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Homo-condensation of acetophenones toward imidazothiones†

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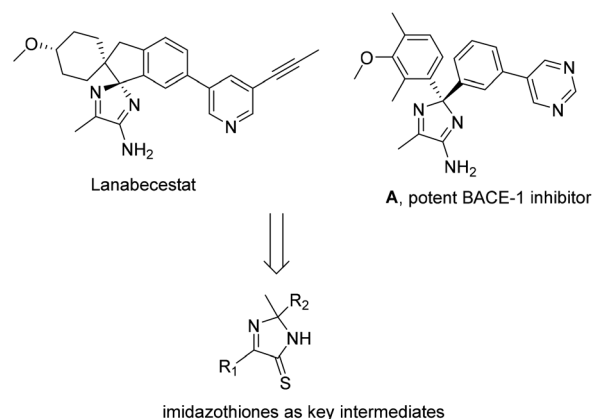
Direct synthesis of imidazothiones from simple, commercial substrates is not known. We report a method for the condensation of acetophenones, elemental sulfur, and ammonium acetate as a nitrogen source to obtain the hitherto challenging five-membered heterocycles. Functionalities such as halogen, trifluoromethyl, 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.^{5f} 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.

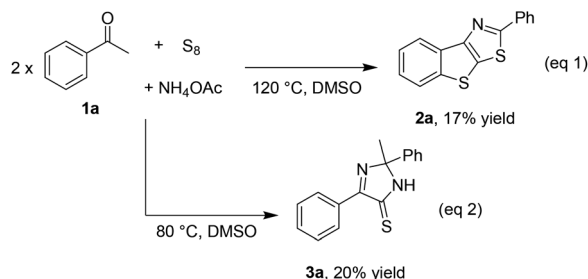
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Scheme 2 An early observation of imidazothione.

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 NH_4OAc to obtain benzothienothiazole **2a** (eqn (1), Scheme 2),^{3f} 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,^{3f} urea could not be used to incorporate nitrogen atoms into the product (entry 4). Since NH_3 did not give the product, the presence of acetate anion was pivotal to the formation of **3a** (entry 5). No

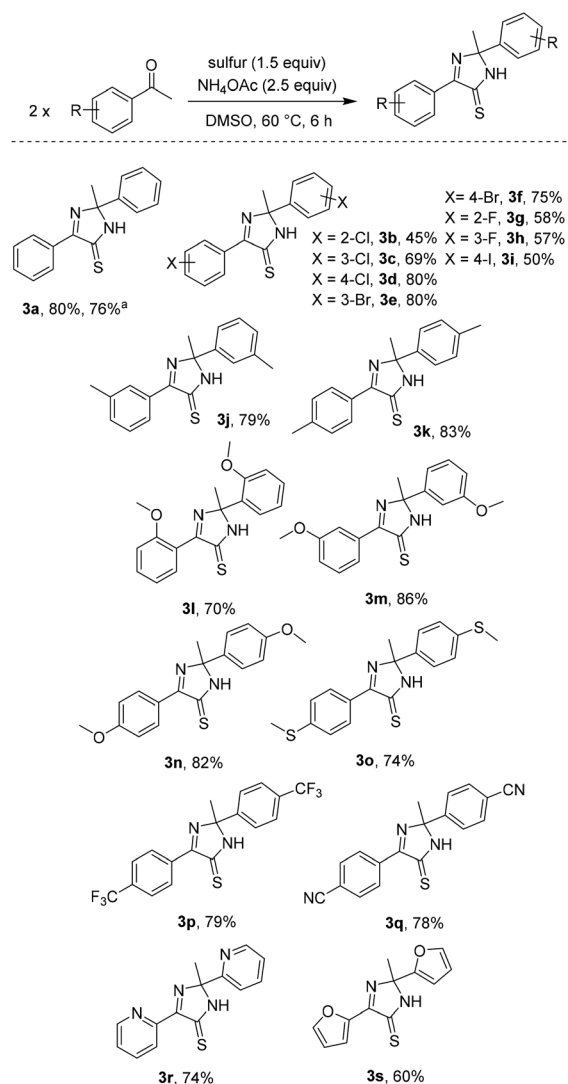
Table 1 Studies of reaction conditions^a

Entry	Temperature (°C)	Nitrogen source	Solvent	Yield of 3a (%)
1	r.t.	NH_4OAc	DMSO	Trace
2	60	NH_4OAc	DMSO	84
3	70	NH_4OAc	DMSO	71
4	60	Urea	DMSO	n.d.
5 ^b	60	NH_3	DMSO	n.d.
6	60	NH_4OAc	Dioxane	n.d.
7	60	NH_4OAc	DMF	n.d.
8 ^c	60	NH_4OAc	DMSO	84

^a Acetophenone (0.2 mmol), elemental sulfur (0.3 mmol, 32 g mol^{-1}), nitrogen source (0.5 mmol, based on nitrogen), solvent (1 mL, [**1a**] = 0.2 M), for 24 h. Yields of **3a** are GC yields using diphenyl ether internal standard. ^b NH_3 as a 28% aqueous solution. ^c 6 h. Abbreviations: r.t. = room temperature, n.d. = not determined.

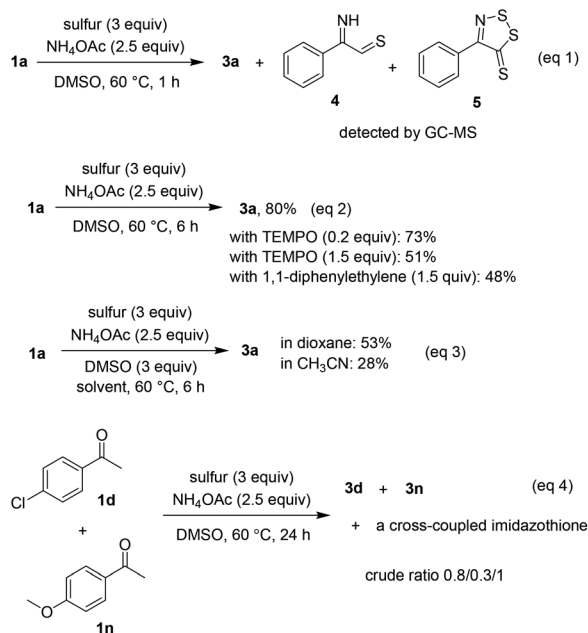
solvents rather than DMSO were effective in this transformation (entries 6 and 7). Lastly, the reaction could reach to the equilibrium only after 6 h (entry 8).

Substrate scope with respect to acetophenones was next studied (Scheme 3). Structures of some imidazothiones were confirmed by the results of HMQC and HMBC spectra.⁶ 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.^{1d} Methyl (**3j**, **3k**), methoxy (**3l–3n**), and methylthio (**3o**) functionalities were all compatible with reaction conditions. Uses of acetophenones containing electron-withdrawing groups were also attempted. Tri-fluoromethyl- (**3p**) and cyano- (**3q**) substituted imidazothiones



Scheme 3 Reaction scope with respect to acetophenones. Reagents and conditions: acetophenones (0.2 mmol), sulfur (0.3 mmol, 32 g mol^{-1}), NH_4OAc (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. ^a 2 mmol scale.



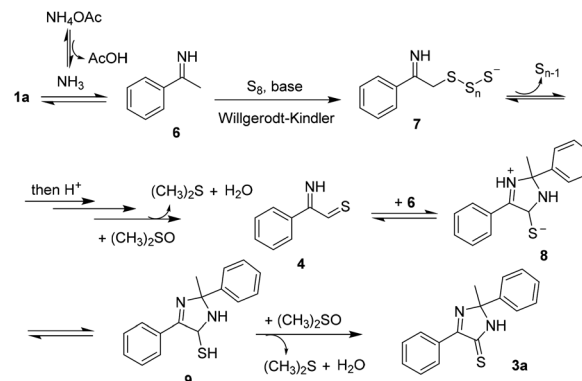


Scheme 4 Mechanistic considerations.

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-acetyltheteroarenes 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 CH_3CN , 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_4OAc , 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** \rightarrow **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_4OAc . 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.

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