Homo-condensation of acetophenones toward imidazothiones†

Phuc Hoang Pham, Thuy Thu Bui, Hien Nhat Tra, Thung Thanh Nguyen and Nam Thanh Son Phan

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-2H-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. Until now, available methods for the synthesis of amino-2H-imidazoles often proceed through substitution of imidazothiones with ammonia. It should be noted that this approach suffers from the use of toxic, flammable hydrogen sulfide gas. Development of continuous-flow conditions has recently increased the synthetic practicality. 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. 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. Many methods for incorporation of small molecules into polycyclic S-heterocycles have been reported. 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. A few examples of furnishing benzothienothiazoles via functionalization of C–H bonds in acetophenone oximes have been reported. Nevertheless, the available methods have required a two-step prefunctionalization of aryk 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. The substrate scope was limited to simple functional groups such as alkyls, alkoxyis, and halogens. Our group has recently presented an annulation of acetophenones, elemental sulfur, and urea as a nitrogen source. 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.
ammonium acetate has been developed. It should be noted that such an one-pot formation of quaternary carbon from simple reagents is relatively rare in the literature.

While optimizing the reaction of acetophenone 1a with elemental sulfur and a nitrogen source such as NH4OAc to obtain benzothienothiazole 2a (eqn (1), Scheme 2), we early observed the formation of imidazothione 3a, especially at the lower temperature (eqn (2), Scheme 2). Our study then commenced on obtaining the simplest diphenyl imidazothione 3a from homocoupling of acetophenone 1a. The reaction was optimized with respect to temperature, nitrogen source, and solvent. The results are presented in Table 1. A trace amount of the desired product was detected when running the reaction at room temperature (entry 1). Increasing the temperature up to 60 °C dramatically increased the yield of 3a (entry 2). However, above 60 °C some by-products could be detected, thus leading to drops in yield (entry 3). Unlike our previous report, urea could not be used to incorporate nitrogen atoms into the product (entry 4). Since NH3 did not give the product, the presence of acetate anion was pivotal to the formation of 3a (entry 5). No solvents rather than DMSO were effective in this transformation (entries 6 and 7). Lastly, the reaction could reach to the equilibrium only after 6 h (entry 8).

Substrate scope with respect to acetophenones was next studied (Scheme 3). Structures of some imidazothiones were confirmed by the results of HMOC and HMB spectra. The simple diphenyl imidazothione 3a was isolated in good yield, even in a 2 mmol scale. Halo-substituted acetophenones afforded the products regardless of positions of the substituents (3b–3i). Since synthesis of bromo- (3e, 3f) and iodo- (3i) containing imidazothiones was viable, late stage functionalization of such molecules could be possible. Methyl (3j, 3k), methoxy (3l–3n), and methythio (3o) functionalities were all compatible with reaction conditions. Uses of acetophenones containing electron-withdrawing groups were also attempted. Trifluoromethyl- (3p) and cyano- (3q) substituted imidazothiones were isolated in good yield.

### Table 1  Studies of reaction conditions

| Entry | Temperature (°C) | Nitrogen source | Solvent  | Yield of 3a (%) |
|-------|-----------------|-----------------|----------|----------------|
| 1     | r.t.            | NH4OAc          | DMSO     | Trace          |
| 2     | 60              | NH4OAc          | DMSO     | 84             |
| 3     | 70              | NH4OAc          | DMSO     | 71             |
| 4     | 60              | Urea            | DMSO     | n.d.           |
| 5b    | 60              | NH3             | DMSO     | n.d.           |
| 6b    | 60              | NH4OAc          | Dioxane  | n.d.           |
| 7b    | 60              | NH4OAc          | DMF      | n.d.           |
| 8b    | 60              | NH4OAc          | DMSO     | 84             |

* Acetophenone (0.2 mmol), elemental sulfur (0.3 mmol, 32 g mol⁻¹), nitrogen source (0.5 mmol, based on nitrogen), solvent (1 mL, [acetophenones] = 0.2 M), for 24 h. Yields of 3a are GC yields using diphenyl ether internal standard. NH3 as a 28% aqueous solution. 6 h. Abbreviations: r.t. = room temperature, n.d. = not determined.

Scheme 2  An early observation of imidazothione.

Scheme 3  Reaction scope with respect to acetophenones. Reagents and conditions: acetophenones (0.2 mmol), sulfur (0.3 mmol, 32 g mol⁻¹), NH4OAc (0.5 mmol), DMSO (1 mL, [acetophenones] = 0.2 M), 60 °C, 6 h. Yields are isolated yields. Please see the ESI† for more details. 2 mmol scale.
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 polycyclic imidazothiones ($3_r$, $3_s$). 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,$^{36}$ compounds afforded by oxidative sulfuration of $\alpha$ 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 more effective than other solvents, we envisaged that it could play important 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 CH$_3$CN, 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 NH$_4$OAc, 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 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 NH$_4$OAc. 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**

1. 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. Fälting, S. B. Haeberlein, A. R. Kugler, R. C. Alexander and G. Cebers, *J. Alzheimer’s Dis.*, 2016, 50, 1109; (d) Y. Gravenfors, J. Viklund, J. Blied, 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. Fälting, 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.*
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.