Reactions of Thioaroylketene *S,N*-Acetals with 1,3-Dicarbonyl Compounds in the Presence of Mercury(II) Acetate: A General Route to 2-Acyl- and 2-Aroyl-3-(alkylamino)-5-arylthiophenes and 2-(Ethoxycarbonyl)-3-(methylamino)-5-arylthiophenes

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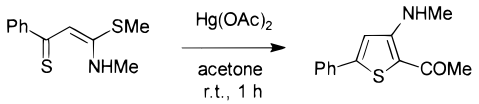
Acyl- and aroylketene *S,N*-acetals have been extensively studied by Junjappa and co-workers[1] and utilized for the synthesis of a variety of heteroatom compounds. Surprisingly, much less attention has been focused on their analogues, thioaroylketene *S,N*-acetals **1**.[2] This might be due to the difficulty of access to the compounds **1**. Recently, we reported a facile and convenient method for the synthesis of compounds **1**, which involves the reactions of 2-alkyl-3-(alkylthio)-5-arylisothiazolium iodides with $NaBH_4$ in a mixture of $CHCl_3$ and EtOH at room temperature.[3] We have shown that compounds **1** are useful for the synthesis of various heterocyclic compounds.[4]

As a part of our study on exploring the synthetic potential of compounds **1**, 3-(methylamino)-3-(methylthio)-1-phenylthioxopropene (**1a**) (0.172 mmol) was treated with mercury(II) acetate (0.172 mmol) in acetone (10 mL) for 1 h at room temperature in order to obtain information about a possible interaction between mercury(II) ion and the thione sulfur. Chromatography (silica gel, 70−230 mesh, ASTM) of the reaction mixture gave 2-acetyl-3-(methylamino)-5-phenylthiophene (**2a**) in 75% yield. The involvement of acetone as a reagent in this reaction prompted us to investigate the reactions of **1** with readily enolizable 1,3-dicarbonyl compounds. We report the preliminary results.



1a **2a**

The stereochemistry of compounds **1** has been established by an X-ray crystallographic analysis of 3-(benzylthio)-3-(methylamino)-1-phenylthioxopropene (**1b**), which shows clearly that the C=S bond and the methylamino group are syn to each other (Figure 1).

Treatment of a mixture of compounds **1** (0.17−0.31 mmol) and mercury(II) acetate (1.5 molar equiv) in CH_2Cl_2 (10−15 mL) with 1,3-diketones (0.2−1.0 mmol) at room temperature gave 2-acyl- and 2-aroyl-3-(alkylamino)-5-arylthiophenes **2** in good to moderate yields. Yields and melting points of **2** are summarized in Table 1.

Compounds **2** are all new except for **2g**.[5] The structures of compounds **2** were determined on the basis of the spectroscopic and mass spectral data and elemental analyses.

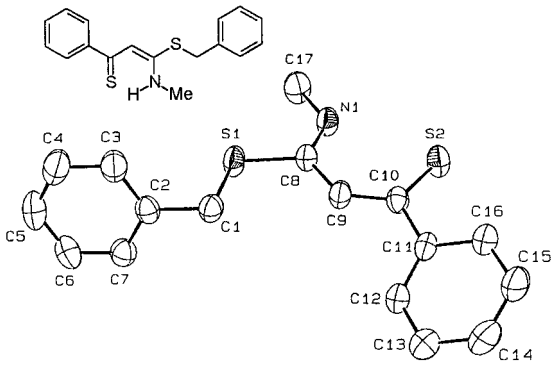
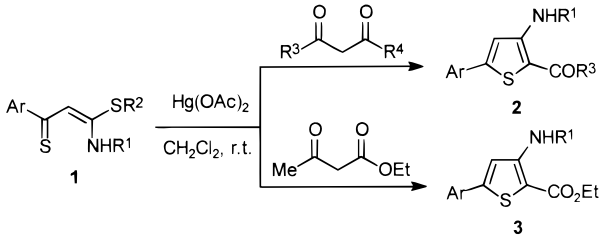


Figure 1. ORTEP drawing of 1b.



2-Acylthiophenes can be readily synthesized by acylation with acyl anhydrides or acid chlorides, using mild Friedel-Craft catalysts, acylations of 2-thienylmetal derivatives, or the reaction of 2-thenoyl chloride with organocadmium.[6] However, synthesis of 2-acyl- and 2-aroyl-3-aminothiophenes has received little attention. It appears to be another report that involves the reaction of the condensation product of malononitrile and carbonoxy sulfide in sodium ethoxide solution, with phenacyl bromide, giving 3-amino-2-benzoyl-4-cyano-5-hydroxythiophene.[7] This method is, however, not applicable to the synthesis of compounds **2**.

It is noteworthy that a benzoyl (R^4 = Ph) group and a trifluoroacetyl (R^4 = CF_3) group are removed from unsymmetrical 1,3-diketones, i.e., 1-phenyl-1,3-butanedione and 1,1,1-trifluoro-2,4-pentanedione, in the course of the reaction leading to compounds **2a** (Table 1, entry 2) and **2g**−**j** (Table 1, entries 8−11), respectively.

Similarly, compounds **1** (0.13−0.31 mmol) reacted with ethyl acetoacetate (1.5 molar equiv) under the same conditions to give 5-aryl-2-(ethoxycarbonyl)-3-(methylamino)-thiophenes **3** in excellent yields. Yields and melting points of **3** are summarized in Table 2.

Synthesis of 2-(alkoxycarbonyl)-3-aminothiophenes has been achieved by treatment of either β-chlorocinnamonitriles with thioglycolic acid esters in the presence of a base[8] or a base-catalyzed cyclization of β-alkylthio-α-cyanocinnamonitriles.[9] Treatment of 2,5-diphenylisothiazolium perchlorate with dimethylsulfonium carbethoxymethylide gave 2-(ethoxycarbonyl)-5-phenyl-3-(phenylamino)thiophenes as a minor product.[10]

It is interesting to find that treatment of **1** with methyl phenylsulfinyl acetate under the same conditions as for **3** gave **3d** in 89% yield, whereas with ethyl methanesulfonyl

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Table 1. Yields and Melting Points of 2-Acyl- and 2-Aroyl-3-(alkylamino)-5-arylthiophenes 2

entry	Ar	R^1	R^2	R^3	R^4	time (h)	compd	yield[a] (%)	mp (°C)
1	Ph	Me	Me	Me	Me	1	**2a**	91	80−81
2	Ph	Me	Me	Me	Ph	0.5	**2a**	90	80−81
3	Ph	Et	Me	Me	Me	1	**2b**	86	77−78
4	3-$MeOC_6H_4$	Me	Me	Me	Me	2	**2c**	90	50−51
5	3-$MeOC_6H_4$	Et	Me	Me	Me	1	**2d**	81	liquid
6	3-ClC_6H_4	Me	Me	Me	Me	2	**2e**	92	92−93
7	3-ClC_6H_4	Et	Me	Me	Me	2	**2f**	84	58−59
8	Ph	Me	Me	Ph	CF_3	3	**2g**	47	118−119 (lit.[5] 108−109)
9	3-$MeOC_6H_4$	Me	Me	Ph	CF_3	4	**2h**	47	128−130[b]
10	Ph	Me	Me	2-naphthyl	CF_3	6	**2i**	38	112−114
11	3-$MeOC_6H_4$	Me	Me	2-naphthyl	CF_3	8	**2j**	47	119−121

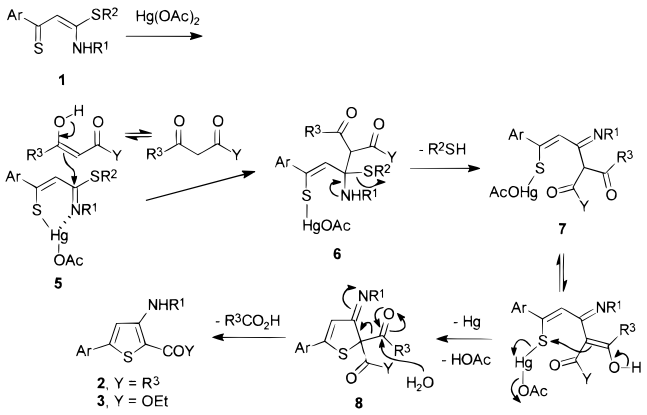
[a] Isolated yields. [b] Recrystallized from a mixture of CH_2Cl_2 and MeOH, otherwise from a mixture of EtOAc and *n*-hexane.

Table 2. Yields and Melting Points of 5-Aryl-2-(ethoxycarbonyl)-3-(methylamino)thiophenes 3

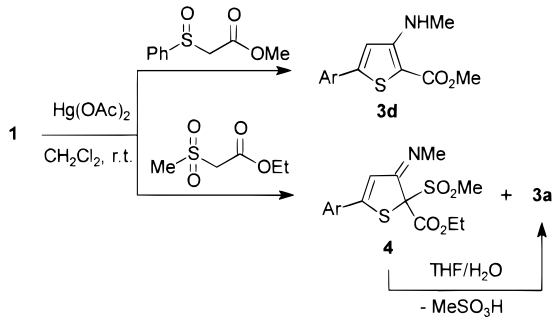
compd	Ar	time (h)	yield[a] (%)	mp (°C)
3a	Ph	3	94	55−57[b]
3b	3-$MeOC_6H_4$	3	82	77−78[c]
3c	3-ClC_6H_4	3	87	101−102[c]

[a] Isolated yields. [b] Recrystallized from a mixture of CH_2Cl_2 and MeOH. [c] Recrystallized from a mixture of EtOAc and *n*-hexane.

Scheme 1



acetate under the same conditions compounds **4** and **3a** were isolated in 64% and 16% yields, respectively. Compound **4** was readily converted to **3a** (58% yield) in aqueous THF. The isolation of **4** and its transformation to **3a** suggests the following mechanism (Scheme 1) for the formation of compounds **2**−**4** from the reactions of **1** with active methylene compounds.



Mercury(II) acetate dissolves in CH_2Cl_2 containing thioaroylketene *S*,*N*-acetals **1** to form a complex **5** having an iminothiolester functionality. The imino carbon is thought to be far more electron deficient by the interaction of the imino nitrogen with mercury acetate bonding to the thione sulfur. The electron-deficient imino carbon would be readily attacked by an enolic carbon of 1,3-dicarbonyl compounds to give an intermediate **6**, which has an amino group and a methylthio group at the same carbon atom. Loss of a methanethiol molecule from **6** gives an intermediate **7**, which is a 1,3-dicarbonyl compound having an enimino group at C-2. Intramolecular nucleophilic attack of the enolic carbon to sulfur concomitant with the formation of mercury and acetic acid leads to an intermediate **8**. Subsequent hydrolysis of **8** gives compounds **2** and **3**. Deacylation of the intermediate **8** is certainly promoted by the driving force derived from aromatization.

The fact that no 2-acylthiophene derivatives are isolated from the reaction with the β-keto esters indicates that an acyl group is more susceptible to hydrolysis than an ester functionality. Similar deacylation was proposed for the formation of pyrrole-2-carboxylate esters from oximinomalonate esters.[11] The formation of an isolable intermediate **4** can be explained on the same grounds. Here, demethanesulfonylation occurs. The aqueous THF was very acidic, which indicates the formation of methanesulfonic acid. When two different acyl groups of the intermediate **8** (R^3 = CF_3CO, Y = MeCO) are in competition for hydrolysis, the CF_3CO group is more hydrolyzable because of the electron-withdrawing effects of the CF_3 group (entries 8−11). On the same grounds, an acetyl group is lost in preference to a benzoyl group (entries 8 and 9).

In conclusion, we have developed a facile method for the synthesis of 3-(alkylamino)-5-arylthiophenes having acyl-, aroyl, and ethoxycarbonyl substituents at C-2 using thioaroylketene *S*,*N*-acetals, mercury(II) acetate, and active methylene compounds, i.e., 1,3-diketones, ethyl acetoacetate, and β-sulfinyl, and β-sulfonyl esters. The reactions did not occur in the absence of mercury(II) acetate.

Full details as to the reactions of the other types of active methylene compounds will be reported in due course.

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Supporting Information Available: Copies of ^{1}H NMR, IR, elemental analyses of **2a**−**j**, **3a**−**c**, and **4**, and X-ray crystallographic data of **1b** (9 pages).

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