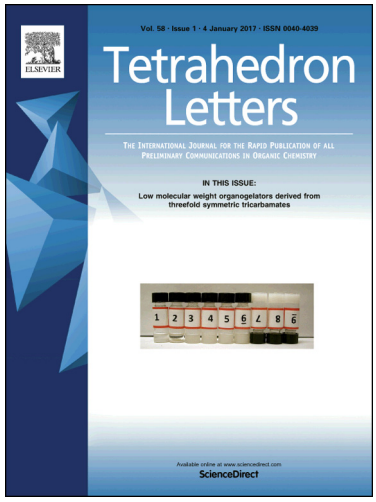

A reactant promoted solvent free synthesis of synthesis of 3,4-dihydropyrimidin-2(*1H*)-thione analogues using ammonium thiocyanate

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Graphical Abstract

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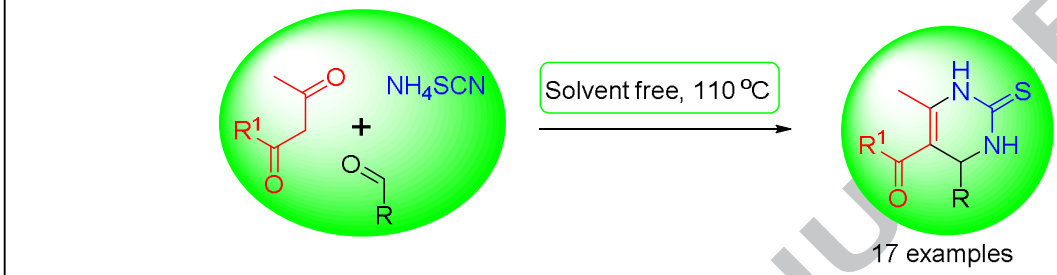

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ABSTRACT

This is the first-time ammonium thiocyanate (NH_4SCN) has been used as a self-promoting reactant for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones. This report describes a greener, efficient and economic protocol for one pot three-component synthesis of Biginelli compounds using various aldehydes, β-ketoesters and ammonium thiocyanate. Ammonium thiocyanate being a weak acid, accelerate the rate of reaction to obtain Biginelli compounds in solvent-free condition at 110 °C. The key advantages of the present method are high yields, short reaction time, solvent free condition, easy workup and ability to tolerate a variety of functional groups. Ammonium thiocyanate is readily available, cheaper, safer and industrial acceptable material which gives economical as well as ecological rewards to the present method.

Green, atom-efficient, eco-friendly and economic transformations of easily available starting materials into complex organic molecules are especially desirable in the green chemistry.[1] With the emphasis on the search for new synthetic methodology using domino and multicomponent reactions have appeared as powerful strategies which allow quicker and economical access to complex compounds.[2,3]

The present method extended the scope of the Biginelli reaction through the use of ammonium thiocyanate in place of thiourea. Ammonium thiocyanate has many greener and economic benefits over thiourea. As thiourea is prepared from ammonium thiocyanate,[4] so it's an energy efficient to use precursor itself. Thiourea is basic in nature whereas ammonium thiocyanate is weakly acidic,[5] which presumably self-promoting the reaction, and it is more reactive which results in increased rate of reaction and ceases the use of other expensive acid catalysts. Moreover, ammonium thiocyanate is safer than thiourea; with LD_{50}=750 mg/kg staging no carcinogenic/teratogenic effect, whereas thiourea with LD_{50}=125 mg/kg has a teratogenic effect which reasonably anticipated as carcinogenic (carcinogen IARC: Group 3). As per as economical aspects are concern ammonium thiocyanate is a better alternative to thiourea due to its relatively lower cost.

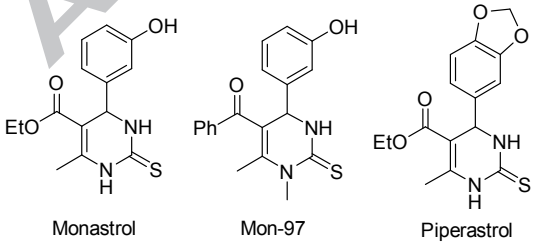

Fig. 1 Pharmacologically active 3, 4-dihydropyrimidin-2(1*H*)-thiones.

More than a century ago a multicomponent synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones was reported by an Italian chemist Pietro Biginelli.[6] However, in last few years, its attractiveness and demand have grown in the field of organic and medicinal chemistry. Much effort has covered for new synthetic methodologies, due to their wide pharmacological properties such as anti-bacterial, anti-inflammatory, anti-viral, anti-tumor, anti-hypertensive and most importantly, as calcium channel modulators.[7,8]

Monastrol is a 3, 4-dihydropyrimidin-2(1*H*)-thione, which blocks mitosis by specifically inhibiting the motor activity of the mitotic kinesin Eg5 and it is a lead molecule for the development of new anticancer drugs. Whereas promising anticancer activity is also reported with Mon-97 and piperastrol (Fig. 1).[9,10]

The most simple and straightforward reaction reported by Biginelli involves the one-pot three component condensation of an aldehyde, ethyl acetoacetate, and urea/thiourea.[6,11] However, this procedure suffered from shortcomings such as the harsh reaction conditions, long reaction time and frequently low yields. This has rekindled development of new methodologies for the Biginelli reaction, which involves the use of a number of Bronsted and Lewis acid catalysts such as sulfated silica tungstic

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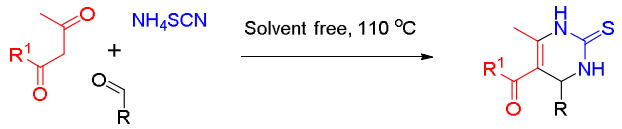


Scheme 1 Ammonium thiocyanate promoted 3, 4-dihydropyrimidin-2(1*H*)-thiones synthesis under solvent free condition.

acid,[12] sulfated tungstate,[13] sulfated polyborate,[14] $SnCl_2.2H_2O$,[15] organosilane sulfonated graphene oxide nanocatalyst,[16] and ZnO nanoparticles.[17] However, some of the newer literature methods suffer from drawbacks of unsatisfactory yields, longer reaction time, and extractive product isolation procedures with toxic organic solvents, use of expensive, metal-based, toxic/corrosive catalysts, which limits their use due to environmental and economic issues.

Despite many advances in the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-thiones, the reagent variety has been limited to β-ketoesters, aldehydes and use of the catalysts. During the last decade, tremendous endeavors have been made to devise efficient synthetic routes to access 3,4-dihydropyrimidin-2(1*H*)-thiones by using various β-ketoesters such as 2-oxosuccinic acid,[18] acetylaldehydes,[19] cyclic and acyclic ketones,[20,21] β-oxo dithioesters,[22] diketenes,[23] and enaminones.[24] On the other hand, aldehydes are also replaced with acetals,[25] and benzyl alcohols.[26]

In continuation of green chemistry interest of MCRs, herein, we described a one-pot multicomponent synthesis of 3, 4-dihydropyrimidin-2(1*H*)-thiones using ammonium thiocyanate; a self-promoting reactant, aldehydes, and β-ketoesters (Scheme 1).

The study was structured to investigate the suitability of ammonium thiocyanate for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-thiones at different reaction conditions. For the preliminary experiment benzaldehyde (4 mmol), a representative substrate, ethyl acetoacetate (4 mmol) and ammonium thiocyanate (4.8 mmol) were used to afford Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxylate (Table 1 and 2).

The effect of the amount of ammonium thiocyanate on reaction time and yield was assessed under solvent free conditions. It was observed that 1.0 equivalent gave lower yield (Table 1, entry 1), whereas, 1.2 equivalent gave good yield in shorter reaction time (Table 1, entry 2). Further increasing the amount of NH_4SCN had no improvement on the reaction time and yield (Table 1, entries 3 and 4). Hence, 1.2 equivalent amount of NH_4SCN was chosen for further study.

Temperature played an important role in the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-thiones (Table 1, entries 2 and 5-7). The temperature effect was examined at ambient, 70 °C, 90 °C and 110 °C under the solvent free condition. The reaction proceeded

Table 1
Optimization of reaction conditions

Entry	NH_4SCN (equiv)	Solvent	Tempera-ture (°C)	Time (h)	Yield[a] (%)
1	1	Solvent free	110	1	81
2	1.2	Solvent free	110	1	90
3	1.5	Solvent free	110	1	90
4	2	Solvent free	110	1	89
5	1.2	Solvent free	rt	6	10
6	1.2	Solvent free	70	2	78
7	1.2	Solvent free	90	2	86

[a]Isolated Yield.

Table 2
The effect of various solvents on synthesis of 3, 4-dihydropyrimidin-2(1*H*)-thiones

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	Solvent free	110	1	90
2	IPA	Reflux	3	85
3	MeCN	Reflux	4	84
4	THF	Reflux	4	80
5	Water	Reflux	6	25
6	Toluene	Reflux	2	85
7	DMF	110	2	88

[a]Isolated Yield.

at room temperature but took longer reaction time with a poor yield (Table 1, entry 5). An increase in the temperature to 70 °C and 90 °C resulted in improved product yield (Table 1, entries 6 and 7). Further increase in temperature to 110 °C gave the highest yield in shorter reaction time (Table 1, entry 2). Therefore, 110 °C was chosen as optimum temperature for the reaction.

The effect of various solvents on time and yield of the reaction was evaluated (Table 2, entries 1-7). None of the solvents has the advantage of time and yield over solvent free condition (Table 2, entry 1). Hence, the solvent free condition was regarded as best for the environmental as well as economical acceptability.

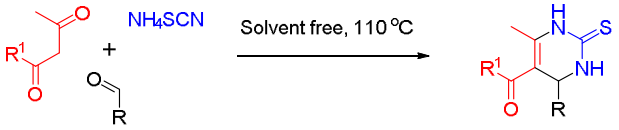
To investigate the substrate scope, optimized reaction condition was applied to substituted aromatic/aliphatic aldehydes and β-ketoesters variants.[37] All the substrate variants reacted well and afforded higher yields of the corresponding 3, 4-dihydropyrimidin-2(1*H*)-thiones within short reaction time (Table 3). Aromatic aldehydes bearing electron-donating or electron-withdrawing groups at different positions on the aromatic ring reacted efficiently and smoothly under the optimized conditions. Electron-donating substituents took longer time than electron-withdrawing substituents to afford the compounds in good to excellent yields (Table 3, entries 2-12), whereas, aliphatic aldehyde have also afforded the corresponding products in good yield (Table 3, entries 13 and 14). This protocol is also extendable to β-ketoester variants under optimized conditions to afford excellent yield in shorter reaction time (Table 3, entries 15 and 16). The model reaction (Table 3, entry 1) was scalable up to 5 gm (47 mmol) with mechanical overhead stirring resulted similar product yield.

The present protocol was also applied for the synthesis of monastrol, an anticancer drug. The reaction of 3-hydroxybenzaldehyde, ethyl acetoacetate and ammonium thiocyanate under optimized reaction condition afforded 89% yield of monastrol in 110 min (Table 3, entry 17).

Conclusion

In conclusion, a one-pot three-component protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones was developed, wherein greener, cheaper and readily available ammonium thiocyanate was used as a self-promoting reactant. The present methodology displayed general applicability for various aldehydes and β-ketoesters with an ability to tolerate a wide variety of substituents. An efficient catalyst, solvent free milder reaction conditions, shorter reaction time, higher yields and ease of workup are the key features of present protocol which give economical as well as ecological rewards to present method.

Table 3 Substrate scope for ammonium thiocyanate promoted synthesis of 3, 4-dihydropyrimidin-2(1*H*)-thiones under solvent free condition[37]



Entry	Aldehydes (R)	β-Ketoesters (R^1)	Time (min)	Yield[a] (%)	Melting Point (°C)	
					Obs.	Lit.
1	C_6H_5	OCH_2CH_3	60	90	207-208	207-208 [14]
2	4-O_2N-C_6H_4	OCH_2CH_3	50	94	112-113	111-112 [27]
3	4-Br-C_6H_4	OCH_2CH_3	60	86	189-190	190-191 [28]
4	4-Cl-C_6H_4	OCH_2CH_3	50	92	182-183	181-182 [14]
5	4-F-C_6H_4	OCH_2CH_3	60	85	185-186	186-187 [28]
6	4-CH_3-C_6H_4	OCH_2CH_3	110	86	191-192	191-193 [29]
7	4-CH_3O-C_6H_4	OCH_2CH_3	110	86	156-157	155-156 [14]
8	4-HO-C_6H_4	OCH_2CH_3	110	85	203-204	205-206 [27]
9	4-$(CH_3)_2N$-C_6H_4	OCH_2CH_3	120	83	206-207	207-209 [27]
10	2-O_2N-C_6H_4	OCH_2CH_3	60	92	213-214	215-216 [27]
11	2-Cl-C_6H_4	OCH_2CH_3	60	90	216-217	216-217 [14]
12	2-CH_3O-C_6H_4	OCH_2CH_3	110	88	185-187	188-189 [14]
13	*c*-C_6H_{11}	OCH_2CH_3	60	92	190-191	189-192 [30]
14	H	OCH_2CH_3	60	90	213-214	212-213 [31]
15	C_6H_5	OCH_3	60	88	220-221	220-222 [28]
16	2-Cl-C_6H_4	OCH_3	60	90	175-176	176-177 [32]
17	3-HO-C_6H_4	OCH_2CH_3	110	89	182-183	182-184 [28]

[a]Isolated Yield.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/00.0000/

References and notes

1. B.M. Trost, Angew. Chem Int. Ed Engl, 34 (1995) 259–281.
2. V. Sridharan, P.T. Perumal, C. Avendano, J.C. Menendez, Tetrahedron 63 (2007) 4407–4413.
3. H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, Chem. Eur. J. 6 (2000) 3321–3329.
4. D.M. Considine, G.D. Considine, Van Nostrand's Scientific Encyclopedia, Springer Science & Business Media, 2013.
5. A.C. Society, A.C.S.C. on A. Reagents, Reagent Chemicals: Specifications and Procedures: American Chemical Society Specifications, Official from January 1, 2006, Oxford University Press, 2006.
6. P. Biginelli, Gazz. Chim. Ital 23 (1893) 360–413.
7. C.O. Kappe, Eur. J. Med. Chem. 35 (2000) 1043–1052.
8. Â. de Fátima, T.C. Braga, L. da S. Neto, B.S. Terra, B.G.F. Oliveira, D.L. da Silva, L. V Modolo, J. Adv. Res. 6 (2015) 363–373.
9. S. Gore, S. Baskaran, B. Koenig, Green Chem. 13 (2011) 1009–1013.
10. A. Canto, R. F. S.; Bernardi, A.; Battastini, V.L. M.O.; Russowsky, D.; Eifler-Lima, J. Brazillian Chem. Soc. 22 (2011) 1379–1388.
11. N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan, L.-Z. Gong, J. Am. Chem. Soc. 131 (2009) 15301–15310.
12. N. Ahmed, Z.N. Siddiqui, J. Mol. Catal. A Chem. 387 (2014) 45–56.
13. S.D. Salim, K.G. Akamanchi, Catal. Commun. 12 (2011) 1153–1156.
14. C.K. Khatri, D.S. Rekunge, G.U. Chaturbhuj, New J. Chem. 40 (2016) 10412–10417.
15. O.M. Singh, M.L. Singh, S.J. Singh, Heterocycl. Commun. 13 (2007) 277–282.
16. J. Safari, S. Gandomi-Ravandi, S. Ashiri, New J. Chem. 40 (2016) 512–520.
17. A. Hassanpour, J. Abolhasani, R.H. Khanmiri, J. Korean Chem. Soc. 58 (2014) 445–449.
18. J.C. Bussolari, P.A. McDonnell, J. Org. Chem. 65 (2000) 6777–6779.
19. C.D. Bailey, C.E. Houlden, G.L.J. Bar, G.C. Lloyd-Jones, K.I. Booker-Milburn, Chem. Commun. (2007) 2932–2934.
20. J.-P. Wan, Y. Lin, K. Hu, Y. Liu, Beilstein J. Org. Chem. 10 (2014) 287–292.
21. Z.-L. Shen, X.-P. Xu, S.-J. Ji, J. Org. Chem. 75 (2010) 1162–1167.
22. G.C. Nandi, S. Samai, M.S. Singh, J. Org. Chem. 75 (2010) 7785–7795.
23. A. Shaabani, M. Seyyedhamzeh, A. Maleki, F. Hajishaabanha, Tetrahedron 66 (2010) 4040–4042.
24. J.-P. Wan, Y.-J. Pan, Chem. Commun. (2009) 2768–2770.
25. A.R. Khosropour, M.M. Khodaei, M. Beygzadeh, Heteroat. Chem. 18 (2007) 684–687.
26. E. Kolvari, M.A. Zolfigol, M. Mirzaeean, Helv. Chim. Acta 95 (2012) 115–119.
27 Q. Liu, N. Pan, J. Xu, W. Zhang, F. Kong, Synth. Commun. 43 (2013) 139–146.
28. S. Nagarajan, T.M. Shaikh, E. Kandasamy, J. Chem. Sci. 127 (2015) 1539–1545.
29. J. Safari, S. Gandomi-Ravandi, New J. Chem. 38 (2014) 3514–3521.
30. D.L. da Silva, F.S. Reis, D.R. Muniz, A.L.T.G. Ruiz, J.E. de Carvalho, A.A. Sabino, L. V Modolo, Â. de Fátima, Bioorg. Med. Chem. 20 (2012) 2645–2650.
31. L.M. Ramos, B.C. Guido, C.C. Nobrega, J.R. Correa, R.G. Silva, H.C.B. de Oliveira, A.F. Gomes, F.C. Gozzo, B.A.D. Neto, Chem. Eur. J. 19 (2013) 4156–4168.
32. M. Ertan, A. Balkan, S. Saraç, S. Uma, J.F. Renaud, Y. Rollad, Arch. Pharm. (Weinheim). 324 (1991) 135–139.
33. F. Sweet, J.D. Fissekis, J. Am. Chem. Soc. 95 (1973) 8741–8749.
34. J. Ma, L. Zhong, X. Peng, R. Sun, Green Chem. 18 (2016) 1738–1750.
35. A. Burrows, J. Holman, A. Parsons, G. Pilling, G. Price, Chemistry[3]:

Introducing Inorganic, Organic and Physical Chemistry, Oxford University Press, 2013.

36. H.G.O. Alvim, E.N. da Silva Júnior, B.A.D. Neto, RSC Adv. 4 (2014) 54282–54299.
37. *General procedure for 3,4-dihydropyrimidin-2(1H)-thiones:* A mixture of aldehyde (4 mmol), β-ketoester (4 mmol), and ammonium thiocyanate (4.8 mmol) was heated at 110 °C. The reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was cooled to room temperature and quenched with water (5 mL); solid precipitated was filtered at vacuum pump, washed with water (3 X 5 mL), dried under vacuum and recrystallized from methanol and acetone (8:2) to afford the pure products.

Highlights:

- Green, economic and scalable synthesis of 3,4-dihydropyrimidin-2(1*H*)-thiones.
- Ammonium thiocyanate was used as a self-promoting reactant in place of thiourea.
- Ammonium thiocyanate is readily available, cheaper and safer than thiourea.
- Key advantages are high yields, short reaction time and simple work-up procedure.
- Method tolerates various functional groups and extendable to multiple substrates.