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PREPARATION OF ACYLTHIOPHENES BY IRON(III) CHLORIDE CATALYZED REACTIONS OF TRIS(2-THIENYL)STIBANES WITH ACYL CHLORIDES

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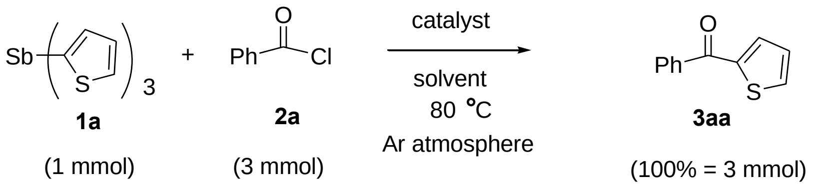
Abstract – The reactions of tris(2-thienyl)stibanes with various acyl chlorides, using a catalytic amount of iron(III) chloride, afforded 2-acylthiophenes. Iron(III) chloride is presumed to act as a Lewis acid, and the ipso substituent of each 2-thienyl group of tris(2-thienyl)stibane is replaced with an acyl group. The reaction is highly atom-efficient in that all three thiophene rings of tris(2-thienyl)stibane take part in the reaction. The reaction procedure is so simple that it can also be carried out under solvent-free and aerobic conditions.

The acylthiophene moiety is an important building block for the synthesis of functional organic materials,[1] pharmaceuticals,[2] and biologically active compounds.[3] Much attention has been given to the development of general and efficient methods for the synthesis of acylthiophenes. Typical methods involve the Lewis acid mediated Friedel–Crafts acylation of thiophene,[4] transition-metal-catalyzed cross-coupling reactions,[5] carbonylative coupling reactions,[6] oxidative arylation of thiophene-2-aldehyde,[7] and oxidation of 1-(2-thienyl)ethanols with mild oxidants.[8] These methods for the functionalization of electron-rich five-membered heteroaromatic compounds often have some disadvantages. For example, the conventional Friedel–Crafts acylation suffers from the requirement of a stoichiometric amount of a moisture-sensitive Lewis acid, low regioselectivity, and poor compatibility with functional groups. With respect to cross-coupling reactions, expensive and toxic transition metals are needed as catalysts, and complicated phosphine ligands tend to easily undergo oxidation in air. Carbonylative coupling reactions are often conducted under high pressures of carbon monoxide. Therefore, a simple and atom-efficient reaction for the preparation of acylthiophenes, using an air- and moisture-stable catalyst with a reasonable price, is still desired.

As part of our studies on organoantimony compounds,[9] we have investigated the reaction of tris(2-thienyl)stibane derivatives (**1**)[10] with acyl chlorides (**2**), using a catalytic amount of iron(III) chloride, to find that acylthiophenes were formed in high yields. Advantages of the use of tris(2-thienyl)stibanes (**1**) are mild reaction conditions and high atom efficiencies, resulting from the high reactivity of organoantimony compounds. In addition, iron is an attractive transition-metal catalyst because of its high abundance, reasonable cost, low toxicity, and environmentally benign nature. Iron-catalyzed reactions have been the focus of attention and many reports have recently been published.[11] We now report an operationally simple and atom-efficient procedure for the synthesis of acylthiophenes from tris(2-thienyl)stibanes and acyl chlorides, using an iron(III) chloride catalyst.

Optimization experiments were conducted using **1a** and benzoyl chloride (**2a**) as model substrates, and the results are summarized in Table 1. A mixture of **1a** and **2a** was heated at 80 °C without a transition-metal catalyst. Although the reaction did not proceed at all (even after prolonged heating) in the solvent 1-methyl-2-pyrrolidone (NMP), the slow formation of 2-benzoylthiophene (**3aa**) was observed in benzene and 1,2-dichloroethane (1,2-DCE). The reaction can also be conducted under solvent-free conditions to give 2-benzoylthiophene (**3aa**) (Table 1, entries 1–4).

Table 1. Screening of reaction conditions



Entry	Solvent	Catalyst (10 mol%)	Time (h)	Yield (%)
1	NMP	---	20	0
2	benzene	---	24	96
3	1,2-DCE	---	24	96
4	None	---	24	96
5	1,2-DCE	$Pd(OAc)_2$	3	18
6	1,2-DCE	$PdCl_2(PPh_3)_2$	17	29
7	1,2-DCE	$Pd(PPh_3)_4$	4	31
8	1,2-DCE	TsOH	24	84
9	1,2-DCE	$BF_3{\cdot}OEt_2$	6	71
10	1,2-DCE	$AlCl_3$	1	78
11	1,2-DCE	$TiCl_4$	20	46
12	1,2-DCE	$ZnCl_2$	20	87
13	1,2-DCE	$Yb(OTf)_3$	24	90
14	1,2-DCE	$FeCl_3$	1	96
15	None	$FeCl_3$	0.1	93

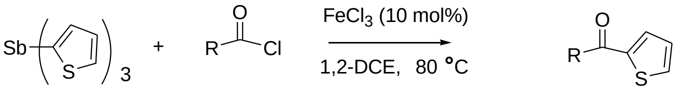
Several types of catalysts were added to the reaction mixture to accelerate the reaction. With palladium catalysts, quick consumption of **1a** was observed by TLC; however, the yield of **3aa** was moderate (entries 5–7). The addition of *p*-toluenesulfonic acid as a protic acid catalyst did not shorten the reaction time, nor did it increase the yield (entry 8). Screening of several Lewis acid catalysts revealed that the reaction completed in a short time with a catalytic amount of boron trifluoride etherate and aluminum chloride (entries 9 and 10). Titanium tetrachloride, zinc chloride, and ytterbium(III) trifluoromethanesulfonate were not effective in reducing the reaction time (entries 11–13). Further examination revealed that a catalytic amount (10 mol%) of iron(III) chloride promoted the reaction to give **3aa** in 96% yield within 1 h in the solvent 1,2-DCE (entry 14). The yield of **3aa** was calculated based on **2a**, suggesting that all three thiophene rings of **1a** take part in the reaction. We employed these optimized conditions in the following reaction because of its atom efficiency. Moreover, the iron(III) chloride catalyzed reaction was shown to proceed under solvent-free conditions. When iron(III) chloride was added directly, under aerobic conditions, to the mixture of **1a** and **2a**, an exothermic reaction occurred and the formation of **3aa** was observed instantly (entry 15).

Having determined the optimized conditions,[12] we next investigated the reaction of **1a** with various acyl chlorides (**2a–l**). In the case of aromatic acyl chlorides, electron-donating substituents such as methyl and methoxy groups on the aromatic ring facilitated the reaction to afford diaryl ketones in good yields in a short time (Table 2, entries 2 and 3). Electron-rich 2-thiophenecarboxylic acid chloride (**2d**) was also found to be a good substrate (entry 4). On the contrary, benzoyl chlorides with electron-withdrawing substituents exhibited lower reactivities. The reaction of **1a** with *p*-cyano-, *p*-nitro-, and *p*-trifluoromethyl-substituted benzoyl chlorides (**2e–g**) required prolonged reaction times and the yields of the products were moderate (entries 5–7). Aliphatic acyl chlorides were also found to be good substrates. The reaction of **1a** with acid chlorides with secondary and tertiary α-carbons gave alkyl 2-thienyl ketones in good yields within 1 h (entries 8–11). However, 2,2-dimethylpropanoyl chloride (**2l**), which has a quaternary carbon in the α-position, gave an inferior result (entry 12). Aliphatic acyl chlorides are generally poorer substrates than aromatic acyl chlorides in palladium-catalyzed cross-coupling reactions.[13]

For the preparation of alkyl 2-thienyl ketones, our iron-catalyzed reaction is superior to conventional palladium-catalyzed cross-coupling reactions.

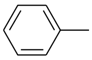
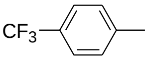
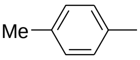
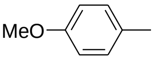
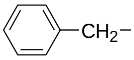
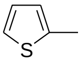
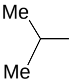
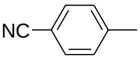
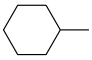
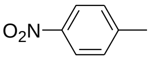
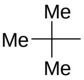
Iron(III) chloride catalyzed reactions of substituted tris(2-thienyl)stibanes (**1b–d**) with benzoyl chloride (**2a**) were also attempted (Scheme 1). 5-Sbstituted tris(2-thienyl)stibanes (**1b,c**) underwent ipso acylation exclusively to give **3ba** and **3ca**, respectively, while the reaction of tris(3-methyl-2-thienyl)stibane (**1d**) with benzoyl chloride (**2a**) gave a mixture of ipso-benzoylated **3da** and 2-benzoyl-3-methylthiophene **3′da**. Benzoylation of tris(3-methyl-2-thienyl)stibane (**1d**) occurred at the less hindered α-position of the thiophene ring, because the ipso position is sterically hindered by the adjacent methyl substituent.

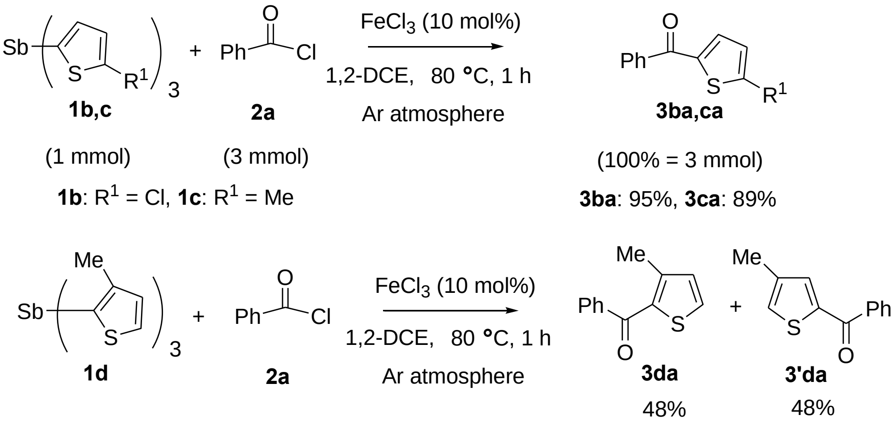
Table 2. Reaction of tris(2-thienyl)stibane (**1a**) with various acyl chlorides (**2a–l**)



Ar atmosphere

1a (1 mmol) **2a-l** (3 mmol) **3aa-l** (100% = 3 mmol)

Entry		R	Time (h)	Yield (%)	Entry		R	Time (h)	Yield (%)
1	**2a:**		1	96	7	**2g:**		12	60
2	**2b:**		3	93	8	**2h:**	C_4H_9—	1	80
3	**2c:**		1	92	9	**2i:**		1	85
4	**2d:**		1	95	10	**2j:**		1	67
5	**2e:**		24	62	11	**2k:**		1	91
6	**2f:**		24	51	12	**2l:**		1	17



1b,c (1 mmol) **2a** (3 mmol) **3ba,ca** (100% = 3 mmol)

1b: R^1 = Cl, **1c**: R^1 = Me

3ba: 95%, **3ca**: 89%

1d **2a** **3da** 48% **3'da** 48%

Scheme 1. Reaction of substituted tris(2-thienyl)stibanes (**1b–d**) with benzoyl chloride (**2a**)

In conclusion, we have found that iron(III) catalyzed reactions of tris(2-thienyl)stibane with various acyl chlorides give ipso-substituted acylthiophenes in good yields. The reaction can also be conducted under solvent-free conditions. Further investigations of this reaction, including the reaction mechanism,[14] are in progress.

ACKNOWLEDGMENTS

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12. Experimental procedure for **3aa**: A mixture of tris(2-thienyl)stibane (370 mg, 1.00 mmol), benzoyl chloride (422 mg, 3.00 mmol), and $FeCl_3$ (16.2 mg, 0.10 mmol) in 1,2-dichloroethane (DCE)(3 mL) was stirred for 1 h at 80 °C under an argon atmosphere. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography using hexane/EtOAc (10:1) as eluent to afford 541 mg (96% yield) of **3aa** as a yellow oil. Recrystallization from hexane/Et_2O gave yellow needle crystals: mp 56–57 °C. LRMS (EI): *m/z* 188 (M^+). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (1H, t, *J* = 4.35 Hz), 7.49 (2H, t, *J* = 7.79 Hz), 7.58 (2H, t, *J* = 7.79 Hz), 7.64 (1H, d, *J* = 4.35 Hz), 7.71 (1H, d, *J* = 4.35 Hz), 7.85 (1H, d, *J* = 7.79 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.9 (d), 128.4 (d), 129.2

(d), 132.3 (d), 134.2 (d), 134.8 (d), 138.1 (s), 143.6 (s), 188.2 (s). IR (KBr): ν 1635 cm^{-1} (C=O).

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14. A plausible reaction mechanism: Slightly negatively charged carbon atom at ipso position of **1a** attacked **2a,** activated by $FeCl_3$ catalyst, to form acyl-stibanothiophene adduct (**4**). Elimination of bis(2-thienyl)antimony(III) chloride from **4**, accompanied by aromatization of thiophene, furnished **3aa**. Two thiophene rings of bis(2-thienyl)antimony chloride undergo similar reaction sequence successively.