Synthetic Methods

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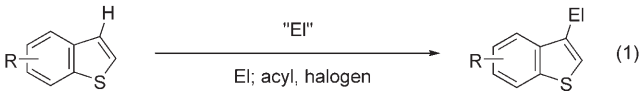
Gold-Catalyzed Intramolecular Carbothiolation of Alkynes: Synthesis of 2,3-Disubstituted Benzothiophenes from (α-Alkoxy Alkyl) (*ortho*-Alkynyl Phenyl) Sulfides

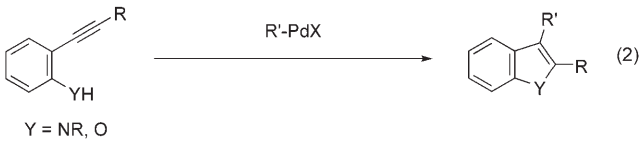
Itaru Nakamura, Takuma Sato, and Yoshinori Yamamoto*

Facile synthesis of benzothiophenes bearing a substituent at the C3 position is of great interest as this structural framework is often seen in biologically active compounds such as raloxifene and sertaconazole.[1,2] In general, functionalization of the C3 position is carried out by electrophilic substitution reactions such as Friedel–Crafts acylation and halogenation [Eq. (1)].[3] However, it is difficult to attach an alkyl group



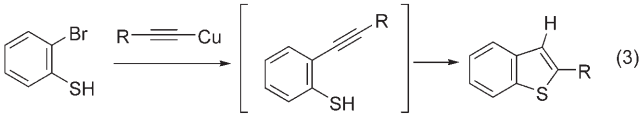
(1)

such as (α-alkoxy alkyl), benzyl, or allyl group because the corresponding alkyl halides are less reactive than acyl halides; in those cases, lithiation at the C3 position by using *sec*-BuLi is required prior to alkylation.[4] Cyclization of *ortho*-alkynyl anilines and *ortho*-alkynyl phenols with organopalladium species is one of the common methods for the direct synthesis of 2,3-disubstituted indoles and benzofurans [Eq. (2)].[5] This



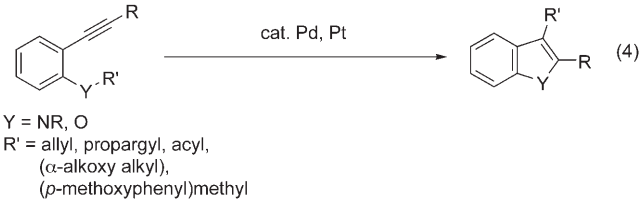
(2)

methodology is, however, inapplicable to the direct synthesis of 2,3-disubstituted benzothiophenes as the substrates, *ortho*-alkynyl benzenethiols, are not accessible by Sonogashira coupling of *ortho*-halo benzenethiols; the palladium-catalyzed reaction does not proceed due to catalyst poisoning by the mercapto group. The substrates can be synthesized through a stoichiometric reaction by using copper acetylides, but they are immediately cyclized under the reaction conditions to give 2-monosubstituted benzothiophenes [Eq. (3)].[6] Accordingly, the direct synthesis of 2,3-disubstituted benzothiophenes is not possible, which is in contrast to the syntheses of 2,3-disubstituted indoles and benzofurans.



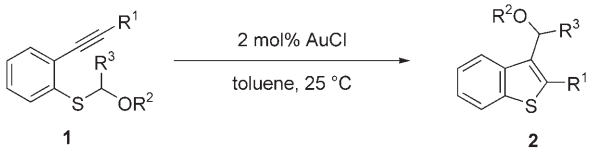
(3)

Recently, several groups, including ourselves, developed the transition metal-catalyzed cyclization of *ortho*-alkynyl anilines and (*ortho*-alkynyl phenyl) ethers, which have a migration group (R′), such as an allyl,[7] propargyl,[8] acyl,[9] (α-alkoxy alkyl),[10] or (*para*-methoxyphenyl)methyl group,[10b] at the Y position. The migration of R^1 from Y to the C3 position takes place readily to produce the corresponding 2,3-disubstituted indoles and benzofurans in excellent yields [Eq. (4)].



(4)

It occurred to us that a similar migration may take place in (*ortho*-alkynyl phenyl) sulfides by judicious choice of catalyst. Herein, we report the gold-catalyzed cyclization of (α-alkoxy alkyl) (*ortho*-alkynyl phenyl) sulfides, **1**, under mild conditions to give 2,3-disubstituted benzothiophenes, **2**, in excellent yields (Scheme 1).[11] The starting materials, **1**, are available through acetalization of *ortho*-bromobenzenethiol followed by Sonogashira coupling.



Scheme 1. Gold-catalyzed cyclization of (α-alkoxy alkyl) (*ortho*-alkynyl phenyl) sulfides, **1**.

The results are summarized in Table 1. The reaction of methoxymethyl-*ortho*-(1-pentynyl)phenyl sulfide (**1a**) in the presence of 2 mol% of AuCl in toluene at 25 °C gave 2-methoxymethyl-3-propylbenzothiophene (**2a**) in 93% yield (Table 1, entry 1). The reaction of **1a** in the presence of $AuCl_3$ or $PtCl_2$ instead of AuCl gave **2a** in a similar yield, whereas $AuBr_3$, $PtCl_4$, AgOTf, or $InCl_3$ did not induce the reaction. Other catalysts, such as $PdCl_2$, PdI_2, $CuCl_2$, and $Yb(OTf)_3$, also did not promote any reaction. The reaction in hexane as solvent, instead of toluene, proceeded slowly over 24 h and gave **2a** in 95% yield, whereas the reaction in CH_2Cl_2 gave **2a**

[*] Dr. I. Nakamura, T. Sato, Prof. Dr. Y. Yamamoto
Department of Chemistry
Graduate School of Science
Tohoku University
Sendai 980-8578 (Japan)
Fax: (+81) 22-795-6784
E-mail: itaru-n@mail.tains.tohoku.ac.jp

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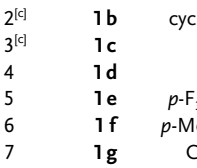
Table 1: Gold(I)-catalyzed cyclization of (α-alkoxy alkyl) (*ortho*-alkynyl phenyl) sulfides **1**.[a]

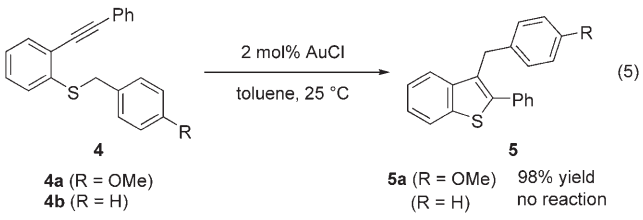
Entry	1	R^1	R^2	R^3	2	Yield [%][b]
1	**1a**	*n*Pr	Me	H	**2a**	93
2[c]	**1b**	cyclohexyl	Me	H	**2b**	92
3[c]	**1c**	*t*Bu	Me	H	**2c**	96
4	**1d**	Ph	Me	H	**2d**	99
5	**1e**	*p*-$F_3CC_6H_4$	Me	H	**2e**	quant.
6	**1f**	*p*-$MeOC_6H_4$	Me	H	**2f**	96
7	**1g**	CO_2Et	Me	H	**2g**	85
8	**1h**	Ph	TBS[d]	H	**2h**	99
9	**1i**	Ph	MPM[e]	H	**2i**	95
10	**1j**	Ph	TMSE[f]	H	**2j**	92
11	**1k**	*n*Pr	Et	Me	**2k**	92
12	**1l**	Ph	Et	Me	**2l**	98
13	**1m**	*n*Pr	$-(CH_2)_4-$		**2m**	98
14	**1n**	Ph	$-(CH_2)_4-$		**2n**	93

[a] The reaction of **1** (0.25 mmol) was carried out in the presence of AuCl (2 mol%) in toluene (1.25 mL) at 25 °C for 2 h. [b] Yield of isolated product. [c] 10 mol% of AuCl was used. [d] TBS = *tert*-butyldimethylsilyl. [e] MPM = (*p*-methoxyphenyl)methyl. [f] TMSE = 2-(trimethylsilyl)ethyl.

in 73% yield along with a small amount (16%) of bis(benzothienyl) methane **3** as a by-product. The use of CH_3CN, THF, or MeOH did not give any reaction. Substrates **1b** and **1c**, which have bulkier substituents at the R^1 position, afforded the desired products, **2b** and **2c**, respectively, in excellent yields with 10 mol% AuCl (Table 1, entries 2 and 3). The reactions of **1d**, **1e**, and **1f**, which bear an aryl group on the alkynyl moiety, gave the corresponding 2-aryl benzothiophenes **2d**, **2e**, and **2f**, respectively, in excellent yields (Table 1, entries 4–6). Ynoate **1g** was converted into the corresponding 2-benzothiophene carboxylate, **2g**, in 85% yield (Table 1, entry 7).[12] Substrates **1h**, **1i**, and **1j**, which had protective groups at the R^3 position, gave the corresponding protected 3-benzothienyl methanols **2h**, **2i**, and **2j** in 99, 95, and 92% yields, respectively (Table 1, entries 8–10). The reactions of 1-ethoxyethyl sulfides, **1k** and **1l**, and tetrahydropyranyl sulfides, **1m** and **1n**, proceeded smoothly (Table 1, entries 11–14). The (*p*-methoxyphenyl)methyl sulfide, **4a**, was converted into the corresponding benzothiophene, **5a**, in 98% yield in the presence of 2 mol% of AuCl, whereas benzyl sulfide **4b** did not react at all [Eq. (5)]. The reaction of



3



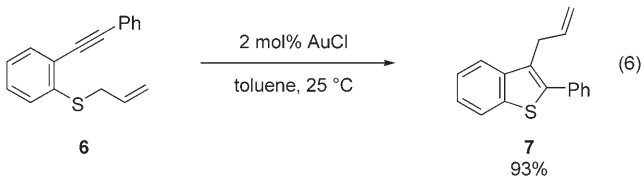
4 **5**

4a (R = OMe)
4b (R = H)

5a (R = OMe) 98% yield
(R = H) no reaction

(5)

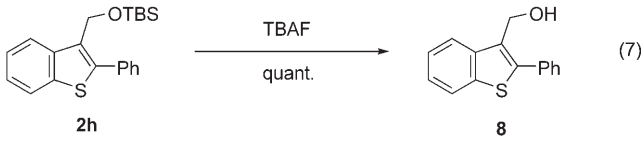
the allyl sulfide **6** proceeded smoothly to give the 3-allylbenzothiophene **7** in 93% yield [Eq. (6)]. (2-Phenylbenzothien-3-yl)methanol (**8**) was obtained quantitatively



6 **7**
93%

(6)

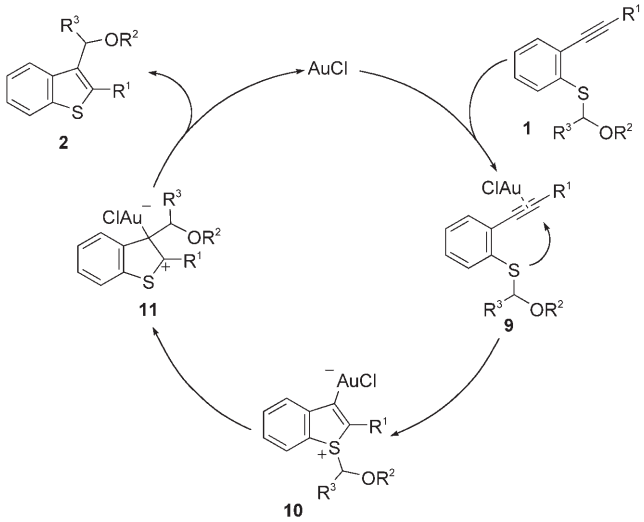
from **2h** by treatment with tetra-*n*-butylammonium fluoride [TBAF, Eq. (7)].



2h **8**

(7)

A plausible mechanism for the gold-catalyzed reaction of **1** is illustrated in Scheme 2. Gold(I) chloride is coordinated by



Scheme 2. Plausible mechanism for the catalytic formation of **2** from **1**.

the triple bond of substrate. Nucleophilic attack of the sulfur atom of **9** at the alkynyl moiety gives the cyclized intermediate **10**. Migration of the (α-alkoxy alkyl) group of **10** to the carbon atom bonded to the gold atom produces the intermediate **11**. Elimination of gold chloride from **11** gives the product **2**; the nature of this migration is not yet known.

In conclusion, we are now in a position to synthesize 2,3-disubstituted benzothiophenes in an efficient manner. As the present reaction proceeds through carbon–sulfur bond addition, so-called carbothiolation,[13] this methodology provides an atom-economic way of synthesizing sulfur-containing heteroarenes. Although multisubstituted benzothiophenes are often seen in biologically active compounds and organic materials, the catalytic construction of benzothiophene skeletons has been rarely investigated.[14] We expect this methodology to be useful in synthesizing biologically active or molecular-materials-oriented benzothiophene derivatives.[15]

Experimental Section

Substrate **1** (0.25 mmol) in toluene (0.5 mL) was added to AuCl (1.16 mg, 0.005 mmol) in toluene (0.75 mL) in a pressure vial under an argon atmosphere. After the reaction mixture had been stirred at 25 °C for 2 h, it was filtered through a short column of silica gel by using ethyl acetate as eluent. The crude product was purified by silica-gel column chromatography with hexane/ethyl acetate as eluent to give **2**.

2a: IR (neat): $\tilde{\nu}$ = 3060, 2959, 2929, 2871, 2817, 1573, 1460, 1436, 1093, 760, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.2 Hz, 3H), 1.75 (m, 2H), 2.93 (t, J = 7.8 Hz, 2H), 3.38 (s, 3H), 4.46 (s, 2H), 7.27 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.35 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.76 ppm (m, 1H), 7.79 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.82, 24.99, 30.47, 57.76, 65.62, 121.75, 121.99, 123.71, 124.07, 127.60, 138.18, 140.10, 145.28 ppm; HRMS (ESI): m/z calcd for $C_{13}H_{16}OS$: 243.0814 $[M+Na]^+$; found: 243.0815.

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