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Synthesis of Quinoline-2-thiones via Tandem Indium(III)-Promoted Friedel–Crafts Alkenylation–Cyclization of 2-Alkynylphenyl Isothiocyanates

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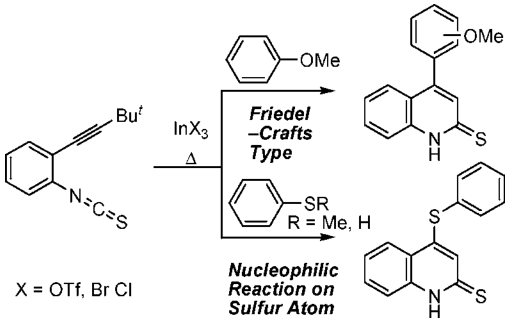
ABSTRACT



A new approach to the synthesis of 4-aryl- or 4-arylthioquinoline-2-thiones via indium(III) reagent-mediated tandem Friedel–Crafts alkenylation–cyclization of 2-alkynylphenyl isothiocyanates is described.

The quinoline ring system is commonly found in a broad range of both natural and synthetic biologically active compounds. Although the structural core of quinolines can be prepared using various conventional methods such as Skraup, Friedländer, Döbner−Miller, Pfitzinger, and Conrad−Limpach syntheses, the development of new synthetic methods for these species is always of fundamental importance in organic chemistry. For example, quinoline-2-thiones have been investigated from a variety of viewpoints, such as synthetic intermediates,[1] biologically active compounds,[2] sulfur−nitrogen mixed donor ligands,[3] and protective groups of thiols.[4] The synthesis of quinoline-2-thiones is usually achieved by thiation of corresponding quinoline-2-ones[2,5] or 2-haloquinolines.[1a,6] However, direct synthetic methods that involve construction of a quinoline skeleton with simultaneous introduction of a thiocarbonyl have hardly been

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[1] For examples, see: (a) Alhaider, A. A.; Abdelkader, M. A.; Lien, E. J. *J. Med. Chem.* **1985**, *28*, 1394. (b) Segawa, J.; Kitano, M.; Kazuno, K.; Matsuoka, M.; Shirahase, I.; Ozaki, M.; Matsuda, M.; Tomii, Y.; Kise, M. *J. Med. Chem.* **1992**, *35*, 4727. (c) Jinbo, Y.; Taguchi, M.; Inoue, Y.; Kondo, H.; Miyasaka, T.; Tsujishita, H.; Sakamoto, F.; Tsukamoto, G. *J. Med. Chem.* **1993**, *36*, 3148.

[2] For example, see: Joseph, B.; Darro, F.; Behard, A.; Lesur, B.; Collignon, F.; Decaestecker, C.; Frydman, A.; Guillaumet, G.; Kiss, R. *J. Med. Chem.* **2002**, *45*, 2543.

[3] For examples, see: (a) Xavier, J. *Fresenius' J. Anal. Chem.* **1958**, *163*, 182. (b) Nakano, S.; Yoshida, T.; Taniguchi, H.; Suzuki, N. *Chem. Pharm. Bull.* **1977**, *25*, 1658. (c) Leeaphon, M.; Ondracek, A. L.; Thomas, R. J.; Fanwick, P. E.; Walton, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 9715.

[4] For examples, see: (a) Zhang, J.; Matteucci, M. D. *Tetrahedron Lett.* **1999**, *40*, 1467. (b) Nakamura, S.; Furutani, A.; Toru, T. *Eur. J. Org. Chem.* **2002**, 1690.

[5] For examples, see: (a) Albert, A.; Barlin, G. B. *J. Chem. Soc.* **1959**, 2384. (b) Wilhelm, M.; Schmidt, P. *Helv. Chim. Acta* **1970**, *53*, 1697.

[6] For examples, see: (a) Tanasescu, I.; Denes, I.; Rusu, G. *Chem. Ber.* **1957**, *90*, 1295. (b) Ismail, M. M.; Abass, M.; Hassan, M. M. *Molecules* [online computer file] **2000**, *5*, 1224. (c) Nithyadevi, V.; Sampathkumar, N.; Rajendran, S. P. *Asian J. Chem.* **2004**, *16*, 1594.

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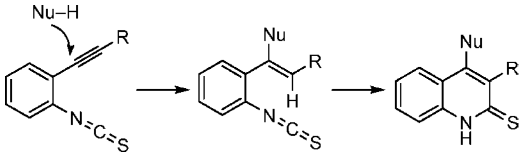
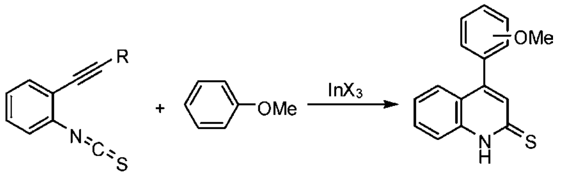
reported so far.[7] From our ongoing interests in the synthesis of nitrogen-containing heterocycles using functionalized azacumulenes as key intermediates,[8] we envisioned that a tandem nucleophilic reaction−cyclization of *N*-(2-alkynylphenyl)isothiocyanate[9] would be a convenient synthetic method for quinoline-2-thiones if the nucleophile first attacks the alkyne and a subsequent cyclization involving the cumulene function occurs (Scheme 1). To achieve this strategy, important points are the choice of the nucleophile (NuH) and activation of the alkyne moiety because a nucleophile usually first attacks an isothiocyanate group of higher reactivity than an alkyne moiety.[10] In this context, metal-promoted Friedel−Crafts (FC) alkenylation[11] of arenes with alkynes would be the choice of triggered reaction for this tandem reaction. We now wish to report our preliminary results for the synthesis of 4-arylquinoline-2-thiones via indium(III)-promoted tandem FC alkenylation−cyclization of 2-alkynylphenyl isothiocyanates.

Scheme 1



With the expectation of obtaining 3-unsubstituted quinolines, we first selected 2-ethynylphenyl isothiocyanate (**1a**) as a substrate, electron-rich anisole as an arene, and In(OTf)$_3$ which is known as an effective catalyst for the Friedel−Crafts alkenylation[11a] (Table 1). The reaction in the presence of 1.0 equiv of In(OTf)$_3$ proceeded at 150 °C to give the expected quinoline **3a** as a mixture of *o*- and *p*-isomers, but the yield was unsatisfactory (37%, entry 1). Interestingly, the same compound **3a** was obtained by use of the masked **1a**, 2-(trimethylsilylethynyl)phenyl isothiocyanate (**1b**), and 2-(3,3-dimethylbutynyl)phenyl isothiocyanate (**1c**), giving **3a** in 86 and 94% yields, respectively (entries 2 and 3). The formation of 3-*tert*-butyl or 3-trimethylsilylquinoline-2-thione was not observed in the crude mixture. Among the alkynes **1a**−**c** examined, **1c** was found to provide the best yield of **3a**, and hereafter we used **1c**.[12] Indium(III) halides[13] were also effective catalysts for these reactions. InCl$_3$ required 2.0 equiv amounts and longer reaction time to give **3a** in quantitative yield (entry 4). InBr$_3$ shortened the reaction time while maintaining a 95% yield of **3a** (entry 5). When the amount of InBr$_3$ was reduced to 0.40 equiv, the yield decreased to 38% (entry 6). These results suggest that the reaction requires a stoichiometric amount of the indium(III) reagent. To prove the superiority of In(III) reagents, some other Lewis acids were examined in the reaction of **1c** with anisole at 150 °C. Sc(OTf)$_3$, which was successfully used in the Friedel−Crafts alkenylation of 1-phenyl-1-propyne,[11a] gave only a trace amount of **3a** with recovery of the majority of **1c**. Among other Lewis acids tested, only BF$_3$·Et$_2$O promoted the reaction to give the expected **3a** in 21% yield. Using AlCl$_3$, Cu(OTf)$_2$, and PdCl$_2$(PPh$_3$)$_2$ resulted in the formation of complex mixtures.

Table 1. Optimization of Alkyne Moiety and Reagent[a]



1a–c **2a** **3a**

entry	1	R	InX$_3$ X	InX$_3$ equiv	conditions	yield[b]	*o*:*p* [c]
1	**1a**	H	OTf	1.0	150 °C, 3 h	37	29:71
2	**1b**	TMS	OTf	1.0	150 °C, 1 h	86	47:53
3	**1c**	*t*-Bu	OTf	1.0	120 °C, 1 h	94	47:53
4	**1c**	*t*-Bu	Cl	2.0	150 °C, 9 h	99	37:63
5	**1c**	*t*-Bu	Br	1.5	150 °C, 2 h	95	40:60
6	**1c**	*t*-Bu	Br	0.4	150 °C, 7 h	38	43:57

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

On the basis of these results, we examined the reaction of **1c** with a variety of arenes in the presence of InBr$_3$ or

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[7] Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron Lett.* **1989**, *30*, 2847.

[8] (a) Saito, T.; Nakane, M.; Endo, M.; Yamashita, H.; Oyamada, Y.; Motoki, S. *Chem. Lett.* **1986**, 1350. (b) Saito, T.; Nakane, M.; Miyazaki, T.; Motoki, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2140. (c) Saito, T.; Ohmori, H.; Furuno, E.; Motoki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 22. (d) Saito, T.; Ohkubo, T.; Maruyama, K.; Kuboki, H.; Motoki, S. *Chem. Lett.* **1993**, 1127. (e) Saito, T.; Ohmori, H.; Ohkubo, T.; Motoki, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1802. (f) Saito, T.; Tsuda, K.; Saito, Y. *Tetrahedron Lett.* **1996**, *37*, 209. (g) Saito, T.; Tsuda, K. *Tetrahedron Lett.* **1996**, *37*, 9071. (h) Saito, T.; Ohkubo, T.; Kuboki, H.; Maeda, M.; Tsuda, K.; Karakasa, T.; Satsumabayashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3065. (i) Saito, T.; Shiotani, M.; Otani, T.; Hasaba, S. *Heterocycles* **2003**, *60*, 1045. (j) Saito, T.; Sugizaki, K.; Otani, T.; Suyama, T. *Org. Lett.* **2007**, *9*, 1239. (k) Saito, T.; Nihei, H.; Otani, T.; Suyama, T.; Furukawa, N.; Saito M. *Chem. Commun.* In press.

[9] For synthesis and radical cyclization of *N*-(2-alkynylphenyl)isothiocyanate, see: (a) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *J. Org. Chem.* **2003**, *68*, 3454.

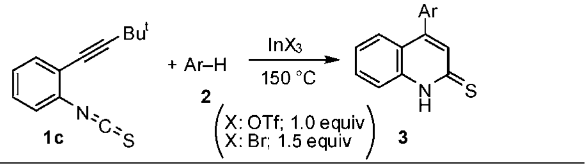
[10] There are examples in which a nucleophile (amine, alcohol, thiol) first attacked the heterocumulene followed by subsequent cyclization onto an alkyne or alkene; see refs 8f, 8g, and 9.

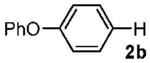
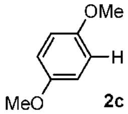
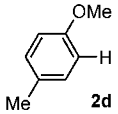
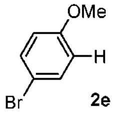
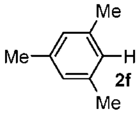
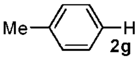
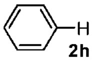
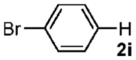
[11] (a) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, T. *Chem. Commun.* **2000**, 1573. (b) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264. (c) Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 2454. (d) Song, C. E.; Jung, D.; Choung, S. Y.; Roh, E. J.; Lee, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6183. (e) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1336. (f) Tsuchimoto, T. *J. Synth. Org. Chem., Jpn.* **2006**, *64*, 752. (g) Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542. (h) Li, R.; Wang, S. R.; Lu, W. *Org. Lett.* **2007**, *9*, 2219. (i) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462.

[12] The reaction of **1** bearing another substituent in R, e.g., *n*-Bu, with 1,4-dimethoxybenzene in the presence of 1.0 equiv of In(OTf)$_3$ at 120 °C for 4 h gave 3-butyl-4-(2,5-dimethoxyphenyl)-2(1*H*)-quinolinethione in 53% yield.

[13] (a) Zhang, J.; Li, C.-J. *J. Org. Chem.* **2002**, *67*, 3969. (b) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126. (c) Angeli, M.; Bandini, M.; Garelli, A.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Org. Biomol. Chem.* **2006**, *4*, 3291.

Table 2. Scope of Arenes[a]

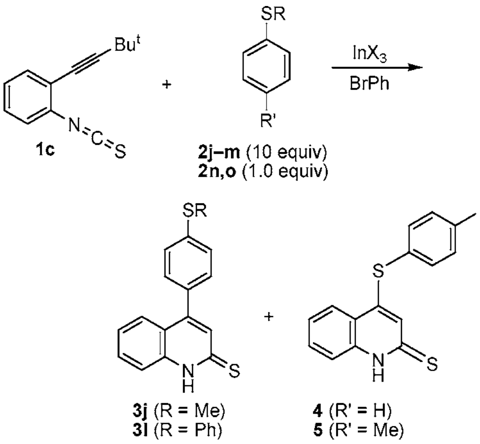


entry	2: Ar–H	X	time/h	3 (%)[b]	p:o[c]
1	 2b	Br	3	**3b** (66)	> 95:5
2	 2c	Br	1	**3c** (99)	–
3	 2d	Br	1	**3d** (99)	82:18[d]
4	 2e	Br	1	**3e** (69)	> 95:5[d]
5	 2f	OTf	1	**3f** (88)	–
6[e]	 2g	OTf	2	**3g** (74)	76:24
7[f,g]	 2h	OTf	60	**3h** (52)	–
8[e,f,h]		OTf	8	**3h** (71)	–
9[h,i]	 2i	OTf	10	**3i** (12)	> 95:5

[a] All reactions were carried out with 0.50 mmol of **1c** in 2 mL of **2**. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Ratio of *o*:*m* with respect to MeO group. [e] At 120 °C. [f] In(OTf)$_3$ (2 equiv) was used. [g] At 80 °C. [h] In a sealed tube. [i] At 200 °C.

In(OTf)$_3$ (Table 2). Electron-rich arenes bearing an alkoxy or aryloxy group reacted smoothly to afford the corresponding quinolinethiones in up to 99% yield (entries 1−4). Weakly nucleophilic mesitylene and toluene also reacted under similar conditions to afford **3f** and **3g** in good yields (entries 5 and 6). Benzene was less reactive as the yield of **3h** was 52% (entry 7), even when the reaction was carried out using 2.0 equiv of In(OTf)$_3$ at refluxing temperature (80 °C) for 60 h. By heating at 120 °C in a sealed tube for 8 h, the yield was improved to 71% (entry 8). In the reactions with electron-poor arenes, bromobenzene **3i** was obtained in a 12% yield after heating at 200 °C for 10 h in a sealed tube (entry 9). The reaction with weak nucleophiles, such as chlorobenzene and ethyl benzoate, at 150 °C for 10 h failed to give the expected products with recovery of **1c** (ca. 80%).

Table 3. Reaction of **1c** with Aryl Sulfide and Thiol[a]



entry	2	R	R′	InX$_3$ X	InX$_3$ equiv	conditions	product yield[b] (%)
1	**2j**	Me	H	OTf	1.5	130 °C, 7 h	**4** (31)
2	**2j**	Me	H	Br	1.5	130 °C, 5 h	**4** (67)
3	**2j**	Me	H	Cl	2.0	130 °C, 2 h	**4** (60)
4	**2k**	Et	H	Br	1.5	150 °C, 5 h	**4** (55)
5	**2l**	Ph	H	Br	1.5	150 °C, 2 h	**3** (61)
6	**2m**	Me	Me	Br	2.0	150 °C, 6 h	**5** (53)
7	**2n**	H	H	–	0	150 °C, 25 h	**4** (9)
8	**2n**	H	H	OTf	1.0	150 °C, 25 h	**4** (66)
9	**2n**	H	H	Br	1.0	150 °C, 25 h	**4** (72)
10	**2n**	H	H	Cl	1.0	150 °C, 25 h	**4** (64)
11	**2o**	H	Me	Br	1.2	150 °C, 12 h	**5** (75)

[a] All reactions were carried out using 0.50 mmol of **1c** in 2 mL of chlorobenzene for entries 1−3 and bromobenzene for entries 4−11. [b] Isolated yield.

Aryl sulfides and arenethiols were also subjected to the indium(III)-mediated tandem reaction of **1c** in chlorobenzene or bromobenzene as the solvent (Table 3). The reaction of **1c** with thioanisole (10 equiv) in the presence of In(OTf)$_3$ gave 4-phenylthioquinolinethione **4** in 31% yield instead of the expected FC-type adduct **3j** (entry 1). As far as we know, this is the first example of the intermolecular C−S bond-forming reaction of alkynes with thioanisole.[14] The yield was improved by use of InBr$_3$ (67%) or InCl$_3$ (60%) (entries 2 and 3). With ethyl phenyl sulfide **2k**, the reaction (InBr$_3$) also afforded **4** in 55% yield (entry 4), whereas the reaction with diphenyl sulfide **2l** gave the FC-type adduct **3l** in 61% yield (entry 5). Similarly, 4-*p*-tolylquinolinethione **5** was obtained in 53% yield (entry 6). For a more straightforward synthesis of **4** or **5**, hydrothiolation[15] of **1c** was examined by exposing **1c** to thiophenol (1.0 equiv) (entries 7−11). Without an In(III) reagent, the reaction with thiophenol **2n** was sluggish and resulted in a lower yield (9%) of **4** (entry 7). In the presence of 1.0 equiv of In(OTf)$_3$, InBr$_3$, and InCl$_3$, the reactions proceeded smoothly to afford **4** in 66, 72, and 64% yield, respectively (entries 8−10). In the same way, *p*-toluenethiol afforded **5** in a satisfactory yield (75%) (entry 11).

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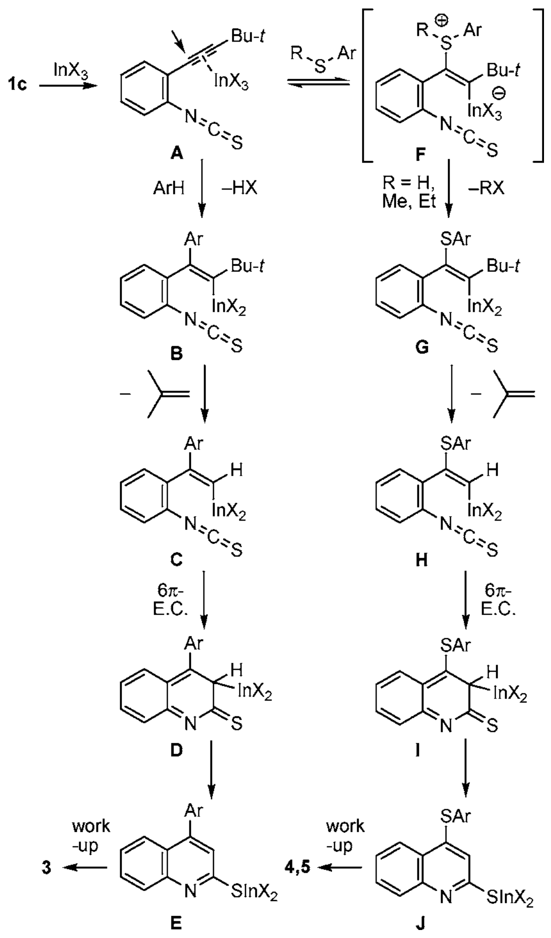
(14) Intramolecular C−S bond-forming reaction: (a) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011. (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905.

(15) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108.

Scheme 2. A Possible Pathway



An assumed pathway for the formation of **3**−**5** is illustrated in Scheme 2. First, the In(III) reagent (InX_3) coordinates to an acetylene bond to form an alkyne−InX_3 complex **A**, and following regioselective addition of an aromatic nucleophile to the benzylic alkynyl carbon atom in a Friedel−Crafts manner gives an alkenylisocyanate **B**. The regioselectivity in these cases agrees with reported reactions of aryl-substituted alkynes.[11] Meanwhile, alkyl aryl sulfides **2j**, **2k**, and **2m** and aryl thiols **2n** and **2o** react preferentially on the more nucleophilic sulfur atom to give a sulfonium salt **F**, from which elimination of RX proceeds to form an arylthioalkenyl indium intermediate **G**. In the case of diphenyl sulfide (R = Ph), such an elimination does not occur because of the poor leaving ability of the phenyl group in **F**. Under such acidic conditions, alkenyl intermediates **B** and **G** eliminate the *t*-Bu group, which was trapped by aromatic nucleophiles.[16] 6π-Electrocyclization and successive aromatization of **C** and **H** led to quinolines **E** and **J** via **D** and **I**.[17] Their tautomerization and/or aqueous workup furnished quinoline-2-thiones **3**−**5**.

In summary, we have developed an indium(III)-mediated tandem FC alkenylation−cyclization method for straightforward and facile synthesis of 4-aryl- or 4-arylthioquinoline-2-thiones from 2-alkynylphenyl isothiocyanates. The application of this method to the synthesis of variously substituted quinoline-2-thiones and extending the method are currently underway in our laboratory.

Supporting Information Available: Spectroscopic data and experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] 2-*tert*-Butyl-1,4-dimethoxybenzene was actually isolated in 20% yield (Table 2, entry 2).

[17] NMR monitoring of the reaction of (3,3-dimethylbut-1-ynyl)benzene with **2c** in 10 mol % of $In(OTf)_3$ revealed an initial formation of 2,5-dimethoxy-1-[(1*Z*)-3,3-dimethyl-1-phenyl-1-butenyl]benzene and its subsequent decomposition leading to 2-*tert*-butyl-1,4-dimethoxybenzene and 1-(2,5-dimethoxyphenyl)-1-phenylethene, albeit in low yield. These results support the pathways **1c** to **C** via **A** and **B** in Scheme 2.