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An efficient one-pot synthesis of substituted 2-arylbenzo[*b*]thiophene derivatives

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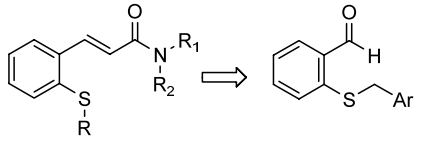
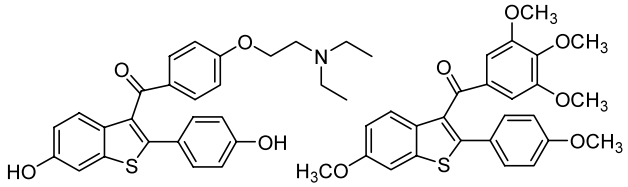
Abstract—This communication describes an efficient one-pot procedure for the synthesis of 2-arylbenzo[*b*]thiophene derivatives via reaction of *o*-halo or nitro aryl carbonyl compounds with benzyl mercaptans in the presence of an excess of anhydrous K_2CO_3 at elevated temperature.

During our work on 2-(arylmercapto)cinnamic acid derivatives **1** as soluble guanylate cyclase activators,[1] we intended to expand the SAR study to 2-(benzylmercapto) cinnamic acid analogs (R = CH_2Ar). An attempt to synthesize 2-(benzylmercapto)benzaldehyde **2** via a nucleophilic displacement reaction between benzyl mercaptan and 2-nitrobenzaldehyde, resulted in unexpected isolation of 2-arylbenzo[*b*]thiophene as the only product. This finding led us to further investigate the scope of this methodology to access substituted 2-arylbenzo[*b*]-thiophene derivatives.



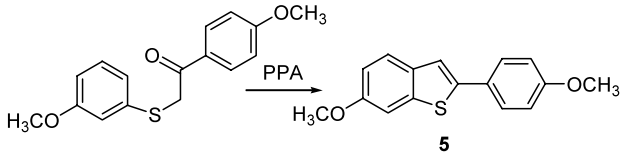
1 **2**

2-Arylbenzo[*b*]thiophene derivatives are found within the structural core of several biologically active compounds.[1–4] For example, Raloxifene® (Evista®) **3**,[2] a selective estrogen receptor modulator (SERM) for the treatment and prevention of osteoporosis in postmenopausal women; an anti-tubulin agent **4** being investigated as a human cancer cell growth inhibitor;[3] and recently described ERβ agonists for central nervous system disorders,[4] contain 2-arylbenzo[*b*]thiophene moiety.



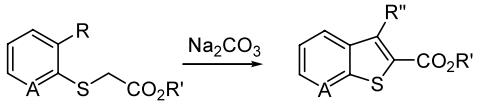
3 **4**

The methods of synthesis of 2-arylbenzo[*b*]thiophenes reported in the literature span a variety of approaches.[2–8] The key step in these syntheses involves formation of the benzothiophene ring via either an electrophilic or a nucleophilic cyclization (Schemes 1 and 2). Electrophilic cyclization methodology was employed to obtain Raloxifene® intermediate, 6-methoxy 2-(4-methoxyphenyl) benzo[*b*]thiophene **5**[3] (Scheme 1). Another approach



5

Scheme 1.



R = CN, CHO, CO_2H
A = CH or N
R' = Et

R" = NH_2, H, OH
A = CH or N

Scheme 2.

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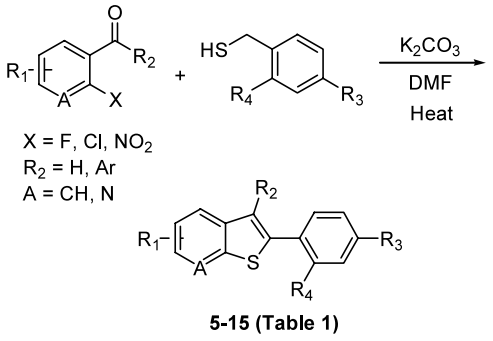
involves Pd/Cu-catalyzed coupling of *o*-iodothioanisole and terminal alkynes, followed by electrophilic cyclization with a variety of electrophiles[5] such as I_2, Br_2, NBS, etc.

Nucleophilic cyclization of strongly activated sulfides, like arylthioacetic acid ester has been reported in the literature to give benzo[*b*]thiophene-2-carboxylic acid-methyl ester[6a,b] (Scheme 2). Similar reactions of highly substituted pyridines have been reported to give 3-amino and 3-hydroxy-thieno[2,3-*b*]pyridines in the presence of Na_2CO_3.[6c,d] Base-promoted cyclizations of 2-(benzylthio)arenecarboxamides,[6g] 2-(4-nitrobenzylthio)benzoic acids[6h] with alkoxide base and 2-(benzylthio)benzoic esters[6i] with LDA have been reported to give 2-aryl-3-hydroxybenzo[*b*]thiophenes.

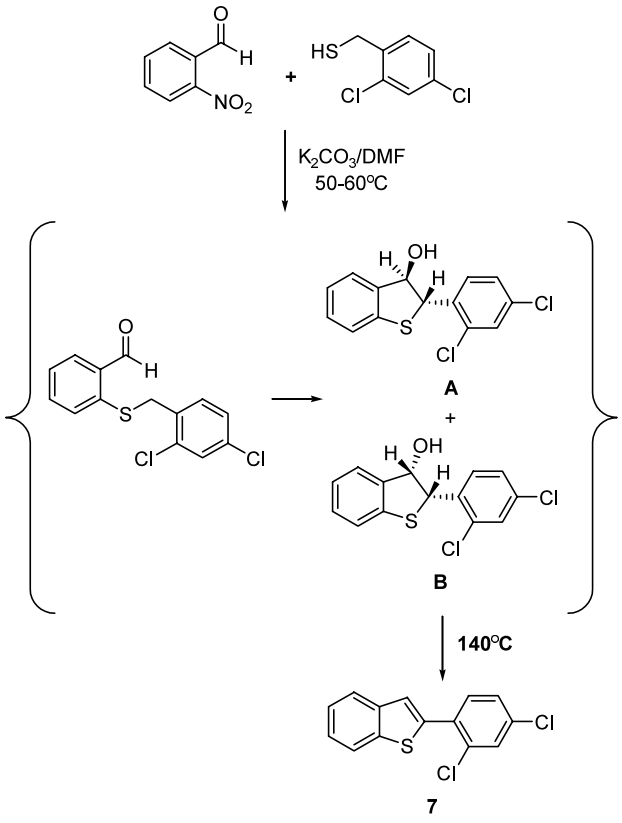
Herein we report our methodology for the synthesis of substituted 2-arylbenzo[*b*]thiophene derivatives.[9] Aryl aldehydes bearing *ortho* leaving groups undergo nucleophilic displacement with weakly activated benzylmercaptans followed by ring closure in the presence of excess anhydrous K_2CO_3 at elevated temperature (Scheme 3).

As mentioned earlier, during the synthesis of 2-(4-chloro-benzylsulfanyl)benzaldehyde from benzylmercaptan and 2-nitrobenzaldehyde in the presence of 4-fold excess anhydrous K_2CO_3, at 50–60°C for 26 h, 2-(4-chloro-phenyl)benzo[*b*]thiophene **6** was unexpectedly isolated as the only product. Under the same conditions, from reaction between sterically hindered 2,4-dichlorophenyl-methanethiol and 2-nitrobenzaldehyde, only cyclized products **A** and **B** (Scheme 4) were isolated. Higher temperature (140°C); additional 5-fold of K_2CO_3; 14 h reaction time for *cis* isomer **B**, and 2 h for *trans* isomer **A**; were required to obtain the dehydration product **7**.

An initial study of the potential scope of this methodology is shown in Table 1. Substituted benzaldehydes bearing various leaving groups such as F, Cl, and NO_2 were used as substrates. This methodology was also extended to benzophenones, heteroaryl aldehydes and benzonitriles.



Scheme 3.



Scheme 4.

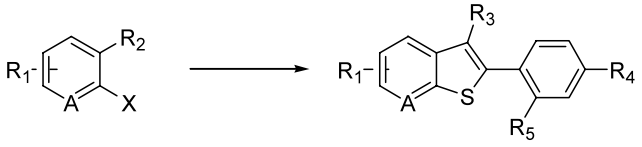
The reaction temperature was modified to drive the reaction to completion and obtain desired final dehydration products.

Typical experimental procedure

A reaction mixture of 2-nitrobenzaldehyde (4.5 g, 30 mmol) and 4-chlorobenzylmercaptane (4.7 mL, 35 mmol) in DMF (100 mL) in the presence of K_2CO_3 (13.8 g, 100 mmol) was heated at 50–60°C for 26 h. The mixture was then treated with water and extracted with ethyl acetate. The acetate extract was washed with water, brine, dried with $MgSO_4$ and concentrated under reduced pressure to small volume (~20 mL). Hexane was added and the solid was filtered to provide 5.5 g (75%) of compound **6**, mp 194–196°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40 (m, 2H), 7.55 (d, $J=9$ Hz, 2H), 7.82 (m, 3H), 7.92 (s, 1H), 8.00 (m, 1H); MS (DCI-NH_3) m/z 245 $(M+H)^+$. Anal. calcd for $C_{14}H_9ClS$: C, 68.71; H, 3.71. Found: C, 68.46; H, 3.76.

In summary, the method described provides a highly efficient one-pot procedure for the synthesis of substituted 2-arylbenzo[*b*]thiophenes and thieno-heteroaryl derivatives, from readily available starting materials.

Table 1. Synthesis of differentially substituted 2-arylbenzo[b]thiophenes



Compound	X	A	R_1	R_2	R_3	R_4	R_5	Temperature conditions*	Yield (%)[a]
5	F	CH	5-OMe	CHO	H	OMe	H	**A**	55
6	NO_2	CH	H	CHO	H	Cl	H	**B**	75
7	NO_2	CH	H	CHO	H	Cl	Cl	**B**	80[b]
8	F	CH	5-Br	CHO	H	Cl	H	**B**	62
9	F	CH	4-F	CHO	H	Cl	H	**C**	49
10	NO_2	CH	3,4-Methylenedioxy	CHO	H	Cl	Cl	**D**	82
11	F	CH	H	COPh	Ph	CH_3	H	**D**	60
12	F	CH	H	-COPh-*p*-OCH_3	4-OCH_3-Ph	CH_3	H	**D**	55
13	F	N		COPh	Ph	Cl	H	**D**	75
14	Cl	CH	H	CN	NH_2	Cl	H	**E**	55
15	Cl	N	H	CN	NH_2	Cl	H	**E**	95

* Temperature conditions: **A**. 60°C, 18 h, 160°C, 48 h; **B**. 50°C, 14 h, 160°C, 14 h; **C**. 80°C, 1 h, 120°C, 18 h; **D**. 120°C, 6 h; **E**. 60°C, 12 h, 120°C, 16 h.

[a] Isolated yields after column chromatography. All the products were characterized by ^{1}H NMR, MS and elemental analysis. The starting materials were purchased from Aldrich, Acros or Lancaster.

[b] Isomer A gave the desired benzothiophene in 14 h and isomer B in 2 h at 140°C. Average yield from the *cis* and *trans* isomers A and B is reported.

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