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Sulfurative Self-Condensation of Ketones and Elemental Sulfur: a Three-Component Access to Thiophenes Catalyzed by Aniline Acid-Base Conjugate Pairs

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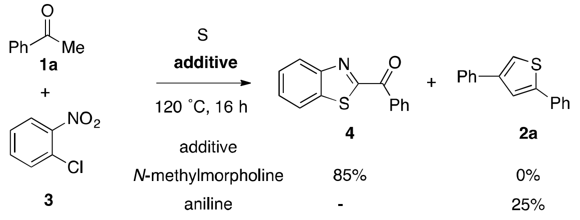
A sulfurative self-condensation method for constructing thiophenes 2 by reaction between ketones 1 with elemental sulfur is reported. The reaction, which is catalyzed by anilines and their salt with strong acids, starts from readily available and inexpensive materials, and releases only water as a by-product.

Thiophene heterocyclic compounds are omnipresent in natural products,[1] bioactive molecules[2] and functional materials[3] (light emitting diodes, organic conductors, and semiconductors…). Consequently they have received much attention in recent years. The development of efficient and versatile synthetic methods to this class of useful molecules represents a continuing interest. These synthetic strategies can be divided into two categories: (a) functionalization of the pre-constructed thiophene nucleus,[4] and (b) construction of thiophene ring from open chain precursors. The second approach is based on cyclization[5] or cycloaddition[6] and related reactions involving two[7] or three[8] starting components or from higher thia heterocycles via fragmentation.[9] According to this classification, direct incorporation of elemental sulfur to the thiophene rings belongs to the second approach. Since elemental sulfur has been demonstrated to be an excellent precursor for the synthesis of sulfur containing compounds,[10] the expected reactions and would provide an economical and flexible, especially in a multicomponent combination.

Herein, we report a novel synthesis of substituted thiophenes **2** based on multicomponent redox condensation of readily available ketones and elemental sulfur.

The redox condensation of acetophenone **1a** and sulfur to 2,4-diphenylthiophene **2a** was somewhat serendipitously, found, which started with our study on the redox condensation of *o*-chloronitrobenzene **3** and acetophenone **1a** with elemental sulfur leading to 2-benzoylbenzothiazole **4** (Scheme 1).[11] A base additive was intentionally used to promote the reaction and to act as scavenger of hydrochloride, a by-product of the reaction. *N*-Methylmorpholine was found to be an excellent base additive for such a role, leading to **4** in excellent yield. When aniline, a weaker base than *N*-methylmorpholine and related aliphatic amines, was employed, **4** was formed only in trace quantities. We detected also the presence of 2,4-diphenylthiophene **2a** in the crude mixtures.



Scheme 1. Initial observation

Although the initial reaction mixture contains four components, the formation of **2a** arose unambiguously from the reaction of two acetophenone molecules and one sulfur atom with the removal of two water molecules. To gain further insight to this expected reaction, we first wanted to confirm if acetophenone could react directly with elemental sulfur to yield **2a** without any other components (Table 1, entry 1). While such reactions at higher temperatures (> 200 °C) were previously documented,[12] the formation of **2a** was not observed. At this point, we wondered if aniline might play any role in promoting the condensation of acetophenone with sulfur. Once again, this control experiment resulted in the recovery of all starting materials (Table 1, entry 2). As previously noted, the presence of *o*-chloronitrobenzene as a sole additive was not effective to provide any detectable condensed product. Both *o*-chloronitrobenzene and acetophenone remained unchanged according to ^{1}H NMR analysis of the crude mixture (Table 1, entry 3).

The initial reaction presented in Scheme 1 was repeated and considered carefully (Table 1, entry 4). Among by-products of the reaction, 2,2’-dinitrodiphenyl disulfide was observed. The

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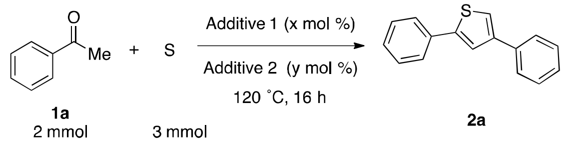
formation of this disulfide arose from a nucleophilic attack of a disulfide species on *o*-chloronitrobenzene and implied a formation of HCl (as anilinium salt). We reasoned that this hydrochloric acid as anilinium along with free aniline could be responsible for the formation of thiophene **2a**. Indeed, when HCl (10 mol %) was introduced to the reaction mixture (as aniline•HCl), thiophene **2a** was formed in excellent yield (Table 1, entry 5). Similar results were also observed when other strong acids (CSA, methanesulfonic acid, sulfuric acid, PTSA•H_2O) were used in place of $PhNH_2$•HCl (Table 1, entries 6-9) or when aniline derivatives of comparable basic strength were used instead of aniline (2- or 4-chloroaniline, *p*-anisidine) (Table 1, entries 10-12). The reaction failed when a weaker acid such as acetic acid was used as the second additive (Table 1, entry 13) or when weakly basic anilines (*p*-nitroaniline, 4-aminopyidine) (Table 1, entries 14-15) or sterically more demanding anilines (*N*-methyl- or *N*,*N*-dimethylaniline) were used as the first additive (Table 1, entries 16-17). While modifying the amount of aniline did not lead to any improvement (Table 1, entries 18-19), the catalyst loading of PTSA•H_2O could be further lowered to 5 mol % (Table 1, entry 20 vs. 21). Finally, the conversion was incomplete at lower temperature (Table 1, entry 22).

Table 1. Optimization of the reaction conditions

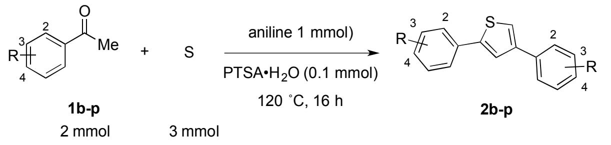


Entry[a]	Additive 1 (x)	Additive 2 (y)	Yield (%)[b]
1	-	-	0[c]
2	aniline (50)	-	0[c]
3	-	*o*-$ClC_6H_4NO_2$ (100)	0[c]
4	aniline (50)	*o*-$ClC_6H_4NO_2$ (100)	25
5	aniline (40)	$PhNH_2$•HCl (10)	71
6	aniline (50)	CSA[d] (10)	66
7	aniline (50)	CH_3SO_3H (10)	65
8	aniline (40)	$PhNH_2$•1/2H_2SO_4 (10)	57
9	aniline (50)	PTSA•H_2O (10)	74
10	4-$ClC_6H_4NH_2$ (50)	PTSA•H_2O (10)	72
11	2-$ClC_6H_4NH_2$ (50)	PTSA•H_2O (10)	71
12	4-$MeOC_6H_4NH_2$ (50)	PTSA•H_2O (10)	73
13	aniline (50)	HOAc (10)	0[c]
14	4-$O_2NC_6H_4NH_2$ (50)	PTSA•H_2O (10)	31
15	4-aminopyridine (50)	PTSA•H_2O (10)	0[c]
16	PhNHMe (50)	PTSA•H_2O (10)	0[c]
17	$PhNMe_2$ (50)	PTSA•H_2O (10)	0[c]
18	aniline (100)	PTSA•H_2O (10)	71
19	aniline (20)	PTSA•H_2O (10)	52
20	**aniline (50)**	**PTSA•H_2O (5)**	**75**
21	aniline (50)	PTSA•H_2O (2)	45
22[d]	aniline (50)	PTSA•H_2O (10)	53

[a] Reaction conditions: **1a** (2 mmol), S (3 mmol, 96 mg), additive 1 (x mol %), additive 2 (y mol %), 120 °C, 16 h, under an argon atmosphere (50 mol % corresponds to 1 mmol). [b] Isolated yield. [c] Determined by ^1H NMR of the crude reaction mixture. [d] camphorsulfonic acid. [d] Reaction performed at 100 °C.

The scope of the reaction was subsequently investigated using the optimized reaction conditions (Table 1, entry 20). Representative results are shown in Table 2. The sulfurative self-condensation of acetophenones **1b**-**o** bearing at different position of the benzene ring alkyl substituents (Table 2, entries 1-3), electron-donating groups (Table 2, entries 4-8), and halogens (Table 2, entries 9-14), proceeded smoothly to provide the expected 2,4-diarylthiophenes **2b**-**o** in moderate-to good yields. The reaction with 2-acetonaphthone **1p** occurred uneventfully and afforded 2,4-dinaphthylthiophene **2p** in 79% yields under optimized conditions. This compound is potentially interesting thiophene-based functional materials[13] as it contains many functionalizable C-H bonds for further extension of polyaromaticity. The structure of **2f** was confirmed by X-ray crystallography.

Table 2. Thiophenes 2b-p from Acetophenones 1b-p



X-ray structure for **2f**

Entry[a]	Ketone **1**	R	Thiophene **2**	Yield (%)[b]
1	**1b**	4-Me	**2b**	72
2	**1c**	3,4-Me_2	**2c**	68
3	**1d**	4-*i*Pr	**2d**	77
4	**1e**	4-MeO	**2e**	88
5	**1f**	4-EtO	**2f**	81
6	**1g**	3-MeO	**2g**	71
7	**1h**	3,4-$(MeO)_2$	**2h**	81
8	**1i**	2-MeO	**2i**	51
9	**1j**	4-F	**2j**	74
10	**1k**	4-Cl	**2k**	69
11	**1l**	4-Br	**2l**	48
12	**1m**	3-Cl	**2m**	73
13	**1n**	3-Br	**2n**	80
14	**1o**	2-Cl	**2o**	69
15	**1p**	3,4-(C_4H_4)	**2p**	79

[a] Reaction conditions: **1b-p** (2 mmol), S (3 mmol, 96 mg), aniline (1 mmol, 93 mg), PTSA•H_2O (0.1 mmol, 18 mg), 120 °C, 16 h, under an argon atmosphere. [b] Isolated yield.

The reaction conditions were next applied to cycloalkanones. Cyclopentanone was shown to be highly reactive, and afforded the expected tricyclic tetrasubstituted thiophene in moderate yield despite the total disappearance cyclopentanone in the crude mixture. This result is in consistent with the low boiling point of cyclopentanone (bp 131 °C). Reactions with other higher cycloalkanones (cyclohexanone, cycloheptanone) led to more complex mixtures. In these cases, although the ^1H NMR spectra of crude mixture indicated the presence of the desired tricyclic products, their purification by column chromatography failed due to contamination of products

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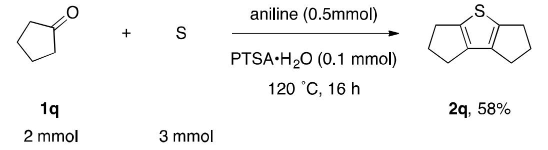
issued from polycondensation of the starting cycloalkanones. These results indicated that the reaction is sensitive to steric hindrance at the enolizable carbon center of the ketone.

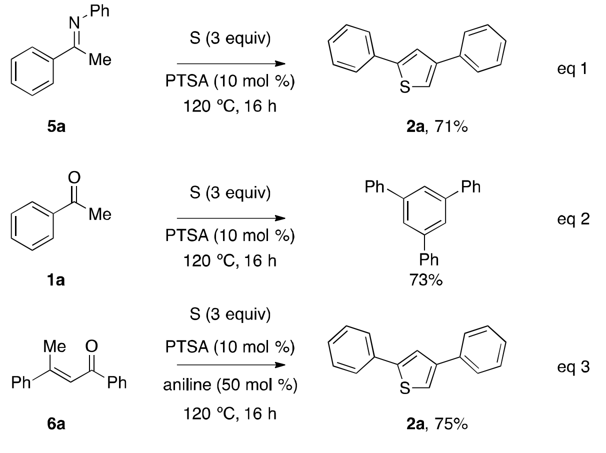


Scheme 2. Thiophene 2q from cyclopentanone 1q

Because *N*-methyl- and *N*,*N*-dimethylanilines were found to be inactive to catalyze the formation of thiophene **2a** from **1a** (Table 1, entries 16-17), it is possible that imine **5a** resulting from ketone **1a** and aniline is the main intermediate responsible for the present transformation. Indeed, trace amounts of **5a** were found in the crude mixture (by ^{1}H NMR). To confirm this hypothesis, imine **5a** was allowed to react with sulfur in the presence of a catalytic amount of PTSA•H$_2$O. As expected, thiophene **2a**, was obtained in high yield (Scheme 3, eq. 1).

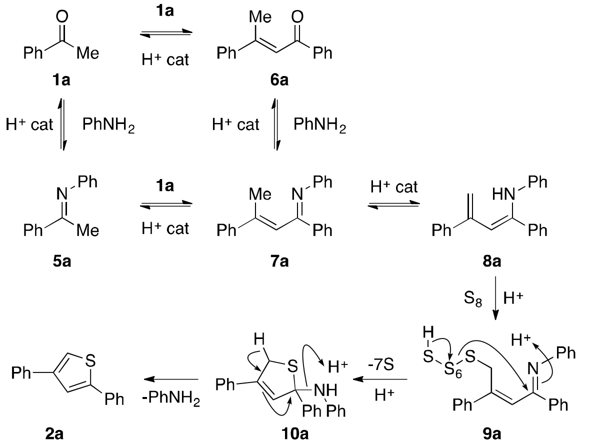
Next, we performed a reaction under the standard conditions (Table 1, entry 20) in the absence of aniline. In this case, no trace of thiophene **2a** was observed. 1,3,5-Triphenylbenzene was obtained as the main product as a result of a condensation of three acetophenone molecules without any sulfuration (eq 2). Such a trimerization of acetophenones in acidic media was previously observed.[14]

Consequently, dypnone **6a**, the corresponding dimer of acetophenone, was proposed to be another intermediate. As anticipated, the controlled experiment starting with dypnone **6a** under the standard conditions provided cleanly thiophene **2a** (Scheme 3, eq. 3).



Scheme 3. Control experiments

Based on the above observations, a possible reaction mechanism for sulfurative self-condensation of ketones to thiophenes is outlined in Scheme 3. The first step would be the formation of dypnone imine **7a** from acetophenone **1a** via two different pathways. In the presence of an acid catalyst, the self-condensation of acetophenone **1a** into dypnone **6a** occurred. Subsequent condensation of dypnone **6a** with aniline provides dypnone imine **7a**. Alternatively, this imine could be formed by a condensation between acetophenone imine **5a** with acetophenone **1a**. The resulting dypnone imine **7a** could exist in an equilibrium with its enamine tautomer **8a**. Sulfuration of dypnone enamine **8a** with elemental sulfur would lead to polysulfane **9a**. Cyclization of **9a** with simultaneous desulfurative fragmentation would lead to dihydrothiophene **10a**. Final deaminative aromatization of **10a** would provide 2,4-diphenylthiophene **2a**.



Scheme 4. Proposed mechanism

Conclusions

In conclusion, we have demonstrated the sulfurative self-condensation of ketones using elemental sulfur. The acid-base conjugate pairs of anilines were shown to be excellent catalysts to provide substituted thiophenes in good yields. The methodology is tolerant of both electron-donating and electron-withdrawing functionality when substituted acetophenones were used, leading to a wide range of 2,4-diarylthiophenes. Application of this methodology to the synthesis of other sulfa heterocycles is underway and the results of these studies will be disclosed in due course.

Conflicts of interest

There are no conflicts to declare.

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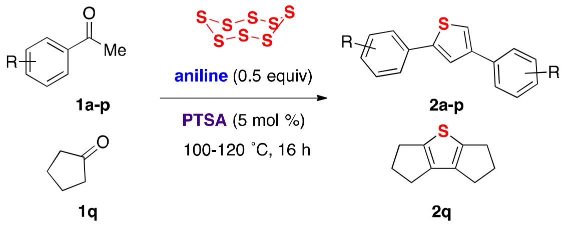

An aniline/acid-catalyzed method for constructing thiophenes **2** from inexpensive ketones **1** and elemental sulfur is reported.