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HPLC purification technique: synthesis of unsymmetrical thiobarbituric acids

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ABSTRACT

Synthesis of thiobarbituric acids by the reaction of 1,3-disubstituted thioureas and malonic acid in acetyl chloride-acetic acid medium and synthesis of cyclized pyrimidin-7-one by the interaction of 1-(2-hydroxyethyl)-aryl thioureas, with malonic acid in *p*-tolyl sulphonic acid and acetyl chloride-acetic acid medium at room temperature stirring has been reported. The present protocol is highly eco-friendly alternative to existing methods, reduces the excess use of acetyl chloride and purity of all synthesized molecules checked with the help of reverse phase high performance liquid chromatography with photo diode array (PDA) detection at 254 nm with spectral characterization by 1H, 13C NMR, and MS spectra.

1. Introduction

Currently, developments of synthetic methodology have great challenge for organic chemists because active methylene group containing compounds are versatile organic precursors with exceptional chemical reactivity. Organic solvent is play a significant role for the synthesis of such active molecule but utilization of huge amount of organic solvents have adverse effect on human health and environment due to emission of volatile organic compounds (VOCs) [1]. Environmental impact for the use of organic solvents in synthesis can be minimizing by replacing non-hazardous solvents [2, 3]. In this regard, use of unsafe solvents in synthesis can represent an issue of health and environmental hazards, hence safer solvent is good alternative for synthesis of organic compound. Therefore, safe synthetic methods under the principle of green chemistry [4, 5, 6, 7] have been used for organic synthesis. The inexpensive, non-hazardous and efficient synthetic approach in recent time is constantly challenged by expanding environmental concern [8], use of natural fruits, vegetables juice [9] also attracting to research groups. Such materials are examples of biocatalyst and carried out organic reactions like preparation of amides [10], triazole [11], Knoevenagel condensation [12], Biginelli reaction [13] etc.

TBAs have gained considerable attention and their biological scaffold such as antimicrobial, antitubercular [14, 15], antifungal [16], antitumor [17], antidiabetic and antibacterial activities [18]. TBAs are good building block to be use in varied organic transformations as precursor [19, 20, 21, 22]. Hence, large number of efforts are being made to find out new routes and methodologies for the synthesis of TBAs [23, 24]. In earlier literature, synthesis of thiobarbituric acids by the reaction of malonic ester with urea in sodium alkoxide [25], malonic acid with thoiureas in Amberlyst-15 [26], acetyl chloride [27, 28, 29, 30, 31, 32], $POCl_3$ [32], malonates with thiourea in potassium tert-butoxide [33] and methyl malonyl chloride with thiourea in dry 1,2-dichloroethane [34] have been reported.

Therefore, higher temperature, long reaction time and excessive use of organic solvent has major drawback of the reactions protocol. We wish to report herein very simple, highly expedient, modified and efficient technique for the synthesis of thiobarbituric acids by the reaction of 1,3-disubstituted thioureas and malonic acid with 1:2 proportion of acetyl chloride-acetic acid medium (Schemes 1 and 2).

2. Material and methods

2.1. General method

Melting points were taken in open capillary tubes and are uncorrected. Purity of all newly synthesized compounds checked by HPLC technique using Dionex Ultimate 3000 with PDA detection in reverse phase column phenyl 5 μm, 150 × 4.6 mm, at 254 nm. ^{1}H (400 MHz) NMR spectra were recorded on a Bruker Advance-II 400 spectrometer from $CDCl_3$ solution with TMS as an internal reference. Chemical shift are recorded as ppm on the δ scale and multiplicities are described as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of

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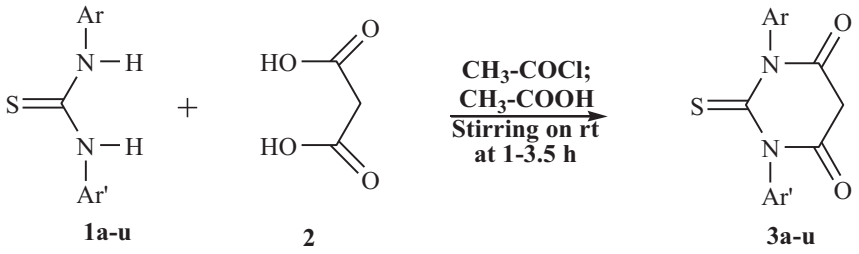
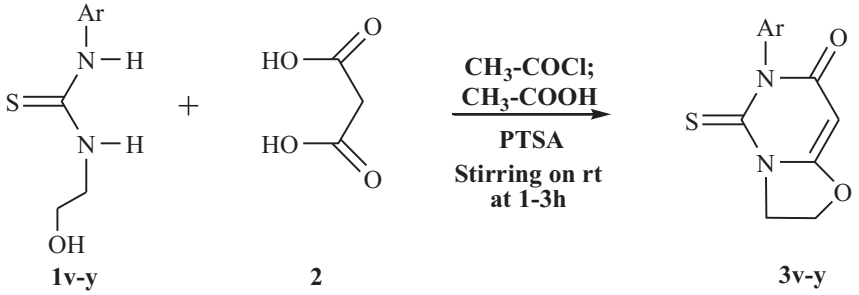


Scheme 1. Reaction of 1a-u with 2.



Scheme 2. Reaction of 1v-y with 2.

doublet), t (triplet), td (triplet of doublet) and q (quar1tet). The MS (ESI) spectra were recorded using Agilent 6890 gas chromatograph coupled with to an Agilent MSD 5973N quadrupole mass spectrometer. Thin layer chromatography (TLC) was performed with E. Merck pre-coated TLC aluminium silica Gel 60 $F_{254,}$ and spot were located with ultraviolet (UV) light.

2.2. Experimental method

2.2.1. Synthesis of 3-phenyl-2-thioxo-1-o-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3a)

Synthesis of 3-phenyl-2-thioxo-1-*o*-tolyl-dihydropyrimidine-4,6(1H, 5H)-dione (3a) was synthesized by the interaction of 1-phenyl-3-*o*-tolyl thiourea (1a, 10 mmol) with malonic acid (2, 10 mmol), acetyl chloride-acetic acid (20:40 mmol). The reaction mixture was stirred for 2.5 h and progress of reaction was monitored by TLC. After completion of reaction, mixture was filtered, washed with water. Purity of all newly synthesized compounds checked with the help of HPLC technique using solvent system acetonitrile-water (4:1) and single peak has been obtained in chromatogram hence compound is in pure form. Yellow solid; mp 105–106 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.493–7.445 (dd, J = 7.6, 4.4 Hz, 2H, C_3, C_6-Ar-H), 7.356–7.309 (dd, J = 6.8, 5.6 Hz, 2H, $C_{4,5}$-Ar-H), 7.215–7.195 (d, J = 8.0 Hz, 3H, $C_{2,4,6}$ Ar–H), 7.111–7.093 (d, J = 7.2 Hz, 2H, $C_{3,5}$ Ar–H), 4.059 (s, 2H, CH_2CO), 2.179 (s, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.72 (C=S), 163.35, 162.86 (C=O), 138.70–127.46 (C–Ar), 41.22 (CH_2), 17.55 (CH_3-Ar). MS (m/z), 310.1 $[M]^+$. Calcd. 310.00 $[M]^+$. Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03; S, 10.33. Found: C, 65.55; H, 4.50; N, 8.97; S, 10.23.

2.2.2. 3-(2-hydroxyethyl)-1-phenyl-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (3b)

Yellow solid; mp 160 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.282–7.251 (t, Ar–H), 7.199 7.182 (d, Ar–H), 4.134–4.098 (t, J = 14.4 Hz, 2H, O–CH_2), 3.840–3.804 (t, J = 14.4 Hz, 2H, N–CH_2), 2.991 (s, 2H, CH_2–CO), 2.052 (s, 1H, OH-(bs). ^{13}C NMR 100 MHz ($CDCl_3$): δ 196.10 (C=S), 168.50, 163.33 (C=O), 137.05–124.03 (C–Ar), 58.08 (CH_2–O), 43.32 (CH_2–N), 36.68 (CH_2). MS (m/z): 219.1 $[M\text{-}NC_2H_5O]^+$. Calcd. 264.3 $[M]^+$. Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: Calcd. C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.57; H, 4.62; N, 10.64; S, 12.11.

2.2.3. 3-(2-hydroxyethyl)-2-thioxo-1-o-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3c)

Yellow solid; mp 148 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.382–7.267 (m, 4 H, Ar–H), 4.460–4.421 (t, J = 15.6 Hz, 2H, O–CH_2), 4.27–4.238 (t, J = 13.2 Hz, 2H, N–CH_2), 3.919 (s, 2H, CH_2–CO), 2.022 (s, 1H, OH-(bs). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.66 (C=S), 171.30, 164.71(C=O), 138.09–128.45 (C–Ar), 61.25 (CH_2–O), 46.74 (CH_2–N), 39.94 (CH_2), 20.86 (CH_3-Ar). MS (m/z): 219.1 $[M\text{-}C_2H_5O]^+$. Calcd. 278.3 $[M]^+$. Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: Calcd. C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.18; H, 5.01; N, 10.06; S, 11.57.

2.2.4. 3-Phenyl-2-thioxo-1-m-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3d)

Yellow solid; mp 206–208 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.49–7.47 (d, J = 7.2 Hz, 2H, C_2, C_6-Ar-H), 7.44 (s, 1H, C_2-Ar-H), 7.39–7.35 (t, J = 7.2 Hz, 1H, C_4-Ar-H), 7.26–7.24 (d, J = 7.2 Hz, 1H, C_6-Ar-H), 7.20–7.19 (d, J = 7.2 Hz, 2H, C_4,C_5-Ar-H), 7.01–6.99 (d, J = 7.6 Hz, 2H, C_3, C_5-Ar-H), 4.06 (s, 2H, CH_2), 2.39 (s, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.67 (C=S), 163.34 (C=O), 139.83–125.59 (C–Ar), 41.27 (CH_2), 21.48 (CH_3-Ar). MS (m/z), 310.95 $[M+1]^+$. Calcd. 311.00 $[M+1]^+$). Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03; S, 10.33. Found: C, 65.63; H, 4.44; N, 9.05; S, 10.26.

2.2.5. 3-(2-hydroxyethyl)-2-thioxo-1-m-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3e)

Yellow solid; mp 120 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.387–7.355 (t, J = 12.8 Hz, 1 H, 5 C, Ar–H), δ 7.267–7.252 (d, J = 6 Hz, 1 H, 6 C, Ar–H), δ 7.040 (s, 1H, 2C, Ar–H), δ 6.996–6.978 (d, J = 7.2 Hz, 2H, 3C, Ar–H), 4.112–4.080 (t, J = 12.4 Hz, 2H, O–CH_2), 3.843 (s, 2H CO–CH2), 2.820–2.785 (t, J = 14 Hz, 2H, N–CH_2), 2.061 (bs, 1H, OH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.66 (C=S), 169.52, 164.42 (C=O), 142.42–119.19 (C–Ar), 61.04 (CH_2–O), 45.99 (CH_2–N), 40.11(CH_2), 22.32(CH_3-Ar). MS (m/z): 219.1 $[M\text{-}C_2H_5O]$. Calcd. 278.3 $[M]^+$. Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: Calcd. C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.15; H, 5.10; N, 10.03; S, 11.55.

2.2.6. 3-Phenyl-2-thioxo-1-o-chlorophenyl-dihydropyrimidine-4,6(1H,5H)-dione (3f)

Dark brown solid; mp 130–131 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ

7.52–7.48 (ddd, J = 8.0, 4.4, 1.2 Hz, 1H, C_3-Ar-H), 7.47–7.42 (ddd, J = 8.4, 4.8, 2.4 Hz, 1H, C_6-Ar-H), 7.29–7.26 (t, J = 7.2 Hz, 3H, C_2,C_4,C_6-Ar-H), 7.29–7.26 (t, J = 7.6, 4.8 Hz, 2H, C_3,C_5-Ar-H), 7.23–7.21 (d, J = 9.2 Hz, 2H, C_4,C_5-Ar-H), 4.07 (s, 2H, CH_2CO). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.35 (C=S), 163.17, 162.57 (C=O), 138.57–125.79 (C–Ar), 41.15 (CH_2). MS (m/z), 330.30 $[M]^+$. Calcd. 330.50 $[M]^+$. Anal. Calcd. for $C_{16}H_{11}ClN_2O_2S$: C, 58.09; H, 3.35; Cl, 10.72; N, 8.47; S, 9.69. Found: C, 57.97; H, 3.27; Cl, 10.66; N, 8.37; S, 9.53.

2.2.7. 3-(2-chlorophenyl)-1-(2-hydroxyethyl)-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (3g)

Yellow solid; mp 130 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.494–7.050 (m, 4H, Ar–H), 4.050–4.014 (t, J = 14.4 Hz, 2H, O–CH_2), 3.211 (s, 2H CO–CH2), 3.068–3.031 (t, J = 14.8 Hz, 2H, N–CH_2), 1.958 (bs, 1H, OH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 196.07 (C=S), 163.35, 162.54 (C=O), 136.49–122.28 (C–Ar), 60.24 (CH_2–O), 43.21 (CH_2–N), 38.90 (CH_2). MS (m/z): 239.1 $[M\text{-}NC_2H_5O]^+$. Calcd. 298.7 $[M]^+$. Anal. Calcd. for $C_{12}H_{11}ClN_2O_3S$: Calcd. C, 48.24; H, 3.71; Cl, 11.87; N, 9.38; S, 10.73. Found: C, 48.31; H, 3.79; Cl, 11.90; N, 9.41; S, 10.72.

2.2.8. 3-Phenyl-2-thioxo-1-m-chlorophenyl-dihydropyrimidine-4,6(1H,5H)-dione (3h)

Yellow solid; mp 166–168 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.57 (s, 1H, C_2-Ar-H), 7.51–7.45 (td, J = 8.8, 4.8, 2.0 Hz, 2H, C_2,C_6-Ar-H), 7.42–7.41 (d, J = 6.0 Hz, 1H, C_4-Ar-H), 7.38–7.36 (t, J = 8.8, 4.4 Hz, 1H, C_5-Ar-H), 7.30–7.29 (d, J = 6.4 Hz, 1H, C_4-Ar-H), 7.23–7.19 (td, J = 7.6, 4.4, 2.0 Hz, 2H, C_3,C_5-Ar-H), 7.11–7.09 (t, J = 8.8, 4.4 Hz, 1H, C_6-Ar-H), 4.07 (s, 2H, CH_2CO). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.18 (C=S), 163.34, 162.89 (C=O), 139.58–117.84 (C–Ar), 41.19 (CH_2). MS (m/z), 329.98 $[M]^+$. Calcd. 330.5 $[M]^+$. Anal. Calcd. for $C_{16}H_{11}ClN_2O_2S$: C, 58.09; H, 3.35; Cl, 10.72; N, 8.47; S, 9.69. Found: C, 58.03; H, 3.18; Cl, 10.59, N, 8.27; S, 9.62.

2.2.9. 3-(3-chlorophenyl)-1-(2-hydroxyethyl)-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (3i)

Yellow solid; mp 142 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.374 (s, 1H, 2C, Ar–H), δ 7.191–7.172 (d, J = 7.6 Hz, 1H, 4C, Ar–H), δ 7.142–7.122 (d, J = 8 Hz, 1H, 5C, Ar–H), δ 7.046–7.030 (d, J = 6.4 Hz, 1H, 6C, Ar–H), 4.051–4.015 (t, J = 14.4 Hz, 2H, O–CH_2), 3.811 (s, 2H CO–CH2), 3.263–3.227 (t, J = 14.4 Hz, 2H, N–CH_2), 1.977 (bs, 1H, OH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 196.19 (C=S), 163.21, 162.97 (C=O), 134–125.76 (C–Ar), 60.04 (CH_2–O), 43.26 (CH_2–N), 39.00 (CH_2). MS (m/z): 239.1 $[M\text{-}NC_2H_5O]^+$. Calcd. 298.7 $[M]^+$. Anal. Calcd. for $C_{12}H_{11}ClN_2O_3S$: Calcd. C, 48.24; H, 3.71; Cl, 11.87; N, 9.38; S, 10.73. Found: C, 48.24; H, 3.73; Cl, 11.85; N, 9.39; S, 10.70.

2.2.10. 3-(4-chlorophenyl)-1-(2-hydroxyethyl)-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (3j)

Yellow solid; mp 118 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.480–7.459 (d, J = 8.4 Hz, 2H, 2, 6C, Ar–H), δ 7.156–7.134 (d, J = 8.8 Hz, 2H, 3,5C, Ar–H), 4.131–4.095 (t, J = 14.4 Hz, 2H, O–CH_2), 3.880 (s, 2H CO–CH_2), 2.833–2.801 (t, J = 12.8 Hz, 2H, N–CH_2), 2.025 (bs, 1H, OH). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.18 (C=S), 164.30, 164.21(C=O), 149.91–129.86 C–Ar), 60.15 (CH_2–O), 44.40 (CH_2–N), 40.09 (CH_2). MS (m/z): 239.1 $[M\text{-}NC_2H_5O]^+$. Calcd. 298.7 $[M]^+$. Anal. Calcd. for $C_{12}H_{11}ClN_2O_3S$: Calcd. C, 48.24; H, 3.71; Cl, 11.87; N, 9.38; S, 10.73. Found: C, 48.29; H, 3.76; Cl, 11.92; N, 9.35; S, 10.71.

2.2.11. 3-o-Tolyl-2-thioxo-1-p-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3k)

Dark brown solid, mp 95 - 95 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.61–7.59 (d, J = 8.0 Hz, 2H, C_3,C_6-Ar-H), 7.31–7.29 (d, J = 6.8 Hz, 2H, C_4,C_5-Ar-H), 7.19–7.17 (d, J = 8.8 Hz, 2H, C_3,C_5-Ar-H), 7.01–6.99 (d, J = 8.0 Hz, 2H, C_2,C_6-Ar-H), 4.06 (s, 2H, CH_2CO), 2.40 (S, 3H, CH_3-Ar), 2.18 (S, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.86 (C=S), 163.46, 162.89 (C=O), 139.36–127.47 (C–Ar), 41.24 (CH_2), 21.47 (CH_3-Ar), 17.56 (CH_3-Ar). MS (m/z), 324.20 $[M]^+$. Calcd. 324.09 $[M]^+$. Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.49; H, 4.85; N, 8.58; S, 9.76.

2.2.12. 3-m-Tolyl-2-thioxo-1-p-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3l)

Yellow solid, mp 135–136 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.38–7.34 (t, J = 7.6 Hz, 1H, C_4-Ar-H), 7.29–7.23 (dd, J = 8.0 Hz, 1H, C_5-Ar-H), 7.20–7.18 (d, J = 8.0 Hz, 1H, C_6-Ar-H), 7.10 (s, 1H, C_2-Ar-H), 7.08–7.06 (d, J = 8.0 Hz, 2H, C_3,C_5-Ar-H), 7.00–6.98 (d, J = 8.8 Hz, 2H, C_2,C_6-Ar-H), 4.03 (s, 2H, CH_2CO), 2.39 (s, CH_3-Ar), 2.38 (s, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.79 (C=S), 163.43, 163.35 (C=O), 139.75–125.58 (C–Ar), 41.25 (CH_2), 21.44 (CH_3-Ar). MS (m/z), 324.20 $[M]^+$. Calcd. 324.09 $[M]^+$. Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.61; H, 4.75; N, 8.48; S, 9.69.

2.2.13. 1-p-Tolyl-2-thioxo-3-o-chlorophenyl-dihydropyrimidine-4,6(1H,5H)-dione (3m)

Dark brown solid, mp 110–112 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.53–7.51 (dd, J = 6.8, 4.8 Hz, 1H, C_4-Ar-H), 7.41–7.38 (ddd, J = 6.4, 3.6, 1.2 Hz, 1H, C_6-Ar-H), 7.33–7.28 (ddd, J = 8.0, 4.0, 1.6 Hz, 2H, C_3, C_5-Ar-H), 7.11–7.09 (d, J = 8.0 Hz, 2H, C_2,C_6-Ar-H), 7.08–7.06 (d, J = 8.4 Hz, 2H, C_3, C_5-Ar-H), 4.08 (s, 2H, CH_2CO), 2.40 (s, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.50 (C=S), 163.26, 162.59 (C=O), 139.42–128.11 (C–Ar), 41.19 (CH_2), 21.47 (CH_3-Ar). MS (m/z), 345.30 $[M+1]^+$. Calcd. 345.50 $[M+1]^+$. Anal. Calcd. for $C_{18}H_{17}ClN_2O_2S$: C, 59.91; H, 4.75; Cl, 9.82; N, 7.76; S, 8.89. Found: C, 60.03; H, 4.69; Cl, 9.68, N, 7.65; S, 8.77.

2.2.14. 1-p-Tolyl-2-thioxo-3-m-chlorophenyl-dihydropyrimidine-4,6(1H,5H)-dione (3n)

Yellow solid, mp 163–164 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.43–7.41 (dd, J = 8.4, 3.2 Hz, 1H, C_6-Ar-H), 7.31–7.29 (d, J = 8.0 Hz, 1H, C_2, C_6-Ar-H), 7.25–7.23 (d, J = 8.8 Hz, 2H, C_3, C_5-Ar-H), 7.13–7.11 (dd, J = 8.0, 3.2 Hz, 1H, C_4-Ar-H), 7.11–7.07 (dd, J = 8.0 Hz, 1H, C_5-Ar-H), 7.06 (s, 1H, C_2-Ar-H), 4.08 (s, 2H, CH_2CO), 2.41 (s, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.32 (C=S), 163.45, 162.86 (C=O), 139.64–127.10 (C–Ar), 41.20 (CH_2), 21.48 (CH3-Ar). MS (m/z), 345.00 $[M]^+$. Calcd. 344.50 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}ClN_2O_2S$: Calcd. C, 59.91; H, 4.75; Cl, 9.82; N, 7.76; S, 8.89. Found: C, 59.78; H, 4.58; Cl, 9.71, N, 7.61; S, 8.81.

2.2.15. 3-o-Tolyl-2-thioxo-1-p-anisole-dihydropyrimidine-4,6(1H,5H)-dione (3°)

Yellow solid, mp 123–124 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.34–7.31 (t, J = 7.2 Hz, 1H, C_5-Ar-H), 7.249–7.22 (d, J = 8.4 Hz, 1H, C_4-Ar-H), 7.20–7.18 (d, J = 8.0 Hz, 2H, C_3,C_6-Ar-H), 7.11–7.09 (d, J = 8.0 Hz, 2H, C_3,C_5-Ar-H), 7.00–6.98 (d, J = 8.8 Hz, 2H, C_2,C_6-Ar-H), 4.07 (s, 2H, CH_2CO), 3.83 (s, 3H, CH_3O–Ar), 2.18 (s, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.07 (C=S), 163.57, 162.88 (C=O), 159.92, 159.86 (O–C-Ar), 137.89–114.95 (C–Ar), 55.55 (CH_3O–Ar), 41.26 (CH_2), 17.56 (CH_3-Ar). MS (m/z), 340.00 $[M]^+$. Calcd. 340.08 $[M]^+$. Anal. Calcd. for $C_{18}H_{16}N_2O_3S$: Calcd. C, 63.51; H, 4.74; N, 8.23; S, 9.42. Found: C, 63.31; H, 4.63; N, 8.09; S, 9.29.

2.2.16. 3-m-Anisole-2-thioxo-1-p-anisole-dihydropyrimidine-4,6(1H,5H)-dione (3p)

Yellow solid, mp 112–113 °C, ^1H NMR 400 MHz ($CDCl_3$): δ 7.41–7.37 (t, J = 8.0 Hz, 1H, C_5-Ar-H), 7.25 (s, 1H, C_2-Ar-H), 7.11–7.09 (d, J = 8.8 Hz, 2H, C_3,C_5-Ar-H), 6.99–6.97 (d, J = 8.8 Hz, 2H, C_2,C_6-Ar-H), 6.80–6.72 (dd, J = 7.6 Hz, 2H, C_4,C_6-Ar-H), 4.06 (s, 2H, CH_2), 3.82 (s, 3H, CH_3O–Ar), 3.80 (s, 3H, CH_3O–Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.73 (C=S), 163.53–163.20 (C=O), 160.62; 159.86 (C–O-Ar), 139.80–110.02 (C–Ar) 55.53 (CH_3O–Ar); 54.64 (CH_3O–Ar); 41.27 (CH_2). MS (m/z), 356.10 $[M]^+$. Calcd. 356.08 $[M]^+$. Anal. Calcd. for $C_{18}H_{16}N_2O_4S$: Calcd. C, 60.66; H, 4.53; N, 7.86; S, 9.00. Found: C, 60.49;

Table 1
Optimization of reaction conditions for 1-*o*-tolyl-3-phenyl thiourea and malonic acid[b].

Entry	CH_3COCl (mmol)	Solvent (mmol)	Time (h)	Yield[c] (%)
1	Neat	Neat	10.0	0
2	10	Neat	8.0	20
3	20	Neat	9.0	32
4	20	C_6H_6 (20)	5.0	42
5	20	$CHCl_3$ (20)	5.5	45
6	20	C_2H_5OH (20)	5.0	50
7	20	DMF (20)	4.0	62
8	20	DMSO (20)	4.0	67
9	20	CH_3COOH (20)	3.5	75
10	20	CH_3COOH (25)	3.5	81
11	20	CH_3COOH (35)	3.0	87
12	20	CH_3COOH (40)	3.0	96

[b] *General reaction conditions:* 1-*o*-tolyl-3-phenyl thiourea *(*10 mmol*), malonic acid (*10 mmol*).*
[c] *present yield, rt-room temperature.*

H, 4.46; N, 7.76; S, 8.93.

2.2.17. 3-m-Tolyl-2-thioxo-1-p-anisole-dihydropyrimidine-4,6(1H,5H)-dione (3q)

Yellow solid, mp 106–108 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.38–7.35 (t, J = 7.2 Hz, 1H, C_5-Ar-H), 7.25–7.24 (d, J = 6.8 Hz, 2H, C_3,C_5-Ar-H), 7.10–7.08 (d, J = 8.0 Hz, 2H, C_2,C_6-Ar-H), 7.00–6.97 (t, J = 7.6 Hz, 2H, C_4,C_6-Ar-H), 6.88 (s, 1H, C_2-Ar-H), 4.05 (s, 2H, CH_2CO), 3.82 (s, 3H, CH_3O–Ar), 2.38 (s, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 182.02 (C=S), 163.56, 163.36 (C=O), 159.85 (C–O-Ar), 139.78–114.92 (C–Ar), 55.52 (CH_3O–Ar), 41.29 (CH_2), 21.45 (CH_3-Ar). MS (m/s) 340.10 $[M]^+$. Calcd. 340.08 $[M]^+$. Anal. Calcd. for $C_{18}H_{16}N_2O_3S$: Calcd. C, 63.51; H, 4.74; N, 8.23; S, 9.42. Found: C, 63.43; H, 4.59; N, 8.17; S, 9.33.

2.2.18. 3-o-Anisole-2-thioxo-1-p-anisole-dihydropyrimidine-4,6(1H,5H)-dione (3r)

Yellow solid, mp 161–163 °C. ^{1}H NMR 400 MHz $CDCl_3$: δ 7.43–7.40 (t, J = 7.6 Hz, 2H, C_3, C_6-Ar-H), 7.15–7.11 (dd, J = 6.4 Hz, 2H, C_4,C_5-Ar-H), 7.06–7.04 (d, J = 7.6 Hz, 2H, C_2,C_6-Ar-H), 6.99–6.97 (d, J = 8.8 Hz, 2H, C_3, C_5-Ar-H), 4.03 (s, 2H, CH_2CO), 3.82 (s, 3H, CH_3O–Ar), 3.81 (s, 3H, CH_3O–Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.79 (C=S), 163.79, 162.96 (C=O), 159.78 (O–C-Ar), 154.45 (O–C-Ar), 131.50–112.33 (C–Ar), 56.02 (CH_3O–Ar), 55.50 (CH_3O–Ar), 41.26 (CH_2). MS (m/z): 356.10 $[M]^+$. Calcd. 356.08 $[M]^+$. Anal. Calcd. for $C_{18}H_{16}N_2O_4S$: Calcd. C, 60.66; H, 4.53; N, 7.86; S, 9.00. Found: C, 60.49; H, 4.46; N, 7.76; S, 8.93.

2.2.19. 3-o-Chlorophenyl-2-thioxo-1-p-anisole-dihydropyrimidine-4,6(1H,5H)-dione (3s)

Yellow solid, mp 178–179 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.53–7.51 (dd, J = 7.2, 4.4 Hz, 1H, C_3-Ar-H), 7.41–7.38 (td, J = 6.0, 3.2 Hz, 1H, C_4, C_5-Ar-H), 7.30–7.27 (dd, J = 7.2, 4.4 Hz, 1H, C_6-Ar-H), 7.14–7.12 (d, J = 8.8 Hz, 2H, C_2, C_6-Ar-H), 7.00–6.98 (d, J = 8.8 Hz, 2H, C_3, C_5-Ar-H), 4.09 (s, 2H, CH_2CO), 3.83 (s, 3H, CH_3-Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.68 (C=S), 163.40, 162.60 (C=O), 159.94 (C_2–Ar), 136.27–114.24 (C–Ar), 55.55 (CH_3-OAr), 41.19 (CH_2). MS (m/z): 356.1 $[M]^+$. Calcd. 356.10 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}ClN_2O_3S$: Calcd. C, 57.37; H, 4.55; Cl, 9.41; N, 7.43; S, 8.51. Found: C, 57.28; H, 4.49; Cl, 9.33; N, 7.36; S, 8.46.

2.2.20. 3-m-Chlorophenyl-2-thioxo-1-p-anisole-dihydropyrimidine-4,6(1H,5H)-dione (3t)

Yellow solid, mp 144–145 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.43–7.41 (d, J = 7.2 Hz, 2H, C_4,C_6-Ar-H), 7.26 (s, 1H, C_2-Ar-H), 7.25–7.23 (d, J = 7.6 Hz, 2H, C_3, C_5-Ar-H), 7.11–7.08 (dd, J = 6.0 Hz, 1H, C_5-Ar-H), 7.00–6.98 (d, J = 8.0 Hz, 2H, C_2, C_6-Ar-H), 4.06 (s, 2H, CH_2CO), 3.84 (s, 3H, CH_3O–Ar). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.51

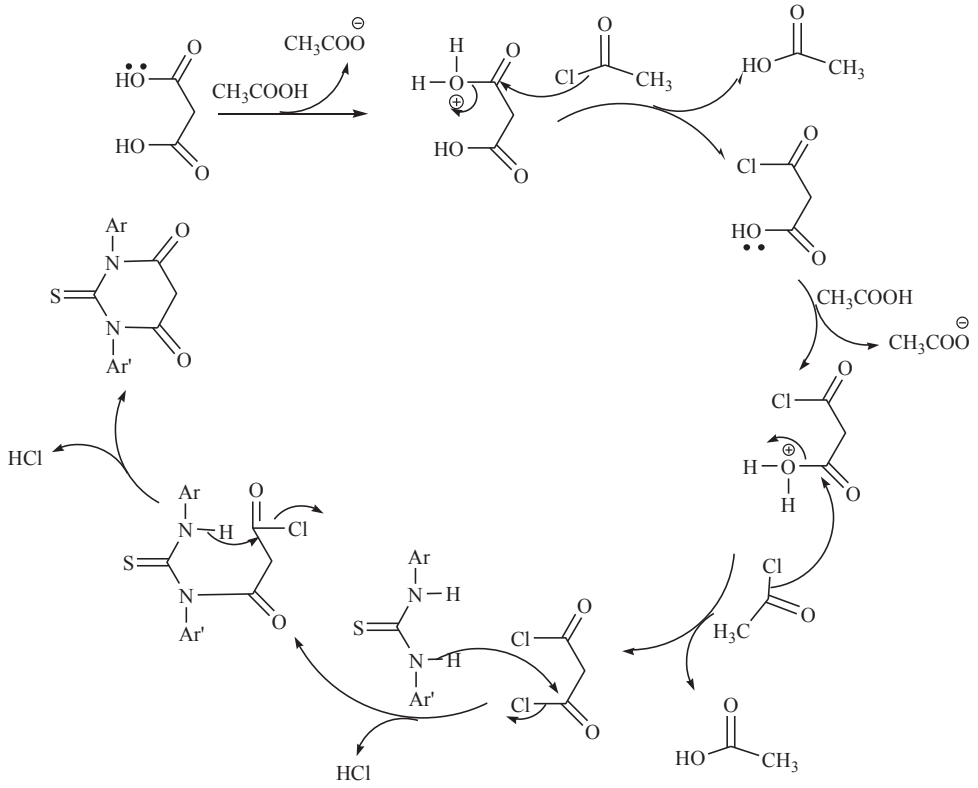


Fig. 1. Mechanistic pathway for the formation of TBA.

Table 2
Optimization of reaction conditions for 1-(2-hydroxyethyl)-3-*p*-tolyl thiourea and malonic acid[b].

Entry	Catalyst	Amount of Catalyst (mmol)	CH_3COCl–CH_3COOH (mmol)	Time (h)	Yield[c] (%)
1	–	–	20:20	24	0
2	–	–	20:40	24	0
3	–	–	20:60	24	0
4	HCl	10	20:40	24	12
5	H_2SO_4	10	20:40	24	67
6	A-15	10	20:40	24	32
7	A-35	10	20:40	24	37
8	PTSA	10	20:40	3.0	88
9	PTSA	7	20:40	3.5	75
10	PTSA	5	20:40	3.5	62
11	PTSA	2	20:40	3.5	52

[b] *General reaction conditions:* 1-(2-hydroxyethyl)-3-p-tolyl thiourea (10 mmol), *malonic acid* (10 mmol).

[c] *present yield,* rt-room temperature, A-15-Amberlyst-15, A-35-Amberlyst-35, PTSA-p-Tolyl Suphonic Acid.

(C=S), 163.35, 163.14 (C=O), 159.93, 159.84 (O–C-Ar), 139.70–114.94 (C–Ar), 55.55 (CH_3O–Ar), 41.18 (CH_2). MS (m/s), 359.97 $[M]^+$. Calcd. 360.50 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}ClN_2O_3S$: Calcd. C, 57.37; H, 4.55; Cl, 9.41; N, 7.43; S, 8.51. Found: C, 57.28; H, 4.49; Cl, 9.33; N, 7.36; S, 8.46.

2.2.21. 1-p-Chlorophenyl-2-thioxo-3-ethyl-dihydropyrimidine-4,6(1H,5H)-dione (3u)

Orange solid, mp 147–149 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.45–7.43 (d, J = 8.4 Hz, 2H, C_2, C_6-Ar-H), 7.07–7.05 (d, J = 8.4 Hz, 2H, C_3, C_5-Ar-H), 4.47–4.42 (q, J = 6.8 Hz, 2H, CH_2–CH_3), 3.89 (s, 2H, CH_2CO), 1.30–1.26 (t, J = 7.2 Hz, 3H, CH_3–CH_2). ^{13}C NMR 100 MHz ($CDCl_3$): δ 180.74 (C=S), 163.21, 162.94 (C=O), 137.48–126.44 (C–Ar), 43.79 (CH_2–N), 40.89 (CH_2), 12.38 (CH_3–CH_2). MS (m/z): 282.10 $[M]^+$. Calcd. 282.5 $[M]^+$. Anal. Calcd. for $C_{12}H_{11}ClN_2O_2S$: Calcd. C, 50.97; H, 3.92; Cl, 12.54; N, 9.91; S, 11.34. Found: C, 51.01; H, 4.03; Cl, 9.88; N, 9.79; S, 11.28.

2.2.22. Synthesis of 5-thioxo-6-p-tolyl-2,3,5,6-tetrahydrooxazolo[3,2-f] pyrimidin-7-one (3v)

Synthesis of 5-thioxo-6-*p*-tolyl-2,3,5,6-tetrahydrooxazolo [3,2-f] pyrimidin-7-one was synthesized by the reaction of 1-(2-hydroxyethyl)-*p*-tolyl thiourea (1v, 10 mmol) with malonic acid (2, 10 mmol), in presence of PTSA (10 mmol) and acetyl chloride-acetic acid (20:40 mmol). The reaction mixture was stirred for 3h and progress of reaction was monitored by TLC. After completion of reaction, mixture was filtered, washed with water. The product was further purified by recrystallization in aqueous ethanol. Purity of all newly synthesized compounds checked with the help of HPLC technique using solvent system acetonitrile-water (4:1) and single peak has been obtained in chromatogram hence compound is in pure form. Yellow solid; mp 160 °C. ^1H NMR 400 MHz ($CDCl_3$): δ 7.309–7.289 (d, J = 8 Hz, 2H, $C_{2,6}$ Ar–H), δ

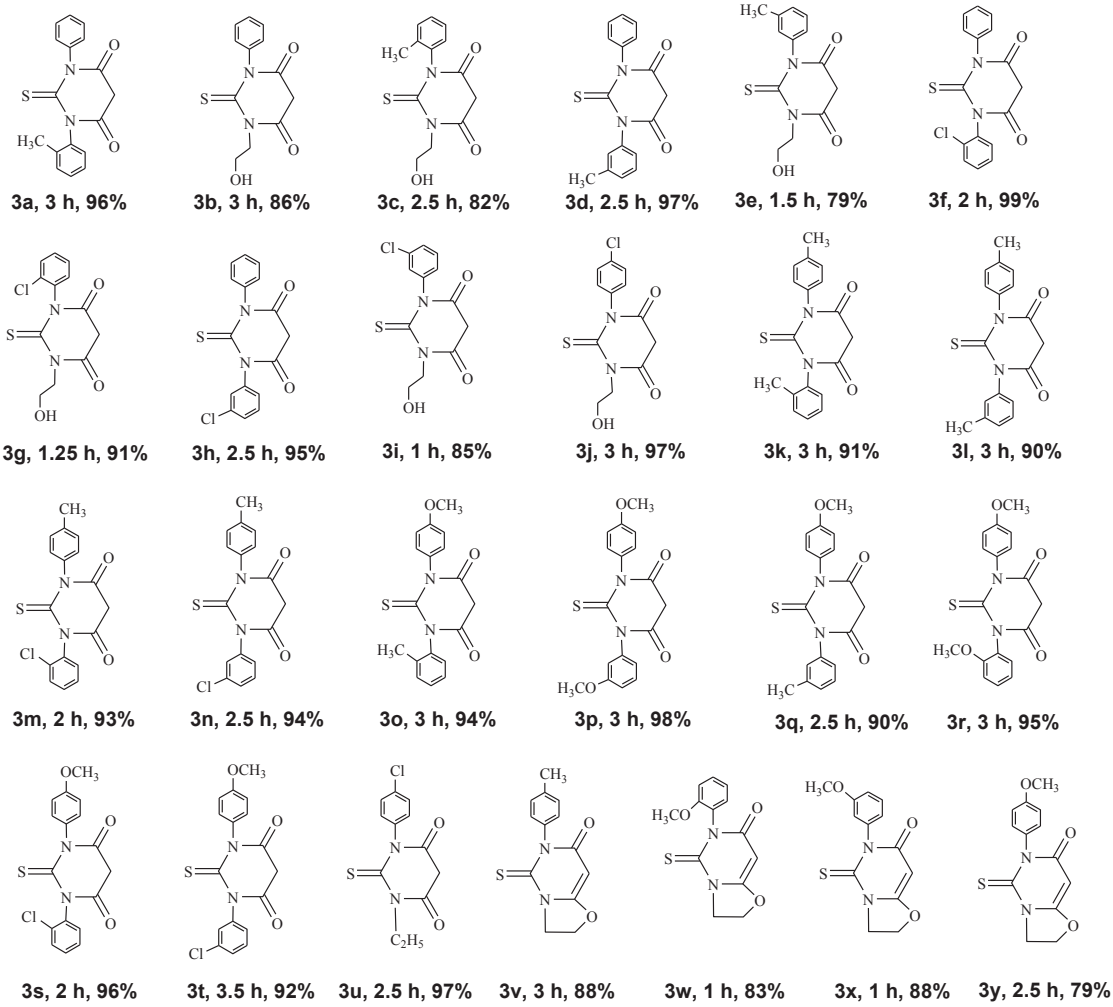


Fig. 2. Structure of different functionalized products.

7.087–7.060 (d, J = 10.8 Hz, 2H, $C_{3,5}$ Ar–H), 4.589 (s, 1 H HC = C), 4.128–4.092 (t, J = 14.4 Hz, 2H, O–CH_2), 3.882–3.852 (t, J = 12 Hz, 2H, N–CH_2), 2.405 (s, 3H, CH_3). ^{13}C NMR 100 MHz ($CDCl_3$): δ 178.04 (C=S), 168.86 (C=O), 164.45 (C–O), 139.59 (C–N), 131.36–128.06 (C–Ar), 84.48 (C–H), 65.16 (CH_2–O), 60.12 (CH_2–N), 22.37 (CH_3-Ar). MS (m/z): 219 $[M\text{-}C_2HO]^+$. Anal. Calcd. for $C_{13}H_{12}N_2O_2S$: Calcd. C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 59.95; H, 4.68; N, 10.81; S, 12.35.

2.2.23. 6-(2-anisyl)-5-thioxo-2,3,5,6-tetrahydrooxazolo[3,2-f]pyrimidin-7-one (3w)

Light orange solid; mp 112 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.419–7.401 (d, J = 7.2 Hz, 2H, 2 C, Ar–H), δ 7.246–7.227 (d, J = 7.6 Hz, 2H, 3 C, Ar–H), δ 7.170–7.150 (d, J = 8 Hz, 2H, 4 C, Ar–H), δ 7.015–6.995 (d, J = 8 Hz, 2H, 5 C, Ar–H), 4.836 (s, 1H HC = C), 4.487–4.451 (t, J = 14.4 Hz, 2H, O–CH_2), 4.291–4.254 (t, J = 14.8 Hz, 2H, N–CH_2), 3.796 (s, 3H, OCH_3). ^{13}C NMR 100 MHz ($CDCl_3$): δ 178.83 (C=S), 171.17(C=O), 171.17 (C–O), 164.76(C–N), 150.93–112.33 (C–Ar), 84.99 (C–H), 62.79 (CH_2–O), 61.68 (CH_2–N), 55.84 (CH_3–O). MS (m/z): 276.31 $[M\text{-}C_2HO]^+$. Calcd. 276.31 $[M]^+$. Anal. Calcd. for $C_{13}H_{12}N_2O_3S$: Calcd. C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.55; H, 4.41; N, 10.19; S, 11.55.

2.2.24. 6-(3-anisyl)-5-thioxo-2,3,5,6-tetrahydrooxazolo[3,2-f]pyrimidin-7-one (3x)

Light orange solid; mp 150 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.413–7.393 (dd, J = 8 Hz, 1H, 5, 4C, Ar–H), δ 7.373–7.353 (dd, J = 8 Hz, 1H, 5, 6C, Ar–H), 6.999–6.978 (d, J = 8.4 Hz, 1H, 4C, Ar–H), 6.749–6.730 (d, J = 7.6 Hz, 1H, 6C, Ar–H), 6.691 (s, 1H, 2C, Ar–H), 4.749 (s, 1H, HC = C), 4.480–4.444 (t, J = 14.4 Hz, 2H, O–CH_2), 3.955–3.919 (t, J = 14.4 Hz, 2H, N–CH_2), 3.812 (s, 3H, OCH_3). ^{13}C NMR 100 MHz ($CDCl_3$): δ 181.44 (C=S), 171.31 (C=O), 163.80 (C–O), 150.12–114.78 (C–Ar), 85.88 (C–H), 70.04 (CH_2–O), 61.34 (CH_2–N), 55.57 (CH_3–O). MS (m/z): 276.30 $[M]^+$. Calcd. 276.31 $[M]^+$. Anal. Calcd. for $C_{13}H_{12}N_2O_3S$: Calcd. C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.51; H, 4.38; N, 10.14; S, 11.60.

2.2.25. 6-(4-anisyl)-5-thioxo-2,3,5,6-tetrahydrooxazolo[3,2-f]pyrimidin-7-one (3y)

Light orange solid; mp 98 °C. ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.115–7.093 (d, J = 8.8 Hz, 2H, 6C, Ar–H), 7.000–6.979 (d, J = 8.4 Hz, 2H, 3,5C, Ar–H), 4.454 (s, 1H, HC = C), 4.114–4.077 (t, J = 14.8 Hz, 2H, O–CH_2), 3.845–3.814 (t, J = 12.4 Hz, 2H, N–CH_2), 3.749 (s, 3H, OCH_3). ^{13}C NMR 100 MHz ($CDCl_3$): δ 197.07 (C=S), 171.10 (C=O), 164.63 (C–O), 160.06 (C–N) 129.40–115.26 (C–Ar), 96.04 (C–H), 62.78 (CH_2–O), 61.03 (CH_2–N) 55.61 (CH_3–O). MS (m/z): 276.31 $[M\text{-}C_2H_5]^+$. Calcd. 276.31 $[M]^+$. Anal. Calcd. for $C_{13}H_{12}N_2O_3S$: Calcd. C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.51; H, 4.38; N, 10.14; S, 11.60.

2.3. Supporting information

^{1}H, ^{13}C NMR and MS spectra of all synthesized compounds is provided in supplementary file.

3. Results and discussion

Initially, the reaction of 1-*o*-tolyl-3-phenyl thiourea **1a** and malonic acid **2**, was screened in varying molar proportion of acetyl chloride at room temperature stirring (Table 1). In order to investigate the role of acetyl chloride in presence or absence of solvent on C–N coupling reaction was executed. First we have carried out the reaction without acetyl chloride and solvent, no reaction in progress (Table 1, entry 1). We attempted the same reaction with acetyl chloride (10 mmol) without solvent for comparison, we realized that 20% amount of product was obtained (Table 1, entry 2). When we optimized same reaction with increased the molar proportion of acetyl chloride (20 mmol) with solvent free condition which offered 32% of product (Table 1, entry 3). Hence we have found that, the dominating role of acetyl chloride on C–N coupling pathways because *in situ* malonyl chloride as an intermediate was obtained.

Thus, encouraged the result of acetyl chloride, we focused on the optimization to increase the yield of **3a**. We optimized the reaction conditions with preset proportion of acetyl chloride (20 mmol) with different solvents like C_6H_6, $CHCl_3$, C_2H_5OH, DMF, DMSO and CH_3COOH (20 mmol), 42–75% yields were obtained but did not put any remarkable results even stretching reaction time (Table 1, entry 4–9). Upon screening for the appropriate solvent, we found to give relatively good outcome in acetic acid medium (Table 1, entry 10–11). The finest result was achieved in presence of acetyl chloride and acetic acid (20:40 mmol) (Table 1, entry 12). Acetic acid as solvent which play a significant role on the C–N coupling reaction because acetyl chloride was react faster in presence of acetic acid medium. Hence, acetic acid is good initiator on an account of completion of reaction.

Therefore we have chosen the proportion of acetyl chloride and acetic acid (20:40 mmol) for rest of the reactions and finally synthesized various TBAs without affecting any functional group. The structure of **3a** is confirmed by spectral, analytical data and further supported by mechanistic pathway as shown in Fig. 1.

In next cyclization, by the reaction of 1-(2-hydroxyethyl)-3-*p*-tolyl thiourea **1v** and malonic acid **2** was screened with molar proportion of acetyl chloride-acetic acid in presence of PTSA (10 mmol) at room temperature stirring as shown in Table 2.

In previous reactions, acetyl chloride-acetic acid is played a vital role but in cyclization, no reaction has been carried out without catalyst (Table 2, entry 1–3). The various types of catalysts like HCl, H_2SO_4, Amberlyst-15 and 35 (10 mmol) were used for the comparison but did not give any progressive outcome on screening the cyclization reaction (Table 2, entry 4–7). When same reaction was carried out in presence of PTSA (10 mmol), which afforded the desired product with good yield (Table 2, entry 8) rather than changing the proportion of PTSA (Table 2, entry 9–11). The structure of **3v** is confirmed by spectral and analytical data. Therefore, we followed the same pathway for rest of the cyclization reactions and results are shown in Fig. 2.

The progress of reaction was monitored by TLC using appropriate eluent. Purity of all newly synthesized products (**3a-y**) checked by reverse phase high performance liquid chromatography with PDA detection at 254 nm and method has been developed skillfully using acetonitrile and water (4:1).

4. Conclusion

This is the first report of a simple, inexpensive and efficient synthesis of unsymmetric TBA by the interaction of unsymmetrical 1,3-disubstituted thioureas with malonic acid and acetyl chloride in acetic acid medium at room temperature. We have also first time reporting, reaction of 1-(2-hydroxyethyl)-3-aryl thioureas and malonic acid with molar proportion of acetyl chloride-acetic acid on room temperature stirring in presence of PTSA. We believe that, the present protocol provides the simple, high yielding, advantageous and commercially available for synthesis of variety of TBAs and their cyclized products.

Declarations

Author contribution statement

Madhukar G. Dhonde: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Vinod D. Deotale: Performed the experiments; Wrote the paper.

Manish M Katiya: Performed the experiments; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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