AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

H_2O-Mediated Efficient Tandem Synthesis of Barbituryl Thiocarbamides using Amberlyst-15 As A Heterogeneous Solid Catalyst

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ABSTRACT

H_2O-mediated efficient, tandem synthesis of barbituryl thiocarbamides by the nucleophilic addition reaction of uramil and aryl isothiocyanates using Amberlyst-15 as a heterogeneous solid catalyst is being reported. The novel and clean methodology offers the advantages that includes short reaction time, good yields, and operational simplicity, less leaks, environmentally benign procedure apart from recyclable, reusable catalyst.

Keywords; Thiocarbamides, green synthesis, Amberlyst-15.

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Received 01 January 2014, Accepted 09 January 2014

Please cite this article in press as: Dhonde MG.*et al.*, H_2O-Mediated Efficient Tandem Synthesis of Barbituryl Thiocarbamides Using Amberlyst-15 As A Heterogeneous Solid Catalyst . American Journal of PharmTech Research 2014.

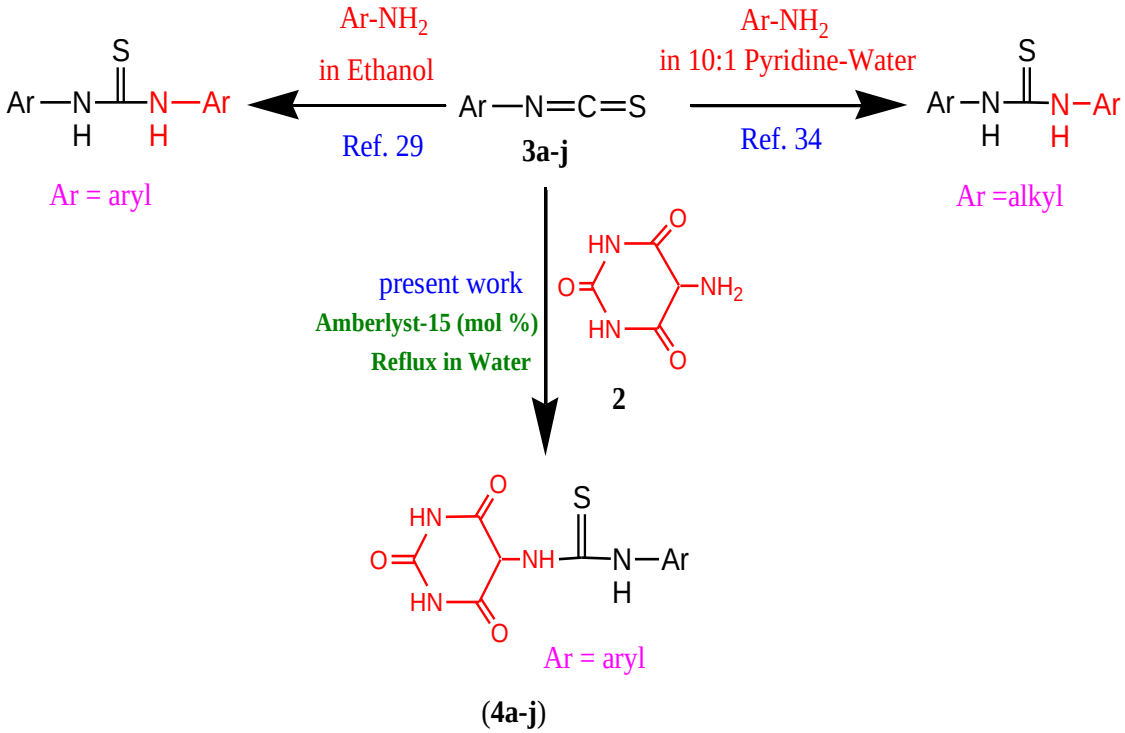
INTRODUCTION

Barbiturates bear structural merits, found in many biological, medicinal and pharmaceutically active compounds and have been used as an important moiety in several pharmaceutical transformations. The barbituric acid and their derivatives exhibit a wide range of medicinal activities such as hypnotic, sedative, and anesthetic drugs[1], including antitumor[2], anticancer[3], and anti-osteoporosis[4] treatments. Barbiturates play an important role in the treatment of a variety of disorders such as anxiety, sleep, seizure and muscle spasm also have proven useful to neurosurgery[5-8]. The heterogeneous catalyst Amberlyst-15 is inexpensive, readily available, easily recyclable and reusable. It was found that Amberlyst-15 is being added to the ever-growing collection of highly active solid catalyst and efficiently catalyses cyclization[9], Aza-Michael addition reaction of amines with α, β–-unsaturated carbonyls and nitriles[10], N-acylation and alkylation of indoles[11], chemoselective thioacetalization of carbonyl group[12], dethioacetalization reaction[13], deprotection of Boc-protected amines[14], epoxide ring opening reaction[15] and various C-N coupling reaction[16-19]. The main advantage of heterogeneous catalyst Amberlyst-15 includes reduced equipment corrosion, easy experimental and product isolation, less contamination in waste streams and recyclability[20, 21]. Water as a solvent is inexpensive, environmentally benign and offer better yields with completely new reactivity[22, 23]. Non toxic, non-corrosive, non-flammable nature and relatively high vapour pressure as compared to organic solvents are favorable individually to render water as sustainable alternative[24, 25]. This is the reason why safer and eco-friendly reaction conditions in an aqueous medium using well known acidic ion exchange resin Amberlyst-15 was considered as a better choice.

Literature survey reveals that the active methylene group of barbituric acid is very reactive and different types of reaction took place at this position. A large number of 5-substituted barbituric acid derivatives have been reported to exhibit a broad spectrum of biological activity like anticonvulsant activity[26]. 5-monoalkylated barbiturates like 5-(benzoxy) benzyl barbituric acid are used in the treatment of cancer and AIDS via inhibition of human uridine phosphorylase[27] and its derivatives are valuable pharmaceuticals[28]. A large number of general thiocarbamides have been synthesized by the interaction of aryl isothiocyanates with various amines[29] and they have been reported to show remarkable medicinal properties i.e. inhibition of HIV[30].

Active methylene group of barbituric acid at 5-position took part in the reaction to give disubstituted product indicating controlled reaction is difficult but some researcher have done the work on controlled and selective nitration of barbituric acid by using fuming nitric acid to give 5-

nitrobarbituric acid[31, 32] followed by reduction of 5-nitrobarbituric acid in presence of Sn in HCl to give 5-amino barbituric acid[32, 33]. Our literature investigation of general thiocarbamides revealed that, diaryl thiocarbamides have been synthesized by the action of aryl amine with aryl isothiocyanates[29] while dialkyl thiocarbamides have been synthesized by the interaction of alkyl amine with alkyl isothiocyanates[34]. To best of our knowledge nucleophilic addition reaction using heterogeneous catalyst Amberlyst-15 is not yet reported (Scheme **1**).



Scheme 1 Different reaction path way for 1- 3-disubstituted thiocarbamides involving isothiocyantes

MATERIAL AND METHODS

General Remark

Melting points were taken in open capillary tube and are uncorrected. Unless otherwise indicated, ^{1}H NMR (400 MHz) spectra were recorded on a Bruker DSX-300/AV-III 400L NMR Spectrometer from DMSO-d6 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), t (triplet) and m (multiplet). The MS spectra were recorded using QUATRO MICRO API-WATER mass spectrometer. IR spectra were recorded on a Shimadzu (4000-450 cm^{-1}) FTIR Spectrophotometer. Thin layer chromatography (TLC) was performed with E. Merck pre-coated TLC plates, aluminium silica Gel_{60} $F_{254,}$ and spots were located with ultra violet (UV) light or Iodine vapors and by charring with suitable charring agent. All other reagents, solvents and solid

heterogeneous catalyst Amberlyst-15 were used without further purification.

General procedure for the synthesis of barbituryl thiocarbamides (**4a-j**)

Barbituryl thiocarbamides were synthesized by the interaction of 5-aminobarbituric acid (**2**, 4.1 mmol) with aryl isothiocynates (3a-j, 4.1 mmol) using Amberlyst-15 (3 mol %) as a catalyst in aqueous medium. The reaction mixture was refluxed for 1-3 h, reaction was monitored by TLC. After completion of the reaction, mixture was filtered, washed with excess of water. The Amberlyst-15 was readily removed at the end of the reaction, it was washed with water followed by ether and dried at 70-80 ^{0}C for 4-5 h and again reused for further transformation. The products were further purified by re-crystallization in aqueous ethanol. The identity of new synthesized compounds is based on spectroscopic comparison IR, ^{1}H NMR, and Mass spectral data spectra's of all newly synthesized compounds 4(a-j) are shown in supplementary file.

Characterization data of (**4a-j**)

1-phenyl-3-(2,4,6-trioxohexahydropyrimidin-5-yl)thiocarbamide (**4a**):

yellow solid, M.p. 278-82 d, IR (KBr, cm^{-1}): 3180.62, 3113 (NH st), 3049.46 (Ar-C-H st), 2983.88 (C-H st), 1730.15 (C=O st), 1219.50 (C=S st), 1159.22 (C-O st), 752.24 (Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.02 (s, 2H, NH), 7.69-7.20 (m, 5H, Ar-H), 7.17 (s, 1H, CH), 3.29 (s, 1H, NH), 2.02 (s, 1H, NH) ppm; MS: m/z 278 (M^+), 142 (BA-NH^+), 127 (BA^+); Anal. Calcd. for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.59; N, 20.14; S, 11.51 %. Found: C, 47.44; H, 3.54; N, 19.87; S. 11.28 %.

1-(2-Methylphenyl)-3-(2,4,6-trioxohexahydropyrimidin-5-yl) thiocarbamide (**4b**)*:* colorless solid, M.p. 306-08 d, IR (KBr, cm^{-1}): 3076.46 (NH st), 3059 (Ar-C-H st), 2987.74 (C-H st), 1730 (C=O st), 1219 (C=S st), 1159.22 (C-O st), 754 (1, 2-Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 2H, NH), 7.251-7.003 (m, 4H, Ar-H), 6.749 (s, 1H, CH), 3.290 (s, 1H, NH), 2.377 (s, 3H, Ar-CH_3), 2.075 (s, 1H, NH) ppm; MS: m/z 292 (M^+), 150 ($^+$C (=S)-NH-C_6H_4-CH_3), 142 (BA-NH^+), 93 ($^+C_6H_4$-CH_3); Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.31; H, 4.10; N, 19.17; S, 10.95 %. Found: C, 49.26; H, 4.08; N, 18.98; S, 10.87 %.

1-(3-Methylphenyl)-3-(2,4,6-trioxohexahydropyrimidin-5-yl) thiocarbamide (**4c**):

brown solid, M.p. 314-16 d, IR (KBr, cm^{-1}): 3072.60 (NH st), 2980 (Ar-C-H st), 2860.40 (C-H st), 1730 (C=O st), 1219 (C=S st), 1159.22 (C-O st), 765.74 (1, 3-Ar-H) cm^{-1}; ^{1}H NMR (400 MHZ, DMSO-d_6): δ 10.303 (s, 2H, NH), 7.524-7.204 (m, 4H, Ar-H), 7.008 (s, 1H, CH), 3.295 (s, 1H, NH), 2.359 (s, 3H, Ar-CH_3), 2.075 (s, 1H, NH) ppm; MS: m/z 292 (M^+), 127 (BA^+), 106 ($^+$NH-C_6H_4-CH_3); Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.31; H, 4.10; N, 19.17; S, 10.95 %. Found: C, 49.25; H, 4.07; N, 18.87; S, 10.78 %.

1-(4-Methylphenyl)-3-(2,4,6-trioxohexahydropyrimidin-5-yl) thiocarbamide (**4d**)*:*

pale yellow solid, M.p. 310 d, IR (KBr, cm^{-1}): 3074.53 (NH st), 2981.95 (Ar-C-H st), 2848.86 (C-H st), 1730 (C=O st), 1219 (C=S st), 1159.22, 1103.28 (C-O st), 869.90 (1, 4-Ar-H) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.312 (s, 2H, NH), 7.331-7.315 (d, J = 6.4 Hz, 2H, Ar-H), 7.125-7.105 (d, J = 8.0 Hz, 2H, Ar-H), 6.904 (s, 1H, CH), 3.266 (s, 1H, NH), 2.345 (s, 3H, Ar-CH_3), 2.075 (s, 1H, NH) ppm; MS: m/z 292 (M^+), 165 ($^+$NH-C (=S)-NH-C_6H_4-CH_3), 127 (BA^+); Anal. Calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.31; H, 4.10; N, 19.17; S, 10.95 %. Found: C, 49.27; H, 4.05; N, 19.38; S, 11.19 %.

1-(2-Chlorophenyl)-3-(2,4,6-trioxohexahydro pyrimidin-5-yl) thiocarbamide (**4e**):

yellow solid, M.p. 308-12 d, IR (KBr, cm^{-1}): 3091.90 (NH st), 3039.81 (Ar-C-H st), 2983.88 (C-H st), 1768.72 (C=O st), 1219 (C=S st), 1159.22 (C-O st), 754 (1, 2- Ar-H) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.392 (s, 2H, NH), 7.681-7.341 (m, 4H, Ar-H), 7.075 (s, 1H, CH), 3.296 (s, 1H, NH), 2.075 (s, 1H, NH) ppm; MS: m/z 313 (M^+), 171 ($^+$C-(=S)-NH-C_6H_4-Cl), 127 ($^+$NH-C_6H_4-Cl); Anal. Calcd. for $C_{11}H_9N_4O_3SCl$: C, 42.24; H, 2.88; N, 17.92; S, 10.24; Cl, 11.36 %. Found: C, 42.19; H, 2.84; N, 17.56; S 9.68; Cl, 11.31 %.

1-(3-Chlorophenyl)-3-(2,4,6-trioxohexahydro pyrimidin-5-yl) thiocarbamide (**4f**):

Red solid, M.p. 295-98 d, IR (KBr, cm^{-1}): 2983.88 (Ar-H st), 2845 (C-H st), 1730.15 (C=O st), 1259 (C=S st), 1159.22 (C-O st), 765.74 (1, 3-Ar-H) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.027 (s, 2H, NH), 7.661-7.168 (m, 4H, Ar-H), 6.938 (s, 1H, CH), 3.293 (s, 1H, NH), 2.075 (s, 1H, NH) ppm; MS: m/z 313 (M^+), 126 ($^+$NH-C_6H_4-Cl); Anal. Calcd. for $C_{11}H_9N_4O_3SCl$: C, 42.24; H, 2.88; N, 17.92; S, 10.24; Cl, 11.36 %. Found: C, 42.20; H, 2.85; N, 17.82; S, 10.08; Cl, 11.31 %.

1-(4-Chlorophenyl)-3-(2,4,6-trioxohexahydro pyrimidin-5-yl) thiocarbamide (**4g**):

White solid, M.p. 288-90 d, IR (KBr, cm^{-1}): 3076.46 (NH st), 3037.89 (Ar-C-H st), 2989.66 (C-H st), 1730.55 (C=O st), 1219 (C=S st), 1159.22 (C-O st), 866 (1, 4-Ar-H) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.901 (s, 2H, NH), 7.635-7.609 (d, J = 10.4 Hz, 2H, Ar-H), 7.404-7.379 (d, J = 10 Hz, 2H, Ar-H), 6.969 (s, 1H, CH), 3.292 (s, 1H, NH), 2.076 (s, 1H, NH) ppm; MS: m/z 313 (M^+), 171 ($^+$C-(=S)-NH-C_6H_4-Cl), 127 ($^+$NH-C_6H_4-Cl); Anal. Calcd. for $C_{11}H_9N_4O_3SCl$: C, 42.24; H, 2.88; N, 17.92; S, 10.24; Cl, 11.36 %. Found: C, 42.18; H, 2.84; N, 17.97; S, 10.17; Cl, 11.32 %.

1-(2-Methoxyphenyl)-3-(2,4,6-trioxohexahydro pyrimidin-5-yl) thiocarbamide (**4h**):

Yellow solid, M.p. 328 d, IR (KBr, cm^{-1}): 2943.37 (Ar-C-H st), 2858.51 (C-H st), 1730 (C=O st), 1219 (C=S st), 1159.22 (C-O st), 754 (1, 2-Ar-H) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ

10.313 (s, 2H, NH), 7.846-7.455 (m, 4H, Ar-H), 6.984 (s, 1H, CH), 3.815 (s, 3H, Ar-OCH_3), 3.295 (s, 1H, NH), 2.075 (s, 1H, NH) ppm; MS: m/z 308 (M^+), 165 ($^+$C-(=S)-NH-C_6H_4-OCH_3), 142 (BA-NH^+), 127 (BA^+); Anal. Calcd. for $C_{12}H_{12}N_4O_4S$: C, 46.75; H, 3.89; N, 18.18; S, 10.38 %. Found: C, 46.69; H, 3.84; N, 17.88; S, 9.96 %.

1-(3-Methoxyphenyl)-3-(2,4,6-trioxohexahydropyrimidin-5-yl) thiocarbamide (**4i**): Brown solid, M.p. 294 d, IR (KBr, cm^{-1}): 3562.52, 3415.93, 3304 (NH st), 3076.46 (Ar-C-H st), 2989.66 (C-H st), 1730 (C=O st), 1219 (C=S st), 1159.22 (C-O st), 763 (1, 3-Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.371 (s, 2H, NH), 7.349-7.012 (m, 4H, Ar-H), 6.945 (s, 1H, CH), 3.794 (s, 3H, Ar-OCH_3), 3.234 (s, 1H, NH), 2.075 (s, 1H, NH) ppm; MS: m/z 308 (M^+), 165 ($^+$C-(=S)-NH-C_6H_4-OCH_3), 127 (BA^+); Anal. Calcd, for $C_{12}H_{12}N_4O_4S$: C, 46.75; H, 3.89; N, 18.18; S, 10.38 %. Found: C, 46.71; H, 3.86; N, 18.09; S, 10.32 %.

1-(4-Methoxyphenyl)-3-(2,4,6-trioxohexahydro pyrimidin-5-yl) thiocarbamide (4j):

red solid, M.p. 310-15 d, IR (KBr, cm^{-1}): 3093.82 (NH st), 3005.10 (Ar-C-H st), 2987.74 (C-H st), 1730.15 (C=O st), 1219 (C=S st), 1182.36, (C-O st), 867.97, 837.11 (1, 4-Ar-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.103 (s, 2H, NH), 7.301-7.275 (d, J = 10.4 Hz, 2H, Ar-H), 7.140-7.115 (d, J = 10 Hz, 2H, Ar-H), 6.907 (s, 1H, CH), 3.732 (s, 3H, Ar-OCH_3), 3.293 (s, 1H, NH), 2.075 (s, 1H, NH) ppm; MS: m/z 308 (M^+), 165 ($^+$C-(=S)-NH-C_6H_4-OCH_3), 127 (BA^+), 107 ($^+C_6H_4$-OCH_3); Anal. Calcd. for $C_{12}H_{12}N_4O_4S$: C, 46.75; H, 3.89; N, 18.18; S, 10.38 %. Found: C, 46.71; H, 3.84; N, 17.97; S, 10.27 %.

RESULTS AND DISCUSSION

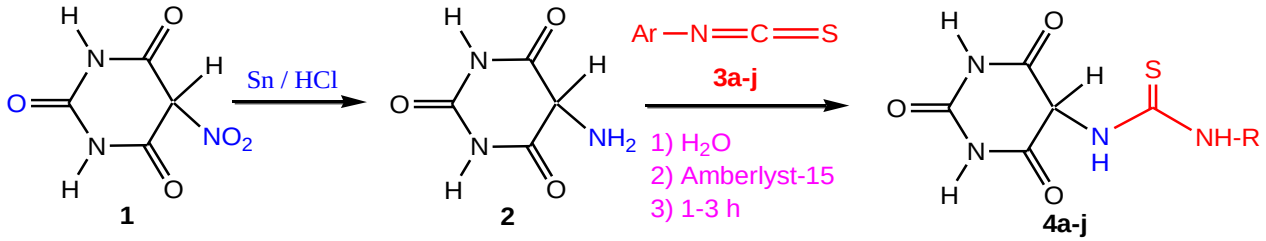
We commenced our studies with novel aqueous synthesis of barbituryl thiocarbamides (4a-j) by the interaction of 5-aminobarbituric acid (2) as a precursor and aryl isothiocyanates (3a-j) without any catalyst giving poor yields and required very large time for the completion of reactions (Table 1).

Table 1: synthesis of barbituryl thiocarbamides in aqueous medium without catalyst

Entry	3	Ar	Time (h)	Product (4)	Yield[a] (%)
1	a	C_6H_5	7	a	45
2	b	2-CH_3-C_6H_4	8	b	48
3	c	3-CH_3-C_6H_4	8	c	36
4	d	4-CH_3-C_6H_4	7	d	52
5	e	2-Cl-C_6H_4	8	e	55
6	f	3-Cl-C_6H_4	8	f	41
7	g	4-Cl-C_6H_4	10	g	58
8	h	2-CH_3O-C_6H_4	8	h	54
9	i	3-CH_3O-C_6H_4	8	i	47
10	j	4-CH_3O-C_6H_4	7	j	58

[a]-Isolated yield without catalyst

We then repeated same experiment with environmental friendly Amberlyst-15 as a solid heterogeneous catalyst in universal solvent water. During initial exploratory reaction, the nucleophilic addition reaction between 5-aminobarbituric acid and aryl isothiocyanates was investigated to establish the feasibility of our strategy and to optimize reaction conditions in aqueous medium using Amberlyst-15 as a catalyst. Optimization was done by varying proportion of catalyst and maximum yield was obtained as observed in case of 3a & 3j (Table 2). The rest of the products have been synthesized by using 3 mol % of catalyst and best results were obtained (Table 3). The catalyst Amberlyst-15 gave a good yield of nucleophilic addition products within very short period of time. The completion of the reaction was monitored by TLC. The product work- up was done by simple method, and alkaline plumbite test of the product showed positive result for C=S group which indicated that direct nucleophilic addition was effected (Scheme 2).



Scheme 2

Table 2: Optimization of barbituryl thiocarbamides using Amberlyst-15 in aqueous medium

Entry	3 (mmol)	Catalyst[a]	Time (h)	Yield[a] (%)
1	**3a** (4.1)	3 mol %	1	75
2	**3a** (4.1)	5 mol %	1	72
3	**3a** (4.1)	10 mol %	1	68
4	**3j** (5.2)	3 mol %	3	78
5	**3j** (5.2)	5 mol %	3	72
6	**3j** (5.2)	10 mol %	3	69

a- isolated yield of different mol % of Amberlyst-15 with different reaction time.

Table 3: Amberlyst-15 catalyzed synthesis of barbituryl thiocarbamides in aqueous medium

Entry	3	Ar	Time (h)	Product (4)	Yield[a] (%)
1	a	C_6H_5	1	a	75
2	b	2-CH_3-C_6H_4	1.5	b	76
3	c	3-CH_3-C_6H_4	1.5	c	69
4	d	4-CH_3-C_6H_4	2	d	79
5	e	2-Cl-C_6H_4	1.5	e	80
6	f	3-Cl-C_6H_4	2	f	71
7	g	4-Cl-C_6H_4	3	g	82
8	h	2-CH_3O-C_6H_4	1	h	75
9	i	3-CH_3O-C_6H_4	2.5	i	71
10	j	4-CH_3O-C_6H_4	3	j	78

a- isolated yield of different mol % of Amberlyst-15 with different reaction time.

The attack of nucleophile in presence of catalyst increased the yield of product and rate of reaction in aqueous medium. It was further clear that electron donating substituent on para position (Table **3**, entry, 4, 7, 10) enhanced the nucleophilic attack than ortho (entry, 2, 5, 8) but meta substituent (entry, 3, 6, 9) slowed down the nucleophilic attack.

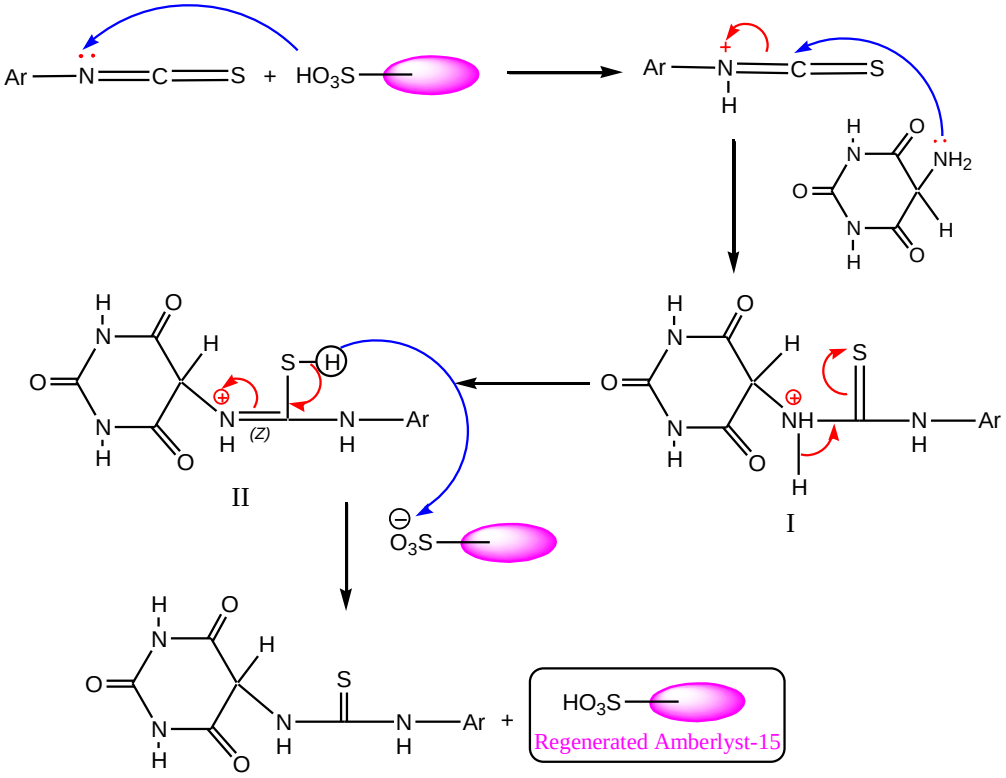


Figure 1 Probable mechanism for formation of thiocarbamide

The probable mechanism for the formation of thiocarbamide is shown in Figure 1. The Amberlyst-15 can donate proton to electron rich nitrogen of isothiocyanate and generate the electrophilic carbon. Then weak nucleophile uramil which can easily donate the electron to electrophilic carbon due to presence of Amberlyst-15 to form intermediate I and II, finally intermediate release the proton and original catalyst is easily regenerated.

Recyclability of catalyst*:*

We emphasized on studying the recyclability and reusability of the catalyst so that our protocol can become more environment-friendly and thus could belong to the domain of green chemistry methods. Upon the completion of the reaction, the catalyst was separated by filtration, further washed with water and then ether, dried at 70-80^0 C for 4-5 h. The activated catalyst was used for two or more subsequent cycles, interestingly consistent performance of the catalyst was observed in all the cycles without appreciable loss of its catalytic activity (fig ure 2, 3).

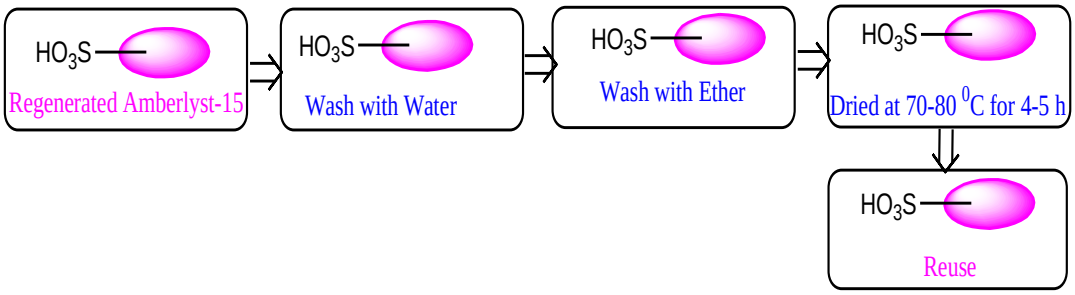


Figure 2 Recovery of Amberlyst-15 & Reuse

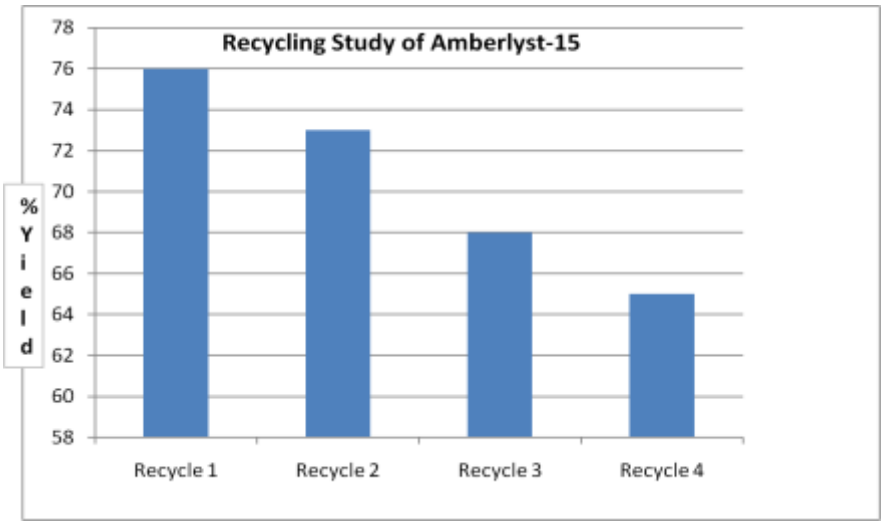


Figure 3 Recycle study of Amberlyst-15 for the reaction of Uramil with o-Tolyl isothiocyanate

CONCLUSION

Use of Amberlyst-15 is responsible for high yield and environmental benign methodology for nuclophilic addition of 5-amino barbituric acid and aryl isothiocyanate in aqueous medium. This synthetic methodology has been developed at 5-position of barbituric acid which supports the generality of this reactions and this is remarkable to make the method economically valuable using Amberlyst-15 as a greener catalyst in aqueous medium. Therefore, present catalytic method is efficient, mild, simple, convenient and applicable for variety of thiocarbamides.

ACKNOWLEDGEMENTS

Authors are thankful to University Grants Commission, New Delhi, India for providing financial assistance (File no. 90/2011-5/7/2011). The authors are also grateful to Shri Shivaji Science College, Akola, Indian Institute of Science, Bangalore and Vishnu Chemical, Hyderabad for recording the IR, NMR and Mass spectra. Thanks are also due to Dr. S.G. Charalwar, Principal, Shri Mathuradas Mohota college of Science and Dr. L.J.Paliwal RTM Nagpur University for encouragement and providing necessary facilities.

REFERENCES

1. Carter MK. The story of barbituric acid. J. Chem. educ., 1951; 28: 524. (b) Vogel's, Textbook of practical Organic chemistry, 3rd ed.; Wiley, New York, 1966. (c) Bojarski JT, Mokrosz JL, Barton HJ, Paluchowska MH. Adv. Heterocyclic Chem., 1985; 38: 229.
2. Gulliya KS. Patent US 5869494, Chem. Abstr., 1999.
3. KG. Patent US 5674870, Chem. Abstr., 1997.
4. Sakai K, Satoh Y. PCT International Patent W09950252A3, Chem Abstr., 2000.
5. Nogrady T. Medicinal Chemistry, Oxford University Press, New York, 1988.
6. Hardman JG, Limbird LE. The Pharmacological basis of therapeutics, 10th ed.; Mc Graw-Hill, 2001.
7. Nadkarni S, Lajoie J, Devinsky O. Current treatments of epilepsy. Neurology, 2005; 64: S2-S11.
8. Jain KS, Chitra TS, Miniyar PB, Kathiravan MK, Bendre VS, Veer VS, Shahane RS, Shishoo CJ. Synthesis of novel barbiturate from 1-chloro-2,4-dinitrobenzene as an anticonvulsant agent. Current Science, 2006; 90: 793-803.
9. Pandit SS, Bhalerao SK, Aher US, Adhav GL, Pandit VU. Amberlyst-15 reusable catalyst for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted-1H-imidazoles under mw irradiation. J. Chem. Sci., 2011; 123(4): 421-426.
10. Das B, Chowdhury N. Amberlyst-15: An efficient reusable heterogeneous catalyst for aza-Michael reactions under solvent-free conditions. J. Mol. Catal. A Chem., 2007; 263: 212.
11. Das B, Pal R, Banerjee J, Mahender G, Holla H, Venkateswarlu K. Amberlyst-15 catalyzed acetylation of heteroaromatics with acetic anhydride under solvent free conditions. Ind. J. Chem., 2005; 44(B): 198.
12. Perni RB. Amberlyst-15 as a Convenient Catalyst for Chemoselective Thioacetalization. Syn. Commun., 1989; 19: 2383.
13. Ballini R, Petrini M. A New Procedure for Dethioacetalization via Equilibrium Exchange with Aqueous Acetone, Paraformaldehyde and Amberlyst 15 as Acidic Catalyst. Synthesis, 1990; 4: 336.
14. Liu YS, Zhao C, Bergbreiter DE, Romo D. Simultaneous Deprotection and Purification of BOC-amines Based on Ionic Resin Capture. J. Org. Chem., 1998; 63: 3471.
15. Vijiender M, Kishore P, Narender P, Satyanarayana B. Amberlist-15 as heterogeneous reusable catalyst for regioselective ring opening of epoxides with amines under mild conditions. J. Mol. Catal. A Chem., 2007; 266; 290.

16. Das B, Banerjee J. Silica-supported Sodium Hydrogen Sulfate and Amberlyst-15 : Two Efficient Heterogeneous Catalysts for Single-step Synthesis of 4(3*H*)-Quinazolinones from Anthranilic Acid, Ortho Esters, and Amines under Solvent Free Conditions. Chem. Lett., 2004; 33: 960.
17. Das B, Damoder K, Chowdhury N, Kumar RA. Application of heterogeneous solid acid catalysts for Friedlander synthesis of quinolines. J. Mol. Catal. A Chem., 2007; 274: 148.
18. Hou RS, Wu JL, Cheng HT, Xie YT, Chen LC. Amberlyst-15 Catalyzed Novel Synthesis of Quinoline Derivatives in Ionic Liquid. J. Chin. Chem. Soc., 2008; 55: 915.
19. Abonia R, Cuervo P, Insuasty B, Quiroga J, Nogueras M, Cobo J, Meier H, Lotero E. An Amberlyst-15® Mediated Synthesis of New Functionalized Dioxoloquinolinone Derivatives. Open Org. chem. J., 2008; 2: 26.
20. Clark JH. Catalysis of Organic Reactions by supported Reagents, VCH, NY, USA, 1994, J.H. Clark, Ed. Chemistry of Waste Minimization, 1995; 86-115.
21. Sheldon RA, Bekkum VH. Fine Chemicals through Heterogeneous Catalysis (Wiley-VCH, Weinheim, Germany), 2002.
22. Li CJ, Chen L. Organic chemistry in water**.** Chem. Soc. Rev., 2006; 35: (1), 68-82.
23. Molteni V, Hamilton MM, Mao L, Crane CM, Termin AP, Wilson DM. Aqueous One-Pot Synthesis of Pyrazoles, Pyrimidines and Isoxazoles Promoted by Microwave Irradiation. Synthesis, 2002; 12: 1669-74.
24. Polshettiwar V, Varma RS. Aqueous microwave chemistry: a clean and green synthetic tool for rapid drug discovery. Chem. Soc. Rev., 2008; 37: 1546-57.
25. Polshettiwar V. Aqueous Microwave Assisted Chemistry: Synthesis and Catalysis (RSC, UK), 2010.
26. Goodman LS, Gilman A. ln the pharmacological basis of therapeutics, Ed.: Mc Graw mosby co., Saint Louis, 1991; 358.
27. Guerin DJ, Mozeas D, Musale MS, Nauguib FNM, Safarjalani ONA, Kouni MH, Panzica RP. Uridine phosphorylase inhibitors: Chemical modification of benzyloxybenzyl-barbituric acidits effect on UrdPase inhibition Bioorg. Med. Chem. Lett., 1999; 9: 1477.
28. Jursic BS, Stevens ED. Mono *C*-alkylation and mono *C*-benzylation of barbituric acids through zinc/acid reduction of acyl, benzylidene, and alkylidene barbiturate intermediates. Tetrahedron Lett., 2003; 44: 2203-10.
29. Katritzky AR, Kirichenko N, Rogovoy BV, Kister J, Tao H. Synthesis of mono-and N,N-disubstituted thioureas and N-acylthioureas. Synthesis, 2004; 11**:** 1799-1805.

30. Wilkerson WM, Daxs, Cheatham WW. Nonsymmetrically Substituted Cyclic Urea HIV Protease Inhibitors J. Med. Chem., 1997; 40: 4079-88.
31. Bergman J, Bergman S. Formation of 3,3,5,7- tetranitrooxindole and 3,5,7-trinitroindazole by nitration of oxindole. Tetrahedron Lett., 1996; 37: 9263-66.
32. Vogel's, Textbook of practical organic chemistry, 5th ed.; Addison Wesley Longman Ltd, England, 1989; 1177.
33. Hartman WW, Sheppard OE. Uramil. Organic Synthesis Coll., 1943: 2: 617. 1932**;** 12: 84.
34. Jose LJB, Claudio SB, Jaun MB, Carmen OM, Jose E, Francisco SG, Jose MGF. A practical amine-free synthesis of symmetric ureas and thioureas by self-condensation of isothiocyanates. Synthesis, 1999; 11: 1907-14.