A Novel Synthesis of Spiro(imidazolidine-2,3′-benzo[*b*]thiophene) by One-Pot Reaction of Arynes, Aryl Isothiocyanates and N-Heterocyclic Carbenes

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Received 6 January 2007

Abstract: A novel synthesis of spiro(imidazolidine-2,3′-benzo[b]thiophene) by one-pot reaction of aryl isothiocyanates, N-heterocyclic carbenes and arynes using (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate as precursor is reported.

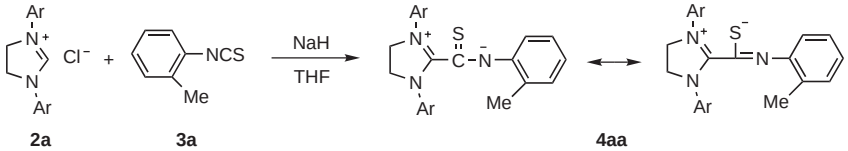
Key words: one-pot reaction, arynes, N-heterocyclic carbenes, aryl isothiocyanates, spiro heterocyclic compounds

As one of the most important active intermediates, arynes have attracted considerable attention for their synthetic applications.[1] The common way for the generation of arynes is dehydrohalogenation of halogenated aromatic compounds with strong bases, which is unfavorable for the substrates bearing base-sensitive functional groups. This disadvantage can be overcome by the Kobayashi method that is employed for the generation of arynes which involves elimination of trimethylsilyltriflate from 2-(trimethylsilyl)phenyl triflate (**1a**) under mild conditions.[2] Recently, the chemistry of 2-(trimethylsilyl)phenyl triflate has been extended to insertion of σ-bonds,[3] multicomponent reactions[4] and transition-metal-catalyzed reactions.[5] Therefore, this aryne precursor has been widely used in the construction of complex organic compounds and polysubstituted arenes.

The addition of 1,3-dipolar compounds to alkenes and alkynes has been developed extensively for the synthesis of five-membered-ring heterocycles.[6] Most of the 1,3-dipolar systems reported to date contain a central heteroatom (N or O), because its lone-pair electrons can participate in the stabilization of the dipolar resonance structures. Only few examples of 1,3-dipolar compounds containing a central carbon have been reported owing to their poor stability.[7] Especially, no reaction of carbon-centered 1,3-dipoles with arynes was reported.[8] Recently 2-arylthiocarbamoylimidazolinium inner salts have been reported to be a unique type of stable ambident C–C–S and C–C–N 1,3-dipolar system, which are able to undergo highly efficient and regioselective 1,3-dipolar cycloaddition reactions.[7c] Herein we wish to report our results on the 1,3-dipolar cycloaddition reactions of arynes generated from (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate (**1b**),[9] aryl isothiocyanate and N-heterocyclic carbenes to synthesize spiro(imidazolidine-2,3′-benzo[*b*]thiophene) in one pot.

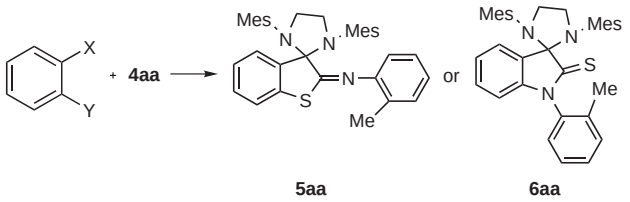
Initially, we examined the cycloaddition reaction of 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (**2a**) with one equivalent of 2-tolyl isothiocyanate (**3a**) in the presence of 1.2 equivalents of NaH (65% in mineral oil) at room temperature for 12 hours, which provided the 1,3-bis(2,4,6-trimethylphenyl)-2-*N*-phenylthiocarbamoyl imidazolinium inner salt (**4aa**) in 97% yield (Scheme 1).[10]

The cycloaddition reaction of arynes with **4aa** was then studied (Scheme 2). When we treated one equivalent of inner salt **4aa** with one equivalent of **1a** in the presence of one equivalent of KF and one equivalent of 18-crown-6 in THF (10 mL) at room temperature for 14 hours, a single spiro product was obtained in 35% yield. The product might be **5aa** or **6aa** according to the regioselectivity of the reaction. In order to determine the pathway of the 1,3-dipolar reaction, we tried to obtain the single crystal of the spiro product. But we could not get the crystal because the melting point of the spiro product is too low.



Scheme 1

SYNLETT 2007, No. 10, pp 1533–1536
Advanced online publication: 07.06.2007
DOI: 10.1055/s-2007-980380; Art ID: W00207ST

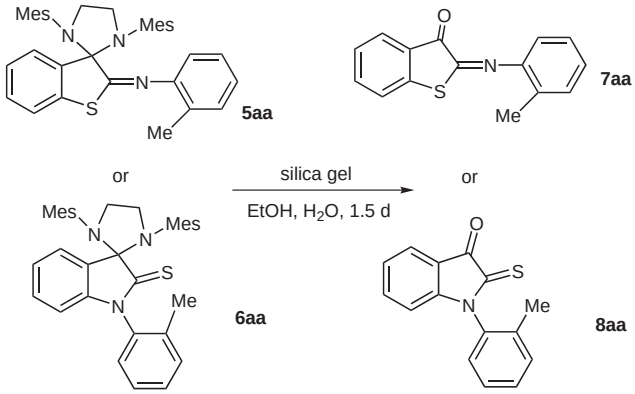


1a: X = TMS, Y = OTf, 14 h, 35%
1b: X = TMS, Y = I^+PhOTf^-, 15 min, 44%
1c: X = CO_2^-, Y = N_2^+, 4 h, 31%

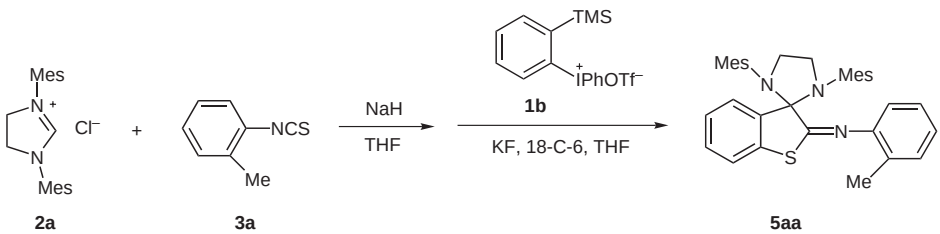
Scheme 2

Fortunately the product could undergo a facile hydrolysis. When the spiro product was treated with silica gel in EtOH–H_2O (1:1) at room temperature for 1.5 days, the hydrolyzed product was isolated in 81% yield (Scheme 3). Recrystallization of the hydrolyzed product from ethanol provided needle-shaped crystal for X-ray diffraction studies.

From the X-ray analysis we could confirm that the structure of the hydrolyzed product was **7aa** (Figure 1).[11] So the spiro compound was 1,3-bis(2,4,6-trimethylphenyl)-2′-(2-tolyliminio)-2′,3′-dihydrospiro(imidazolidine-2,3′-benzo[*b*]thiophene) (**5aa**) and the 1,3-dipolar cycloaddition reaction proceeds in the C–C–S fashion. In order to explain the reaction pathway we calculated the energies of **5aa** and **6aa** on the basis of their RHF/STO-3G optimized structures.[12] The results showed that **5aa** (32.99 kcal/mol) has much higher relative energies than **6aa** (0.00 kcal/mol). The cycloaddition of aryne with **4aa** proceeds through a kinetically favored route to afford thiophene adducts rapidly and irreversibly because arynes have higher reactivity.



Scheme 3



Scheme 4

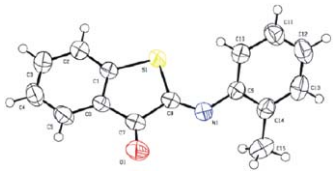


Figure 1 X-ray crystal structure of **7aa**

In an attempt to improve the yield, subsequent work focused on the choice of the precursor of arynes. Another two precursors **1b** and **1c** were selected, which are widely used in arynes chemistry. When **1b** was used as the precursor of aryne under the similar conditions, the spiro product was obtained in 44% yield and the reaction was complete within 15 minutes. However, when benzenediazonium 2-carboxylate (**1c**)[13] was chosen as the precursor of aryne for this reaction, the reaction was complete in four hours and the spiro product was isolated in 31% yield. The experimental results showed that the precursor **1b** has higher efficiency, which was consistent with the previous report.[9b] Thus, phenyl iodonium triflate **1b** was chosen as the optimal precursor of aryne in the reaction.

We then tried to conduct the above two-step reaction in one pot. It was found that one equivalent of 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (**2a**) reacted smoothly with one equivalent of 2-tolyl isothiocyanate (**3a**) in the presence of 1.2 equivalents of NaH within 12 hours and the subsequent cycloaddition reaction with one equivalent of **1b** in the presence of one equivalent 18-crown-6 and one equivalent KF could finish in 15 minutes, affording the product **5aa** in 45% yield (Scheme 4).

With this encouraging result, the 1,3-dipolar cycloaddition reaction of arynes generated from **1b** was examined carefully. As shown in Table 1, when the reaction was carried out in the absence of KF and 18-crown-6, the product **5aa** was not obtained and **4aa** was recovered (Table 1, entry 2). By using two equivalents of **1b**, two equivalents of KF and two equivalents of 18-crown-6, the reaction proceeded smoothly at room temperature to give **5aa** in 52% yield (Table 1, entry 3). On increasing the amount of **1b** to 2.2 equivalents the yield of **5aa** could not be improved dramatically (Table 1, entry 4). Using two equivalents of **1b** and three equivalents of KF and 18-crown-6 in THF at room temperature gave the product in 60% yield (Table 1, entry 5). But increasing the amount of KF and 18-crown-6 up to four equivalents failed to increase the yield of **5aa** (Table 1, entry 6). Therefore, the

Table 1 1,3-Dipolar Cycloaddition Reaction of Arynes[a]

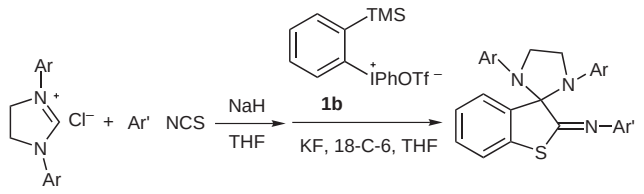
Entry	5 (mmol)	KF (mmol)	18-crown-6 (mmol)	Yield (%)
1	0.5	0.5	0.5	45
2	0.5	0	0	0
3	1	1	1	52
4	1.1	1.1	1.1	50
5	1	1.5	1.5	60
6	1	2	2	61

[a] At ambient temperature, **2a** (0.5 mmol) and **3a** (0.5 mmol) in the presence of NaH (0.5 mmol, 65% in mineral oil) for 12 h, then the mixture was reacted with **1b** in the presence of KF and 18-crown-6 in THF (10 mL).

optimized reaction conditions were two equivalents of **1b**, one equivalent of imidazolium salts and aryl isothiocyanate, 1.2 equivalents of NaH, three equivalents of KF and three equivalents of 18-crown-6 in anhydrous THF at room temperature.

Under these optimal reaction conditions, a series of imidazolium salts **2** and aryl isothiocyanates **3** were chosen for this reaction. Typical results are summarized in Table 2.[14] The yields of the spiro products dropped due to the steric hindrance of the methyl group in the substrates (compare entry 1 with entry 2; compare entries 1 and 6 with entry 9, Table 2). It should be noted that the electron-donating groups in the substrate **3** facilitated the reaction (Table 2, entry 4), but we got only trace product when there was an electron-withdrawing group in the substrate **3** (Table 2, entry 5).

Table 2 1,3-Dipolar Cycloaddition Reaction of Arynes[a]



2 **3** **5**

Entry	Ar	Ar[1]	Products	Yield (%)[b]
1	mesityl	2-MeC_6H_4	**5aa**	60
2		Ph	**5ab**	62
3		4-MeC_6H_4	**5ac**	68
4		2-MeOC_6H_4	**5ad**	75[c]
5		2-FC_6H_4	**5ae**	trace
6	xylyl	2-MeC_6H_4	**5ba**	63
7		Ph	**5bb**	65
8		4-MeC_6H_4	**5bc**	70
9	2-tolyl	Ph	**5cb**	67
10		4-MeC_6H_4	**5cc**	73

[a] Reaction conditions: At ambient temperature, **2** (0.5 mmol) and **3** (0.5 mmol) were stirred in the presence of NaH (0.6 mmol, 65% in mineral oil) for 12 h, then the mixture was treated with **1b** in the presence of KF and 18-crown-6 in THF (10 mL).
[b] Isolated yields based on aryl isothiocyanate.
[c] Crude product.

In summary, a novel synthesis of spiro(imidazolidine-2,3′-benzo[*b*]thiophene) by one-pot reaction of arynes, aryl isothiocyanates and N-heterocyclic carbenes has been developed. It is the first example of a reaction of 1,3-dipolar compounds containing a central carbon atom with arynes. Further studies including the generation methods of arynes, the reaction mechanism and synthetic application of arynes are ongoing in our laboratory.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (20332060, 20472072).

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(10) **Procedure for the Preparation of Compound 4aa**: At ambient temperature, 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (**2a**; 1 mmol) was mixed with phenyl isothiocyanate **3a** (1 mmol) in anhyd THF (20 mL), and then NaH (1.2 mmol, 65% in mineral oil) was added. After 12 h H_2O (5 mL) was added to the mixture. The mixture was then diluted with CH_2Cl_2 (15 mL) and washed. The organic layer was dried over $MgSO_4$, and concentrated to give inner salt **4aa** as yellow crystal. Compound **4aa** was further purified by recrystallization from CH_2Cl_2 and PE, through which the pure inner salt **4aa** was obtained. **Data of 4aa**: yellow solid; mp 252–253 °C. IR (KBr): 1548, 1511, 1480, 1280 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (s, 4 H), 6.82–6.92 (m, 2 H), 6.67–6.71 (t, *J* = 8 Hz, 1 H), 5.96–5.98 (d, *J* = 8 Hz, 1 H), 4.16 (s, 4 H), 2.56 (s, 12 H), 2.27 (s, 6 H), 1.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 150.5, 139.6, 136.8, 130.9, 129.7, 129.5, 128.4, 125.8, 122.1, 119.7, 49.1, 21.0, 18.6, 16.9. MS (EI): *m*/*z* (%) = 455 (72.41) [M^+], 441 (100). Anal. Calcd for $C_{29}H_{33}N_3S$: C, 76.44; H, 7.30; N, 9.22. Found: C, 76.38; H, 7.37; N, 9.19.

(11) **Procedure for the Preparation of Compound 7aa**: The mixture of **5aa** (0.5 mmol) and silica gel (100 mg) in EtOH–H_2O (10 mL, 1:1) was stirred at ambient temperature. When the reaction was complete (monitored by TLC), the mixture was diluted with EtOAc (15 mL) and filtered. The organic layer was dried over $MgSO_4$. Removal of the solvent in vacuum, and purification of the residue by silica gel chromatography with *n*-hexane–EtOAc (10:1) as eluent gave the product **7aa**. **Data of 7aa**: yellow solid; mp 134–136 °C. IR (KBr): 1706, 1591, 1309 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.98 (d, *J* = 8 Hz, 1 H), 7.60–7.64 (t, *J* = 8 Hz, 1 H), 7.33–7.39 (m, 2 H), 7.23–7.29 (m, 2 H), 7.17–7.20 (m, 1 H), 6.96–6.98 (d, *J* = 8 Hz, 1 H), 2.23 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.0, 157.1, 149.2, 144.5, 143.30, 136.90, 130.8, 130.2, 128.1, 127.7, 126.8, 126.6, 126.5, 124.5, 117.3, 17.7. MS (EI): *m*/*z* (%) = 253 (9.80) [M^+], 149 (100). Anal. Calcd for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53. Found: C, 71.04; H, 4.43; N, 5.55. Crystal data for **7aa**: $C_{15}H_{11}NOS$, M = 253.31, T = 293 K, monoclinic, space group: *P*–1/*c*, a = 4.1713 (12), b = 18.949 (5), c = 15.561 (4) Å, α = 90 (4)°, β = 85.469 (4)°, γ = 89.231 (4)°, V = 1223.5 (6) $Å^3$, Z = 4, ρ_{calcd} = 1.375 g cm^{-3}, absorption coefficient: 0.250 mm^{-1}, reflections collected/unique: 6951/2651 [R(int) = 0.1071], final R indices [I >2σ(I)] R1 = 0.0484, R2 = 0.0989. For the crystallographic data in CIF, see CCDC: 641755.

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(14) **Procedure for the Preparation of Compound 5**: At ambient temperature, imidazolinium salt **2** (0.5 mmol) was mixed with aryl isothiocyanate **3** (0.5 mmol) in anhyd THF (10 mL), and then NaH (0.6 mmol, 65% in mineral oil) was added. After 12 h when the reaction was complete (monitored by TLC), phenyl[2-(trimethylsilyl)phenyl]iodonium triflate (**1b**; 1 mmol) and 18-crown-6 (1.5 mmol) in THF (10 mL) were added to the mixture and then KF (1.5 mmol) was added. After completion of the reaction, the mixture was diluted with EtOAc (10 mL) and washed with H_2O and brine. The organic layer was dried over $MgSO_4$. Removal of the solvent in vacuum, and purification of the residue by silica gel chromatography with *n*-hexane–EtOAc (10:1) as eluent gave the product **5**. **Selected data of 5aa**: low melting point solid. IR (neat): 1706, 1623, 1483, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.98 (d, *J* = 8 Hz, 1 H), 7.59–7.63 (t, *J* = 8 Hz, 1 H), 7.34–7.38 (m, 2 H), 7.25–7.27 (m, 2 H), 7.18–7.20 (m, 1 H), 6.96–6.98 (d, *J* = 8 Hz, 1 H), 6.82 (s, 4 H), 3.15 (s, 4 H), 2.28 (s, 12 H), 2.27 (s, 3 H), 2.23 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.1, 157.1, 149.2, 144.5, 143.3, 136.9, 131.5, 130.8, 130.2, 129.7, 129.5, 128.1, 127.7, 126.8, 126.6, 126.5, 125.0, 117.3, 49.1, 20.5, 18.4, 17.8. MS (EI): *m*/*z* (%) = 531 (3.24) [M^+], 148 (100). Anal. Calcd for $C_{35}H_{37}N_3S$: C, 79.05; H, 7.01; N, 7.90. Found: C, 78.96; H, 7.09; N, 7.93.