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Metalated azolo[1,2,4]triazines. II. Generation, C(4)-substituent dependent stability and electrophile trapping of 7-lithiopyrazolo[5,1-*c*][1,2,4]triazines

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ABSTRACT

7-Lithio-3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazines have been generated for the first time using one-pot nucleophilic addition and metal-halogen exchange reactions in 7-bromopyrazolo[5,1-*c*][1,2,4]triazines. It was found that the stability of 7-lithio species depends highly on the substitution pattern at the C(4) ring position. The rate of the pyrazole ring opening reaction roughly followed the order of the electronegativity of substituents: rapid cycle cleavage took place already at −97 °C for C(4) = O, CH—Ar, CH—C≡CPh, while CH—Alk and CH_2 substituted derivatives were stable in these conditions (Ar = Ph, 4-tolyl; Alk = *t*-Bu, *n*-Bu, *n*-Pr). Quantum chemical modeling showed that the ring opening is accompanied with simultaneous shift of the Li atom towards N(6). Calculated free activation energies are in range from 12.7 to 15.0 kcal*mol^{-1}. Electrophile trapping of fairly stable 4-alkyl-1,7-metalated derivatives at −97 °C using H_2O, DMF or PhCHO allowed the selective side-chain functionalization. Tautomeric exo- and endocyclic double bond equilibrium in the isolated 4-oxo and 4-aryl substituted ring opening products is also discussed on the basis of IR, ^{1}H, ^{13}C NMR, high resolution mass spectra and X-ray powder diffraction analysis.

1. Introduction

Fused 1,2,4-triazines exhibit a wide range of useful properties and represent an interesting target for researchers [1–5]. In particular, azolo[1,2,4]triazine derivatives possess diverse biological activities [6–9], and also have been considered as promising high-nitrogen energetic materials [10]. However, the lack of the data on the reactivity and transformations of these compounds inhibits the potential practical applications. A number of unexpected and still poorly understood factors in the way of direct functionalization of the heterocyclic scaffold is also well known [11–15].

Lithiated heterocycles demonstrate interesting chemical properties, which can provide an easy route to otherwise inaccessible compounds [16–19]. Recently, we have explored the reactivity of some metalated pyrazolo[5,1-*c*][1,2,4]triazines and synthesized the highly functionalized 1,2,4- and 1,3,5-triazines [20–23]. 8-Lithio-4-oxopyrazolo[5,1-*c*][1,2,4]triazines were fairly stable at −97° ÷ −84 °C [21], while (1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazin-4-yl) lithiums rearranged into pyrazolo[1,5-*a*][1,3,5]triazines [23]. In the present work, the generation and the reactivity of novel 7-lithiopyrazolo[5,1-*c*][1,2,4]triazines are considered, and factors affecting on their stability are discussed.

2. Results and discussion

Ethyl 7-bromo-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate **1** was synthesized *via* diazotization of the corresponding 7-amino substituted precursor in the presence of TMSBr [24]. Compound **1** easily reacted with NaH in THF at r.t. with evolution of hydrogen. The formed sodium salt was not

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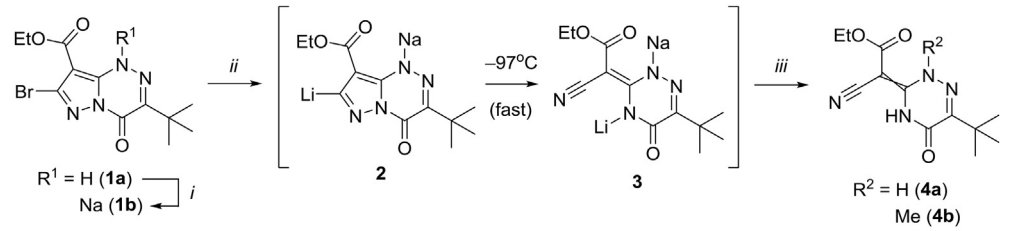


Scheme 1. The reactivity of ethyl 7-bromo-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate **1**. Reagents and conditions: *i*: NaH, THF, 20 °C; *ii*: *n*-BuLi, THF, −97 °C, 5 min; *iii*: KH_2PO_4, H_2O, −97° ÷ 0 °C (**4a**) or 1). *t*-BuOH, −97° ÷ 0 °C; 2). CH_3I, HMPA, THF, 40 °C, 1 h; 3). HCl, H_2O, 0 °C (**4b**).

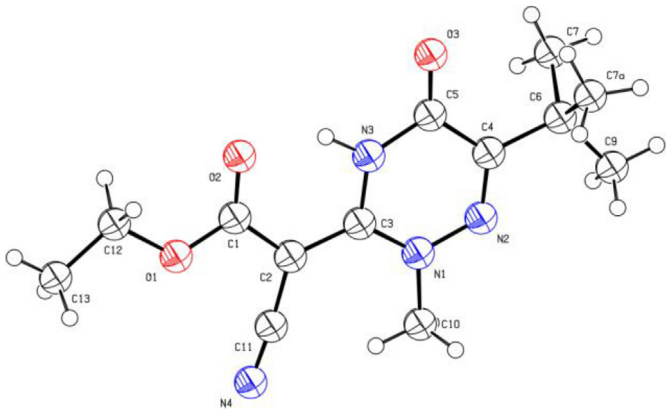
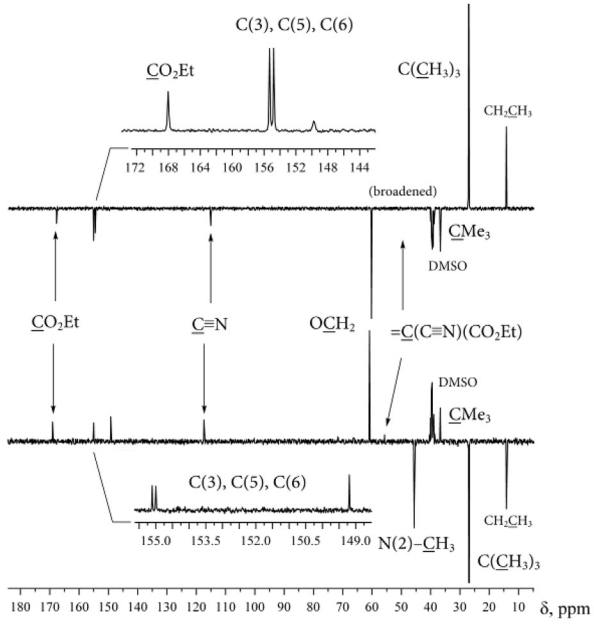


Fig. 1. General view of **4b** in a crystal (powder XRD [26]). Anisotropic displacement parameters for non-hydrogen atoms are drawn at 50% probability.

isolated in its pure form [25] and was directly subjected to metal–halogen exchange using *n*-BuLi at low temperature (−97 °C). We found that the expected 7-lithio derivative **2** underwent a rapid pyrazole ring opening in these conditions [22]. Attempted electrophile trapping of **2** was unsuccessful, and only ethyl 2-(6-*tert*-butyl-5-oxo-4,5-dihydro-1,2,4-triazin-3(2*H*)-ylidene)-2-cyanoacetate (**4a**) was isolated after water quench (Scheme 1). Methylation of the intermediate salt **3** led to the selective formation of N(2)-substituted product **4b**. Unfortunately, we failed to produce an X-ray suitable crystal, however, X-ray powder diffraction was sufficient to confirm the structure of **4b**. It also revealed an intramolecular N–H...O hydrogen bond formed between the N(4)H and the side chain C=O atoms (Fig. 1). The latter led to the preferable stabilization of one of the exocyclic double bond configurational isomers in **4b** (namely, *E*-isomer) and suppressed the double bond rotation. This fact was also supported by the ^{13}C NMR spectra of compounds **4a,b**. Thus, N(2)-unsubstituted compound **4a** exhibited broad signals for one of the 1,2,4-triazine carbons, as well as for the =C(CN)(CO_2Et) carbon atom, due to the rotation of the cyanoacetate moiety (in DMSO-d_6, 20 °C). However, on methylation at the N(2) ring position, both the signals became sharp (Fig. 2).

Reduction of compound **1** using an excess of diborane in the presence of BF_3 [27] in Et_2O/THF at 10°–20 °C for 7 h or 2 weeks, respectively, allowed the synthesis of 8-methyl-4-oxo derivative **5** and 1,2,3,4-tetrahydro pyrazolotriazine **6a** (Scheme 2). Compound **6a** did not react with sodium hydride in various conditions. Interaction of pure compound **6a** with *t*-BuLi at −97 °C was fast and after aqueous work-up led to isolation of C(7)-unsubstituted bicyclic derivative **6b** [27]. No isolable products were formed on attempted electrophile trapping with DMF or PhCHO. This fact can be attributed to the rapid inter- or intramolecular NH hydrogen transfer processes to the metalated C(7) carbon atom. The preliminary



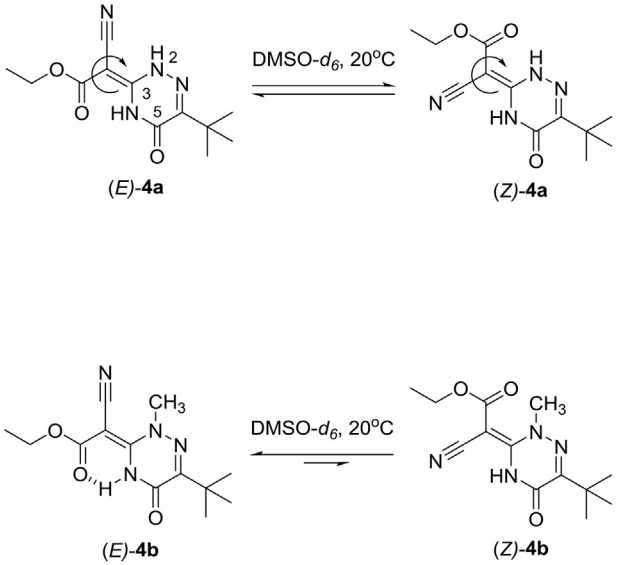
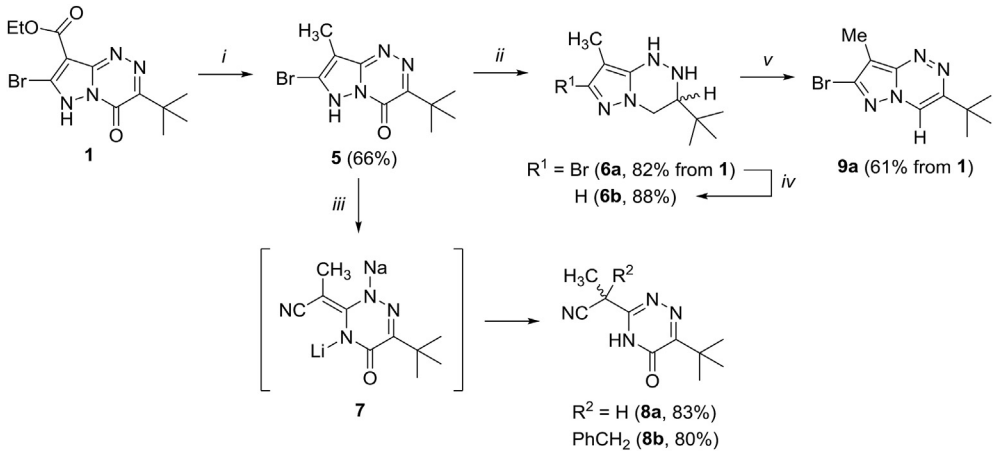


Fig. 2. The *E*/*Z*-exocyclic double bond rotation-induced broadening of the 1,2,4-triazine signals in the ^{13}C NMR (75 or 125 MHz, APT, DMSO-d_6 at r.t.) spectra of **4a,b**.



Scheme 2. Synthesis and reactivity of 7-bromopyrazolo[5,1-*c*][1,2,4]triazines. Reagents and conditions: *i*: 1). BH_3/BF_3, Et_2O/THF, 10 °C, 7 h; 2). KOH, H_2O, $NBu_4^+Br^-$, 80 °C, 30 min (air); *ii*: 1). BH_3/BF_3, Et_2O/THF, 20 °C, 2 weeks; 2). KOH, H_2O, $NBu_4^+Br^-$, 80 °C, 30 min (air); *iii*: 1). NaH, THF, 20 °C; 2). *t*-BuLi, −97 °C, 10 min; 3). H_2O (**8a**) or *t*-BuOH (**8b**), −97° ÷ 0 °C; 4). KH_2PO_4 (**8a**), 0 °C, or $PhCH_2Cl$ (**8b**), HMPA, 40 °C, 1.5 h; *iv*: 1). *t*-BuLi, −97 °C, 10 min; 2). KH_2PO_4, H_2O, −97° ÷ 0 °C; *v*: 1). *t*-BuONO, Δ 40 min (in air); 2). K_2CO_3, EtOH, Δ 40 min.

removal of the acidic hydrogens was accomplished using *n*-butyl magnesium bromide in THF at r.t. However, the resulting bright yellow solution of magnesium hydrazides was remarkably inert toward the lithium-bromine exchange at −97° ÷ −80 °C, even in the presence of a large molar excess of *n*-BuLi or *t*-BuLi. Presumably, this was due to the low solubility or considerable molecular aggregation of polymetalated species.

Interaction of 8-methyl-4-oxopyrazolo[5,1-*c*][1,2,4]triazine **5** with NaH in THF at r.t. and further addition of 4 mol. eq. of *t*-BuLi at −97 °C led to formation of the expected degradation product **8a** after aqueous work-up in 83% yield. Ring opening was fast and completed in several minutes at −97 °C, while only traces of bicyclic derivative could be detected. Alternatively, addition of $PhCH_2Cl$ to the reaction mixture at 40 °C led to the exclusive formation of the side chain alkylation product **8b** (Scheme 2). It is important to emphasize, that in the case of carbonyl substituent in place of CH_3, the ring opening products existed as isomers with exocyclic double bond [22], and alkylation also took place selectively at the N(2) ring position (Scheme 1).

Mechanism of the pyrazole cycle cleavage was modeled at PBE0 [28]-D3 [29]/def2SVP [30] level of theory. PBE0 functional is known to provide accurate results for organometallic chemistry calculations [31] and was recently shown to be well-grounded in theory [32,33]. We have considered a lithiated complex with two sodium cations (full charge: +1), nine explicit THF molecules were included in the model (Fig. 3), and the whole system was surrounded with a polarizable continuum *via* PCM [34] (THF). In the minimum-energy conformation of the substrate ($\mathbf{S_{CO}}$ on Fig. 3), lithium is coordinated with the carbon atom and three THF molecules, one of which is shared with the adjacent sodium ion bound to the N(6) and

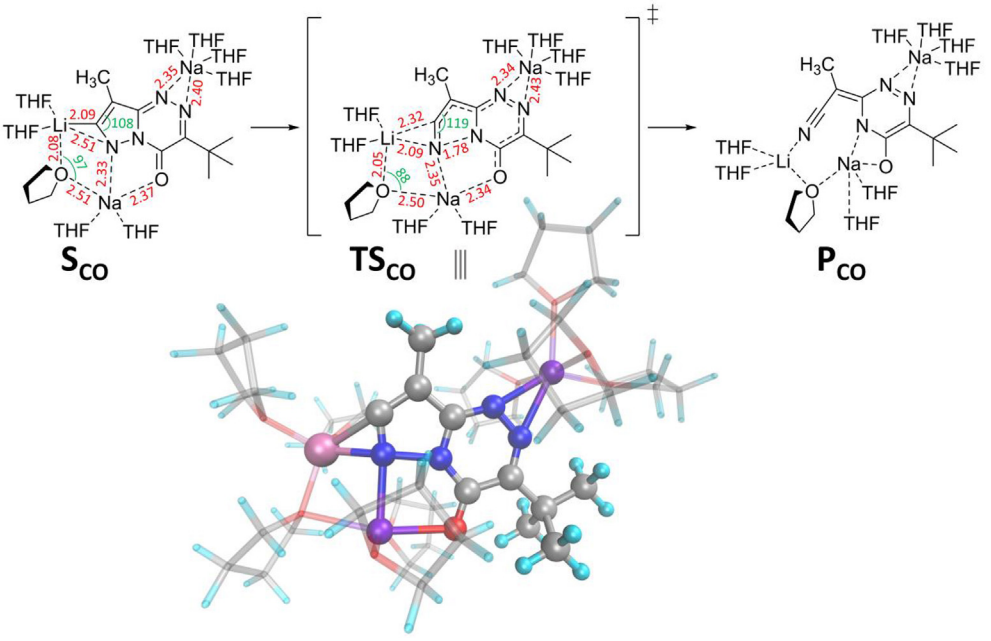
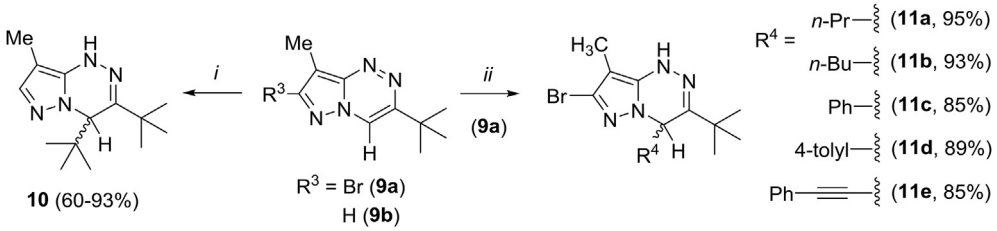


Fig. 3. Computed reaction mechanism. Red numbers designate key bonds lengths in Å, green numbers designate values of key valence angles in degrees. On the molecular visualization, Li atom is colored pink, Na atoms are colored purple and H atoms are light blue; THF molecules are drawn transparent for clarity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



Scheme 3. The reactivity of aromatic pyrazolo[5,1-*c*][1,2,4]triazines **9a,b**. Reagents and conditions: *i*: 1). *t*-BuLi, THF, −97 °C, 10 min; 2). KH_2PO_4, H_2O, −97° ÷ 0 °C; *ii*: 1). R^4MgBr, THF, Δ 15 min (**11a-d**) or 1 h (**11e**); 2). HCl, H_2O, 0 °C.

carbonyl oxygen. The other sodium ion is bound to the N(1)–N(2) bond with almost equal Na…N distances. The reaction proceeds through transition state ($\mathbf{TS_{CO}}$) shown on Fig. 3.

Along the reaction path, as N(5) … N(6) distance increases, the Li atom shifts toward N(6). This is a similar (but reverse) pattern to the recently found in cyclizations of *ortho*-lithiated arylazides [35]. Computed free activation energy of the reaction amounts to 14.2 kcal*mol^{-1}, which is consistent with its speed at −97 °C. Intrinsic reaction coordinate (IRC) following confirmed that the located transition state connects $\mathbf{S_{CO}}$ with product **7** which has $\mathbf{P_{CO}}$ structure.

Aromatization of compound **6a** was achieved using the previously developed method of oxidative nitration/elimination [27]. Thus, heating of cyclic hydrazine **6a** in neat *tert*-butyl nitrite, and further treatment with K_2CO_3 in boiling ethanol led to formation of 7-bromo-3-*tert*-butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazine (**9a**) in 61% overall yield (from **1**). The latter showed interesting reactivity toward the common organometallic reagents. Interaction of triazine **9a** with 1–4 mol eq of *n*-BuLi in THF at −97 °C led to rapid resinification. An application of *t*-BuLi in analogous conditions resulted in color change with formation of a deep blue solution. The color dissipated after several seconds, and compound **10** was isolated in moderate yield after aqueous work-up and chromatographic purification (Scheme 3). Compound **10** could be prepared from C(7)-unsubstituted triazine **9b** [27] in 93% yield. In this case, also, application of *n*-BuLi led only to resinification.

Structure of compound **10** was confirmed by IR, NMR and high resolution mass spectral data. All attempts to selectively perform the Li/Br exchange in triazine **9a** and retard the nucleophilic addition of *t*-BuLi were failed. Application of other types of electrophiles (e.g. DMF or PhCHO) in place of H_2O was also unsuccessful.

The following conclusions were made on the basis of the experimental results: 1). Both the nucleophilic addition and metal-halogen exchange reactions took place easily in these conditions; 2). 7-Lithio-4-*tert*-butyl-1,4-dihydro derivative was stable toward the pyrazole ring opening at −97 °C; 3). Selective Li/Br exchange could not be performed in the presence of the aromatic triazine core.

However, a selective nucleophilic addition of the Grignard reagents without affecting the bromine atom was possible. Thus, interaction of triazine **9a** with various organyl magnesium bromides in boiling THF led to formation of the expected derivatives **11a-e** after acidic work-up in high yields (Scheme 3). Conjugate addition of sp-hybrid PhC≡CMgBr was slow and required prolonged heating. Interestingly, only red tar was formed when PhC≡CLi was employed instead of the corresponding magnesium acetylide, even at −20 °C.

Compounds **11a-e** represented interesting targets for the lithium-bromine exchange and conceivable electrophile trapping. Cleavages of N–N bonds in the C(7)-lithiated pyrazole rings with simple C(4)-aryl (R^4 = Ph, **11c**) and alkyl (R^4 = Me) substituents were modeled at the same level of theory as above, using a similar complexation model (Fig. 4). The located transition states are very similar, but quite differ from $\mathbf{TS_{CO}}$: the Li atom gets off the plane of the pyrazole ring, and the Na atom bounded to the triazine ring is now connected only with N(1). Despite this, the main feature found for the reaction of $\mathbf{S_{CO}}$ (simultaneous N(5)–N(6) bond cleavage and the Li shift towards N(6)) remains. IRC calculations confirmed that the located transition states correspond to the expected reactions. Interestingly, in the minimum-energy conformation of $\mathbf{S_{CHMe}}$, Li and Na ions do not share a THF molecule, like in $\mathbf{S_{CO}}$ and $\mathbf{S_{CHPh}}$. As a result, computed free activation energies of the bond cleavage reactions with Ph and Me substituents R^4 amount to 12.7 and 15.0 kcal*mol^{-1}, respectively. This indicate that 7-lithio-3-*tert*-butyl-8-methyl-4-phenyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine should be more susceptible toward the pyrazole ring opening than the corresponding 4-alkyl substituted ones.

Unfortunately, compounds **11a-e** were inert toward the action of sodium hydride in THF. However, the intermediate magnesium salts formed during the preparation of **11a-e** from **9a** possessed good solubility in THF at low temperature, and were subjected to one-pot metal-halogen exchange using *n*-BuLi or *t*-BuLi as lithium donors (Scheme 4). We found that a large molar excess of an organolithium reagent was required, in order to convert the residual MgBr fragments to MgAlk. The resulting 1,7-metalated species bearing alkyl substituents at the C(4) ring position (**12**, Alk = *n*-Bu, *n*-Pr) were stable toward ring opening at −97 °C, and electrophile trapping using DMF allowed to synthesize aldehyde **13** in 82% overall yield (from **9a**). Application of PhCHO in analogous conditions led to formation of the expected mixture of diastereomers **15** with dr ~3 : 1 (Scheme 4). Attempted reactions of **12** with TMSHal (Hal = Cl, Br) were unsuccessful.

Further nucleophilic addition of H^- and CH_3^- to the aldehyde carbonyl was also possible and was successfully used as another route to C(7)-hydroxymethyl substituted bicyclic derivatives (Scheme 4). Thus, one-pot reduction of compound **13** with $NaBH_4$ led to formation of alcohol **14a**, and N(1)-alkylated derivative **14b** was also synthesized. Highly functionalized compound **18** was synthesized from triazine **9a** using the following one-pot procedure. Nucleophilic addition of *n*-BuMgBr in boiling THF with subsequent C(7)–Br/C(7)–Li and Mg–Br/Mg–*n*-Bu exchange by means of 10–15 mol. eq. of *n*-BuLi at −97 °C, and electrophile trapping using an excess of DMF led to the intermediate aminoacetal salt. Treatment of the latter with $PhCH_2Cl$ at 40 °C for 2 h led to alkylation of both the N(1) and oxygen atoms (compound **16**, detected by TLC). Work-up using hot aqueous HCl and further extraction furnished the N(1)–Bn protected aldehyde **17** (^{1}H NMR ($CDCl_3$), δ C<u>H</u>O = 9.94 ppm), which we failed to purify by means of chromatography on SiO_2. However, reaction of impure **17** with an excess of MeLi in THF/Et_2O at 0 °C led to isolation of the expected secondary alcohol as a *ca.* 1 : 1 mixture of diastereomers **18** in 66% overall yield from **9a** (Scheme 4). In the ^{1}H NMR spectrum, the major isomer showed the expected singlet of C(8)–C<u>H</u>$_3$ at 1.95 ppm and a doublet of the C<u>H</u>$_3$–CH(OH) at 1.34 ppm with $^3J_{H,H}$ = 6.5 Hz.

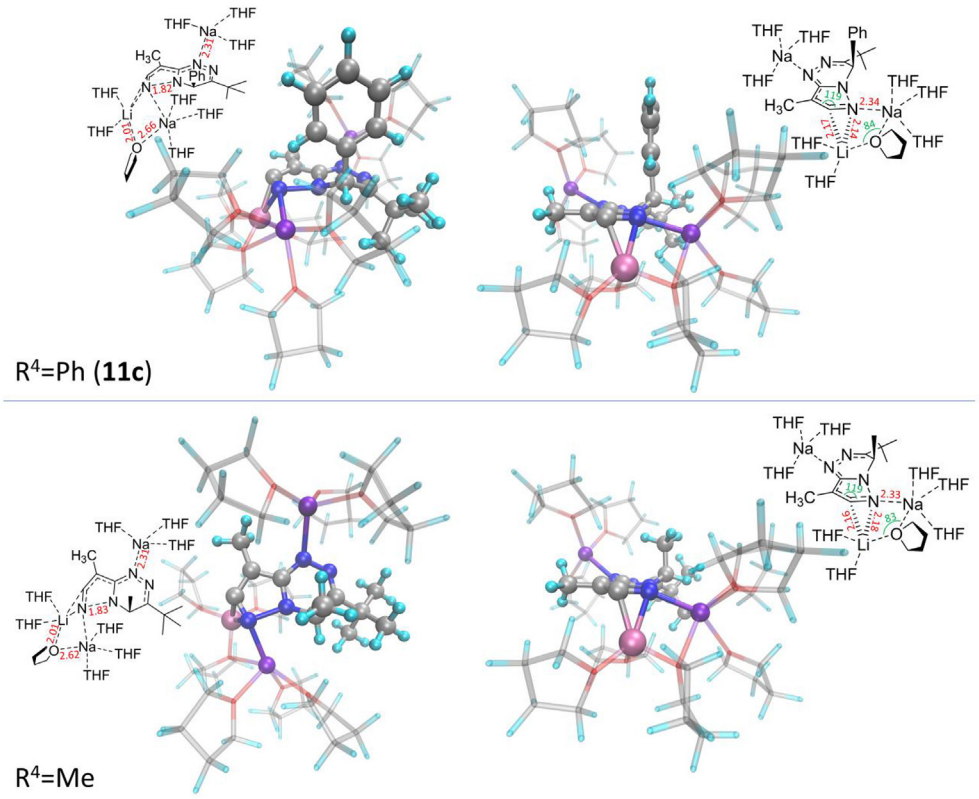
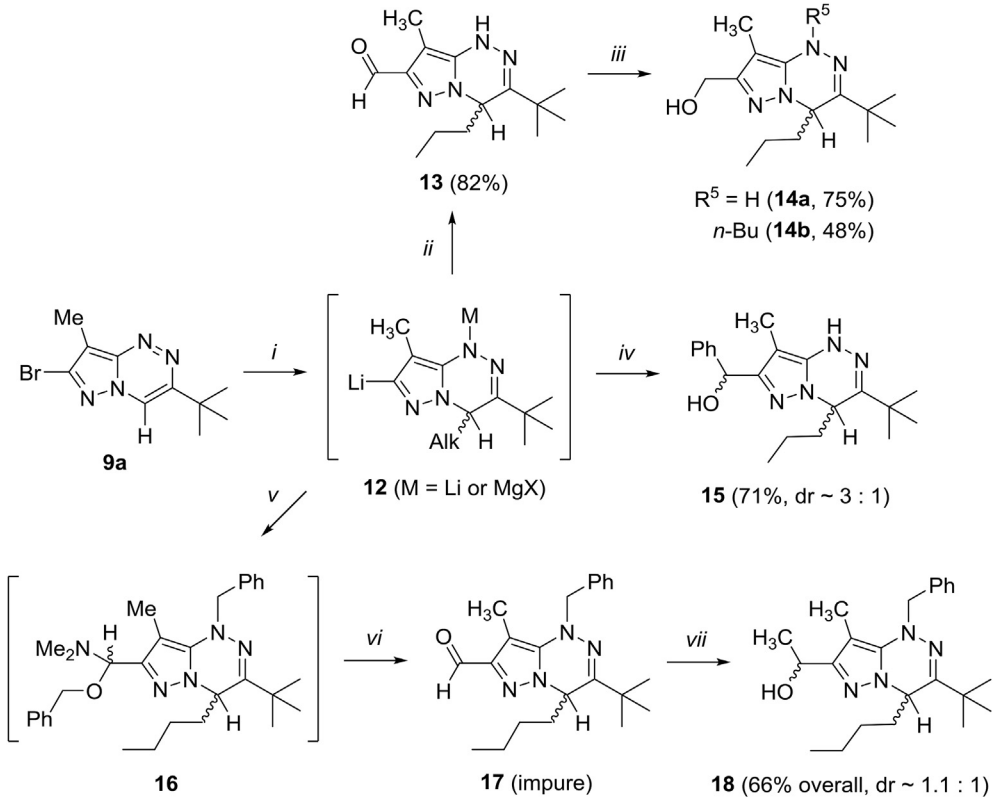
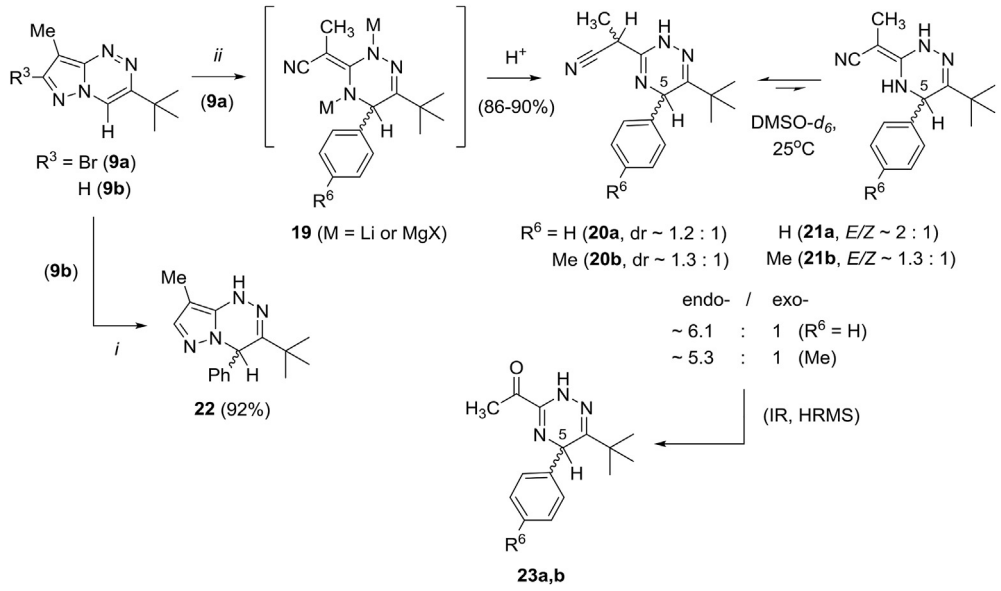


Fig. 4. Structures of located transition states for 7-lithio-3-*tert*-butyl-8-methyl-4-R^4-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines. Red numbers designate key bonds lengths in Å, green numbers designate values of key valence angles in degrees. On the molecular visualizations, Li atom is colored pink, Na atoms are colored purple and H atoms are light blue; THF molecules are drawn transparent for clarity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



Scheme 4. The generation and reactivity of 7-lithio-4-alkyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines **12**. Reagents and conditions: *i*: 1). AlkMgBr, THF, Δ 15 min; 2). *n*-BuLi, THF, −97 °C, 15 min; *ii*: 1). DMF, THF, −97° ÷ −30 °C, 30 min; 2). H_2O, HCl, 0 °C; *iii*: 1). $NaBH_4$ or $NaBH_4$/*n*-BuBr, EtOH/EtOAc, 20 °C, 4–48 h; 2). KH_2PO_4, H_2O, 20 °C; *iv*: 1). PhCHO, THF, −97° ÷ −30 °C, 30 min; 2). KH_2PO_4, H_2O, 0 °C; *v*: 1). DMF, THF, −97° ÷ 0 °C, 40 min; 2). $PhCH_2Cl$, 40 °C, 2 h; *vi*: HCl, H_2O, 50 °C, 1 h; *vii*: 1). MeLi, THF/Et_2O, 0 °C, 20 min; 2). KH_2PO_4, H_2O, 0 °C.



Scheme 5. Ring opening in 7-lithio-4-aryl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines. Reagents and conditions: *i*: 1). PhMgBr, THF, Δ 15 min; 2). HCl, H_2O, 0 °C; *ii*: 1). ArMgBr, THF, Δ 15 min; 2). *n*-BuLi, THF, −97 °C, 15 min; 3). H_2O, HCl, −97° ÷ 0 °C.

Diastereotopic multiplets of the benzyl group methylene protons and the signals of the corresponding carbons were located at 5.06–4.94 ppm (^{1}H) and 56.2, 56.0 ppm (^{13}C). HRMS data contained the characteristic peaks at *m/z* = 383.2796 [M + H, 100%], 405.2624 [M + Na, 5%].

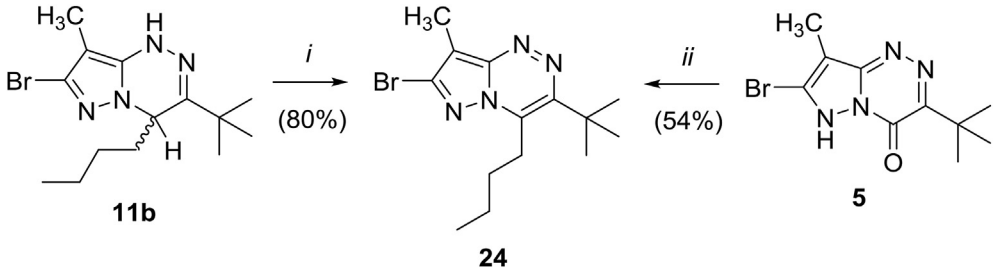
Next, the reactivity of C(4)–Ar substituted C(7)–lithio species was investigated. The resulting polymetalated intermediates were significantly less stable at −97 °C than the corresponding C(4)–Alk substituted derivatives, in agreement with the computational results. The ring opening reaction could be monitored using TLC. Thus, quenching of samples taken from the reaction mixture with an aqueous HCl solution resulted in formation of a mixture of C(7)–unsubstituted 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines (e.g. **22**) and the corresponding ring opening products **20** (Scheme 5).

The degradation was fast and practically complete in 5–15 min already at −97 °C, as no traces of compound **22** (for Ar = Ph) could be detected after the given time. The latter was also synthesized independently from the aromatic triazine **9b** and PhMgBr. The isolated ring opening products **20** exhibited completely different spectral and chromatographic data compared to **22** and were identified as monocyclic 1,2,4-triazines which existed as complex mixtures of tautomers. For example, triazine **20a** existed in DMSO-d_6 solution at 25 °C in a tautomeric equilibrium of endocyclic double bonds diastereomers with dr ~7 : 6, and *ca.* 2 : 1 mixture of the two exocyclic *E/Z*-double bond isomers **21a** (Scheme 5). A total endo-/exo-double bond isomers ratio was approx. equal to 6 : 1. Thus, the peaks of the side chain CH_3 for endo-isomers **20a** in the ^{1}H NMR spectrum were observed as doublets with $^3J_{H,H}$ = 7.2 Hz at 1.26 ppm for the major diastereomer and at 1.40 ppm for the minor one, while for the two *E*- and *Z*-exo-isomers **21a** it showed singlets at 1.57 and 1.49 ppm. The significant broadening of the C(5)–H ring carbon signals in the ^{13}C NMR (APT) spectra of the ring opening products is also worth mentioning.

Interestingly, the experimental HRMS data for compounds **20a, 21a** and **20b, 21b** showed the signals with the maximal spectral intensities at *m/z* = 258.1598 and 272.1765, respectively, which were assigned to [(M − HCN + O) + H] (structures **23a,b**, Scheme 5). The expected peaks of M + H at *m/z* = 269.1753 or 283.1918 with moderate spectral intensities (70% and 20% for **20a, 21a** and **20b, 21b**, respectively) were also observed. Presumably, compounds **20a,b** and **21a,b** could oxidize with transformation of Me–CH(CN)–C(3) group to Me–CO–C(3). This assumption was also substantiated by the IR spectra (recorded in KBr pellets), which showed the characteristic absorption bands at 2251, 2175 (C≡N) and 1703 (C=O) cm^{-1} (for **20a, 21a**) or at 2248, 2168 (C≡N) and 1703 (C=O) cm^{-1} (for **20b, 21b**). However, such anomalies were not observed in the spectra of the related 5-oxo-1,2,4-triazines **4a,b** and **8a,b**, and further investigations are under way.

In a separate experiment, in order to determine the stability of the 4-alkyl-7-lithio species, a solution of metalated derivative **12** (for Alk = *n*-Pr) in THF was slowly heated from −97 °C to *ca.* −60 °C over 30 min. The expected ring opening products were not observed (TLC), and further heating led only to resinification. Despite numerous attempts, we were not able to isolate any analytically pure products from the Br/Li exchange reaction in acetylene **11e**. Interaction of compound **11e** with *t*-BuLi or *n*-BuLi at −97 °C resulted in rapid resinification. In one case, an unidentified, presumably oligomeric compound was isolated, and the ^{1}H NMR spectrum showed several diastereotopic multiplets in the areas characteristic for the side-chain NCC<u>H</u>–CH_3 protons of the previously explored ring opening products.

Aromatization of 7-bromo-3-*tert*-butyl-4-butyl-8-methyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **11b** was achieved using *tert*-butyl nitrite [27] at r.t. for 24 h and further treatment with K_2CO_3 in boiling EtOH (Scheme 6). However, only decomposition was observed in the case of C(4)–Ar substituted 1,4-dihydro derivatives, presumably, due to the competing aryl nitration processes. Triazine **24** was also synthesized in moderate yield from the reaction of *n*-BuMgBr with 7-bromo-3-*tert*-butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-one **5** in neat HMPA [20] at elevated temperature (Scheme 6). Structure of the product **24** was proved by IR, ^{1}H and ^{13}C NMR, and HRMS data. Compound **24** is an interesting target for further investigations of the metal-halogen exchange reaction in azolo[1,2,4]triazine series, and the respective studies are under way.



Scheme 6. Syntheses of 7-bromo-3-*tert*-butyl-4-butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazine (**24**). Reagents and conditions: *i*: 1). *t*-BuONO, 20 °C, 24 h; 2). K_2CO_3, EtOH, Δ 30 min; *ii*: 1). *n*-BuMgBr, HMPA (neat), 70 °C, 30 min; 2). H_2O, HCl, 0 °C.

3. Conclusion

In summary, 7-lithiopyrazolo[5,1-*c*][1,2,4]triazines have been generated for the first time using one-pot nucleophilic addition and the metal-halogen exchange reactions. The rate of the pyrazole ring opening reaction roughly followed the order of the electronegativity of substituents: rapid cycle cleavage took place already at −97 °C for C(4) = O, CH—Ar, CH—C≡CPh, while CH—Alk and CH_2 substituted derivatives were stable in these conditions (Ar = Ph, 4-tolyl; Alk = *t*-Bu, *n*-Bu, *n*-Pr). Quantum chemical modeling showed that the ring opening is accompanied with simultaneous shift of the Li atom towards N(6). Calculated free activation energies are in range from 12.7 to 15.0 kcal*mol^{-1}. Electrophile trapping of the fairly stable 4-alkyl-1,7-metalated derivatives at −97 °C using H_2O, DMF or PhCHO and further nucleophilic addition and alkylation reactions allowed the selective C(7) and N(1) functionalization. It was found that the isolated 8-methyl-4-oxo and 4-aryl substituted ring opening products in DMSO-d_6 solutions at r.t. predominantly existed as the endocyclic double bond tautomers, and benzylation also took place selectively in the side chain, while the ester group stabilized the exocyclic double bond and promoted the ring N(2) methylation. The presented results provide a strong basis for further investigations of reactivity of metalated polycyclic triazines. The transformations described can also be effectively used for the preparation of novel highly functionalized pyrazolo[5,1-*c*][1,2,4]triazine and 1,2,4-triazine derivatives.

4. Experimental section

4.1. General information

Melting points were determined on a STUART Melting point SMP30 apparatus. IR spectra were recorded in KBr pellets using Agilent Cary 660 FTIR infrared spectrophotometer. NMR spectra were recorded on Bruker AM-300, DRX-500, or AV-600 spectrometers operating at working frequencies of 300 or 500 MHz (^{1}H), 75, 126 or 151 MHz (^{13}C). Chemical shifts were related to that of the DMSO-d_5 or $CHCl_3$ (^{1}H), DMSO-d_6 or $CDCl_3$ (^{13}C). High resolution mass spectra were recorded on a Bruker MicroTOF II instrument in positive ion mode (capillary voltage 4500 V) using electrospray ionisation (ESI) and methanol or acetonitrile as a solvent. Elemental analysis was performed on a PerkinElmer Series II 2400 Elemental Analyzer. The X-ray powder diffraction was performed on a Bruker AXS D8 Advance Vario X-ray powder diffractometer equipped with primary monochromator (Cu-$K_{\alpha 1}$, λ = 1.54056 Å) and 1D LynxEye PSD. The inner temperature of the reaction mixtures was monitored using Pt100 RTD and a Dwyer Series 32B 1/32 DIN Temperature/Process Controller (precision ±0.1 K). Flash and column chromatography were performed using Merck Silica gel for chromatography (60–200 μm). All operations, except for chromatography, were carried out under an atmosphere of dry argon. Tetrahydrofuran and diethyl ether were boiled with potassium/sodium alloy and distilled in argon atmosphere from K/Na immediately prior to use. HMPA was distilled from CaH_2 at reduced pressure and stored in argon atmosphere over molecular sieves. Phenyl acetylene was distilled at reduced pressure and further passed through a layer of calcined Al_2O_3. Commercial *n*-BuLi (2.5 M in hexane, Acros Organics) and *t*-BuLi (1.7 M in pentane, Sigma-Aldrich) solutions were used. Starting compounds **1** and **9b** were prepared according to the literature procedures [24,27], and MeLi was prepared from *n*-BuLi and MeI as described in Ref. [36]. Alkyl and aryl magnesium bromides were prepared as described in Refs. [37,38]. Diborane, lithium organometallics and the related compounds are highly toxic and flammable. In the case of spontaneous ignition, liq. N_2 should be used to fight the fire.

4.1.1. Computational details

Quantum chemical calculations were performed using PBE0 [28]-D3 [29] density functional with def2SVP [30] basis set; Gaussian09 D.01 [39] program package was used for all calculations. The PBE0 functional was chosen because it is known to be accurate for organic chemistry calculations [31] and has recently been shown to be well-grounded in theory. Harmonic frequencies were calculated for every located stationary point to ascertain its type. Free energies were calculated based on the computed harmonic frequencies using GoodVibes program [40] with Grimme quaziharmonic entropic correction [41] at 176.15 K and concentration 0.035 mol*l^{-1}.

4.2. General procedure for the preparation of compounds ***4a,b***

NaH (60% suspension in mineral oil, 0.10 g, 2.5 mmol) was added in one portion to a solution of compound **1a** (0.35 g, 1.02 mmol) in THF (30 ml) at 20 °C. Gas evolution was observed (formation of **1b**, not isolated). The resulting mixture was stirred at r.t. for 10 min and cooled to −97 °C (CH_2Cl_2/liq. N_2 bath). Next, a pre-cooled (−25 °C) solution of *n*-BuLi (2.5 M in hexane, 0.5 ml, 1.25 mmol) was added dropwise over 3 min with vigorous stirring. The resulting bright red reaction mixture was further stirred for 2–3 min at −97 °C (TLC monitoring). Next, a pre-cooled (0 °C) solution of H_2O (1 ml, 55.5 mmol, for the synthesis of compound **4a**) or *t*-BuOH (0.2 g, 2.70 mmol, for the synthesis of compound **4b**) in THF (5 ml) was added dropwise over 3 min with vigorous stirring. The cooling bath was removed, and the resulting mixture was stirred for 30 min (the internal temperature reached 0 °C). Then, crystalline KH_2PO_4 (1 g, 7.35 mmol, for **4a**) or NaH (60% dispersion in mineral oil, 0.15 g, 3.75 mmol), HMPA (0.5 ml) and CH_3I (0.5 ml, 8.03 mmol, for **4b**) were added in one portion.

For the preparation of **4a**, water (50 ml) and EtOAc (30 ml) were added, the organic phase was separated, and the mother liquor was further extracted with EtOAc (3 × 30 ml). The combined organic layers were dried with anhydrous $MgSO_4$ and filtered. The solvents

were evaporated *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:10–1:5) to give **4a**.

Alternatively, the reaction mixture was stirred at 40 °C for 1 h (TLC monitoring for **4b**). Then, cooled water (0 °C, 100 ml) and conc. HCl/H_2O solution (3 ml) were slowly added. The resulting mixture was stirred for 10 min and extracted with EtOAc (4 × 30 ml). The combined organic layers were washed with cooled 1% HCl/H_2O solution (0 °C, 1 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were evaporated *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:10–1:5) to give **4b**.

4.2.1. Ethyl (E/Z)-2-(6-tert-butyl-5-oxo-4,5-dihydro-1,2,4-triazin-3(2H)-ylidene)-2-cyanoacetate (*4a*)

White powder, yield 0.25 g (93%). M.p. and spectral data for compound **4a** coincided with those described in Ref. [22].

4.2.2. Ethyl (E)-2-(6-tert-butyl-2-methyl-5-oxo-4,5-dihydro-1,2,4-triazin-3(2H)-ylidene)-2-cyanoacetate (*4b*)

Colorless needles, yield 0.24 g (85%). M.p. and spectral data for compound **4b** coincided with those described in Ref. [22]. Sample of **4b** was placed between two polyimide films and mounted on a Bruker AXS D8 Advance Vario X-ray powder diffractometer equipped with primary monochromator (Cu-$K_{\alpha 1}$, $\lambda = 1.54056$ Å) and 1D LynxEye PSD. Data were collected at room temperature in the range 2–90° 2θ with a 0.01° 2θ step size in transmission mode.

The diffraction pattern was indexed using the SVD (singular value decomposition) index algorithm [42] as implemented in Bruker TOPAS 5.0 [43], and space group determination was carried out using systematic absences analysis. Parallel tempering, as implemented in FOX [44] was used to solve the crystal structure in direct space. Additional symmetry was found and the space group was changed from $P2_1$ to $P2_1/m$. The restrained Rietveld refinement (in Bruker TOPAS 5.0) was carried out using the methodology described elsewhere [45]. Agreement between the Rietveld refined structures and the PWDFT-D optimized ones was good [46].

PW-DFT-D calculations was performed in VASP 5.4.4 [47–50] using PBE functional [51] corrected by Grimme D3 van der Waals correction [29] with Becke-Jonson damping [52]. A plane-wave basis set with 'normal' projector augmented wave (PAW) pseudopotentials [53,54] as supplied with VASP was employed. Optimizations with both fixed and optimized unit-cell parameters were performed using energy cutoff of 600 eV and 4 k-points.

4.3. General procedure for the preparation of compounds *5*, *6a* and *9a*

$LiBH_4$ (7 g, 321 mmol) was added in small portions over 1.5 h and with vigorous stirring to a stirred solution of compound **1** (15 g, 43.7 mmol) in a mixture of Et_2O (30 ml), THF (30 ml) and $BF_3 \cdot Et_2O$ (45 ml, 365 mmol) at 0 °C. After the addition was complete, the resulting mixture was further stirred at 10 °C for 7 h (for the synthesis of **5**) or 2 weeks at 15°–20 °C (for the synthesis of **6a**, **9a**). Then, the red reaction mixture was added dropwise over 1 h to a cooled (0 °C) solution of KOH (30 g, 535 mmol) in H_2O (200 ml) and *n*-butanol (5 ml) with vigorous stirring. After the addition was complete, $NBu_4^+Br^-$ (0.5 g, 1.55 mmol) and EtOAc (20 ml) were added. Next, Et_2O was completely removed by gentle heating, and the reaction mixture was stirred vigorously at 80 °C for 30 min in air atmosphere. Then, it was cooled and the precipitate formed was filtered and washed with water (5 × 30 ml). The solid obtained was extracted with hot $CHCl_3$ (50 °C, 5 × 50 ml). For the preparation of compound **5**, the combined organic extracts were washed with 15% HCl/H_2O solution (5 × 100 ml) and H_2O (5 × 100 ml), in order to remove traces of hydrazine **6a**. The organic phase was dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give a residue, which was purified *via* flash chromatography (eluent 100% $CHCl_3$) to give **5**.

Alternatively, the organic extracts were evaporated *in vacuo* (for the synthesis of **6a**, **9a**) to give a residue, which was purified *via* flash chromatography (eluent EtOAc: hexane = 1:6–1:2) to give **6a**. For the synthesis of **9a**, freshly distilled *t*-BuONO (150 ml) was added to the residue (crude compound **6a**), and the resulting mixture was boiled under reflux (50 °C) for 40 min in air atmosphere. Then, the solvents were removed *in vacuo*, and 95% aqueous EtOH (50 ml) and K_2CO_3 (15 g, 109 mmol) were added in one portion. The resulting mixture was boiled under reflux for 40 min. Then, it was cooled, and hexane (150 ml) was added. The precipitate formed was filtered and washed with hot hexane (50 °C, 5 × 30 ml). The combined organic filtrates were evaporated *in vacuo* to give a residue, which was purified *via* flash chromatography (eluent EtOAc: hexane = 0:1–1:50) to give **9a**.

4.3.1. 7-Bromo-3-tert-butyl-8-methylpyrazolo[5,1-c][1,2,4]triazin-4(6H)-one (*5*)

Colorless crystals, yield 8.21 g (66%), mp 295–305 °C (sublimation). IR ν_{max} (KBr): 3254, 3188, 3143 (NH), 3083, 3057, 2956, 2929, 2868 (CH), 1691 (CO), 1625, 1560, 1536, 1486, 1475, 1458, 1392, 1374, 1344, 1288, 1215, 1188, 1137, 1073, 1019, 953, 848, 793, 778, 744, 721, 676, 623, 543, 524 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.82 (s, 1H, N<u>H</u>), 2.06 (s, 3H, C(8)–C<u>H</u>$_3$), 1.37 (s, 9H, *t*-Bu).^{13}C-NMR APT (126 MHz, DMSO-d_6): δ 147.49, 144.29, 141.52, 137.49 (C(3), C(4), C(7), C(8a)), 95.89 (C(8)), 37.08 (<u>C</u>(CH$_3$)$_3$), 28.30 (C(<u>C</u>H$_3$)$_3$), 7.75 (C(8)–<u>C</u>H$_3$). HRMS *m/z* (%) Calcd for $C_{10}H_{13}BrN_4O$ M + H = 285.0346, 287.0325, M + Na = 307.0165, 309.0145. Found: 285.0349, 287.0328 [M + H, 100%], 307.0164, 309.0143 [M + Na, 70%]. *Anal.* Calcd for $C_{10}H_{13}BrN_4O$: C, 42.12; H, 4.60; N, 19.65. Found: C, 42.10; H, 4.64; N, 19.63.

4.3.2. 7-Bromo-3-tert-butyl-8-methyl-1,2,3,4-tetrahydropyrazolo[5,1-c][1,2,4]triazine (*6a*)

Colorless crystals, yield 9.84 g (82%), mp 163–164 °C (decomp.). IR ν_{max} (KBr): 3275, 3237 (NH), 3067, 2965, 2931, 2900, 2873, 2755, 2719 (CH), 1582, 1537, 1490, 1466, 1437, 1398, 1384, 1366, 1338, 1263, 1254, 1196, 1176, 1127, 1090, 1064, 1033, 949, 932, 904, 863, 797, 776, 743, 695, 666, 631, 609, 542, 507, 488, 437 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.23 (d, J = 3.6 Hz, 1H, N(1)–<u>H</u>), 4.27–4.22, 3.96–3.90 (2 diastereotopic m, 1H + 1H, C(4)<u>H</u>$_2$), 3.66 (t, J = 11.3 Hz, 1H, C(3)–<u>H</u>), 2.65–2.55 (m, 1H, N(2)–<u>H</u>), 1.73 (s, 3H, C(8)–C<u>H</u>$_3$), 0.95 (s, 9H, *t*-Bu). ^{13}C-NMR APT (126 MHz, DMSO-d_6): δ 143.72 (C(7)), 126.49 (C(8a)), 94.52 (C(8)), 61.41 (<u>C</u>(4)H$_2$), 46.81 (<u>C</u>(3)–H), 32.47 (<u>C</u>(CH$_3$)$_3$), 26.87 (C(<u>C</u>H$_3$)$_3$), 7.74 (C(8)–<u>C</u>H$_3$). HRMS *m/z* (%) Calcd for $C_{10}H_{17}BrN_4$ M + H = 271.0553, 273.0533. Found: 271.0555, 273.0558 [M + H, 100%]. *Anal.* Calcd for $C_{10}H_{17}BrN_4$: C, 43.97; H, 6.27; N, 20.51. Found: C, 43.95; H, 6.32; N, 20.52.

4.3.3. 7-Bromo-3-tert-butyl-8-methylpyrazolo[5,1-c][1,2,4]triazine (*9a*)

Yellow crystals, yield 7.15 g (61%), mp 118–119 °C. IR ν_{max} (KBr): 2968, 2922, 2872 (CH), 1548, 1467, 1383, 1366, 1335, 1315, 1279, 1260, 1235, 1207, 1173, 1088, 1032, 953, 865, 857, 819, 764, 751, 654, 625, 555, 536 cm $^{-1}$.^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.26 (s, 1H, C(4)–<u>H</u>), 2.54 (s, 3H, C(8)–C<u>H</u>$_3$), 1.53 (s, 9H, *t*-Bu). ^{13}C-NMR APT (75 MHz, $CDCl_3$): δ 153.47, 147.00, 136.06 (C(3), C(7), C(8a)), 116.43 (<u>C</u>(4)–H), 108.84 (C(8)), 35.27 (<u>C</u>(CH$_3$)$_3$), 29.53 (C(<u>C</u>H$_3$)$_3$), 7.88 (C(8)–<u>C</u>H$_3$). HRMS *m/z* (%) Calcd for $C_{10}H_{13}BrN_4$ M + H = 269.0396, 271.0376. Found: 269.0401, 271.0380 [M + H, 100%]. *Anal.* Calcd for $C_{10}H_{13}BrN_4$: C, 44.63; H, 4.87; N, 20.82. Found: C, 44.64; H, 4.85; N, 20.80.

4.4. Synthesis of compounds **6b**, **8a,b** and **10**

A pre-cooled solution of *t*-BuLi (0°–5 °C, 1.7 M in pentane, 2.5 ml, 4.25 mmol) was added dropwise with vigorous stirring over 2 min to a solution of the corresponding compound **6a**, **9a** or **9b** (1 mmol, for the synthesis of **6b** or **10**, respectively), or a mixture of NaH (0.11 g, 2.75 mmol) and compound **5** (0.3 g, 1.05 mmol, for **8a,b**) had been stirred at r.t. for 15 min in THF (30 ml), at −97 °C (CH_2Cl_2/liq. N_2 cooling bath). The resulting mixture was further stirred at −97 °C for 10 min. Then, the cooling bath was removed, and a cooled (0 °C) solution of H_2O (1 ml, 55.5 mmol, for **6b**, **8a**, **10**) or *t*-BuOH (0.25 g, 3.37 mmol, for **8b**) in THF (5 ml) was added dropwise with vigorous stirring over 2 min. The reaction mixture was stirred for 40 min (the internal temperature reached 0 °C).

For the synthesis of **6b**, **8a** and **10**, KH_2PO_4 (1 g, 7.35 mmol), water (30 ml) and EtOAc (40 ml) were added with stirring. The organic phase was separated, and the mother liquor was further extracted with EtOAc (5 × 30 ml). The combined organic phases were washed with 1% HCl/H_2O solution (2 × 100 ml, for **8a** and **10** only) and water (2 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:1–2:1 for **6b**; 1:3–1:1 for **8a**; 1:10–1:4 for **10**) to give compounds **6b** (yield 0.17 g, 88%), **8a** or **10**.

For the synthesis of **8b**, NaH (60% dispersion in mineral oil, 0.15 g, 3.75 mmol), HMPA (0.5 ml) and $PhCH_2Cl$ (0.5 ml, 4.35 mmol) were added in one portion, instead of KH_2PO_4. The resulting mixture was stirred at 40 °C for 1.5 h (TLC monitoring). Then, it was cooled to 0 °C, and water (5 ml) was added dropwise with stirring. Next, water (50 ml) and conc. HCl/H_2O solution (7 ml) were added in one portion with stirring. The reaction mixture was extracted with EtOAc (5 × 30 ml). The combined organic phases were washed with 1% HCl/H_2O solution (2 × 100 ml) and water (2 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:10–1:3) to give compound **8b**.

Spectral data and m.p. for compound **6b** coincided with those described in Ref. [27].

4.4.1. 2-(6-tert-Butyl-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl) propanenitrile (**8a**)

White powder, yield 0.18 g (83%), mp 181–182 °C. IR ν_{max} (KBr): 3242 (NH), 3044, 2968, 2930, 2871, 2793 (CH), 2255, 2188 (CN), 1693 (CO), 1648, 1624, 1594, 1560, 1496, 1479, 1457, 1402, 1376, 1364, 1333, 1293, 1273, 1243, 1214, 1159, 1129, 1111, 1076, 1057, 1025, 985, 936, 899, 864, 820, 751, 707, 652, 589, 554, 521, 457, 438, 414 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 14.0–13.6 (br s, 1H, NH), 4.24 (q, J = 7.3 Hz, 1H, NC–CH–CH_3), 1.59 (d, J = 7.2 Hz, 3H, NC–CH–CH_3), 1.29 (s, 9H, *t*-Bu). ^{13}C-NMR APT (126 MHz, DMSO-d_6, signals of C(5), C(6) were not observed due to the broadening): δ 118.88 (CN), 60.18 (C(3)), 37.13 ($C(CH_3)_3$), 30.32 (NC–CH–CH_3), 27.38 ($C(CH_3)_3$), 17.14 (NC–CH–CH_3). HRMS *m/z* (%) Calcd for $C_{10}H_{14}N_4O$ M + H = 207.1240, M + Na = 229.1060, M + K = 245.0799. Found: 207.1243 [M + H, 100%], 229.1052 [M + Na, 60%], 245.0795 [M + K, 10%]. *Anal.* Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.17. Found: C, 58.19; H, 6.89; N, 27.16.

4.4.2. 2-(6-tert-Butyl-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl)-2-methyl-3-phenylpropanenitrile (**8b**)

White solid, yield 0.25 g (80%), mp 165–166 °C. IR ν_{max} (KBr): 3221 (NH), 3090, 3064, 3032, 2961, 2932, 2872 (CH), 2247, 2202 (CN), 1654, 1616 (CO), 1553, 1490, 1477, 1458, 1393, 1361, 1288, 1274, 1203, 1129, 1072, 1026, 1003, 936, 911, 901, 859, 818, 795, 763, 734, 702, 669, 652, 635, 611, 590, 554, 523, 484, 445 cm $^{-1}$.^{1}H-NMR (500 MHz, DMSO-d_6): δ 14.1–13.9 (br s, 1H, NH), 7.35–7.30, 7.18–7.16 (2 m, 5H, Ph), 3.41–3.28 (diastereotopic m, 2H, $PhCH_2$), 1.73 (s, 3H, CH_3), 1.32 (s, 9H, *t*-Bu). ^{13}C-NMR APT (75 MHz, DMSO-d_6, signals of C(3), C(5), C(6) were not observed due to the broadening, also at 126 MHz, see the S.I. file): δ 134.25 (*ipso*-C Ph), 129.91, 128.27, 127.57 (2 *o*-, 2 *m*- and *p*-CH Ph), 119.54 (CN), 44.40 ($PhCH_2$–C(CN)CH_3), 42.87 ($PhCH_2$), 36.65 ($C(CH_3)_3$), 26.93 ($C(CH_3)_3$), 22.47 ($PhCH_2$–C(CN)CH_3). HRMS *m/z* (%) Calcd for $C_{17}H_{20}N_4O$ M + H = 297.1710, M + Na = 319.1529, M + K = 335.1269. Found: 297.1707 [M + H, 100%], 319.1520 [M + Na, 10%], 335.1259 [M + K, 5%]. *Anal.* Calcd for $C_{17}H_{20}N_4O$: C, 68.90; H, 6.80; N, 18.90. Found: C, 68.92; H, 6.85; N, 18.91.

4.4.3. 3,4-di-tert-Butyl-8-methyl-1,4-dihydropyrazolo[5,1-c][1,2,4] triazine (**10**)

Colorless crystals, yield 0.15 g (60%, from **9a**); 0.23 g (93%, from **9b**), mp 170–180 °C (sublimation). IR ν_{max} (KBr): 3252, 3179 (NH), 3096, 3068, 3037, 2967, 2899 (CH), 1619, 1575, 1541, 1499, 1479, 1467, 1459, 1406, 1367, 1341, 1324, 1307, 1276, 1253, 1223, 1200, 1190, 1152, 1121, 1097, 1038, 1029, 988, 920, 879, 847, 819, 797, 768, 727, 689, 650, 638, 606, 540, 444, 427 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.17 (s, 1H, N(1)–H), 7.09 (s, 1H, C(7)–H), 4.88 (s, 1H, C(4)–H), 1.93 (s, 3H, C(8)–CH_3), 1.23 (s, 9H, C(3)–*t*-Bu), 0.86 (s, 9H, C(4)–*t*-Bu). ^{13}C-NMR APT (151 MHz, DMSO-d_6, peaks of CMe_3 were overlapped with the solvent peak): δ 150.79, 138.88 (C(3), C(8a)), 138.49 (C(7)–H), 92.30 (C(8)), 61.27 (C(4)–H), 30.24, 28.41 ($2C(CH_3)_3$), 7.15 (C(8)–CH_3). HRMS *m/z* (%) Calcd for $C_{14}H_{24}N_4$ M + H = 249.2074. Found: 249.2068 [M + H, 100%]. *Anal.* Calcd for $C_{14}H_{24}N_4$: C, 67.70; H, 9.74; N, 22.56. Found: C, 67.71; H, 9.76; N, 22.55.

4.5. Preparation of a solution of (phenylethynyl)magnesium bromide

n-BuMgBr (1 M in Et_2O, 2 ml, 2 mmol) was added dropwise with stirring over 1 min to a cooled (0 °C) solution of PhC≡CH (0.3 ml, 2.73 mmol) in THF (10 ml). The resulting mixture was stirred vigorously for 20 min at 0 °C and used immediately in the next reaction step.

4.6. General procedure for the preparation of compounds **11a-e**, **13**, **14a,b**, **15**, **17**, **18**, mixture of isomers **20a,b** and **21a,b**, and compound **22**

A solution of the corresponding organyl magnesium bromide (2 mmol, in Et_2O or THF) was added in one portion to a solution of compound **9a** (0.3 g, 1.11 mmol) or compound **9b** (0.2 g, 1.05 mmol, for the synthesis of **22**) in THF (30 ml). The resulting mixture was boiled under reflux (60 °C) for 15 min (for **11a-d** and **22**) or 1 h (for **11e**, TLC monitoring), cooled and used immediately in the next lithium-bromine exchange reaction step.

For the isolation of compounds **11a-e** and **22**, the reaction mixture was cooled to 0 °C, and H_2O (5 ml) was added dropwise over 3 min with vigorous stirring. Next, water (50 ml) and conc. HCl/H_2O solution (8 ml) were added in one portion, the resulting mixture was stirred at 0 °C for 5 min and extracted with EtOAc (5 × 30 ml). The combined organic phases were washed with water (1 × 100 ml), dried with anhydrous $MgSO_4$, and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* flash-chromatography (eluent EtOAc:hexane = 1:20–1:8 for **11a,b**; 1:10–1:4 for **11c,d** and **22**; $CHCl_3$:hexane = 1:1–4:1 for **11e**) to give compounds **11a-e** or **22**.

*4.6.1. 7-Bromo-3-tert-butyl-8-methyl-4-propyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine (**11a**)*

White powder, yield 0.33 g (95%), mp 166–167 °C. IR ν_{max} (KBr): 3253, 3190 (NH), 3086, 3060, 2966, 2872 (CH), 1625, 1587, 1536, 1474, 1465, 1434, 1396, 1384, 1365, 1324, 1286, 1251, 1232, 1198, 1139, 1101, 1089, 1054, 1021, 967, 920, 901, 881, 850, 809, 782, 727, 696, 675, 631, 596, 537, 485, 447, 434 cm $^{-1}$.^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.41 (s, 1H, N(1)–H), 5.07–5.03 (diastereotopic m, 1H, C(4)–H), 1.93 (s, 3H, C(8)–CH$_3$), 1.72–1.65 (diastereotopic m, 2H, C(4)–CH$_2$CH$_2$CH$_3$), 1.34–1.26 (diastereotopic m, 2H, C(4)–CH$_2$CH$_2$CH$_3$), 1.23 (s, 9H, *t*-Bu), 0.88 (t, J = 7.3 Hz, 3H, C(4)–CH$_2$CH$_2$CH$_3$). ^{13}C-NMR APT (75 MHz, $CDCl_3$): δ 154.06, 138.00, 127.87 (C(3), C(7), C(8a)), 94.63 (C(8)), 53.97 (C(4)–H), 37.24 (C(CH$_3$)$_3$), 34.99 (C(4)–CH$_2$CH$_2$CH$_3$), 28.87 (C(CH$_3$)$_3$), 18.72 (C(4)–CH$_2$CH$_2$CH$_3$), 13.74 (C(4)–CH$_2$CH$_2$CH$_3$), 7.59 (C(8)–CH$_3$). HRMS *m/z* (%) Calcd for $C_{13}H_{21}BrN_4$ M + H = 313.1022, 315.1002. Found: 313.1013, 315.0994 [M + H, 100%]. *Anal.* Calcd for $C_{13}H_{21}BrN_4$: C, 49.85; H, 6.76; N, 17.89. Found: C, 49.83; H, 6.81; N, 17.86.

*4.6.2. 7-Bromo-3-tert-butyl-4-butyl-8-methyl-1,4-dihydropyrazolo [5,1-c][1,2,4]triazine (**11b**)*

White powder, yield 0.34 g (93%), mp 136–137 °C. IR ν_{max} (KBr): 3254, 3192 (NH), 3083, 2958, 2931, 2870 (CH), 1649, 1625, 1587, 1537, 1466, 1396, 1384, 1364, 1272, 1250, 1199, 1133, 1053, 959, 924, 884, 847, 787, 726, 692, 630, 595, 537, 432 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.28 (s, 1H, N(1)–H), 5.09–5.06 (diastereotopic m, 1H, C(4)–H), 1.85 (s, 3H, C(8)–CH$_3$), 1.71–1.49 (diastereotopic m, 2H, C(4)–CH$_2$CH$_2$CH$_2$CH$_3$), 1.35–1.01 (diastereotopic m, 4H, C(4)–CH$_2$CH$_2$CH$_2$CH$_3$), 1.18 (s, 9H, *t*-Bu), 0.78 (t, J = 6.9 Hz, 3H, C(4)–CH$_2$CH$_2$CH$_2$CH$_3$). ^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 151.00, 138.17, 126.78 (C(3), C(7), C(8a)), 92.96 (C(8)), 52.72 (C(4)–H), 36.77 (C(CH$_3$)$_3$), 32.13 (C(4)–CH$_2$CH$_2$CH$_2$CH$_3$), 28.55 (C(CH$_3$)$_3$), 26.81 (C(4)–CH$_2$CH$_2$CH$_2$CH$_3$), 21.58 (C(4)–CH$_2$CH$_2$CH$_2$CH$_3$), 13.70 (C(4)–CH$_2$CH$_2$CH$_2$CH$_3$), 7.24 (C(8)–CH$_3$). HRMS *m/z* (%) Calcd for $C_{14}H_{23}BrN_4$ M + H = 327.1179, 329.1159. Found: 327.1178, 329.1161 [M + H, 100%]. *Anal.* Calcd for $C_{14}H_{23}BrN_4$: C, 51.38; H, 7.08; N, 17.12. Found: C, 51.41; H, 7.13; N, 17.11.

*4.6.3. 7-Bromo-3-tert-butyl-8-methyl-4-phenyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine (**11c**)*

White powder, yield 0.33 g (85%), mp 235–236 °C. IR ν_{max} (KBr): 3248, 3177 (NH), 3064, 3034, 2964, 2949, 2900, 2868, 1622, 1591, 1542, 1494, 1475, 1457, 1396, 1382, 1362, 1315, 1283, 1258, 1241, 1199, 1158, 1129, 1099, 1061, 1022, 1004, 968, 931, 912, 860, 842, 795, 753, 732, 702, 691, 654, 635, 622, 612, 555, 545, 488, 438, 420 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.62 (s, 1H, N(1)–H), 7.40–7.21 (m, 5H, Ph), 6.18 (s, 1H, C(4)–H), 1.84 (s, 3H, C(8)–CH$_3$), 1.05 (s, 9H, *t*-Bu). ^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 149.85, 139.43, 136.99 (C(3), C(7), C(8a)), 127.85 (*ipso*-C Ph), 128.84, 128.38, 127.57 (2 *o*-, *p*-, and 2 *m*- CH Ph), 93.26 (C(8)), 56.06 (C(4)–H), 37.31 (C(CH$_3$)$_3$), 28.67 (C(CH$_3$)$_3$), 7.22 (C(8)–CH$_3$). HRMS *m/z* (%) Calcd for $C_{16}H_{19}BrN_4$ M + H = 347.0866, 349.0846. Found: 347.0855, 349.0836 [M + H, 100%]. *Anal.* Calcd for $C_{16}H_{19}BrN_4$: C, 55.34; H, 5.52; N, 16.13. Found: C, 55.35; H, 5.57; N, 16.12.

*4.6.4. 7-Bromo-3-tert-butyl-8-methyl-4-(p-tolyl)-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine (**11d**)*

White powder, yield 0.36 g (89%), mp 227–228 °C. IR ν_{max} (KBr): 3246, 3211, 3191 (NH), 3084, 3059, 3015, 2962, 2934, 2864 (CH), 1623, 1590, 1543, 1516, 1484, 1473, 1460, 1396, 1381, 1365, 1351, 1317, 1286, 1254, 1241, 1222, 1193, 1181, 1128, 1094, 1052, 1019, 975, 925, 861, 848, 811, 794, 772, 728, 713, 693, 669, 650, 625, 613, 527, 484, 437 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.56 (s, 1H, N(1)–H), 7.21–7.08 (m, 4H, Ph), 6.11 (s, 1H, C(4)–H), 2.23 (s, 3H, CH$_3$–Ar), 1.83 (s, 3H, C(8)–CH$_3$), 1.05 (s, 9H, *t*-Bu). ^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 149.93, 137.72, 137.01, 136.49, 127.74 (C(3), C(7), C(8a), and 2 *ipso*-C Ph), 129.35, 127.45 (2 *o*- and 2 *m*- CH Ph), 93.15 (C(8)), 55.76 (C(4)–H), 37.26 (C(CH$_3$)$_3$), 28.68 (C(CH$_3$)$_3$), 20.62 (CH$_3$–Ar), 7.19 (C(8)–CH$_3$). HRMS *m/z* (%) Calcd for $C_{17}H_{21}BrN_4$ M + H = 361.1022, 363.1002. Found: 361.1014, 363.0995 [M + H, 100%]. *Anal.* Calcd for $C_{17}H_{21}BrN_4$: C, 56.52; H, 5.86; N, 15.51. Found: C, 56.60; H, 5.89; N, 15.49.

*4.6.5. 7-Bromo-3-tert-butyl-8-methyl-4-phenylethynyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine (**11e**)*

White powder, yield 0.35 g (85%), mp 240–244 °C (decomp.). IR ν_{max} (KBr): 3253, 3180, 3161 (NH), 3088, 3056, 2984, 2968, 2948, 2868, 2835 (CH), 2245, 2215, 2123 (C≡C), 1625, 1588, 1561, 1542, 1509, 1489, 1475, 1459, 1443, 1395, 1380, 1368, 1351, 1323, 1301, 1261, 1244, 1233, 1202, 1193, 1176, 1156, 1132, 1094, 1060, 1028, 1021, 1002, 978, 937, 906, 855, 839, 798, 761, 726, 692, 671, 630, 610, 534, 499, 433 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.76 (s, 1H, N(1)–H), 7.49–7.31 (m, 5H, Ph), 6.34 (s, 1H, C(4)–H), 1.88 (s, 3H, C(8)–CH$_3$), 1.29 (s, 9H, *t*-Bu). ^{1}H-NMR (300 MHz, $CDCl_3$: DMSO-d_6 = 5:1 v/v): δ 9.97 (s, 1H, N(1)–H), 7.00–6.79 (m, 5H, Ph), 5.57 (s, 1H, C(4)–H), 1.54 (s, 3H, C(8)–CH$_3$), 0.93 (s, 9H, *t*-Bu). ^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 146.02, 137.40, 128.76, 120.93 (C(3), C(7), C(8a) and *ipso*-C Ph), 131.29, 129.18, 128.71 (2 *o*-, *p*-, and 2 *m*- CH Ph), 93.49, 84.55 (Ph–C≡C–C(4)), 84.07 (C(8)), 43.39 (C(4)–H), 37.17 (C(CH$_3$)$_3$), 28.27 (C(CH$_3$)$_3$), 7.21 (C(8)–CH$_3$). ^{13}C-NMR APT (75 MHz, $CDCl_3$: DMSO-d_6 = 5:1 v/v): δ 145.30, 137.19, 128.75, 121.02 (C(3), C(7), C(8a) and *ipso*-C Ph), 131.11, 128.67, 128.19 (2 *o*-, *p*-, and 2 *m*- CH Ph), 93.49, 84.02 (Ph–C≡C–C(4)), 84.11 (C(8)), 43.32 (C(4)–H), 36.95 (C(CH$_3$)$_3$), 28.23 (C(CH$_3$)$_3$), 7.08 (C(8)–CH$_3$). HRMS *m/z* (%) Calcd for $C_{18}H_{19}BrN_4$ M + H = 371.0866, 373.0846. Found: 371.0853, 373.0836 [M + H, 100%]. *Anal.* Calcd for $C_{18}H_{19}BrN_4$: C, 58.23; H, 5.16; N, 15.09. Found: C, 58.28; H, 5.22; N, 15.07.

*4.6.6. 3-tert-Butyl-8-methyl-4-phenyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine (**22**)*

Colorless crystals, yield 0.26 g (92%), mp 207–208 °C. IR ν_{max} (KBr): 3262, 3187 (NH), 3075, 2971 (CH), 1628, 1593, 1560, 1541, 1535, 1508, 1498, 1492, 1475, 1458, 1420, 1401, 1364, 1341, 1330, 1319, 1288, 1266, 1240, 1217, 1188, 1155, 1125, 1099, 1078, 1048, 1037, 991, 970, 932, 914, 853, 835, 815, 794, 749, 703, 670, 661, 603, 571, 555, 536, 421 cm $^{-1}$.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.35 (s, 1H, N(1)–H), 7.39–7.19 (m, 5H, Ph), 7.04 (s, 1H, C(7)–H), 6.16 (s, 1H, C(4)–H), 1.89 (s, 3H, C(8)–CH$_3$), 1.07 (s, 9H, *t*-Bu). ^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 146.92, 138.30 (C(3), C(8a)), 137.80 (C(7)–H), 134.27 (*ipso*-C Ph), 126.80, 126.22, 125.75 (2 *o*-, *p*-, and 2 *m*- CH Ph), 91.06 (C(8)), 54.88 (C(4)–H), 35.35 (C(CH$_3$)$_3$), 27.11 (C(CH$_3$)$_3$), 5.27 (C(8)–CH$_3$). HRMS *m/z* (%) Calcd for $C_{16}H_{20}N_4$ M + H = 269.1761. Found: 269.1766 [M + H, 100%]. *Anal.* Calcd for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.60; H, 7.53; N, 20.89.

*4.7. Generation of magnesium (3-tert-butyl-4,8-dimethyl-4H-pyrazolo[5,1-c][1,2,4]triazin-1-id-7-yl)lithiums **12, and Synthesis of compounds 20a,b, 21a,b.***

A pre-cooled (−25 °C) solution of *n*-BuLi (2.5 M in hexane, 6 ml, 15 mmol) was added dropwise over 2 min with vigorous stirring to the prepared solution of magnesium salt of the corresponding compound **11a-e** (1.11 mmol) at −97 °C (CH_2Cl_2/liq. N_2 cooling bath). The reaction mixture was stirred for 3–15 min at −97 °C (TLC monitoring), and the resulting solution of 4-alkyl-7-lithio derivative **12** was used immediately in the next reaction step.

For the isolation of compounds **20a,b, 21a,b**, the cooling bath was removed, and a cooled (0 °C) solution of H_2O (1 ml, 55.5 mmol) in THF (5 ml) was added dropwise with vigorous stirring over 2 min. The reaction mixture was stirred for 40 min (the internal

temperature reached 0 °C). Next, cooled water (0 °C, 50 ml), EtOAc (50 ml) and conc. HCl/H_2O solution (5 ml) were added in one portion with stirring. The resulting mixture was stirred at 0 °C for 5 min. Then, the organic phase was separated, and the mother liquor was further extracted with EtOAc (5 × 30 ml). The combined organic phases were washed with 1% HCl/H_2O solution (2 × 100 ml) and water (2 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:4–1:1 for **20a, 21a**; 1:3–1:2 for **20b, 21b**) to give compounds **20a, 21a** or **20b, 21b**.

4.7.1. Mixture of tautomers 2-(6-tert-Butyl-5-phenyl-2,5-dihydro-1,2,4-triazin-3-yl)propanenitrile (**20a**, mixture of diastereomers) and (E/Z)-2-(6-tert-butyl-5-phenyl-4,5-dihydro-1,2,4-triazin-3(2H)-ylidene)propanenitrile (**21a**)

White powder, yield 0.27 g (90%), mp 115–116 °C. IR ν_{max} (KBr): 3388, 3339 (NH), 3083, 3062, 3028, 2969, 2907, 2872 (CH), 2251, 2175 (CN), 1703, 1648, 1625, 1612, 1561, 1494, 1476, 1460, 1430, 1396, 1365, 1349, 1320, 1305, 1274, 1255, 1202, 1179, 1153, 1122, 1077, 1065, 1050, 1024, 1008, 971, 949, 918, 862, 847, 806, 756, 730, 701, 670, 648, 613, 574, 548, 529, 492, 477, 450, 425, 407 cm^{-1}.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.47 (s, 1H, NH, **20a**, for both diastereomers, and **21a**), 7.38–7.18 (m, 5H, Ph, **20a**, for both diastereomers, and **21a**), 5.33, 5.32 (2 s, 1H, C(5)–H, **20a**, for both diastereomers), 3.81–3.69 (diastereotopic m, 1H, CH_3–CH–CN, **20a**, for both diastereomers), 1.57, 1.49 (2 s, ~0.28H + 0.14H, *E* and *Z*-CH_3–C(CN) = **21a**), 1.40 (d, *J* = 7.2 Hz, ~1.19H, CH_3–C(CN)H, **20a**, for minor diastereomer), 1.26 (d, *J* = 7.2 Hz, ~1.39H, CH_3–C(CN)H, **20a**, for major diastereomer), 1.06, 1.05 (2 s, ~1.44H, *t*-Bu, *E* and *Z*- **21a**), 1.04 (s, ~3.96H, *t*-Bu, **20a**, for major diastereomer), 1.03 (s, ~3.60H, *t*-Bu, **20a**, for minor diastereomer). ^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 150.55, 150.54, 141.62, 141.41, 139.97 (C(6), C(3), and *ipso*-C Ph for **20a, 21a**), 128.72, 128.46, 127.81, 127.40, 127.32, 127.28 (*p*-, *m*- and *o*-CH Ph for **20a, 21a**), 119.53, 119.41 (CN for **20a**, for both diastereomers), 54.97 (C(5)–H, broad, **20a**, for both diastereomers), 49.23 (C(5)–H, *E* and *Z*- **21a**), 36.49, 36.46 ($C(CH_3)_3$, **20a**, for both diastereomers), 29.11, 28.92 (CH_3–CH–CN, **20a**, for both diastereomers), 28.26, 28.25 ($C(CH_3)_3$ for **20a**, for both diastereomers), 28.04 ($C(CH_3)_3$ for *E* and *Z*- **21a**), 16.12, 15.94 (CH_3–CH–CN, **20a**, for both diastereomers), 10.87 (*E* and *Z*-CH_3–C(CN) = **21a**). HRMS *m/z* (%) Calcd for $C_{16}H_{20}N_4$ M + H = 269.1761, (M − HCN + O) + H = 258.1601. Found: 269.1753 [M + H, 70%], 258.1598 [(M − HCN + O) + H, 100%]. *Anal.* Calcd for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.58; H, 7.52; N, 20.89.

4.7.2. Mixture of tautomers 2-(6-tert-Butyl-5-(p-tolyl)-2,5-dihydro-1,2,4-triazin-3-yl)propanenitrile (**20b**, mixture of diastereomers) and (E/Z)-2-(6-tert-butyl-5-(p-tolyl)-4,5-dihydro-1,2,4-triazin-3(2H)-ylidene)propanenitrile (**21b**)

White powder, yield 0.27 g (86%), mp 146–147 °C (decomp.). IR ν_{max} (KBr): 3313 (NH), 3095, 3058, 3028, 2968, 2930, 2870 (CH), 2248, 2168 (CN), 1703, 1629, 1612, 1513, 1459, 1420, 1395, 1380, 1364, 1329, 1303, 1289, 1273, 1222, 1185, 1154, 1123, 1072, 1024, 1010, 972, 953, 941, 866, 815, 785, 739, 675, 661, 631, 613, 575, 549, 505, 495, 480, 452, 419 cm^{-1}.^{1}H-NMR (300 MHz, DMSO-d_6): δ 10.42 (s, 1H, NH, **20b**, for both diastereomers, and **21b**), 7.18–6.98 (m, 5H, Ph, **20b**, for both diastereomers, and **21b**), 5.27, 5.26 (2 s, 1H, C(5)–H, **20b**, for both diastereomers), 3.79–3.67 (diastereotopic m, 1H, CH_3–CH–CN, **20b**, for both diastereomers), 2.31, 2.27, 2.25 (3 s, 3H, CH_3–Ar, **20b**, for both diastereomers, and **21b**), 1.56, 1.48 (2 s, ~0.27H + 0.21H, *E* and *Z*- CH_3–C(CN) = **21b**), 1.39 (d, *J* = 7.1 Hz, ~1.08H, CH_3–C(CN)H, **20b**, for minor diastereomer), 1.26 (d, *J* = 7.2 Hz, ~1.44H, CH_3–C(CN)H, **20b**, for major diastereomer), 1.06, 1.04 (2 s, ~2.25H, *t*-Bu, *E* and *Z*- **21b**), 1.03 (s, ~2.70H, *t*-Bu, **20b**, for minor diastereomer), 1.02 (s, ~4.05H, *t*-Bu, **20b**, for major diastereomer).^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 150.38, 150.37, 138.75, 138.52, 137.03, 136.37, 136.34 (C(6), C(3), and *ipso*-C Ph for **20b, 21b**), 129.24, 129.18, 129.08, 129.00, 127.45, 127.40, 127.28, 127.22 (*m*- and *o*-CH Ph for **20b, 21b**), 119.53, 119.41 (CN for **20b**, for both diastereomers), 54.72 (C(5)–H, broad, **20b**, for both diastereomers), 48.90 (C(5)–H, *E* and *Z*- **21b**), 36.43, 36.40 ($C(CH_3)_3$ for **20b**, for both diastereomers), 29.05, 28.89 (CH_3–CH–CN, **20b**, for both diastereomers), 28.28, 28.26 ($C(CH_3)_3$, **20b**, for both diastereomers), 28.03 ($C(CH_3)_3$ for *E* and *Z*- **21b**), 20.61 (CH_3–Ar for *E* and *Z*- **21b**), 20.59 (CH_3–Ar, **20b**, for both diastereomers), 16.09, 15.90 (CH_3–CH–CN, **20b**, for both diastereomers), 10.82 (*E* and *Z*-CH_3–C(CN) = **21b**). HRMS *m/z* (%) Calcd for $C_{17}H_{22}N_4$ M + H = 283.1917, (M − HCN + O) + H = 272.1757. Found: 283.1918 [M + H, 20%], 272.1765 [(M − HCN + O) + H, 100%]. *Anal.* Calcd for $C_{17}H_{22}N_4$: C, 72.31; H, 7.85; N, 19.84. Found: C, 72.30; H, 7.91; N, 19.83.

4.8. Synthesis of compounds **13** and **14a,b**

A pre-cooled (−25 °C) solution of DMF (4 ml, 51.7 mmol) in THF (10 ml) was added dropwise over 4 min to the solution of 7-lithio derivative **12** (prepared from the magnesium salt of compound **11a** as described above, 1.11 mmol) with vigorous stirring. The resulting mixture was further stirred at −97 °C for 10 min. Then, the cooling bath was removed, and the resulting solution was stirred for 20 min (the internal temperature reached −30 °C). Next, cooled water (0 °C, 50 ml) and EtOAc (20 ml) were added in one portion. Next, conc. HCl/H_2O solution (8 ml) was added dropwise with stirring over 3 min. The resulting mixture was stirred for 5 min at 5–10 °C. The organic phase was separated, and the mother liquor was further extracted with EtOAc (5 × 30 ml). The combined organic phases were washed with 1% HCl/H_2O solution (2 × 50 ml), water (2 × 100 ml), then with a solution of K_2CO_3 (3 g) in H_2O (30 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:30–1:5) to give compound **13**.

For the synthesis of alcohols **14a,b**, the residue (crude compound **13**) was dissolved in a mixture of 95% aqueous EtOH (20 ml) and EtOAc (20 ml). Then, finely powdered $NaBH_4$ (0.5 g, 13.2 mmol, for the synthesis of **14a**) was added in one portion. For the synthesis of compound **14b**, *n*-BuBr (1 ml, 9.27 mmol) was additionally added. The resulting mixture was stirred at 20 °C for 4 h (for **14a**) or 48 h (for **14b**). Next, KH_2PO_4 (5 g) was added at 20 °C over 30 min in small portions and with vigorous stirring. After the addition was complete, the resulting mixture was stirred at 20 °C for 1 h. Then, water (100 ml) and EtOAc (100 ml) were added in one portion with stirring. The organic phase was separated, and the mother liquor was further extracted with EtOAc (5 × 40 ml). The combined organic phases were washed with 1% HCl/H_2O solution (1 × 100 ml) and water (2 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:3–2:1) to give compounds **14a** or **14b**.

4.8.1. 3-tert-Butyl-8-methyl-4-propyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine-7-carbaldehyde (**13**)

Yellow crystals, yield 0.24 g (82%), mp 90–91 °C. IR ν_{max} (KBr): 3254, 3217, 3197 (NH), 3098, 3065, 2964, 2935, 2873, 2820, 2781, 2751 (CH), 1701 (CO), 1626, 1584, 1528, 1459, 1447, 1399, 1381, 1366, 1340, 1328, 1264, 1235, 1212, 1200, 1175, 1145, 1092, 1049, 1020, 1010, 925, 904, 877, 836, 785, 708 cm^{-1}.^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H, CHO), 7.64 (s, 1H, N(1)–H), 5.17–5.13 (diastereotopic

m, 1H, C(4)–H), 2.21 (s, 3H, C(8)–CH_3), 1.80–1.63 (diastereotopic m, 2H, C(4)–$CH_2CH_2CH_3$), 1.42–1.12 (diastereotopic m, 2H, C(4)–$CH_2CH_2CH_3$), 1.25 (s, 9H, *t*-Bu), 0.89 (t, $J = 7.3$ Hz, 3H, C(4)–$CH_2CH_2CH_3$). ^{13}C-NMR APT (75 MHz, $CDCl_3$): δ 188.46 (CHO), 153.78, 147.98, 138.99 (C(3), C(7), C(8a)), 96.10 (C(8)), 54.86 (C(4)–H), 37.23 ($C(CH_3)_3$), 34.56 (C(4)–$CH_2CH_2CH_3$), 28.81 ($C(CH_3)_3$), 18.80 (C(4)–$CH_2CH_2CH_3$), 13.61 (C(4)–$CH_2CH_2CH_3$), 7.11 (C(8)–CH_3). HRMS *m/z* (%) Calcd for $C_{14}H_{22}N_4O$ M + H = 263.1866, M + Na = 285.1686, M + K = 301.1425. Found: 263.1867 [M + H, 100%], 285.1682 [M + Na, 50%], 301.1418 [M + K, 20%], *Anal.* Calcd for $C_{14}H_{22}N_4O$: C, 64.09; H, 8.45; N, 21.36. Found: C, 64.07; H, 8.46; N, 21.34.

4.8.2. (3-tert-Butyl-8-methyl-4-propyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazin-7-yl)methanol (**14a**)

White solid, yield 0.22 g (75%), mp 173–174 °C. IR ν_{max} (KBr): 3275, 3214, 3196 (OH, NH), 3095, 2964, 2875, 2647 (CH), 1626, 1586, 1549, 1507, 1476, 1466, 1396, 1362, 1345, 1293, 1276, 1254, 1221, 1170, 1129, 1107, 1085, 1019, 985, 964, 925, 899, 865, 843, 815, 785, 733, 689, 678, 629, 588, 531 cm $^{-1}$.^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H, N(1)–H), 5.05 (t, $J = 5.6$ Hz, 1H, C(4)–H), 4.60 (s, 2H, CH_2OH), 3.8–2.8 (broad s, 1H, OH), 2.00 (s, 3H, C(8)–CH_3), 1.71–1.64 (diastereotopic m, 2H, C(4)–$CH_2CH_2CH_3$), 1.34–1.15 (diastereotopic m, 2H, C(4)–$CH_2CH_2CH_3$), 1.23 (s, 9H, *t*-Bu), 0.84 (t, $J = 7.3$ Hz, 3H, C(4)–$CH_2CH_2CH_3$). ^{13}C-NMR APT (75 MHz, $CDCl_3$): δ 153.69, 150.09, 138.24 (C(3), C(7), C(8a)), 92.15 (C(8)), 57.58 (CH_2OH), 53.88 (C(4)–H), 37.15 ($C(CH_3)_3$), 35.07 (C(4)–$CH_2CH_2CH_3$), 28.91 ($C(CH_3)_3$), 18.78 (C(4)–$CH_2CH_2CH_3$), 13.79 (C(4)–$CH_2CH_2CH_3$), 6.51 (C(8)–CH_3). HRMS *m/z* (%) Calcd for $C_{14}H_{24}N_4O$ M + H = 265.2023, M + Na = 287.1842. Found: 265.2019 [M + H, 100%], 287.1830 [M + Na, 30%]. *Anal.* Calcd for $C_{14}H_{24}N_4O$: C, 63.60; H, 9.15; N, 21.19. Found: C, 63.56; H, 9.25; N, 21.18.

4.8.3. (3-tert-Butyl-1-butyl-8-methyl-4-propyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazin-7-yl)methanol (**14b**)

Colorless liquid, yield 0.17 g (48%), mp < 25 °C. IR ν_{max} (KBr thin layer): 3149 (OH), 2923, 2872 (CH), 1578, 1522, 1479, 1439, 1404, 1385, 1352, 1292, 1204, 1168, 1130, 1104, 1032, 931, 895, 843, 804, 766, 746, 600, 533 cm $^{-1}$.^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28 (s, 1H, N(1)–H), 5.03–5.00 (diastereotopic m, 1H, C(4)–H), 4.60 (s, 2H, CH_2OH), 3.84–3.67 (diastereotopic m, 2H, N(1)–$CH_2CH_2CH_2CH_3$), 3.3–2.3 (broad s, 1H, OH), 2.17 (s, 3H, C(8)–CH_3), 1.83–1.07 (diastereotopic m, 8H, N(1)–$CH_2CH_2CH_2CH_3$ and C(4)–$CH_2CH_2CH_3$), 1.22 (s, 9H, *t*-Bu), 0.97 (t, $J = 7.3$ Hz, 3H, N(1)–$CH_2CH_2CH_2CH_3$), 0.82 (t, $J = 7.2$ Hz, 3H, C(4)–$CH_2CH_2CH_3$). ^{13}C-NMR APT (75 MHz, $CDCl_3$): δ 150.38, 150.19, 138.83 (C(3), C(7), C(8a)), 91.65 (C(8)), 57.90 (CH_2OH), 53.27 (C(4)–H), 52.35 (N(1)–CH_2), 36.99 ($C(CH_3)_3$), 35.42 (C(4)–$CH_2CH_2CH_3$), 30.61 (N(1)–$CH_2CH_2CH_2CH_3$), 29.08 ($C(CH_3)_3$), 19.91, 18.63 (N(1)–$CH_2CH_2CH_2CH_3$ and C(4)–$CH_2CH_2CH_3$), 14.02, 13.88 (N(1)–$CH_2CH_2CH_2CH_3$ and C(4)–$CH_2CH_2CH_3$), 8.83 (C(8)–CH_3). HRMS *m/z* (%) Calcd for $C_{18}H_{32}N_4O$ M + H = 321.2649, M + Na = 343.2468, M + K = 359.2208. Found: 321.2649 [M + H, 100%], 343.2465 [M + Na, 50%], 359.2206 [M + K, 5%]. *Anal.* Calcd for $C_{18}H_{32}N_4O$: C, 67.46; H, 10.06; N, 17.48. Found: C, 67.45; H, 10.12; N, 17.50.

4.9. Synthesis of (3-tert-butyl-8-methyl-4-propyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazin-7-yl)(phenyl)methanol (**15**, mixture of diastereomers)

A pre-cooled (−25 °C) solution of PhCHO (3 ml, 29.4 mmol) in THF (10 ml) was added dropwise over 4 min to the solution of 7-lithio derivative **12** (prepared from the magnesium salt of compound **11a** as described above, 1.11 mmol) with vigorous stirring. The resulting mixture was further stirred at −97 °C for 10 min. Then, the cooling bath was removed, and the resulting solution was stirred for 20 min (the internal temperature reached −30 °C). Then, KH_2PO_4 (5 g, 36.7 mmol), cooled water (0 °C, 50 ml) and EtOAc (50 ml) were added in one portion. The resulting mixture was stirred vigorously for 15 min, the organic phase was separated, and the mother liquor was further extracted with EtOAc (5 × 40 ml). The combined organic phases were washed with water (3 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:30–1:2) to give compound **15**, colorless liquid, yield 0.27 g (71%). IR ν_{max} (KBr): 3288, 3221 (OH, NH), 3086, 3064, 3028, 2961, 2932, 2873 (CH), 1646, 1590, 1542, 1493, 1466, 1453, 1394, 1366, 1345, 1268, 1193, 1103, 1085, 1040, 1025, 924, 900, 849, 804, 756, 700, 667, 597, 489 cm $^{-1}$.^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H, N(1)–H, for both diastereomers), 7.44–7.21 (m, 5H, Ph, for both diastereomers), 5.82 (s, ~0.75H, PhCH–OH, for major diastereomer), 5.81 (s, ~0.25H, PhCH–OH, for minor diastereomer), 5.12–5.07 (diastereotopic m, 1H, C(4)–H, for both diastereomers), 3.7–3.3 (broad s, 1H, OH, for both diastereomers), 1.71 (s, ~0.90H, C(8)–CH_3, for minor diastereomer), 1.70 (s, ~2.10H, C(8)–CH_3, for major diastereomer), 1.77–1.61 (diastereotopic m, 2H, C(4)–$CH_2CH_2CH_3$), 1.36–1.14 (diastereotopic m, 2H, C(4)–$CH_2CH_2CH_3$), 1.25 (s, ~3H, *t*-Bu, for minor diastereomer), 1.24 (s, ~6H, *t*-Bu, for major diastereomer), 0.91–0.85 (m, 3H, C(4)–$CH_2CH_2CH_3$, for both diastereomers). ^{13}C-NMR APT (151 MHz, $CDCl_3$): δ (major diastereomer) 153.09, 151.43, 142.00, 138.10 (C(3), C(7), C(8a), and *ipso*-C Ph), 127.74, 126.81, 126.07 (2 *o*-, 2 *m*-, and *o*-CH Ph), 90.45 (C(8)), 70.47 (Ph–CHOH), 53.10 (C(4)–H), 36.57 ($C(CH_3)_3$, for both diastereomers), 34.54 (C(4)–$CH_2CH_2CH_3$), 28.40 ($C(CH_3)_3$, for both diastereomers), 18.25 (C(4)–$CH_2CH_2CH_3$), 13.23 (C(4)–$CH_2CH_2CH_3$), 6.15 (C(8)–CH_3, for both diastereomers); δ (minor diastereomer) 153.24, 151.22, 142.12, 138.01 (C(3), C(7), C(8a), and *ipso*-C Ph), 127.78, 126.90, 126.27 (2 *o*-, 2 *m*-, and *o*-CH Ph), 90.53 (C(8)), 70.32 (Ph–CHOH), 53.18 (C(4)–H), 34.44 (C(4)–$CH_2CH_2CH_3$), 18.28 (C(4)–$CH_2CH_2CH_3$), 13.21 (C(4)–$CH_2CH_2CH_3$). HRMS *m/z* (%) Calcd for $C_{20}H_{28}N_4O$ M + H = 341.2336, M + Na = 363.2155, M + K = 379.1895. Found: 341.2339 [M + H, 100%], 363.2153 [M + Na, 80%], 379.1890 [M + K, 5%]. *Anal.* Calcd for $C_{20}H_{28}N_4O$: C, 70.56; H, 8.29; N, 16.46. Found: C, 70.59; H, 8.30; N, 16.49.

4.10. Synthesis of compounds **17** and **18**

A pre-cooled (−25 °C) solution of DMF (4 ml, 51.7 mmol) in THF (10 ml) was added dropwise over 4 min to the solution of the corresponding 7-lithio derivative **12** (prepared from the magnesium salt of compound **11b** as described above, 1.11 mmol) with vigorous stirring. The resulting mixture was further stirred at −97 °C for 10 min. Then, the cooling bath was removed, and the resulting solution was stirred for 40 min (the internal temperature reached 0 °C). Next, $PhCH_2Cl$ (1.5 ml, 13.0 mmol) was added in one portion, and the resulting mixture was stirred at 40 °C for 2 h (TLC monitoring of formation of **16**). Then, water (50 ml) and conc. HCl/H_2O solution (15 ml) were added in one portion, and the reaction mixture was stirred vigorously at 50 °C for 1 h (TLC monitoring of formation of **17**). After cooling to 20 °C, water (50 ml) and EtOAc (50 ml) were added with stirring. The organic phase was separated, and the mother liquor was further extracted with EtOAc (4 × 30 ml). The combined organic phases were washed with 1% HCl/H_2O solution (2 × 100 ml), water (2 × 100 ml), dried with $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue,

which was purified *via* chromatography (eluent EtOAc: hexane = 1:30–1:8) to give crude compound **17**.

For the synthesis of compound **18**, the crude aldehyde **17** (0.34 g, 0.93 mmol) was dissolved in a mixture of THF (15 ml) and Et_2O (20 ml). The resulting solution was cooled to 0 °C, and a pre-cooled MeLi solution (0°–5 °C, 0.25 M in Et_2O, 15 ml, 3.75 mmol) was added dropwise with stirring over 5 min. The resulting yellow mixture was stirred vigorously for 15 min at 0 °C. Then, cooled water (0 °C, 5 ml) was added dropwise with stirring over 2 min. Next, KH_2PO_4 (5 g, 36.7 mmol), water (50 ml) and EtOAc (50 ml) were added in one portion. The resulting mixture was stirred vigorously for 15 min, the organic phase was separated, and the mother liquor was further extracted with EtOAc (5 × 40 ml). The combined organic phases were washed with 1% HCl/H_2O solution (1 × 100 ml) and water (2 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified *via* chromatography (eluent EtOAc: hexane = 1:5–1:2) to give compound **18**.

*4.10.1. 1-Benzyl-3-tert-butyl-4-butyl-8-methyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine-7-carbaldehyde (**17**, crude)*

Colorless liquid, yield 0.34 g (83%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.94 (s, 1H, C<u>H</u>O).

*4.10.2. 1-(1-Benzyl-3-tert-butyl-4-butyl-8-methyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazin-7-yl)ethan-1-ol (**18**, mixture of diastereomers)*

Unstable colorless liquid, yield 0.28 g (79% from crude **17**, 66% from **9a**). IR ν_{max} (KBr): 3404 (OH), 2958, 2924, 2855 (CH), 1644, 1457, 1428, 1384, 1285, 1270, 1125, 1076, 1006, 898, 843, 752 cm^{-1}.^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.34–7.21 (m, 5H, Ph, for both diastereomers), 5.09–5.07 (diastereotopic m, 1H, *n*-Bu–C(4)–<u>H</u>, for both diastereomers), 5.06–4.94 (diastereotopic m, 2H, PhC<u>H</u>$_2$, for both diastereomers), 4.82 (d, J = 4.7 Hz, ~0.48H, CH–O<u>H</u>, for minor diastereomer), 4.79 (d, J = 5.2 Hz, ~0.52H, CH–O<u>H</u>, for major diastereomer), 4.67–4.61 (m, 1H, CH_3–C<u>H</u>–OH, for both diastereomers), 1.96 (s, ~1.28H, C<u>H</u>$_3$–C(8), for minor diastereomer), 1.95 (s, ~1.72H, C<u>H</u>$_3$–C(8), for major diastereomer), 1.71–1.64, 1.59–1.51 (2 diastereotopic m, 1 + 1H, C(4)–C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$, for both diastereomers), 1.34 (d, J = 6.5 Hz, 3H, C<u>H</u>$_3$–CH–OH, for both diastereomers), 1.26–1.03 (diastereotopic m, 4H, C(4)–CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$, for both diastereomers), 1.19, 1.18 (2 s, ~4.5H + 4.5H, *t*-Bu, for both diastereomers), 0.80–0.76 (m, 3H, C(4)–CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$, for both diastereomers). ^{13}C-NMR APT (126 MHz, DMSO-d_6, for both diastereomers): δ 154.00, 153.95, 150.69, 150.57, 139.55, 139.53, 138.23, 138.17 (C(3), C(7), C(8a), and *ipso*-<u>C</u> Ph), 128.80, 127.38, 127.35, 127.06 (*o*-, *m*-, and *p*-<u>C</u>H Ph), 91.37, 91.29 (C(8)), 63.39, 63.11 (<u>C</u>H–OH), 56.16, 56.04 (Ph<u>C</u>H$_2$), 52.85, 52.70 (<u>C</u>(4)–H), 37.11, 37.10 (<u>C</u>(CH$_3$)$_3$), 33.09, 33.06 (C(4)–<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 29.12, 29.10 (C(<u>C</u>H$_3$)$_3$), 27.38, 27.34 (C(4)–CH$_2$<u>C</u>H$_2$CH$_2$CH$_3$), 23.04, 22.94 (<u>C</u>H$_3$–CH–OH), 22.20, 22.18 (C(4)–CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 14.31 (C(4)–CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$), 8.84 (C(8)–<u>C</u>H$_3$). HRMS *m/z* (%) Calcd for $C_{23}H_{34}N_4O$ M + H = 383.2805, M + Na = 405.2625. Found: 383.2796 [M + H, 100%], 405.2624 [M + Na, 5%]. *Anal.* Calcd for $C_{23}H_{34}N_4O$: C, 72.21; H, 8.96; N, 14.65. Found: C, 72.19; H, 9.01; N, 14.63.

*4.11. Preparation of 7-bromo-3-tert-butyl-4-butyl-8-methylpyrazolo[5,1-c][1,2,4]triazine (**24**)*

Method A. A solution of compound **11b** (0.3 g, 0.92 mmol) in freshly distilled *t*-BuONO (30 ml, 252 mmol) was stirred at 20 °C for 24 h (TLC monitoring). Next, the solvents were removed *in vacuo*, and 95% aqueous EtOH (20 ml) and crystalline K_2CO_3 (5 g, 36.2 mmol) were added in one portion. The resulting mixture was boiled under reflux for 30 min with stirring. Then, it was cooled, and hexane (50 ml) was added. The precipitate formed was filtered and washed with hexane (3 × 20 ml). The combined organic filtrates were evaporated *in vacuo* to give a residue, which was purified *via* flash chromatography (eluent EtOAc: hexane = 0:1–1:200) to give **24** as a yellow powder, yield 0.24 g (80%), mp 61–62 °C.

Method B. In a 500 ml round-bottom flask, *n*-BuMgBr (1 M in Et_2O, 40 ml, 40 mmol) was added in one portion to a solution of compound **5** (0.5 g, 1.75 mmol) in HMPA (20 ml), and diethyl ether was completely removed from the reaction mixture *in vacuo*. The resulting yellow solution was stirred at 70 °C for 30 min (the color changed to deep red). After cooling to 0 °C, hexane (100 ml) was added in one portion, and water (20 ml) was added dropwise with vigorous stirring over 10 min. Next, cooled water (0 °C, 150 ml) and conc. HCl/H_2O solution (50 ml) were added in one portion. The resulting mixture was stirred vigorously at 0 °C for 30 min, the organic phase was separated, and the mother liquor was further extracted with hexane (4 × 50 ml). The combined organic phases were washed with 5% HCl/H_2O solution (3 × 100 ml) and water (3 × 100 ml), dried with anhydrous $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give a residue, which was purified as described above to give **24** as a yellow powder, yield 0.31 g (54%), mp 61–62 °C. IR ν_{max} (KBr): 2958, 2930, 2870 (CH), 1576, 1511, 1477, 1467, 1399, 1384, 1366, 1323, 1275, 1249, 1223, 1208, 1186, 1129, 1101, 1073, 1049, 1016, 986, 962, 935, 902, 799, 779, 730, 681, 652, 612, 557, 538 cm^{-1}.^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.28–3.24 (m, 2H, C(4)–C<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 2.40 (s, 3H, C(8)–C<u>H</u>$_3$), 1.74–1.64 (m, 2H, C(4)–CH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.57–1.48 (m, 2H, C(4)–CH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 1.55 (s, 9H, *t*-Bu), 0.96 (t, J = 7.3 Hz, 3H, C(4)–CH$_2$CH$_2$CH$_2$C<u>H</u>$_3$). ^{13}C-NMR APT (75 MHz, DMSO-d_6): δ 149.16, 146.72, 135.23, 134.72 (C(3), C(4), C(7), C(8a)), 106.47 (C(8)), 36.99 (<u>C</u>(CH$_3$)$_3$), 30.80 (C(<u>C</u>H$_3$)$_3$), 26.94, 26.90 (C(4)–<u>C</u>H$_2$CH$_2$CH$_2$CH$_3$), 22.45 (C(4)–CH$_2$CH$_2$<u>C</u>H$_2$CH$_3$), 13.43 (C(4)–CH$_2$CH$_2$CH$_2$<u>C</u>H$_3$), 7.57 (C(8)–<u>C</u>H$_3$). HRMS *m/z* (%) Calcd for $C_{14}H_{21}BrN_4$ M + H = 325.1022, 327.1002. Found: 325.1021, 327.1002 [M + H, 50%], 334.3224 [100%]. *Anal.* Calcd for $C_{14}H_{21}BrN_4$: C, 51.70; H, 6.51; N, 17.23. Found: C, 51.68; H, 6.54; N, 17.19.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article (IR, ^{1}H, ^{13}C NMR spectra, HRMS, detailed computational and X-ray powder diffraction data can be found, in the online version, at https://doi.org/10.1016/j.jorganchem.2019.06.009.

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