


 Cite this: *RSC Adv.*, 2020, 10, 40225

 Received 4th April 2020
 Accepted 30th October 2020

DOI: 10.1039/d0ra03047c

rsc.li/rsc-advances

Homo-condensation of acetophenones toward imidazothiones†

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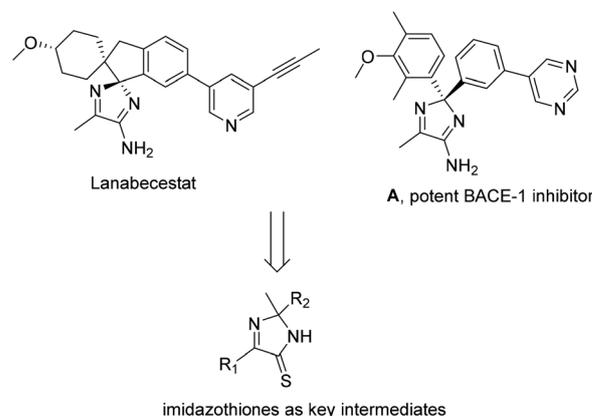
Direct synthesis of imidazothiones from simple, commercial substrates is not known. We report a method for the condensation of acetophenones, elemental sulfur, and ammonium acetate as a nitrogen source to obtain the hitherto challenging five-membered heterocycles. Functionalities such as halogen, trifluoromethyl, cyano, methylthio, and heteroaryl groups were well tolerated.

Amino-2*H*-imidazoles such as commercial lanabecestat or a pyrimidine derivative, **A** (Scheme 1) are potent inhibitors against BACE-1 (β -site APP cleaving enzyme), and are thus useful in studies for treating Alzheimer's disease.¹ Until now, available methods for the synthesis of amino-2*H*-imidazoles often proceed through substitution of imidazothiones with ammonia.^{1d} It should be noted that this approach suffers from the use of toxic, flammable hydrogen sulfide gas.² Development of continuous-flow conditions has recently increased the synthetic practicality.^{2b,c} In 2012, Gravenfors and co-workers reported a rare study of substrate scope with respect to synthesis of 2,5-diaryl imidazothiones from acetophenones, α -oxoacetates, and ammonia, followed by sulfur exchange of the amide intermediates.^{1d} Arguably, methods for directly assembling simple, commercial substrates to obtain such five-membered heterocycles are still deficient.

Studies of using elemental sulfur in organic synthesis has been extensively investigated over the last few years, probably because it is cheap, abundant, and easy to handle. The element has replaced the need of heavy phosphorus–sulfur complexes such as Lawesson's reagent and P₂S₅ in synthesis of thioamides.³ Many methods for incorporation of small molecules into polycyclic *S*-heterocycles have been reported.⁴ In such transformations, C–H bonds in acetophenones or pseudo oxime esters have been considered as the major targets.

Oxime-assisted annulation of elemental sulfur and activated C–H bonds α to carbonyl group often afford synthetically challenging polyheterocycles.⁵ A few examples of furnishing

benzothienothiazoles *via* functionalization of C–H bonds in acetophenone oximes have been reported.^{5b,c} Nevertheless, the available methods have required a two-step prefunctionalization of aryl ketones. Arguably it would be more advantageous if C–H bonds in acetophenones could be directly functionalized, thus avoiding the unnecessary preparation of oxime substrates. Only a couple of reports, to our best knowledge, have described attempts to convert methyl C–H bonds of acetophenones without the need of *N*-oxime esters. Nguyen reported a synthesis of 2,4-diarylthiophenes *via* homo-annulation of acetophenones and elemental sulfur.^{5e} The substrate scope was limited to simple functional groups such as alkyls, alkoxy, and halogens. Our group has recently presented an annulation of acetophenones, elemental sulfur, and urea as a nitrogen source.^{3f} The reactions afforded benzothienothiazoles that were compatible with many functionalities such as methylthio, protected alcohol, and heterocycle groups. As a continuation of our interests in functionalization of C–H bonds in absence of transition metals, herein a method for synthesis of imidazothiones from simple acetophenones, elemental sulfur, and



Scheme 1 Importance of imidazothiones.

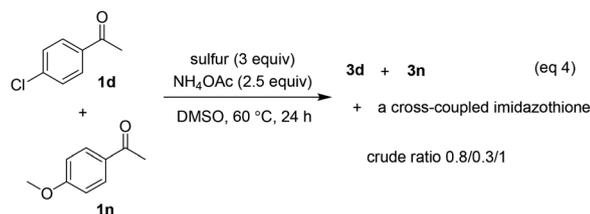
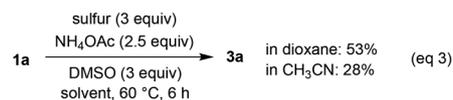
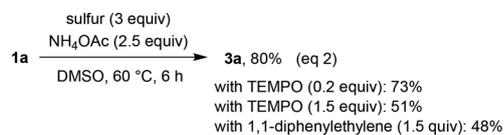
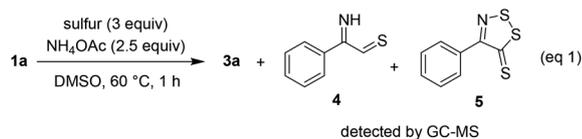
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† Electronic supplementary information (ESI) available: Details of optimization, experimental procedures, and characterization of unknown compounds. See DOI: 10.1039/d0ra03047c

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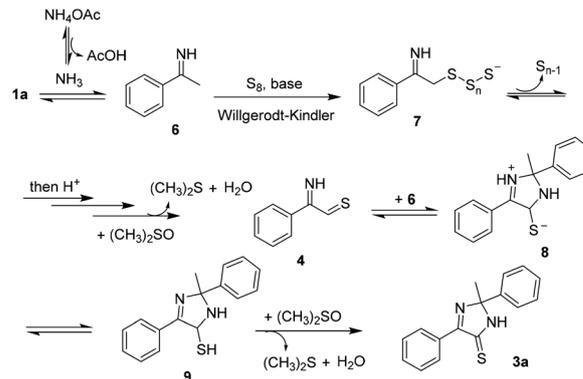


Scheme 4 Mechanistic considerations.

could be obtained in good yields. However, running the reaction of 4-nitroacetophenone did not give the desired product. Furthermore, our conditions were applied for synthesis of polyheterocyclic imidazothiones (**3r**, **3s**). It should be noted that 2-acetylheteroarenes sometimes were not competent substrates.

Although most of possible intermediates were unstable and difficult to independently prepare, some mechanistic studies still have been investigated (Scheme 4). Similar to previous studies,^{5f,g} compounds afforded by oxidative sulfuration of α C–H bonds were detected by GC-MS if the coupling of **1a** and **2a** was stopped after 1 h (eqn (1)). The annulation was somewhat affected by the presence of radical quenchers such as TEMPO or 1,1-diphenylethylene, especially if excess amount of these compounds was used (eqn (2)). Since DMSO was much effective more than other solvents, we envisaged that it could play roles in oxidation steps. Indeed, 53% and 28% of product **3a** were obtained if 3 equivalents of DMSO were used in solvents 1,4-dioxane and CH₃CN, respectively (eqn (3)). Analysis of the crude mixture obtained from the reaction of 4'-chloroacetophenone and 4'-methoxyacetophenone disclosed a 0.8/0.3/1 ratio of three coupling products, as the major was the heterocoupling imidazothione (eqn (4)). Given that only one cross-coupled product was obtained, it was likely that electronic properties of substituents have played a somewhat important role during reaction course. Ongoing experiments will include the isolation of synthetically challenging cross-coupled imidazothiones.

With the results in hand, we proposed a possible mechanism for the annulation (Scheme 5). An imine **6** was obtained when acetophenone **1a** reacted with NH₄OAc, followed by a Willgerodt–Kindler sulfuration to afford the intermediate **7**. Oxidation, presumably promoted by DMSO, would furnish an iminothial **4**. This intermediate was unstable, either generating



Scheme 5 Plausible mechanism.

a dithiazolethione **5** or reacting with **6** following a [3 + 2] cycloaddition to afford **8**. After isomerization (**8** → **9**) and oxidation of C–S bond, the imidazothione **3a** was obtained.

Conclusions

In conclusion, we have developed a simple method for synthesis of imidazothiones from annulation of methyl C–H bonds in acetophenones with elemental sulfur and NH₄OAc. DMSO was used as a solvent as well as oxidant in these reactions. A wide range of functionalities including halogen, methylthio, cyano groups were compatible with reaction condition. Heteroaryl methyl ketones were also competent substrates. The method would offer a rapid route to assemble complex polycyclic structures from simple, commercial substrates.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The Vietnam National Foundation for Science and Technology Development (NAFOSTED) is acknowledged for supporting this research under project code 104.01-2019.340.

Notes and references

- For reviews: (a) K. Lao, N. Ji, X. Zhang, W. Qiao, Z. Tang and X. Gou, *J. Drug Targeting*, 2019, **27**, 164; (b) A. K. Ghosh and H. L. Osswald, *Chem. Soc. Rev.*, 2014, **43**, 6765. Selected examples; (c) S. Eketjäll, J. Janson, K. Kaspersson, A. Bogstedt, F. Jeppsson, J. Fältling, S. B. Haerberlein, A. R. Kugler, R. C. Alexander and G. Cebers, *J. Alzheimer's Dis.*, 2016, **50**, 1109; (d) Y. Gravenfors, J. Viklund, J. Blid, T. Ginman, S. Karlström, J. Kihlström, K. Kolmodin, J. Lindström, S. von Berg, F. von Kieseritzky, C. Silvo, B.-M. Swahn, L.-L. Olsson, P. Johansson, S. Eketjäll, J. Fältling, F. Jeppsson, K. Strömberg, J. Janson and F. Rahm, *J. Med. Chem.*, 2012, **55**, 9297; (e) E. G. Vega-Hissi, R. Tosso, R. D. Enriz and L. J. Gutierrez, *Int. J. Quantum*



- Chem.*, 2015, **115**, 389; (f) F. Asinger, H. Offermanns, D. Neuray and F. A. Dagga, *Monatsh. Chem.*, 1970, **101**, 500.
- 2 (a) F. Asinger, W. Schäfer and F. Haaf, *Justus Liebigs Ann. Chem.*, 1964, **672**, 134; (b) D. Cantillo, P. A. Inglesby, A. Boyd and C. O. Kappe, *J. Flow Chem.*, 2017, **7**, 29; (c) D. Znidar, D. Cantillo, P. Inglesby, A. Boyd and C. O. Kappe, *Org. Process Res. Dev.*, 2018, **22**, 633.
- 3 (a) T. Guntreddi, R. Vanjari and K. N. Singh, *Org. Lett.*, 2014, **16**, 3624; (b) P. Zhang, W. Chen, M. Liu and H. Wu, *J. Org. Chem.*, 2018, **83**, 14269.
- 4 For review: (a) T. B. Nguyen, *Adv. Synth. Catal.*, 2017, **359**, 1066. Selected examples; (b) B. Wu and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 10496; (c) T. B. Nguyen, L. Ermolenko, P. Retailleau and A. Al-Mourabit, *Angew. Chem., Int. Ed.*, 2014, **53**, 13808; (d) L. Meng, T. Fujikawa, M. Kuwayama, Y. Segawa and K. Itami, *J. Am. Chem. Soc.*, 2016, **138**, 10351; (e) J.-R. Guo, J.-F. Gong and M.-P. Song, *Org. Biomol. Chem.*, 2019, **17**, 5029; (f) Y. Xie, X. Chen, Z. Wang, H. Huang, B. Yi and G.-J. Deng, *Green Chem.*, 2017, **19**, 4294.
- 5 (a) X. Wang, X. Qiu, J. Wei, J. Liu, S. Song, W. Wang and N. Jiao, *Org. Lett.*, 2018, **20**, 2632; (b) H. Huang, Z. Xu, X. Ji, B. Li and G.-J. Deng, *Org. Lett.*, 2018, **20**, 4917; (c) H. Huang, Q. Wang, Z. Xu and G.-J. Deng, *Adv. Synth. Catal.*, 2019, **361**, 591; (d) Y. Liao, Y. Peng, H. Qi, G.-J. Deng, H. Gong and C.-J. Li, *Chem. Commun.*, 2015, **51**, 1031; (e) T. B. Nguyen and P. Retailleau, *Green Chem.*, 2018, **20**, 387; (f) P. H. Pham, K. X. Nguyen, H. T. B. Pham, T. T. Nguyen and N. T. S. Phan, *Org. Lett.*, 2019, **21**, 8795; (g) P. Zhou, Y. Huang, W. Wu, J. Zhou, W. Yu and H. Jiang, *Org. Lett.*, 2019, **21**, 9976.
- 6 Please see the ESI† for details.

