One-Pot Synthesis of Benzo[*b*]thiophenes and Naphtho[2,1-*b*]thiophenes in the Presence of Acidic and Basic Supported Reagents

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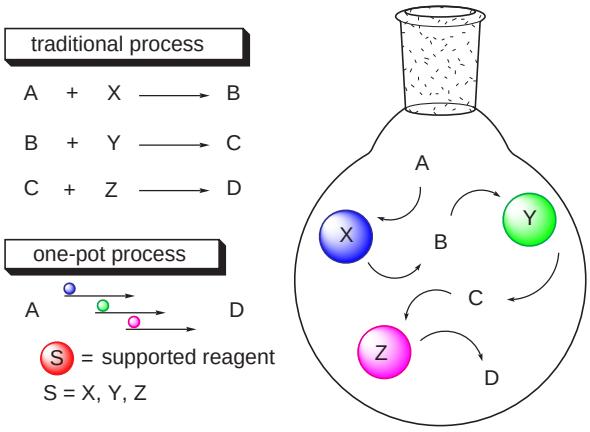
Received 28 July 2005

Abstract: A simple and efficient method has been developed for the synthesis of benzo[*b*]thiophenes and naphtho[2,1-*b*]thiophenes from aryl thiols and α-halo ketones by using an acid- and a base-supported reagent system, Na_2CO_3/SiO_2–PPA/SiO_2. Reaction of α-halo ketones with aryl thiols is promoted by Na_2CO_3/SiO_2 to afford α-phenylthio ketones, which cyclizes in the presence of PPA/SiO_2 to give the corresponding arylthiophenes in one-pot.

Key words: one-pot synthesis, benzo[*b*]thiophenes, naphtho[2,1-*b*]thiophenes, supported reagents

Currently, one-pot synthesis, which can carry out multi-step reactions or multiple reactions in one pot, is very attractive in organic synthesis. In traditional process, the reaction and the isolation of products have to be carried out more than once to synthesize the target compounds. One-pot processes, however, can provide the target compounds in not only a single operation and with low cost, but also in high total yield. Much effort has been devoted to the development of one-pot reaction processes. One-pot synthesis using inorganic solid-supported reagents is unique because, if three kinds of inorganic solid-supported reagents are used in one pot, three different reaction stages are able to exist separately in the same vessel.[1d] Thus, synthesis of a compound which is prepared stepwise in homogeneous solution could be possible in one pot if each step in the multi-step reaction can be achieved using inorganic solid-supported reagents (Scheme 1).

We have demonstrated the possibility of multi-step reactions in one pot by using a couple of supported reagents, e.g., $ZnCl_2/SiO_2$–K_2CO_3/Al_2O_3,[1a] $CuBr_2/Al_2O_3$–KSCN/SiO_2,[1b] KSCN/SiO_2–RNH_3OAc/Al_2O_3[1c,e] and $CuBr_2/Al_2O_3$–Na_2CO_3/Al_2O_3.[1d] These analogous soluble reagents react with each other rapidly in solution. An acid and a base cannot coexist in a homogeneous solution in order to neutralize each other. A multi-step reaction process using an acid and a base is applicable for many chemical transformations. For instance, benzo[*b*]thiophenes are synthesized from acid-catalyzed intramolecular cyclocondensation of α-phenylthio ketones, which was prepared by the reaction of α-halo ketones and thiols under basic conditions.[2] Thiochromans and thiocoumarins were also synthesized by using a base and an acid. First, precursors of thiochromans and of thiocoumarins were formed from the Michael reaction under the basic conditions, and then the intramolecular cyclocondensation was carried out in the presence of an acid.[3] We tried to carry out the two-step reactions in one pot using an inorganic solid-supported acid and base in which the first step is promoted by the base and second step is catalyzed by the acid. The synthesis of benzo[*b*]thiophene and naphtho[2,1-*b*]thiophene was chosen as a model for this process. Benzo[*b*]thiophenes and naphtho[2,1-*b*]thiophenes were very useful compounds. For instance, benzo[*b*]thiophene derivatives present interesting synthetic targets and encompass numerous biological activities,[4] and naphtho[2,1-*b*]thiophene derivatives were used as C_1-symmetric ligands for homogeneous stereoselective catalysts.[5] Many synthetic methods have been developed for these compounds,[6–16] but the most common method starts from thiophenols, reacting with α-haloketones, followed by cyclization using a strong acid. Herein, we report one-pot synthesis of benzo[*b*]thiophenes and naphtho[2,1-*b*]thiophenes using a couple of supported reagents, Na_2CO_3/SiO_2 and PPA/SiO_2 as a base and an acid.



Scheme 1 One-pot multi-step synthesis using supported reagents system

First, we examined whether both the acidic and basic supported reagents are able to function as an acid and a base, respectively, in a model reaction of thiophenol and 3-bromo-4-phenyl butane-2-one (**1a**) in chlorobenzene (Table 1). The desired product **3a** was obtained in 80%

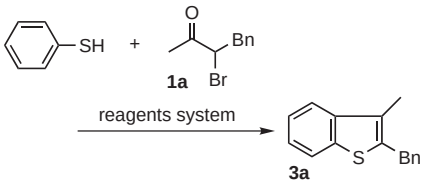
SYNLETT 2005, No. 18, pp 2739–2742
Advanced online publication: 10.10.2005
DOI: 10.1055/s-2005-918928; Art ID: U25005ST

yield[17] when the reaction was carried out in the presence of silica gel supported sodium carbonate (Na_2CO_3/SiO_2)[18] and silica gel supported polyphosphoric acid (PPA/SiO_2).[19] When Na_2CO_3 and PPA were used for the reaction, **3a** was not detected. Using the reagents system of Na_2CO_3–PPA/SiO_2 or only PPA/SiO_2, **3a** was formed in moderate yields along with diphenyldisulfide as a by-product. The reagents system, Na_2CO_3/SiO_2–PPA, gave **3a** in 46% yield along with 4-phenyl-3-phenylthiobutan-2-one (**2a**) in 41% yield. These results suggest that Na_2CO_3/SiO_2 and PPA/SiO_2 are able to coexist in the same vessel and function as a base and an acid, respectively. The reagents system Na_2CO_3/SiO_2 promotes the reaction of thiophenol with **1a**, and PPA/SiO_2 catalyzes the intramolecular cyclocondensation of **2a** to afford **3a**. A series of thiophenols was used for similar reactions. The results obtained are shown in Table 2. The reaction of *p*-toluene thiol with **1a** gave a desired compound **3b** in 71% yield along with the 4-phenyl-3-(*p*-tolylthio)butan-2-one (**2b**) in 20% yield. *o*-Toluene thiol was completely consumed and **3d** was obtained in 94% yield. Using *m*-toluene thiol, **3c** and **3c′** were formed in 34% and 61% yields, respectively (entry 2). These yields were determined by using ^{1}H NMR spectroscopy. The reactions of **1a** with 4-bromothiophenol and 4-methoxythiophenol gave 3-(4-bromophenylthio)-4-phenylbutan-2-one (**2e**) and 3-(4-methoxyphenylthio)-4-phenylbutan-2-one (**2f**) as a main product. For instance, the reaction with 4-bromothiophenol gave **2e** in 90% yield and a trace amount of **3e** was observed. When the reaction temperature was increased to 180 °C in dichlorobenzene, the intramolecular cyclocondensation of **2e** and **2f** occurred to give the corresponding benzo[*b*]thiophenes. Compounds **3e** and **3f** were formed in 8% and 30% yield, respectively. The intramolecular cyclocondensation on a naphthalene ring occurred at the first position in preference to the third position. Thus, the reaction of β-naphthalene thiol selectively produced 2-benzyl-1-methylnaphtho[2,1-*b*]thiophene (**3g**) in 97% yield.

The results of the reaction of β-naphthalene thiol and α-haloketones were summarized in Table 3. The reactions with acyclic α-haloketones gave the corresponding naphtho[2,1-*b*]thiophenes in moderate to excellent yields. The cyclic α-haloketone also reacted with β-naphthalene thiol under similar conditions to give the corresponding naphthothiophene. For example, α-chlorocyclohexanone gave **3j** in 87% yield (entry 3). When α-chloroacetoacetic acid ethyl ester was used as a starting material, unexpected side reactions occurred. Undesired compound **3h** was formed in 54% yield as a main product, and the desired compound **3k** was obtained in 39% yield (entry 4). The reaction of α-bromobenzyl phenyl ketone gave **3m** in 57% yield, and debrominated compound, benzyl phenyl ketone, was also detected in 19% yield.

In conclusion, we developed a simple and efficient method for the synthesis of benzo[*b*]thiophenes and naphtho[2,1-*b*]thiophenes in one pot using supported reagents system Na_2CO_3/SiO_2–PPA/SiO_2.[20] Aryl thiols and α-haloketones are commercially available, and some of

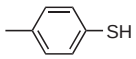
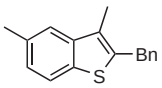
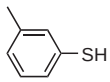
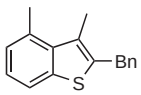
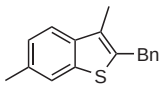
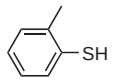
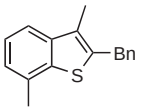
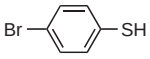
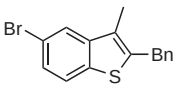
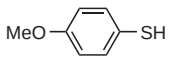
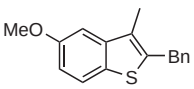
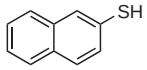
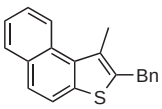
Table 1 Synthesis of 2-Benzyl-3-methylbenzo[*b*]thiophene Using Various Reagents Systems



Reagents system		Yield (%)[a]
Na_2CO_3	PPA	0
	PPA/SiO_2	44
Na_2CO_3	PPA/SiO_2	27
Na_2CO_3/SiO_2	PPA	46 (41)[b]
Na_2CO_3/SiO_2	PPA/SiO_2	80

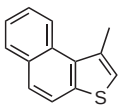
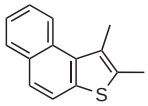
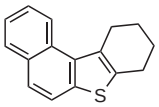
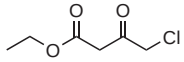
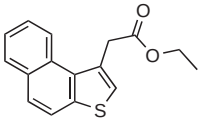
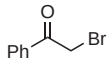
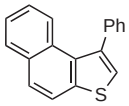
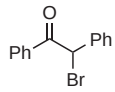
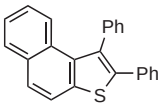
[a] Isolated yield.
[b] A figure in parentheses indicates the yield of the intermediate.

Table 2 One-Pot Synthesis of Benzo[*b*]thiophenes and Naphtho[2,1-*b*]thiophenes from **1a** and Various Arylthiols

Entry	Aryl thiol	Product		Yield (%)[a]
1			**3b**	71 (20)[b]
2			**3c**	34[c]
			**3c′**	61[c]
3			**3d**	94
4			**3e**	8[d]
5			**3f**	30[d]
6			**3g**	97

[a] Isolated yield.
[b] A figure in parentheses indicates the yield of the intermediate.
[c] Yield was determined by ^{1}H NMR.
[d] At 180 °C for 6 h in *o*-dichlorobenzene.

Table 3 One-Pot Synthesis of Naphtho[2,1-*b*]thiophenes from Various Haloketones and 2-Naphthalene Thiol

Entry	Haloketone	Product		Yield (%)[a]
1			**3h**	89
			**3i**	92
3			**3j**	87
4			**3k**	39 (54)[b]
5			**3l**	94
6			**3m**	57 (19)[c]

[a] Isolated yield.
[b] A figure in parentheses indicates the yield of compound **3h**.
[c] A figure in parentheses indicates the yield of benzyl phenyl ketone.

α-bromo ketones are easily synthesized by using our reported methods.[1d] Several chemical transformations using this reagents system are now under investigation.

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(17) **Typical Procedure.**
A mixture of α-haloketone (1 mmol), arylthiol (1 mmol), Na_2CO_3/SiO_2 (1.0 g, 1.5 mmol) and PPA/SiO_2 (3.5 g, 10 wt%) in chlorobenzene (15 mL) was stirred at 135 °C for 6 h, and then used supported reagents were removed by filtration. The filtrate was evaporated to leave crude product, which was purified by flash column chromatography to give the desired product.

(18) **Preparation of Na_2CO_3/SiO_2.**
Silica gel [Wakogel C-200 (Wako Pure Chemical Ind. LTD.), 16.82 g] was added to a solution of sodium carbonate (30 mmol, 3.18 g) in distilled H_2O, and the mixture was stirred at r.t. for 0.5 h. Then, H_2O was removed by rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at 160 °C for 5 h.

(19) **Preparation of PPA/SiO_2.**
The PPA (2.0 g) and $CHCl_3$ (100 mL) were placed in a round-bottom flask, and the mixture was stirred at 50 °C for 1 h. SiO_2 [Wakogel C-200 (Wako Pure Chemical Ind. Ltd.), 18.0 g], which was dried in vacuo at 160 °C for 2 h, was added to the mixture, and the mixture was stirred for another 1 h. Then, $CHCl_3$ was removed with rotary evaporator and the resulting solid was dried in vacuo at r.t. for 3 h.

(20) Compound **3b**: mp 46–47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3 H, s), 2.46 (3 H, s), 4.17 (2 H, s), 7.09 (1 H, d, *J* = 8.3 Hz), 7.18–7.29 (5 H, m), 7.42 (1 H, s), 7.59 (1 H, d, *J* = 8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 21.5, 34.4, 121.5, 121.8, 125.4, 126.4, 127.3, 128.4, 128.5, 133.5, 135.7, 137.7, 139.8, 141.1. HRMS (TOF-CI): *m/z* calcd for $C_{17}H_{17}S$ [MH^+]: 253.1050; found: 253.1056.
Compound **3d**: mp 60–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36 (3 H, s), 2.47 (3 H, s), 4.20 (2 H, s), 7.07 (1 H, d, *J* = 7.3 Hz), 7.18–7.30 (6 H, m), 7.48 (1 H, d, *J* = 7.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 20.2, 34.4, 119.1, 124.1, 124.3, 126.4, 128.3, 128.5, 128.5, 131.6, 137.2, 138.7, 139.8, 140.7. HRMS (TOF-CI): *m/z* calcd for $C_{17}H_{17}S$ [MH^+]: 253.1050; found: 253.1044.

Compound **3e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3 H, s), 4.19 (2 H, s), 7.21–7.32 (5 H, m), 7.36 (1 H, dd, *J* = 8.5, 2.0 Hz), 7.56 (1 H, d, *J* = 8.5 Hz), 7.76 (1 H, d, *J* = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 34.4, 118.0, 123.5, 124.3, 126.6, 126.6, 127.0, 128.5, 128.6, 137.2, 139.3, 139.9, 142.6. HRMS (EI): *m/z* calcd for $C_{16}H_{13}BrS$ [M^+]: 315.9921; found: 315.9922.

Compound **3f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3 H, s), 3.88 (3 H, s), 4.18 (2 H, s), 6.92 (1 H, dd, *J* = 8.8, 2.4 Hz), 7.08 (1 H, d, *J* = 2.4 Hz), 7.21–7.31 (5 H, m), 7.59 (1 H, d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 34.5, 55.6, 104.3, 113.4, 122.8, 126.5, 127.4, 128.4, 128.5, 130.9, 139.1, 139.7, 141.9, 157.4. HRMS (TOF-CI): *m/z* calcd for $C_{17}H_{17}OS$ [MH^+]: 269.1000; found: 269.1001.

Compound **3g**: mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.80 (3 H, s), 4.30 (2 H, s), 7.20–7.32 (5 H, m), 7.48–7.59 (2 H, m), 7.65 (1 H, d, *J* = 8.8 Hz), 7.75 (1 H, d, *J* = 8.8 Hz), 7.93 (1 H, dd, *J* = 8.0, 1.2 Hz), 8.71 (1 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 34.5, 120.7, 123.3, 124.5, 124.7, 125.8, 126.5, 128.4, 128.6, 129.0, 130.4, 130.5, 132.1, 134.7, 136.5, 137.5, 139.8. HRMS (TOF-CI): *m/z* calcd for $C_{20}H_{17}S$ [MH^+]: 289.1050; found: 289.1049.

Compound **3k**: mp 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (3 H, t, *J* = 7.1 Hz), 4.22 (2 H, q, *J* = 7.1 Hz), 4.29 (2 H, s), 7.41 (1 H, s), 7.50–7.62 (2 H, m), 7.72 (1 H, d, *J* = 8.7 Hz), 7.85 (1 H, d, *J* = 8.7 Hz), 7.95 (1 H, dd, *J* = 8.0, 1.2 Hz), 8.43 (1 H, d, *J* = 8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 38.4, 61.1, 121.1, 122.9, 124.9, 125.3, 125.7, 126.2, 129.0, 129.9, 130.8, 131.9, 132.8, 139.4, 170.9. HRMS (TOF-CI): *m/z* calcd for $C_{16}H_{15}O_2S$ [MH^+]: 271.0792; found: 271.0798.

Compound **3m**: mp 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.29 (6 H, m), 7.36–7.45 (6 H, m), 7.51 (1 H, d, *J* = 8.5 Hz), 7.75 (1 H, d, *J* = 8.8 Hz), 7.89 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.4, 123.7, 124.8, 125.6, 125.7, 127.4, 127.8, 128.2, 128.8, 128.9, 129.7, 130.1, 130.8, 132.2, 134.5, 134.5, 135.7, 137.1, 138.3, 139.9. HRMS (TOF-CI): *m/z* calcd for $C_{24}H_{17}S$ [MH^+]: 337.1050; found: 337.1045.