



One-pot Mannich type reaction of thiobarbituric acid, aryl aldehyde and aromatic amine in catalyzed by surfactants

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ABSTRACT

The Thioxopyrimidine-dione derivatives were prepared by one pot multi-component Mannich type reaction involving thiobarbituric acids, substituted aldehydes and aromatic amines in acetonitrile-water as solvent using surfactant, Sodium dodecyl sulphate (SDS) at water bath temperature in good yields. The structures of the compounds were confirmed by elemental analyses and spectral data.

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KEYWORDS

Thioxopyrimidine-dione;
Thiobarbituric acid;
Aldehydes;
Amines;
SDS.

INTRODUCTION

Multicomponent reactions (MCRs) have become powerful tools in organic synthesis due to its advantages like atom efficient, structural diversity, waste free synthesis of complex building blocks of 'drug-like' motifs and for promoting the development of straightforward synthetic routes to bioactive heterocycles^[1-6]. Organic reactions in aqueous media have received much attention not only because water has unique reactivity and selectivity but also because it is an economically and environmentally benign solvent. However the use of water in organic reaction has one disadvantage as most of the organic compounds are insoluble in water and as a result, most reaction are slowed^[7]. Sometimes the solubility of organic compounds can be enhanced by using surfactants which can solubilise organic materials or form colloidal dispersion with water^[8]. The development of new synthetic methods for the construction of nitrogenous molecule has defined the frontier of organic synthesis since its very beginning^[9].

The Mannich reaction is a very powerful tool for

constructing carbon-carbon bond in organic chemistry^[10-13]. The reaction is especially useful for the synthesis of β -amino carbonyl derivatives. Due to the importance of the Mannich products in organic synthesis, various methods for conducting highly diastereoselective and/or enantioselective Mannich reactions have been developed in the past^[14]. The Mannich product so called Mannich bases are 1, 3 amino carbonyls, which are versatile intermediates in organic synthesis and have especially proven their values in the synthesis of alkaloids. This type of conversion by now has also been firmly established as a viable approach to prepare the same products in enantio- and diastereomerically pure form via organocatalysis^[14,15]. Compounds bearing 1,3 arrangements of amino and oxygenated functional groups are frequently found in various biologically active natural products^[16,17].

Some modern variants of Mannich reaction have been developed to avoid substrate limitations and environmental problems using catalyst in combination with surfactant in aqueous medium^[18-22]. As surfactants, at ambient condition in aqueous media, aggregates to

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form micelles with hydrophobic tail and hydrophilic head, micellar surfactants as catalysts are widespread and found to be used in different reactions as a route for synthesis in aqueous solutions^[23]. The studies of surfactant-promoted reactions have been increasing, such as, reaction of 1,4-quinone with oxygen nucleophiles in aqueous micelles^[24] surfactant assisted organic reactions in water^[25], Pictet-Spengler reactions^[26].

In view for the synthesis of various biologically important heterocyclic compounds^[29], we wish to report herein a highly efficient procedure for the preparation of Mannich base type 5-(amino(phenyl)methyl)-dihydro-2-thioxopyrimidine-4,6-(1H,5H)-dione via one pot three component Mannich type reaction using anionic surfactant (Sodium dodecyl sulphate) in water:acetonitrile solvent.

EXPERIMENTAL

General

The chemical reagents are of A.R. grade and were used without further purification. Solvents like ethyl acetate and petroleum ether were used after distillation. Melting points were determined on Buchi M-500 digital melting point apparatus and were uncorrected. IR spectra were recorded in KBr pellets on Shimadzo 8400S FTIR spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AV III 500 MHz or Varian 400 MHz or Bruker 300 MHz spectrometer using TMS as internal standard either CDCl₃ or D₂O as solvent. Chemical shifts (δ) were given in parts per million (ppm) and the coupling constant in hertz (Hz). Mass Spectrometer were measured in LC-MS. Model: Waters ZQ-4000 in electron ionization. Elemental analyses were performed by using Perkin Elmer CHNS/O analyzer 2400.

General procedure for mannich reaction

In general experiment, substituted aldehyde (1mmol), aromatic amine (1mmol), thiobarbituric acid (1mmol) and SDS (0.015 mmol%) were taken in a round bottom flask using water and acetonitrile(1:1) as solvent. The reaction mixture was made to reflux at above 100°C in oil bath. The progress of the reaction was monitored by TLC. After completion of reaction,

the solid was separated and washed out several times to remove the surfactant and washed again with acetonitrile to remove all the starting substrate to give the pure product and recrystallise in DCM.

5-((2-nitrophenylamino)(4-chlorophenyl)methyl)-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1a)

Yellow solid; m.p 205 °C (de) ; IR (KBr): ν_{max} 3340,3000,1650,1100,820; ¹H NMR (DMSO-d₆, 500 MHz) δ 4.1(2H,d),4.3(2H,d),5.2 (1H,s), 6.5-7.5 (8H,m), 11.1(1H,s), 11.5(1H,s); ¹³C NMR (DMSO-d₆, 125 MHz): δ 180.8, 169.06,165.8,137.6, 135.8,130.3,128.3, 128.9,127.1, 126.4,117.0,53.1, 43.1; LCMS (EI) 404.8; Anal. Calcd for: C₁₇H₁₃ClN₄O₄S: C, 58.54; H, 4.09 N, 11.38%. Found: C, 58.50; H, 4.14; N, 11.29%.

5-((4-fluorophenylamino)(3-nitrophenyl)methyl)-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1b)

Yellow solid; m.p 210 °C (de) ;IR (KBr): ν_{max} 3219.31, 1598.08, 1542.14, 1170.83, 822.67; ¹H NMR (DMSO-d₆, 500 MHz) 4.6(1H,s),3.5(2H,d)3.9(2H,d),6.9-9.1(8H,m), 10.1(1H,s), 10.7(1H,s); ¹³CNMR(DMSO-d₆,125MHz): 186.0,174.0,170.6,164.8,161.4, 154.3,146.3,138.7,135.7,135.5,126.8, 122.2,120.3,58.4; H,3.37;N, 14.43%. Found: C, 52.50; H,3.30; N, 14.39. %.

5-((4-chlorophenylamino)(3-nitrophenyl)methyl)-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1c)

Yellow solid; m.p 202 °C (de) ;IR (KBr):ν_{max} 3320, 3100, 1695,1100, 789; ¹H NMR (DMSO-d₆, 500 MHz ; δ 5.3(1H,s),4.0 (2H,d),4.9 (2H,d), 7.2-9.0(8H, m), 11.1(1H,s), 11.5(1H,s); ¹³C NMR (DMSO-d₆, 125 MHz) : δ 192.1,178.5,172.8,161.4,159.4,137.1, 135.6,134.9,139.3,128.3, 127.5,125.3,95.4,30.0; LCMS (EI): 404.8. Anal.Calcd for C₁₇H₁₃ClN₄O₄S : C,50.44; H,3.24;N, 13.75%. Found: C, 50.33; H,3.31; N, 13.71%.

5-((4-chlorophenylamino)(3-chlorophenyl)methyl)-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1d)

White solid; m.p 208 °C (de) ; IR (KBr): ν_{max} 3300,2395, 1550, 1350, 900; ¹H NMR (DMSO-d₆, 500 MHz) δ 5.36(1H,s), 3.9(2H,d),4.5 (2H,d),7-9(8H,m),12.1(1H,s), 12.2(1H,s); ¹³C NMR (DMSO-d₆, 125 MHz): δ 179.4,161.7,159.4,154.0,

144.5,129.2,127.9,125.0,122.5,121.7,56.2,28.8. LCMS (EI):394.3. Anal. Calcd for $C_{17}H_{13}ClN_4O_4S$: C,51.79; H,3.32; N, 10.66%. Found: C,51.73; H,3.32; N, 10.52%.

5-((2-nitrophenylamino)(3-nitrophenyl)methyl)-1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1e)

Yellow solid; m.p 220 °C (de) ; IR (KBr): ν_{max} 3230,2395, 1781, 1595,1292, 1091 1H NMR (DMSO- d_6 , 500 MHz) δ 1.2(4H,q), 1.7(6H,t), 4.0(1H,s), 4.4(2H,d), 4.9(2H,d), 6.5-8(8H,m); ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 176.7,169.0,167.6,141.8,139.0,136.1, 135.8,135.2, 134.1, 134.0,133.8,29.4,14.1 LCMS (EI) : 471.1 Anal. Calcd for $C_{21}H_{21}N_5O_6S$: C,53.50; H,4.49; N, 14.85%. Found: C,53.43; H,4.56; N, 14.80%.

5-((4-nitrophenylamino)(3-nitrophenyl)methyl)-1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1f)

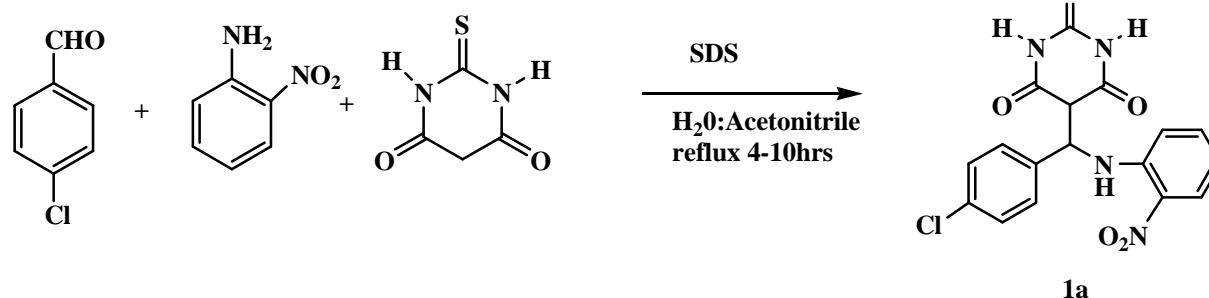
1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1f)

Yellow solid; m.p 218 °C; IR (KBr): ν_{max} 3390,2980,1703,1604,1498, 1501, 1109, 927 1H NMR (DMSO- d_6 , 500 MHz) δ 1.9(6H,t), 2.5(4H,q), 4.5(2H,d), 4.9 (2H,d), 5.2(1H,s), 7.2-7.5 (8H,m); ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 180.1,179.2,179.0,1315,129.3, 128.9, 128.5,121.9,121.4,39.1,32.4 LCMS (EI) :471.5. Anal. Calcd for: $C_{21}H_{21}N_4O_6S$: C,53.50; H,4.49; N, 14.85%. Found: C,53.43; H,4.40; N, 14.80%.

5-((4-nitrophenylamino)(4-chlorophenyl)methyl)-1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1g)

White solid; m.p 222 °C; IR (KBr): ν_{max} 3300,3068, 1650, 1597, 1093,819 1H NMR (DMSO- d_6 , 500

TABLE 1 : Optimisation of reaction conditions



Entry	Surfactant	Solvent	Temperature	Time (hr)	1a (%)
1	SDS (1mmol)	H ₂ O	R.T	-	-
2	SDS (1mmol)	CH ₃ CN: H ₂ O	R.T	-	-
3	SDS (1mmol)	CH ₃ CN: H ₂ O	Reflux	6	75
4	SDS (1.5mmol)	CH ₃ CN: H ₂ O	Reflux	4	85
5	TTAB (1mmol)	CH ₃ CN: H ₂ O	Reflux	18	60
6	CTAB (1mmol)	CH ₃ CN: H ₂ O	Reflux	20	65
7	CPC (1mmol)	CH ₃ CN: H ₂ O	Reflux	12	60
8	TEAB (1mmol)	CH ₃ CN: H ₂ O	Reflux	14	65
9	CPC (1.5mmol)	CH ₃ CN: H ₂ O	Reflux	12	70
10	CPC (1mmol)	H ₂ O	Reflux	24	65

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MHz δ 0.8 (6H,t), 2.2(4H,q), 4.02(2H,d), 4.9(2H,d), 5.5(1H,s), 6.9-7.1(8H,m); ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 177.4, 168.0, 162.8, 143.9, 37.9, 134.7, 132.4, 129.6, 129.4, 123.4, 119.5, 68.7, 578.2, 21.1, 12.0. LCMS (EI) : 460.9. Anal. Calcd for: $\text{C}_{21}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$: C, 54.72; H, 4.59; N, 12.16%. Found: C, 54.68; H, 4.62; N, 12.02%.

5-(3-indole)methyl)-1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1h)

Orange solid; m.p 275°C; IR (KBr): ν_{max} 3300, 2900, 1750, 1610, 1450, 1000. ^1H NMR (DMSO- d_6 , 500 MHz) δ 2.0(6H,t), 5.2(1H,s), 4.8(2H,d), 4.9(2H,d), 6.5-8(10H,m), 9.8 (1H,s), ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 167.7, 165.2, 160.1, 132.1, 131.7, 130.1, 129.1, 128.2, 126.8, 125, 83.2, 80.4, 12.9. LCMS (EI) : 451.5. Anal. Calcd for: $\text{C}_{24}\text{H}_{29}\text{N}_5\text{O}_2\text{S}$: C, 63.83; H, 6.47; N, 15.51%. Found: C, 63.79; H, 6.42; N, 15.48%.

5-((4-methylphenylamino)(4-chlorophenyl)methyl)-1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1i)

Yellow solid; m.p 230 °C; IR (KBr): ν_{max} 3300, 2890, 1650, 1450, 900. ^1H NMR (DMSO- d_6 , 500 MHz) δ 0.83 (6H,t), 2.0(3H,s), 3.9(4H,q), 5.1(1H,s), 4.71(2H,d), 4.8(2H,d), 6.4-7.1(8H,m); ^{13}C NMR (DMSO- d_6 , 125 MHz): δ 180, 176.8, 166.9, 162.0, 145.5, 142.9, 129.5, 127.3, 116.3, 115.9, 63.9, 43.8, 12.1. LCMS (EI) : 429.9. Anal. Calcd for: $\text{C}_{22}\text{H}_{24}\text{ClN}_3\text{O}_2\text{S}$: C, 61.46; H, 5.63; N, 9.77%. Found: C, 61.43; H, 5.60; N, 9.74%.

5-((4-ald-oxophenylamino)(4-chlorophenyl)methyl)-1,3-diethyl-dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (1j)

White solid; m.p 225 °C; IR (KBr): ν_{max} 3100, 2795, 1610, 1450, 820. ^1H NMR (DMSO- d_6 , 500 MHz) δ 1.2 (6H,t), 2.5 (4H,q), 3.95(2H,d), 4.00(2H,d), 5.1(1H,s),

TABLE 2 : Substrate scope for the synthesis of thioxopyrimidine-dione derivatives

Entry	R	R ₁	R ₂	Product 1 (a-j)	Time (in hr)	Yield (%)
1	m-NO ₂ C ₆ H ₄	o-Cl	H	1(a)	7	80
2	m-NO ₂ C ₆ H ₄	p-F	H	1(b)	6	75
3	m-NO ₂ C ₆ H ₄	p-Cl	H	1(c)	8	85
4	p-Cl C ₆ H ₄	p-Cl	H	1(d)	7	70
5	m-NO ₂ C ₆ H ₄	o-NO ₂	CH ₂ CH ₃	1(e)	6	75
6	m-NO ₂ C ₆ H ₄	p-NO ₂	CH ₂ CH ₃	1(f)	6	80
7	p-Cl C ₆ H ₄	p-NO ₂	CH ₂ CH ₃	1(g)	4	85
8	2-indole	p-Cl	CH ₂ CH ₃	1(h)	5	80
9	p-Me C ₆ H ₄	p-Cl	CH ₂ CH ₃	1(i)	7	75
10	p-CHO C ₆ H ₄	p-Cl	CH ₂ CH ₃	1(j)	10	80

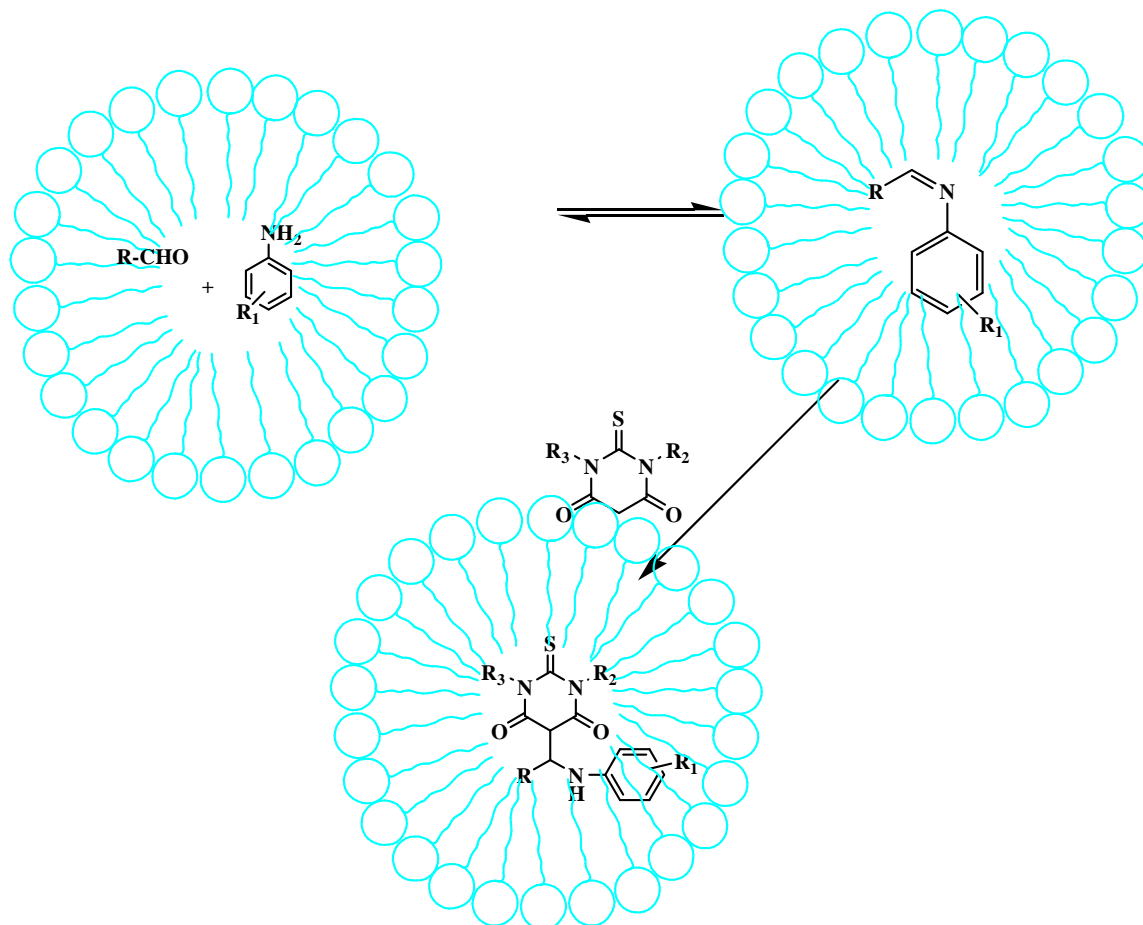
7.2-8.8(8H,m),13.0(1H,s):¹³C NMR (DMSO-d₆, 125 MHz): δ 178.7, 161.7,159.7,147.0,142.1,137.2, 129.6,1 24.7,118.3,113.9,113.4,109.7, 47.9,12.9. LCMS (EI) :443.9. Anal. Calcd for: C₂₂H₂₂ClN₃O₃S: C, 59.52; H, 4.99 N, 9.47%. Found: C, 59.50; H, 4.96; N, 9.45%.

RESULT AND DISCUSSION

Initially, the generation of Mannich base product was set as a model. The reaction of one pot synthesis involved substituted aldehyde, aromatic amine, thiobarbituric acid and a surfactant. Surfactant like sodium dodecylsulphate (SDS), cetyltrimethylammonium bromide (CTAB), cetylpyridinium chloride (CPC), tetradecyltrimethyl ammonium bromide (TTAB), TEAB were employed as catalyst in water alone and in water:acetonitrile (1:1) as solvent for the reaction. Here we tried to select the best surfactant which can give the highest yield by

reacting the components with different surfactants including anionic and cationic surfactants listed in TABLE 1.

At room temperature stirring the substrate gives no product at all TABLE1, entry 1 and at water bath temperature around 100° C the substrate were dissolved in the solvent (water:acetonitrile) giving the product in 4-5 hours. Again as shown in TABLE 1, with different surfactants the yield was found to be different. The reaction when refluxing at oil bath above 100° C using TTAB(1mmol) gives product 1a (60% yield) TABLE 1, entry 5. When CTAB (1 mmol) was employed as catalyst in water:acetonitrile (1:1) solvent, the product 1a was afforded in 65% yield on refluxing at above 100° C, TABLE 1, entry 6; While TTAB, TEAB and CTAB afforded around 60-65% overall yield (TABLE 1), CPC (1 mmol) gave 60% yield (TABLE 1). On taking CPC (1.5 mmol) as catalyst in water:acetonitrile (1:1) as solvent, 1a was obtained as 70% yield TABLE 1, entry 9, and reaction in water



Scheme 1 : Plausible mechanism for Micelle-Promoted multicomponent synthesis of 2-thioxopyrimidine-dione

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afforded 65% yield using CPC (1.0 mmol) as catalyst by refluxing for 24 hr (TABLE 1). The reaction when carried out in presence of SDS (1mmol) and water:acetonitrile(1:1) as solvent refluxing at temperature above 100° C afforded the yield upto 75% of 2a (TABLE 1) but when increased the mol% of SDS the yield percent was found 85% TABLE 1, entry 4. By tabulating the number of hours and yield percentage (TABLE 1), it is found that Sodium dodecyl sulphate catalyst gives good yield (80-90%) with no side product. The amount of SDS as catalyst in the direct Mannich protocol to 1 was investigated and the results are indicated in TABLE 2. The influence of the solvent system was further evaluated. Solvent of moderate-polarity like acetonitrile which is miscible with water is used in various ratios with water as solvent. It is found that use of the mixture of acetonitrile in water enhances the solubility of the substrate and increases the yield of the product 1a. Further studies revealed that increasing the amount of surfactant can increase the yield and the best result was obtained when the surfactant is used at 15mmol% (above CMC). With acetonitrile and water as a solvent the substrate can be solubilised otherwise it is not soluble in water. The amount of water:Acetonitrile ratio is also optimised and found that 50:50 of water: acetonitrile can give the desired product in high yield.

With successful optimisation of the synthesis of 5-(amino(phenyl)methyl)-dihydro-2-thioxopyrimidine-4,6-(1H,5H)- dione with 4-chloro benzaldehyde, 4-chloro aniline and thiobarbituric acid we further studied the reactions of different aldehydes mostly aromatic, aromatic amine and N, N- substituted thiobarbituric acid under similar conditions as shown in TABLE 2.

The formation of desired product indicates that surfactants play an important role to stabilise the imine intermediate which is formed by aromatic amine and aromatic aldehyde. The water molecules generated by imine formation are probably expelled from the micelle due to hydrophobic nature of their interior as shown in Scheme

CONCLUSION

In conclusion we have demonstrated an easy, efficient and almost green protocol of one pot synthesis

of 5-(amino(phenyl)methyl)-dihydro-2-thioxopyrimidine-4,6-(1H,5H)- dione without the formation of side product and in a high yield. The use of water and acetonitrile is to solubilise the insoluble thiobarbituric acid in generating the Mannich base.

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