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TfOH-promoted transformation from 2-alkynylphenyl isothiocyanates to quinoline-2-thiones or indoles

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ABSTRACT

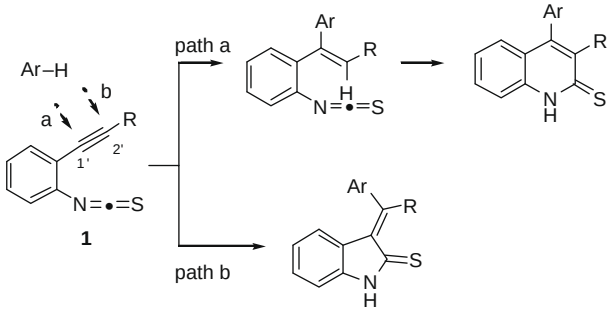
A variety of 4-arylquinoline-2-thiones and 3-arylthieno[2,3-*b*]indoles were synthesized in high yields via TfOH-promoted tandem Friedel–Crafts alkenylation–cyclization reactions of 2-alkynylphenyl isothiocyanates.

Azacumulenes, such as isocyanates, isothiocyanates, and carbodiimides, are versatile building blocks for the synthesis of nitrogen-containing heterocycles because azacumulenes can participate in various cyclizations, serving as an electrophile or a 2π component with high reactivity. For example, multi-functionalized azacumulenes such as *N*-(2-alkynylphenyl)azacumulenes have attracted attention, and their transformation into poly-substituted and/or ring-fused indoles has been investigated intensively.[1] However, their transformation into quinoline derivatives has hardly been reported.[1i,2] Because of our ongoing interest in the reactions of functionalized carbodiimides,[3] we envisioned that a tandem Friedel–Crafts alkenylation[4]–cyclization strategy applied to *N*-(2-alkynylphenyl) isothiocyanates (**1**) could be an alternative for the quinoline and indole syntheses (Scheme 1).

Our initial study showed that In(III) promoted the reaction of 2-(3,3-dimethylbutynyl)phenyl isothiocyanate (**1A**) with arenes to afford 4-arylquinoline-2-thiones with elimination of isobutene from the *t*-Bu group (*R* = *t*-Bu → H) via path a in Scheme 1; however, the reaction required high temperature (>120 °C), and one or more electron-donating groups on the arene.[5] In recent years, stronger Brønsted acids[6] have been used successfully in Friedel–Crafts alkenylation reactions at lower temperatures.[7] Therefore, to widen the scope of our tandem strategy, we examined reactions using Brønsted acids as effective and inexpensive promoters instead of In(III). We report here a trifluoromethanesulfonic acid (TfOH)-induced facile and regioselective transformation from *N*-(2-alkynyl)phenyl isothiocyanates into not only poly-substituted quinoline-2(1*H*)-thiones (Scheme 1, path a) but also indoline-2-thiones (path b).

First, we evaluated the catalytic activity of various Brønsted acids in the reaction of 2-(3,3-dimethylbutynyl)-phenyl isothiocyanate (**1A**) with benzene (Table 1). The catalytic activity of trifluoroacetic acid was very low (entry 1). Similarly, Tf_2NH, $MeSO_3H$, and $C_8F_{17}SO_3H$ did not work sufficiently well for the formation of the required **3a** (entries 2–4). On the other hand, sulfuric acid was found to be a better catalyst (entry 5), and TfOH showed the highest catalytic activity (entry 6 vs entries 1–5). Gratifyingly, isothiocyanate **1A** was completely converted to **3a** in the presence of 3.0 equiv of TfOH in 10 min. (entry 8). Similarly, 2-(2-(trimethylsilyl)ethynyl)phenyl isothiocyanate (**1B**) and 2-(1-ethynyl)phenyl isothiocyanate (**1C**) afforded **3a**. However, the yields (88% and 87%, respectively, of **3a**) are slightly lower than that of the reaction of **1A**. We assumed that an excess of TfOH is required to maintain the high acidity of the reaction mixture because the products are basic compounds and would reduce the acidity of the reaction mixture.

Based on the above results, we examined the reactions of **1A** with a variety of arenes in the presence of 3.0 equiv of TfOH at 0 °C or 20 °C (Table 2). Arenes bearing one or more electron-donating groups reacted smoothly to provide the corresponding quinoline-2-thiones **3b–h** in nearly quantitative yields (entries 1–7). It is noteworthy that even halobenzenes **2i–k** of electron-poor nucleophiles could react with **1A** to provide the corresponding quinolines **3i–k**



Scheme 1.

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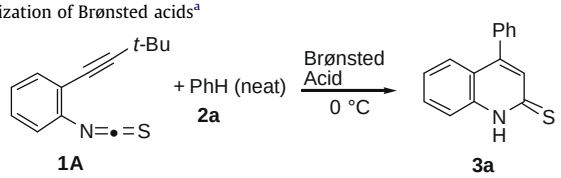
Table 1
Optimization of Brønsted acids[a]



Entry	Brønsted acid	Equiv	Time (h)	NMR yield (%)	
				3Aa	**1A** (S.M.)
1	CF_3COOH	1.0	1.0	2	98
2	Tf_2NH	1.0	1.0	7	93
3	$MeSO_3H$	1.0	1.0	2	98
4	$C_8F_{17}SO_3H$	1.0	1.0	1	99
5	H_2SO_4	1.0	1.0	16	84
6	TfOH	1.0	1.0	28	72
7	TfOH	2.0	1.0	57	43
8	TfOH	3.0	10 min	100	0

[a] All reactions were carried out using 0.50 mmol of **1A** in 2 mL of **2a**.

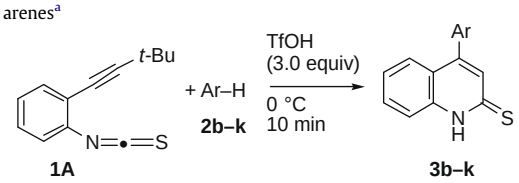
albeit in moderate yields (entries 8–10), because In(III) did not promote the reaction with **2 k** despite heating at 200 °C for 10 h.

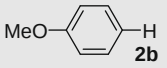
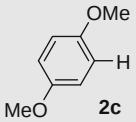
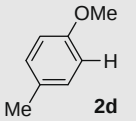
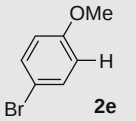
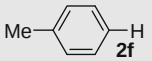
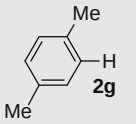
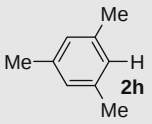
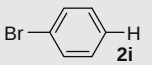
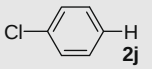
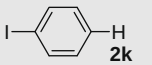
Next, with the expectation of obtaining 3,4-disubstituted quinolines **4Db**, 2-(1-hexynyl)phenyl isothiocyanate (**1D**) was subjected to the TfOH-promoted reaction with anisole (**2b**) (Table 3). To our surprise, **1D** reacted with anisole on the C-2′ atom to provide (*E*)-1,3-dihydro-3-(1-(*p*-methoxy-phenyl)pentylidene)-2*H*-indol-2-thione (**5Db**) exclusively in 83% yield, when the reaction was carried out in the presence of TfOH at −40 °C (entry 1). Although **5Db** is stable in the solid state for months, partial oxidative cyclization occurred in solution to give 8*H*-thieno[2,3-*b*]indole **6Db**. When the separated **5Db** was left in DMF below 20 °C under aerobic conditions for 5 h, **6Db** was obtained in 98% yield. For this reason, **6Db** was indeed obtained instead of **5Db** at 60 °C and 120 °C (entries 3 and 4). Thieno[2,3-*b*]-indoles are expected to have important physiological activities such as growth-promoting and growth-inhibiting activities in rice seedlings,[8] and only a few methods for accessing the ring system have been reported.[9] The present method provides a facile way to create 3-arylthienoindoles **6**. On the other hand, 3-butyl-4-(methoxyphenyl)-2(1*H*)-quinolinethione (**4Db**) was also formed, and the yields increased in accord with rising temperature from 20 °C to 60 °C (entries 2 and 3). At 120 °C, the reaction became messy and the yield of **4Db** decreased slightly (39%, entry 4). When the reaction was carried out in the presence of $In(OTf)_3$ at 120 °C, the highest yield of **4Db** was obtained (53%, entry 5).

Having optimized the conditions (Table 3, entry 1), we wanted to confirm the generality of the protocol for the synthesis of indolines **5** and thienoindoles **6** having a variety of substituents. Thus, isothiocyanates **1D–F** were allowed to react with arenes **2b, 2c, 2g** in the presence of TfOH (3.0 equiv) at −40 °C (Table 4). In all entries, aqueous work-up of the mixture gave the corresponding indoline-2-thiones **5** in an almost pure state, with no quinoline-2-thiones **4** detected. The indolinethiones **5Dg, 5Eb, 5Eg, 5Fg** were isolated while **5Dc, 5Ec, 5Fb, 5Fc** were not, because conversion of the latter compounds to thienoindoles **6** occurred rapidly. Thus, thienoindoles **6** were obtained in good to excellent yields.

It is noteworthy that the arenes added to the C-2′ atom of the alkyne moiety in **1D–F** leading to **5/6** (Table 4). As far as we know, the reported intermolecular Friedel–Crafts alkenylations of aryl alkynes all took place on the C-1′ atom.[4,6] Indeed, when 3-phenyl-1-propyne (**7**), instead of **1E**, was treated with *p*-xylene (**2g**) in the presence of TfOH at −40 °C, the reaction occurred at the C-1 atom of **7** to afford (*Z*)-1-(2,5-dimethylphenyl)-1-phenyl-1-propene (**8**) in 74% yield (Scheme 2). Addition of the arene to the C-2′ atom of the alkyne moiety (Table 4) could be reasonably explained in

Table 2
Scope of arenes[a]



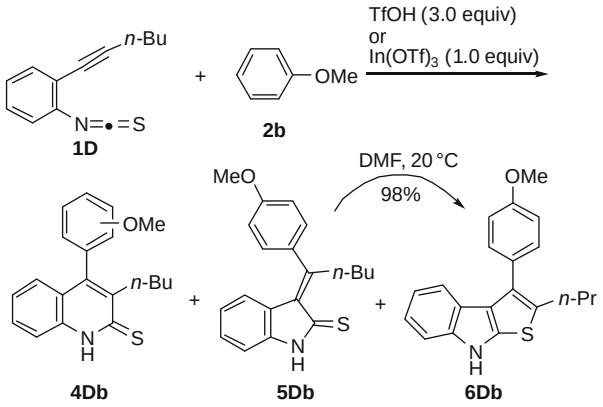
Entry	**2**: Ar–H	Product	Yield[b] (%)	*p*:*o*[c]
1	 **2b**	**3b**	98	55:45
2[d]	 **2c**	**3c**	84	—
3	 **2d**	**3d**	97	76:24[e]
4[e]	 **2e**	**3e**	93	>95:5[e]
5	 **2f**	**3f**	99	78:22
6	 **2g**	**3g**	95	—
7	 **2h**	**3h**	92	—
8[f]	 **2i**	**3i**	61	>95:5
9[f]	 **2j**	**3j**	59	>95:5
10[f]	 **2k**	**3k**	55	>95:5

[a] All reactions were carried out using 0.50 mmol of **1A** in 2 mL of **2**.
[b] Isolated yield of a mixture of *o*- and *p*-isomers.
[c] Ratio determined by ^1H NMR.
[d] Dichloromethane (2 mL) was added as a solvent.
[e] Ratio of *o*:*m* with respect to MeO group.
[f] At 20 °C.

terms of participation of the neighboring isothiocyanate group at an early stage of the reaction of **1D–F**. Thus, the protonated isothiocyanate group might undergo intramolecular reaction with the alkyne moiety of **1D–F**, and vinyl cation **9** could be generated. This cation might react with arene to give **5** as the final product (Scheme 3).

Meanwhile, a possible pathway for the TfOH-promoted formation of quinoline-2-thiones **4** is illustrated in Scheme 4. At a higher temperature, further protonation of the resulting monocation **9**

Table 3
Reactions of **1D** with **2b** under various conditions[a]



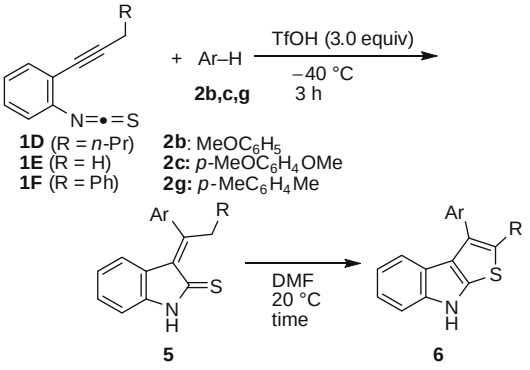
Entry	Acid	Conditions	Isolated yield (%)		
			4Db[b] (*o*:*p*)[c]	**5Db**	**6Db**
1	TfOH	−40 °C, 3 h	—	83	—
2	TfOH	20 °C, 10 min	27 (37:63)	62	—
3	TfOH	60 °C, 10 min	40 (38:62)	—	49
4	TfOH	120 °C, 10 min	39 (35:65)	—	27
5	$In(OTf)_3$	120 °C, 4 h	53 (33:67)	—	—

[a] All reactions were carried out using 0.50 mmol of **1D** in 2 mL of **2b**.
[b] Isolated yield of a mixture of *o*- and *p*-isomers.
[c] Ratio determined by ^1H NMR.

could occur, yielding dication **11**. This dication could react with arene **2** to give **12**, which could cyclize to **4** as the final product.

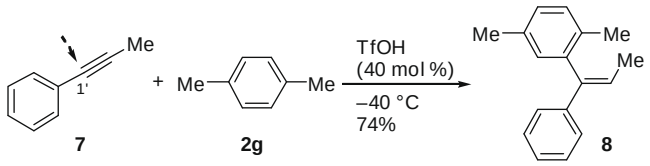
In summary, we have found that TfOH is a superior promoter for the tandem Friedel–Crafts alkenylation–cyclization reaction of 2-alkynylphenyl isothiocyanates. Thus, the reaction between **1A–C** and arenes furnished 4-aryl-3-unsubstituted quinoline-2-thiones **3** at 0 °C. On the other hand, the reaction of **1D–F** produced indoline-2-thiones **5**, which were readily converted to the corresponding thienoindoles **6** via the dehydrogenative cyclization. Applications of this method for the synthesis of a variety of the nitrogen-containing heterocycles are currently under way in our laboratory.

Table 4
Generality of the formation of indoline-2-thiones **5** and thienoindoles **6**[a]

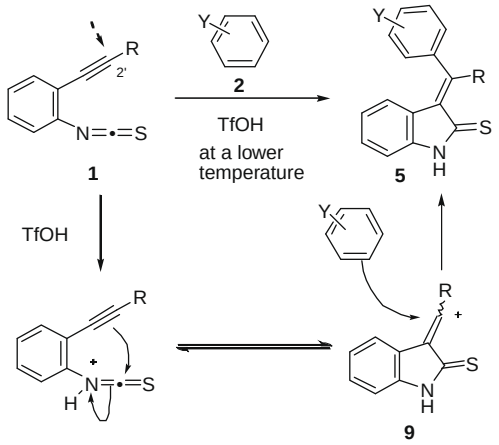


Entry	1	2	5 Yield (%)	Time (h)	6 Yield (%)
1[b]	**1D**	**2c**	—	4	**6Dc** (81)[c]
2	**1D**	**2g**	**5Dg** (82)	25	**6Dg** (96)
3	**1E**	**2b**	**5Eb** (85)	16	**6Eb** (92)[d]
4[b]	**1E**	**2c**	—	5	**6Ec** (80)[c]
5	**1E**	**2g**	**5Eg** (74)	30	**6Eg** (74)
6	**1F**	**2b**	—	4	**6Fb** (57)[c]
7[b]	**1F**	**2c**	—	3	**6Fc** (58)[c]
8	**1F**	**2g**	**5Fg** (52)	10	**6Fg** (97)

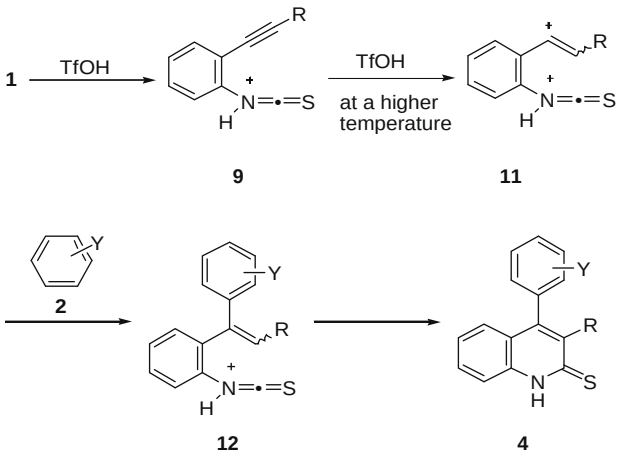
[a] All reactions were carried out using 0.50 mmol of **1** in 2 mL of **2**.
[b] Dichloromethane (2 mL) was added as a solvent.
[c] Two-step yield from **1**.
[d] *p*:*o* = > 95:5.



Scheme 2.



Scheme 3.



Scheme 4.

Supplementary data

Supplementary data (general information, procedure, compound data and NMR spectral data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.045.

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