Synthesis of 2-aminothiazole derivatives from easily available thiourea and alkyl/aryl ketones using aqueous $NaICl_2$

Shrikant M. Ghodse, Vikas N. Telvekar

PII: S0040-4039(14)02054-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.11.140
Reference: TETL 45524

To appear in: *Tetrahedron Letters*

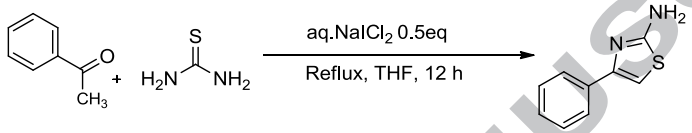
Received Date: 24 September 2014
Revised Date: 28 November 2014
Accepted Date: 30 November 2014

Please cite this article as: Ghodse, S.M., Telvekar, V.N., Synthesis of 2-aminothiazole derivatives from easily available thiourea and alkyl/aryl ketones using aqueous $NaICl_2$, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.11.140

Graphical Abstract

Synthesis of 2-aminothiazole derivatives from easily available thiourea and alkyl/aryl ketones using aqueous $NaICl_2$

Shrikant M. Ghodse, Vikas N. Telvekar*



ELSEVIER

Tetrahedron Letters

journal homepage: www.elsevier.com

Synthesis of 2-aminothiazole derivatives from easily available thiourea and alkyl/aryl ketones using aqueous $NaICl_2$

Shrikant M. Ghodse, Vikas N. Telvekar*

Department of Pharmaceutical Sciences & Technology, Institute of Chemical Technology, Matunga, Mumbai-400 019, India

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Aminothiazole
Thiourea
Ketones
Aqueous Sodium iodine dichloride ($NaICl_2$)

ABSTRACT

A simple methodology was developed to synthesize substituted aminothiazoles from corresponding thiourea and substituted ketones using aqueous $NaICl_2$ at reflux temperature in THF. The products were obtained in good to excellent yields.

Aminothiazole have been recently identified as desired structural element that is screened as part of many drug design processes in medicinal chemistry due to their thiourea like properties and tendency to modulate biological targets.[1] Aminothiazole and its derivatives have broad spectrum of medicinal applications such as antitubercular,[2] anti-inflammatory,[3] antiplatelet,[4] antiviral,[5] anticancer [6] and human lymphatic filarial parasite.[7] Aminothiazole analogs have also been reported as ligands at adenosine receptors,[8] estrogen receptor [9] and inhibitors of human platelet aggregation factor.[10] This heterocyclic core is also reported in many natural products and pharmaceuticals. (Fig. 1)

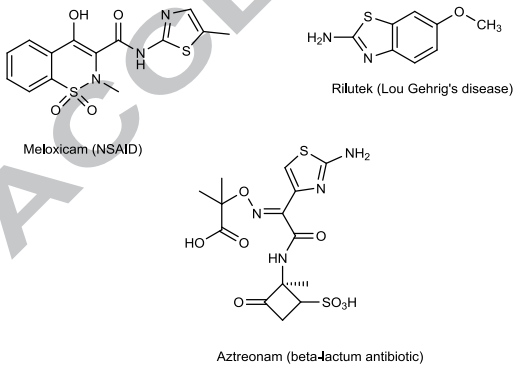
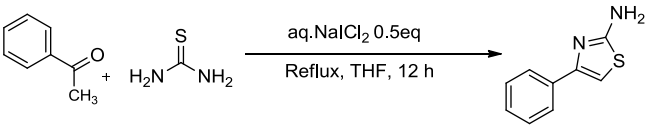


Figure1. Some drugs containing aminothiazole moiety.

Various methodologies such as Hantzsch, Cook Heilborn, and Tchernic for the synthesis of aminothiazole and their derivatives have been reported. Among these, Hantzsch thiazole synthesis is the most widely used, which involves reaction of α-halo carbonyl compounds with thiourea or thioamides.[11] There are very few reports available in which α-halo carbonyl compounds were generated in-situ using ketones and reacted with thiourea to form varieties of aminothiazoles.[12]

Recently, aminothiazole derivatives were also synthesized by using various catalysts such as iodine,[13] silica chloride,[14] 1,3-di-n-butylimidazolium tetrafluoroborate,[15] ammonium 12-molybdophosphate and cyclodextrin.[16-17]

Herein, we report the synthesis of aminothiazoles from thiourea and alkyl/aryl ketones in the presence of aq. $NaICl_2$.



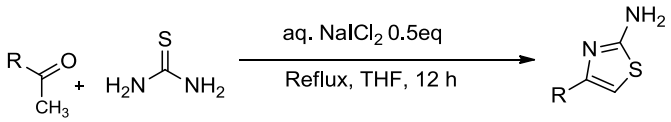
Scheme1. Synthesis of 2-amino 4-(phenyl)-1,3-thiazole using aq..$NaICl_2$

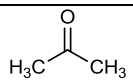
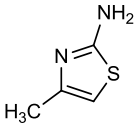
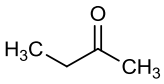
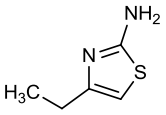
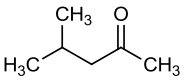
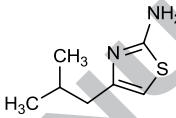
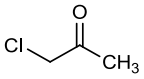
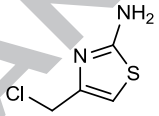
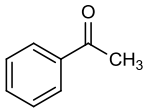
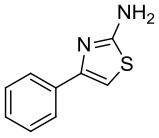
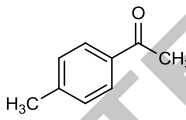
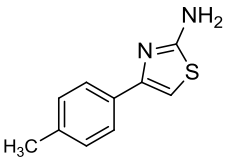
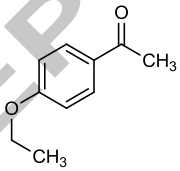
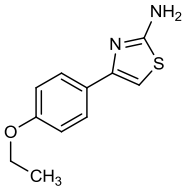
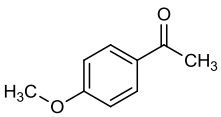
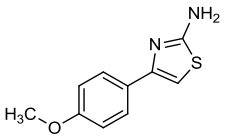
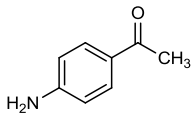
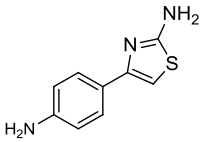
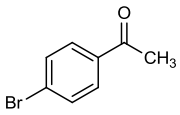
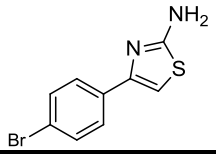
For our initial study, we took thiourea and acetophenone as the model substrates (Scheme 1). The desirable 2-amino-4-(phenyl)-1,3-thiazole was formed when 1 equivalents of thiourea and acetophenone were treated with 1 equivalent of aq. $NaICl_2$ (30% W/W in water) in presence of THF at reflux temperature. Further, it was observed that in the absence of aq. $NaICl_2$ no product was formed. Thus, to optimize the reaction conditions, thiourea and acetophenone were treated with different equimolar ratios and finally, optimum yield of desired aminothiazoles was obtained when 2 equivalents of thiourea reacted with 1 equivalent of acetophenone. It was observed that 0.5 equivalent of aq.$NaICl_2$ was sufficient to carry out the reaction. Further, the effect of temperature on the model reaction was studied and it was showed that the reflux temperature produced best results. The above reaction is also carried out in different solvents, at reflux temperature, such as methanol, ethanol, MDC and toluene instead of THF. No reactions were observed in MDC and toluene, while in methanol and ethanol yields were 30% and 40% respectively. Thus, THF was found to be the most suitable solvent for this reaction.

These optimized reaction conditions were applied to varieties of aliphatic and aromatic ketones in presence of thiourea and aq.$NaICl_2$ to convert into corresponding aminothiazoles and the results are summarized in Table 1.[18]

* Corresponding author. Tel.: + 91 22 3361 2213; fax: +91 22 3361 1020;
E-mail: vikastelvekar@rediffmail.com

Table 1. Aliphatic and aromatic ketones are converted into aminothiazoles [a]



entry	substrate	product	%Yield [b]
1			70
2			85
3			84
4			74
5			91
6			86
7			89
8			83
9			72
10			90

[a] Reaction conditions: thiourea (2 equiv), ketones (1 equiv) and aq. $NaICl_2$ (0.5 equiv) in THF at reflux temperature.
[b] Isolated yields after column chromatography, Structure were confirmed by comparison of IR, ^1H NMR and M.P. with literature reports.[19-25]

Both aliphatic and aromatic ketones are suitable for this conversion (Table 1 entries 1-10). In case of aliphatic substrates like acetone, chloroacetone, methyl acetone and isopropyl acetone, the desired aminothiazoles were obtained in moderate to good yields (Table 1, entries 1- 4). Under these reaction conditions, ether linkages are stable (Table 1, entry 7, 8). In most of the literature, it is reported that *p*-aminoacetophenone does not react with thiourea [26], but in our case aqueous $NaICl_2$ is found to give the desired product (Table1, entry 9).

In conclusion, a novel, facile and highly efficient methodology has been developed to synthesize substituted aminothiazoles using easily available aliphatic and aromatic ketones in presence of aq. sodium iodine dichloride under metal free conditions. The conditions are general and applicable to variety of pharmaceutical intermediate. This methodology is also useful for conversion of substrate like *p*-aminocetophenone to corresponding aminothiazole.

Acknowledgment
SMG thanks University Grants Commission (UGC) and VNT thanks Science and Engineering Research Board (SERB), New Delhi, India, for providing financial support.

References

1. Baell, J. B.; Holloway, G. A. *J. Med. Chem*. **2010**, *53*, 2719.
2. Meissner, A.; Boshoff, H.; Vasan, M.; Duckworth, B. P.; Barry, C. E.; Aldrich, C. C. *Bioorg. & Med. Chem*. **2013,** *21*, 6385.
3. Helal, M. H. M.; Salem, M. A.; El-Gaby, M. S. A.; Aljahdali, M. *Eur. J. Med. Chem.* **2013**, *65*, 517.
4. Pi, Z.; Sutton, J.; Lloyd, L.; Hua, J.; Price, L.; Wu,Q.; Chang, M.; Zheng,J.; Rehfuss, R.; Huang, C. S.; Wexler, R. R.; Lam, P. Y. S. *Bioorg. Med. Chem.* **2013**, *23*, 4206.
5. Liu, R.; Huang, Z.; Murray, M. G.; Guo, X.; Liu, G. *J. Med. Chem.* **2011**, *54*, 5747.
6. Romagnoli, R.; Baraldi, P. G.; Salvador, M. K.; Camacho, M. E.; Preti, D.; Tabrizi, M. A.; Bassetto, M.; Brancale, A.; Hamel, E.; Bortolozzi, R.; Basso, G.; Viola, G. *Bioorg. Med. Chem.* **2012,** *20*, 7083.
7. Sashidhara, K. V.; Rao, K. B.; Kushwaha, V.; Modukuri, R. K.; Verma, R.; Murthy, P. K. *Eur. J. Med.* Chem. **2014** , *81*, 473.
8. Van Tilburg, E. W.; Van der Klein, P. A. M.; De Groote, M. W.; IJzerman, A. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2017.
9. Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellengbogen, J. A. *Chem. Biol*. **1999**, *6*, 205.
10. Umadevi, B. *Eur. J. Med. Chem.* **2007**, *42*, 1144.
11. Hantzsch, A.; Weber, J. H. *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 3118
12. (a) Zhu, Y. P. ; Yuan, J. J.; Zhao, Q.; Lian, M. ; Gao , Q. H. ; Liu, M. C.; Yang ,Y.; Wu, A.X. *Tetrahedron*, **2012**, *68*, 173. (b) Xue, W.J.; Zheng, K. L.; Li, H. Z.; Geo, F. F.; Wu A. X. *Tetrahedron Lett*. **2014,** *55*, 4212.
13. Siddiqui, H. L.; Iqbal, A.; Ahmed, S.; Weaver, G. *Molecules*, **2006**, *11*, 206
14. Karade, H.; Sathe, M.; Kaushik, M. P. *Catal. Commun*. **2007**, *8*, 741.
15. Potewar, T. P.; Ingale, S. A.; Srinivasan, K. V.; *Tetrahedron*, **2007**, *63*, 11066.
16. Das, B.; Reddy, S. V.; Ramu, R. J. *Mol. Catal. A: Chem*. **2006**, 252, 235.
17. Narender, M.; Somi Reddy, M.; Sridhar, R.; Nageswar, K.; Nageswar, K.; Rama Rao, K.. *Tetrahydron Lett*. **2005**, *46*, 7779.
18. **General procedure for the synthesis of 2-aminothiazole:** To a stirred solution of thiourea (2 equiv), and ketone (1equiv) in THF (10 mL) at room temperature was slowly added aqueous $NaICl_2$ (0.5 equiv, 30% W/W aqueous $NaICl_2$). The resultant reaction mixture was refluxed for 12 h. After completion of reaction (TLC), the solvent was evaporated under the vacuum. The resulted residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was separated and washed successively with 10% sodium bisulfate solution (2 x 10 mL), 10% sodium bicarbonate (2 × 10 mL) and water (2 × 15 mL). The organic layer finally dried over anhydrous sodium sulphate and concentrated under the reduced pressure to give crude product. Pure product was obtained after silica gel column chromatography (30% EtOAc-Hexane).
2-amino-4-(phenyl)-1,3-thiazole (Table 1, entry 5):[19] colorless solid, Mp 148-150 ^oC (Lit. Mp 149-151 ^oC); IR (neat): 3325, 3192, 2926, 1616, 1519, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77-7.76 (d, *J* = 7.7, 2H), 7.39-7.36 (d, *J* = 7.4, 2H), 7.30-7.35 (m, 2H), 5.78 (bs, 2H); MS: m/z calcd for $C_9H_8N_2S$ (M): 176.26; found 176.00.
2-amino-4-(methyl)-1,3-thiazole (Table 1, entry 1):[20] **y**ellow oil, ^1H NMR (300 MHz, $CDCl_3$): δ 6.13 (d, *J*= 0.9 Hz, 1H), 5.30 (bs, 2H), 2.18 (d, *J*= 0.9 Hz, 3H)
2-amino-4-(*p*- methylphenyl)-1,3-thiazole (Table 1, entry 6):[21] Mp 129–131 ^oC (Lit Mp 130-132 ^oC); ^1H NMR (300MHz, $CDCl_3$): δ 7.67(d, *J* = 6.8, 2H), 7.16 (d, *J* = 7.2, 2H), 7.10 (s, 1H), 6.90 (s, 2H); MS: m/z calcd for $C_{10}H_{10}N_2S$ (M^+): 190.26; found 190.00
19. Yadav, J. S.; Reddy, B. V. S.; Rao, Y. G.; Narsaiah, A. V. *Tetrahedron Lett.*. **2008**, *49*, 2381.
20. Huang, G.; Sun, H.; Qiu, X.; Jin, C.; Lin, C.; Shen, Y.; Jiang, J.; Wang, L. *Org. Lett*. **2011**, *13*, 5224.
21. Morales-Bonilla, P.; Perez-Cardena, A.; Quintero-Mármol, E.; Arias-Téllez, J. L.; Mena-Rejón, G. J. *Heter. Chem*, **2006**, *17*, 254.
22. Veretennikov, E. A.; Pavlov, A. V. *Russian. J. Org. Chem.* **2013**, *49*, 575.
23. Donohoe, T. J.; Kabeshov, M. A.; Rathi, A.H.; Smith , E. D. *Org. Biomol. Chem*. **2012,** *10*, 1093.
24. Bhargava, P. N.; Singh, P. R. *J. Ind. Chem. Soc*. **1960**, *37*, 241.
25. Pathan S. R.; Ali M. S.; Pathan, J. S.; Purohit, S. S.; Reddy V. V. K.; Nataraj B. R. *Indi. J. Chem.* **2006,** *45*, 1929**.**
26. Caceres-Castillo, D.; Carballo, R. M.; Tzec-Interián, J. A.; Mena-Rejon, G. J. *Tetrahedron Lett.* **2012**, *53*, 3934.