HPLC purification technique: synthesis of unsymmetrical thiobarbituric acids

Vinod D. Deotale, Manish M. Katiya, Madhukar G. Dhonde*  
Department of Chemistry, Shri Mathuradas Mohota College of Science, Nagpur, 444009, MS, India

ARTICLE INFO
Keywords:
Organic chemistry  
Thioureas  
Unsymmetrical thiobarbituric acid  
Cyclized pyrimidines  
HPLC

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], anti-diabetic 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 thioureas in Amberlyst-15 [26], acetyl chloride [27, 28, 29, 30, 31, 32], POCl3 [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 \( \mu \)m, 150 x 4.6 mm, at 254 nm. \(^1\)H (400 MHz) NMR spectra were recorded on a Bruker Advance-III 400 spectrometer from CDCl\(_3\) solution with TMS as an internal reference. Chemical shift are recorded as ppm on the \( \delta \) scale and multiplicities are described as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of triplet).
1. H NMR 400 MHz (CDCl₃): δ 7.493–7.445 (dd, J = 7.6, 4.4 Hz, 2H, C₆–C₇′ Ar-H), 7.356–7.309 (dd, J = 6.8, 5.6 Hz, 2H, C₄–C₅′ Ar-H), 7.215–7.195 (d, J = 8.0 Hz, 3H, C₂–C₄′ Ar-H), 7.111–7.093 (d, J = 7.2 Hz, 2H, C₆–C₇′ Ar-H), 4.059 (s, 2H, CH₂CO), 2.179 (s, 3H, CH₃ Ar). ¹³C NMR 100 MHz (CDCl₃): δ 180.72 (C-S), 163.35, 162.86 (C-O), 138.70–127.46 (C-Ar), 41.22 (CH₂), 17.55 (CH₃ Ar). MS (m/z), 310.1 [M⁺].

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

Yellow solid; mp 120 °C. ¹H NMR 400 MHz (CDCl₃): δ 7.382–7.267 (m, 4H, Ar-H), 4.460–4.421 (t, J = 15.6 Hz, 2H, O-CH₂), 4.27–4.238 (t, J = 13.2 Hz, 2H, N-CH₂), 3.919 (s, 2H, CH₂CO), 2.022 (s, 1H, OH-(bs)).

2.2. Experimental method

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

Synthesis of 3-phenyl-2-thiooxo-1-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3a) was synthesized by the interaction of 1-phenyl-3-thiooxo-1-phenyl-2-thioxo-1-tolyl-dihydropyrimidine-4,6(1H,5H)-dione (3b) with 1H NMR 400 MHz (CDCl₃): δ 7.382–7.267 (m, 4H, Ar-H), 4.460–4.421 (t, J = 15.6 Hz, 2H, O-CH₂), 4.27–4.238 (t, J = 13.2 Hz, 2H, N-CH₂), 3.919 (s, 2H, CH₂CO), 2.022 (s, 1H, OH-(bs)).

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

Yellow solid; mp 160 °C. ¹H NMR 400 MHz (CDCl₃): δ 7.282–7.251 (t, J = 14.4 Hz, 2H, O-CH₂), 7.199–7.182 (d, Ar-H), 4.134–4.098 (t, J = 14.4 Hz, 2H, O-CH₂), 2.840–3.804 (t, J = 14.4 Hz, 2H, N-CH₂), 2.991 (s, 2H, CH₂CO), 2.052 (s, 1H, OH-(bs)). ¹³C NMR 100 MHz (CDCl₃): δ 196.10 (C=S), 168.50, 163.33 (C=O), 137.05–124.03 (C=O), 58.08 (CH₂-OCONH), 43.32 (CH₂-CH₂), 36.68 (CH₂). MS (m/z): 219.1 [M-N₂H₂O⁺].

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

Yellow solid; mp 148 °C. ¹H NMR 400 MHz (CDCl₃): δ 7.493–7.445 (dd, J = 7.6, 4.4 Hz, 2H, C₆–C₇′ Ar-H), 7.356–7.309 (dd, J = 6.8, 5.6 Hz, 2H, C₄–C₅′ Ar-H), 7.215–7.195 (d, J = 8.0 Hz, 3H, C₂–C₄′ Ar-H), 7.111–7.093 (d, J = 7.2 Hz, 2H, C₆–C₇′ Ar-H), 4.059 (s, 2H, CH₂CO), 2.179 (s, 3H, CH₃ Ar). ¹³C NMR 100 MHz (CDCl₃): δ 180.72 (C-S), 163.35, 162.86 (C-O), 138.70–127.46 (C-Ar), 41.22 (CH₂), 17.55 (CH₃ Ar). MS (m/z), 310.1 [M⁺].

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

Yellow solid; mp 206–208 °C. ¹H NMR 400 MHz (CDCl₃): δ 7.49–7.47 (d, J = 7.2 Hz, 2H, C₂–C₃′ Ar-H), 7.44 (s, 1H, C₂–C₃′ Ar-H), 7.39–7.35 (d, J = 7.2 Hz, 1H, C₄–C₅′ Ar-H), 7.26–7.24 (d, J = 7.2 Hz, 1H, C₄–C₅′ Ar-H), 7.20–7.19 (d, J = 7.2 Hz, 2H, C₆–C₇′ Ar-H), 7.01–6.99 (d, J = 7.2 Hz, 2H, C₆–C₇′ Ar-H), 4.06 (s, 2H, CH₂), 2.39 (s, 3H, CH₃ Ar). ¹³C NMR 100 MHz (CDCl₃): δ 181.67 (C-S), 163.34 (C-O), 139.83–125.59 (C=O), 41.27 (CH₂), 21.48 (CH₃ Ar). MS (m/z), 310.95 [M⁺].

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

Yellow solid; mp 120 °C. ¹H NMR 400 MHz (CDCl₃): δ 7.387–7.355 (t, J = 12.8 Hz, 1H, 5 C, Ar-H), δ 7.267–7.252 (d, J = 6 Hz, 1H, 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-CH₂), 3.843 (s, 2H CO-CH₂), 2.820–2.785 (t, J = 14 Hz, 2H, N-CH₂), 2.061 (bs, 1H, OH). ¹³C NMR 100 MHz (CDCl₃): δ 180.66 (C-S), 169.52, 164.42 (C=O), 142.42–119.19 (C=O), 61.04 (CH₂O), 45.99 (CH₂N), 40.11(CH₂), 22.32(CH₃ Ar). MS (m/z): 219.1 [M-C₂H₅O⁺].

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

Dark brown solid; mp 130–131 °C. ¹H NMR 400 MHz (CDCl₃): δ
2.2.7. 3-(2-chlorophenyl)-1-(2-hydroxyethyl)-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione (3p)

Yellow solid; mp 118–120 °C. 1H NMR 400 MHz (CDCl3): δ 8.19–8.19 (m, 3H, C4-Ar-H), 7.98 (t, J = 8.3 Hz, 1H, C5-Ar-H), 7.44 (dd, J = 8.4 Hz, 2H, C3, C5-Ar-H), 7.38–7.39 (m, 4H, C5, C6-Ar-H), 7.06–7.06 (m, 4H, C2, C4-Ar-H). 13C NMR 100 MHz (CDCl3): δ 181.32 (C=O), 180.50 (C=O), 139.43 (C-Ar), 138.49 (C-Ar), 128.82 (C-Ar), 128.39 (C-Ar), 127.77 (C-Ar), 127.26 (C-Ar), 126.76 (C-Ar), 125.96 (C-Ar), 125.46 (C-Ar), 124.86 (C-Ar). MS (m/z): 324.20 [M+1]+. Anal. Calcd. for C18H14N2O5S: C, 59.59; H, 5.87; N, 9.29. Found: C, 59.78; H, 5.76; N, 9.28.

2.2.12. 3-m-Tolyloxy-2-thioxo-1-p-tolyldihydropyrimidine-4,6(1H,5H)-dione (3l)

Yellow solid, mp 112–113 °C. 1H NMR 400 MHz (CDCl3): δ 7.54–7.54 (m, 5H, C6-Ar-H), 7.32 (s, 3H, O-Ar), 7.07–7.07 (m, 3H, C3, C4-Ar-H), 6.93–6.93 (m, 2H, C3, C4-Ar-H), 6.82–6.82 (m, 2H, C3, C4-Ar-H). 13C NMR 100 MHz (CDCl3): δ 180.96 (C=O), 136.48 (C-Ar), 133.30 (C-Ar), 132.52 (C-Ar), 129.67 (C-Ar), 128.49 (C-Ar), 127.88 (C-Ar), 126.69 (C-Ar), 124.00 (C-Ar). MS (m/z): 356.10 [M+1]+. Anal. Calcd. for C18H16N2O5S: C, 60.65; H, 4.63; N, 7.86. Found: C, 60.49; H, 4.53; N, 7.86; S, 9.00.
Table 1
Optimization of reaction conditions for 1-o-tolyl-3-phenyl thiourea and malonic acid.

| Entry | CH3COCl (mmol) | Solvent (mmol) | Time (h) | Yield (%) |
|-------|-----------------|----------------|----------|-----------|
| 1     | Neat            | Neat           | 10.0     | 0         |
| 2     | 10              | Neat           | 8.0      | 20        |
| 3     | 20              | Neat           | 9.0      | 32        |
| 4     | 20              | C6H6 (20)      | 5.0      | 42        |
| 5     | 20              | CH2Cl (20)     | 5.5      | 45        |
| 6     | 20              | CH3OH (20)     | 5.0      | 50        |
| 7     | 20              | DMF (20)       | 4.0      | 62        |
| 8     | 20              | DMSO (20)      | 4.0      | 67        |
| 9     | 20              | CH3COOH (20)   | 3.5      | 75        |
| 10    | 20              | CH3COOH (25)   | 3.5      | 81        |
| 11    | 20              | CH3COOH (35)   | 3.0      | 87        |
| 12    | 20              | CH3COOH (40)   | 3.0      | 96        |

* General reaction conditions: 1-o-tolyl-3-phenyl thiourea (10 mmol), malonic acid (10 mmol).

† present yield, rt-room temperature.

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

2.2.17. 3-m-Toly1-2-thioxo-1-p-anisole-dihydropyrimidine-4,6(1H,5H)-dione (3g)

Yellow solid, mp 106–108 °C. 1H NMR 400 MHz (CDCl3): δ 7.38–7.35 (t, J = 7.2 Hz, 1H, C9-Ar-H), 7.25–7.24 (d, J = 6.8 Hz, 2H, C8,C7-Ar-H), 7.10–7.08 (d, J = 8.0 Hz, 2H, C6,C5-Ar-H), 7.00–6.97 (t, J = 7.6 Hz, 2H, C4,C3-Ar-H), 6.88 (s, 1H, C2-Ar-H), 4.05 (s, 2H, CH2CO), 3.82 (s, 3H, CH3O–Ar), 2.38 (s, 3H, CH3–Ar). 13C NMR 100 MHz (CDCl3): δ 182.02 (C=S), 163.56, 163.36 (C=O), 159.85 (C-O-Ar), 139.78–119.42 (C-Ar), 55.52 (CH3O–Ar), 41.29 (CH2), 21.45 (CH3–Ar). MS (m/z) 340.10 [M]+. Calcd. 340.08 [M]+. Anal. Calcd. for C18H16N2O3S: 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. 1H NMR 400 MHz (CDCl3): δ 7.43–7.40 (t, J = 7.6 Hz, 2H, C8,C7-Ar-H), 7.15–7.11 (dd, J = 6.4 Hz, 2H, C6,C5-Ar-H), 7.06–7.04 (d, J = 7.6 Hz, 2H, C6,C5-Ar-H), 6.99–6.97 (d, J = 8.8 Hz, 2H, C4,C3-Ar-H), 4.03 (s, 2H, CH2CO), 3.82 (s, 3H, CH3O–Ar), 3.81 (s, 3H, CH3O–Ar). 13C NMR 100 MHz (CDCl3): 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 (CH3O–Ar), 55.50 (CH2O-Ar), 41.26 (CH2). MS (m/z): 356.10 [M]+. Calcd. 356.08 [M]+. Anal. Calcd. for C18H16N2O3S: 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. 1H NMR 400 MHz (CDCl3): δ 7.53–7.51 (dd, J = 7.2, 4.4 Hz, 1H, C9-Ar-H), 7.41–7.38 (td, J = 6.0, 3.2 Hz, 1H, C8, C7-Ar-H), 7.30–7.27 (dd, J = 7.2, 4.4 Hz, 1H, C6-Ar-H), 7.14–7.12 (d, J = 8.8 Hz, 2H, C4,C3-Ar-H), 7.00–6.98 (d, J = 8.8 Hz, 2H, C4,C3-Ar-H), 4.09 (s, 2H, CH2CO), 3.83 (s, 3H, CH3–Ar). 13C NMR 100 MHz (CDCl3): δ 180.68 (C=S), 163.40, 162.60 (C=O), 159.94 (C2-Ar), 136.27–114.24 (C-Ar), 55.55 (CH2O–Ar), 41.19 (CH2). MS (m/z): 356.1 [M]+. Calcd. 356.10 [M]+. Anal. Calcd. for C18H16ClN2O3S: Calcd. C, 57.37; H, 4.55; Cl, 4.91; 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. 1H NMR 400 MHz (CDCl3): δ 7.43–7.41 (d, J = 7.2 Hz, 2H, C8,C7-Ar-H), 7.26 (s, 1H, C6-Ar-H), 7.25–7.23 (d, J = 7.6 Hz, 2H, C6,C5-Ar-H), 7.11–7.08 (dd, J = 6.0 Hz, 1H, C5–Ar-H), 7.00–6.98 (d, J = 8.0 Hz, 2H, C4,C3-Ar-H), 4.06 (s, 2H, CH2CO), 3.84 (s, 3H, CH3O–Ar). 13C NMR 100 MHz (CDCl3): 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

| Entry | Catalyst | Amount of Catalyst (mmol) | CH3COC-CH2COOH | Time (h) | Yield (%) |
|-------|----------|---------------------------|-----------------|----------|-----------|
| 1     | –        | –                         | 20:20           | 24       | 0         |
| 2     | –        | –                         | 20:40           | 24       | 0         |
| 3     | –        | –                         | 20:60           | 24       | 0         |
| 4     | HCl      | 10                        | 20:40           | 24       | 12        |
| 5     | H2SO4    | 10                        | 20:40           | 24       | 67        |
| 6     | A-15     | 10                        | 20:40           | 24       | 32        |
| 7     | A-35     | 10                        | 20:40           | 24       | 37        |
| 8     | PTSA     | 7                         | 20:40           | 3.5      | 75        |
| 9     | PTSA     | 5                         | 20:40           | 3.5      | 62        |
| 10    | 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 (CH2=OAr), 41.18 (CH2), MS (m/s), 359.97 [M]+. Calcd. 360.50 [M]+. Anal. Calcd. for C16H14ClN2O2S: Calcd. C, 50.88; H, 3.91; Cl, 10.18; N, 11.17; S, 10.24. Found: C, 50.78; H, 3.85; Cl, 10.02; N, 11.25; S, 10.03.

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 (CDCl3): δ 7.45–7.43 (d, J = 8.4 Hz, 2H, C2, C6-Ar-H), 7.07–7.05 (d, J = 8.4 Hz, 2H, C3, C7-Ar-H), 4.47–4.42 (q, J = 6.8 Hz, 2H, CH2-CH3), 3.89 (s, 2H, CH2=CO), 1.30–1.26 (t, J = 7.2 Hz, 3H, CH3-CH2). 13C NMR 100 MHz (CDCl3): δ 180.74 (C=O), 163.21, 162.94 (C=O), 137.48–126.44 (C-Ar), 43.79 (CH2-N), 40.89 (CH2), 12.38 (CH2=CH2). MS (m/z): 282.10 [M]+. Calcd. 282.5 [M]+. Anal. Calcd. for C12H11ClN2O2S: Calcd. C, 50.97; 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 (CDCl3): δ 7.309–7.289 (d, J = 8 Hz, 2H, C2,6 Ar-H), δ 7.05 (d, J = 8.4 Hz, 2H, C2,6 Ar-H), 6.8 Hz, 2H, CH2). 13C NMR 100 MHz (CDCl3): δ 159.90, 159.81 (C=O). Anal. Calcd. for C10H8ClN2O: Calcd. C, 64.65; H, 4.07; Cl, 9.02; N, 9.60. Found: C, 64.52; H, 4.08; Cl, 9.00; N, 9.63.

Fig. 2. Structure of different functionalized products.
4. Conclusion

This is the first report of a simple, inexpensive and efficient synthesis of unsymmetrical 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-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, H2SO4, 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, analytical data and further supported by mechanistic pathway as 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).

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.
Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2019.e02008.

References

[1] W. Leitner, Green solvents for processes, Green Chem. 9 (2007), 923-223.
[2] C. Capello, U. Fischer, K. Hungerbühler, What is a green solvent? a comprehensive framework for the environmental assessment of solvents, Green Chem. 9 (2007) 927–934.
[3] Y. Gu, F. Jérome, Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry, Chem. Soc. Rev. 42 (2013) 9550–9591.
[4] P.T. Anastas, J.C. Warner, Green Chemistry: Principles and Practice, Oxford University Press, New York, 1998.
[5] P. Anastas, N. Eghbali, Green chemistry: principles and practice, Chem. Soc. Rev. 39 (2010) 301–312.
[6] M. Poliaffo, J.M. Fitzpatrick, T.R. Farren, P.T. Anastas, Green chemistry: science and politics of change, Science 297 (2002) 807–810.
[7] P.T. Anastas, Green Chemistry as Applied to Solvents, ACS Symposium Series, Washington, 2002, pp. 1-9, 1991.
[8] C. Jimenez-Gonzalez, D.J. Constable, S.C. Ponder, Evaluating the ‘greenness’ of chemical processes and products in the pharmaceutical industry—a green metrics primer, Chem. Soc. Rev. 41 (2012) 1485–1498.
[9] T. Pramanik, A.H. Patanah, Dihydropyrimidinone derivatives: green synthesis and effect of electronic factor on their antimicrobial properties, Res. J. Pharmac. Biol. Chem. Sci. 5 (2014) 444–449.
[10] K. Mote, S. Fore, G. Rashinkar, A. Kambhar, R. Salunkhe, Acacia concinna pods: as a green catalyst for highly efficient synthesis of acylation of amines, Arch. Appl. Sci. Res. 2 (2010) 74–86.
[11] H. Sachdeva, R. Saroj, S. Khaturia, D. Dwivedi, Operationally simple green synthesis of some Schiff bases using grinding chemistry technique and evaluation of antimicrobial activities, Green Process. Synth. 1 (2012) 469–477.
[12] M.B. Deshmukh, S.S. Patil, S.D. Jadhav, P.B. Pawar, Green approach for Knoevenagel condensation of aromatic aldehydes with active methylene group, Synth. Commun. 42 (2012) 1177–1183.
[13] S. Patil, S. Jadhav, M.B. Deshmukh, Efficient greener synthesis of 2-aryl-1-aryl-methyl-1-H benzimidazoles using polystyrene sulphonic acid as a catalyst, Arch. Appl. Sci. Res. 3 (2011) 203–208.
[14] V.V. Dabholkar, D.R. Trigathi, Synthesis of Biginelli products of thiobarbituric acids and their antimicrobial activity, J. Serb. Chem. Soc. 75 (2010) 1033–1040.
[15] S. Vijay-Laxmi, Y.T. Reddy, B.S. Kuam, P.N. Reddy, P.A. Crooks, B. Rajitha, Synthesis and evaluation of chromenyl barbiturates and thiobarbiturates as potential antitubercular agents, Bioorg. Med. Chem. Lett 21 (2011) 4329–4331.
[16] M. Kidwai, R. Thakur, R. Mohan, Ecofriendly synthesis of novel antifungal (thio) barbituric acid derivatives, Acta Chim. Slov. 52 (2005) 88–92.
[17] V.I. Bala, I.I. Verginizadis, G.D. Geromichalos, N. Kourkoumelis, I. Male, M.B. Hursthouse, K.H. Repana, E. Yiannaki, K. Charalabopoulou, T. Bala, S.K. Hadijikakou, Synthesis structural characterization and biological studies of the triphenyltin(IV) complex with 2-thiobarbituric acid, Eur. J. Med. Chem. 46 (2011) 2825–2844.
[18] M. Hassan, H.M. Faidallah, A.K. Khalid, Synthesis and biological evaluation of new barbituric and thiobarbituric acid fluro analogs of benzenesulphonamides as antidiabetic and antibacterial agents, J. Fluorine Chem. 142 (2012) 96–104.
[19] S.A. Abdel-Mohsen, Heterocycles derived from 5-(2-Aminothiazol-4-yl)-8-hydroxyquinoline: synthesis and antimicrobial activity, J. Chin. Chem. Soc. 50 (2003) 1085–1092.
[20] K.M. Thakur, D.J. Paghdir, P.T. Chovatia, H.S. Joshi, Synthesis of thiourea derivatives bearing the benz[b]thiophene nucleus as potential antimicrobial agents, J. Serb. Chem. Soc. 70 (2005) 807–815.
[21] D. Pareek, M. Chaudhary, P.K. Pareek, R. Kout, K.G. Ojha, S.M.U. Imaqi, A. Pareek, Synthesis of some biologically important 2-thiobarbituric acid derivatives incorporating benzoazole moiety, Der. Pharmac. Lett. 2 (4) (2010) 274–283.
[22] N. Moraiztranghem, W.S. Laitonjain, A facile synthesis of 7-amino-1,5-diaryl-5-phenyl-2-thiobenzopyran[2,3-d]pyrimidine-4(5H)-ones, Am. Chem. Soc. J. 1 (3) (2011) 58–70.
[23] F.A.G. Nahed, Synthesis reactions structure-activity relationship of 2-benzimidazole analogs as anticancer agents and study their molecular docking, Der. Der Pharma Chem. 5 (5) (2013) 243–257.
[24] L.W. Deady, D. Ganame, A.B. Hughes, N.H. Quazi, S.D. Zanatta, On the synthesis of pyridinythiobarbituric acids, Aust. J. Chem. 55 (2002) 287–289.
[25] J.B. Dickey, A.R. Gray, Barbituric Acid Coll.in Org. Synth, 2, John Wiley & Sons Inc., New York, 1947, p. 60.
[26] M.M. Katyla, M.G. Dhonde, J.M. Gajbhiye, Solvent-free synthesis of thiobarbituric acids using Amberlyst-15 as a green catalyst, Curr. green chem. 4 (11) (2017) 50–56.
[27] A. Singh, V.S. Misra, Synthesis and CVS activity of 1-(2,3,5,2,6 dichlorehenyl)-3-morpholinophenyl-5-substituted benzylidene-thiobarbituric acids, Pharmacol. Res. 21 (1) (1989) 59–64.
[28] M. Kidwai, R.K. Gerg, R.B. Kumar, Novel one pot synthesis of new pyranoquinolines using microwaves, J. Chem. Res., Synop. (2000) 586–587.
[29] A. Shawkat, M. Abdel, Heterocycles derived from 5-(2-aminothiazol-4-yl)-5H-8-hydroxyquinoline: synthesis and antimicrobial activity, J. Chin. Chem. Soc. 50 (2003) 1085–1092.
[30] S. Bondock, A.E.G. Tarhoni, A.A. Fadda, Synthesis and reactions of some new thiobarbituric acid derivatives, Phosphorus Sulfur Silicon Relat, Elements 182 (2007) 1915–1936.
[31] D. Pareek, M. Chaudhary, P.K. Pareek, R. Kout, K.G. Ojha, S.M.U. Imaqi, A. Pareek, Synthesis of some biologically important 2-thiobarbituric acid derivatives incorporating benzoazole moiety, Der. Pharmac. Lett. 2 (4) (2010) 274–283.
[32] V.K. Ahluwaliya, R. Aggarwal, Chemistry of thiobarbituric acid, Proc. Indian natn. Sci. Acad. 62A (5) (1996) 369–413.
[33] B. Ahlem, C. Christophe, V. Patrice, New methodology for the synthesis of thiobarbiturates mediated by manganese(III) acetate, Molecules 17 (2012) 4313–4328.
[34] P.C. Heath, C.Q. Huang, R.F. Lowe, J.R. McCarthy, L.O. Weigle, J.P. Whitten, An efficient acylation/base-catalyzed cyclization of thioureas affords N,N% disubstituted thiobarbituric acids, Tetrahedron 42 (2001) 1607–1610.