Organic Letters

Letter

pubs.acs.org/OrgLett

Nickel-Catalyzed Reaction of Thioisatins and Alkynes: A Facile Synthesis of Thiochromones

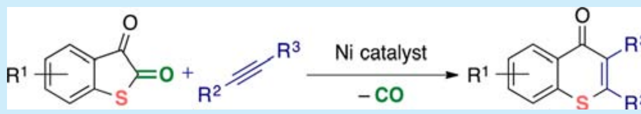
Tasuku Inami,[†] Takuya Kurahashi,*[,†,‡] and Seijiro Matsubara*[,†]

[†]Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

[‡]JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

Supporting Information

ABSTRACT: A new synthetic method for thiochromones was developed by using nickel-catalyzed decarbonylative cycloaddition of readily available thioisatins with alkynes. This reaction proceeded under very mild conditions and has quite high functional group compatibility.

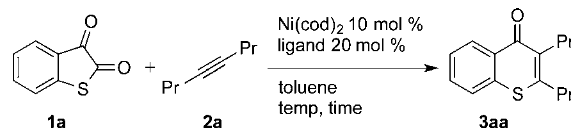


Heterocyclic compounds are predominant structural motifs in many functional molecules, natural products, and bioactive compounds.[1] Among the various heterocyclic compounds, chromone derivatives and their analogues, such as quinolones and thiochromones, constitute part of a large family of biologically active compounds, and thus, the development of a new synthetic method is a research topic of great interest.[2] In particular, thiochromones are also recognized as bioactive compounds; however, synthetic methods for thiochromones are still limited.[3−5] Herein, we report that a nickel-catalyzed decarbonylative cycloaddition reaction of alkynes and thioisatins, which can be easily prepared from thiols, affords a variety of thiochromones with functional group compatibility.

Initially, thioisatin **1a** and 4-octyne (**2a**) were reacted in refluxing toluene in the presence of 10 mol % of $Ni(cod)_2$ and 20 mol % of triphenylphosphine under argon atmosphere to exclusively furnish 2,3-dipropylthiochromone (**3aa**) in quantitative yield (Table 1, entry 1). The nickel complex worked catalytically even at 50 °C to afford **3aa** in 98% yield (entry 2). We then examined various phosphine ligands and IPr (1,3-bis(2,6-diisopropylphenyl)-4-ylidene) and found that triphenylphosphine gave the best result (entries 3−6). The reaction also proceeded at room temperature, although the yield was moderate even with expanded reaction time (entry 7).

After optimization of the reaction conditions, the scope of substrates for this cycloaddition was then evaluated using different thioisatins with various substituents (Scheme 1). 5-Methylthioisatin smoothly reacted with 4-octyne to give the corresponding thiochromone in 87% yield (**3ba**). Electron-donating or -withdrawing groups did not suppress the reaction (**3ca**: 68%, **3da**: 91%). Moreover, a benzo-fused derivative also gave the desired product **3ea** in 82% yield. Various alkynes could be applied to the reaction with thioisatins. 2-Octyne gave the desired products in good yield as a mixture of regioisomers (**3ab**: 91%). 1-(Trimethylsilyl)-1-propyne smoothly reacted to give the desired product in 58% yield as a single regioisomer. The carbon−carbon triple bond of a 1,3-conjugated enyne underwent the regioselective reaction with **1a**. Varieties of

Table 1. Optimization Study of Reaction Conditions[a]



entry	ligand	temp (°C)	time (h)	yield[b] (%)
1	PPh_3	130	1	96
2	PPh_3	50	6	98 (78)[c]
3	PCy_3	50	6	35
4	PPr_3	50	6	<1
5	$PtBu_3$	50	6	20
6	IPr[d]	50	6	0
7	PPh_3	25	24	49

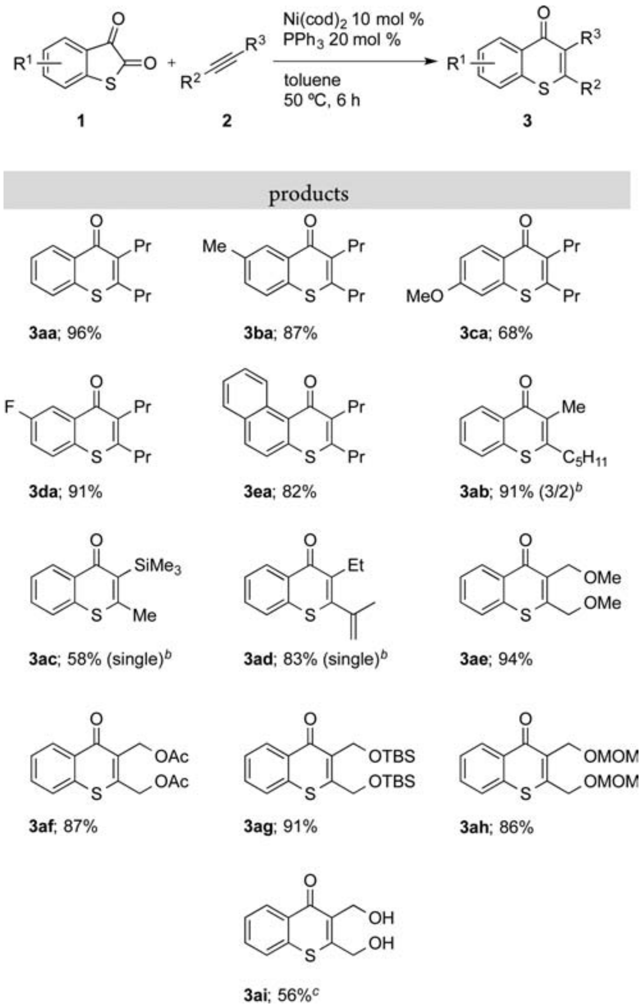
[a]Reaction conditions: $Ni(cod)_2$ (10 mol %), ligand (20 mol %), **1a** (0.2 mmol), and 4-octyne **2a** (0.3 mmol; 1.5 equiv) in 1.0 mL of toluene. [b]Yield was determined by ^1H NMR spectroscopy. [c]5 mol % of $Ni(cod)_2$ and 10 mol % of PPh_3 were used. [d]10 mol % of ligand was used.

functional groups were found to be tolerated under the reaction conditions. For example, alkynes with ether, ester, siloxy, or acetal groups reacted with **1a** without decomposition with good-to-excellent yields (**3ae**: 94%, **3af**: 87%, **3ag**: 91%, **3ah**: 86%). Furthermore, an alkyne with two unprotected hydroxy groups also gave the corresponding product **3ai** in 56% yield.

The derivatives of 2-phenylthiochromone are recognized as good medicinal candidates.[4c−g] We found that various 2-arylthiochromones could be easily synthesized by the nickel-catalyzed reaction of thioisatin with aryl-substituted alkynes (Scheme 2). Diphenylacetylene smoothly reacted with **1a** to give 2,3-diphenylthiochromone **3aj** in 93% yield. 1-Methyl- or 1-cycopropyl-2-phenyl acetylenes gave the corresponding thiochromone derivatives as major products over their regioisomers (**3ak**: 92%, **3al**: 82%). An electronically biased diphenyl acetylene derivative reacted to give the cycloadduct

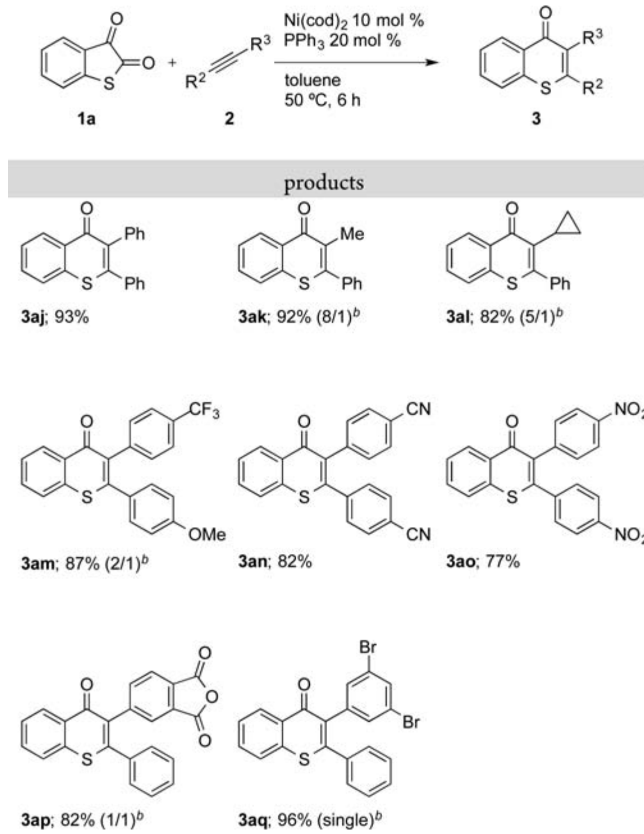
Received: September 3, 2014
Published: October 27, 2014

Scheme 1. Synthesis of Alkyl-Substituted Thiochromones[a]



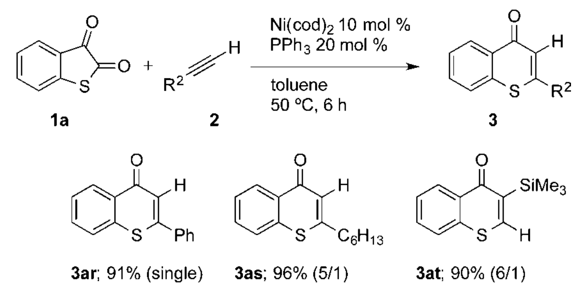
[a]Isolated yields are given. [b]Ratio of ragioisomers. [c]3 equiv of alkyne was used. Ac = acetyl. TBS = *tert*-butyldimethylsilyl. MOM = methoxymethyl.

Scheme 2. Synthesis of Aryl-Substituted Thiochromones[a]

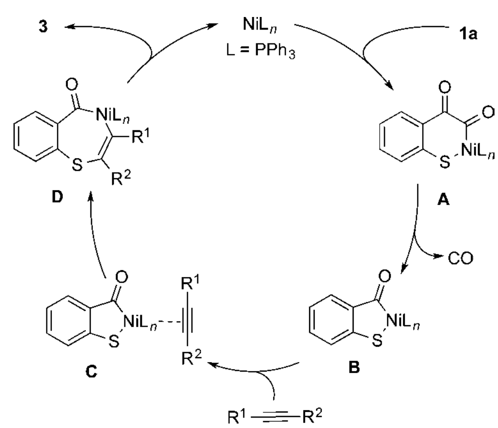


[a]Isolated yields are given. [b]Ratio of ragioisomers.

Scheme 3. Reaction with Terminal Alkynes



Scheme 4. Plausible Reaction Mechanism



3am with a moderate ratio of regioisomers. Cyano- or nitro-substituted tolanes reacted with **1a** to give the cycloadducts in 82% (**3an**) and 77% (**3ao**) yields, respectively. Phthalic anhydride substituted phenylacetylene gave the product **3ap** in 82% yield as a regioisomeric mixture; however, 1-phenyl-2-(3,5-dibromophenyl)ethyne gave the corresponding thiochromone **3aq** in 96% yield as a single regioisomer.

As shown in Scheme 3, terminal alkynes also participated in the reaction to afford thiochromones. For example, phenylacetylene gave **3ar** regioselectively in 91% yield. 1-Octyne also reacted with **1a** in excellent yield (**3as**: 96%). Moreover, (trimethylsilyl)acetylene gave the correspondingly substituted product (**3at**) in 90% yield.

A plausible reaction pathway to account for the formation of thiochromone **3** based on the observed results is outlined in Scheme 4. In view of the mechanism of the previously reported transition-metal-catalyzed insertion reaction of S−CO bond to alkynes, it is reasonable to consider that the catalytic cycle of the present reaction should consist of the oxidative addition of S−CO bond of thioisatin **1a** to a Ni(0) complex to form an intermediate **A**.[6−9] Then, decarbonylation occurs to give a complex **B** followed by the migratory insertion of an alkyne to the C−S bond via **C**. Finally, reductive elimination of nickel from **D** gives the desired product **3**.

In summary, we developed a nickel-catalyzed decarbonylative cycloaddition reaction of thioisatins and alkynes to form various thiochromones. The reaction proceeded under mild conditions; thus, a number of functional groups could be tolerated to afford the correspondingly substituted thiochromones in high yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures including spectroscopic and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: kurahashi.takuya.2c@kyoto-u.ac.jp.
*E-mail: matsubara.seijiro.2e@kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JST, ACT-C, and Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.K. acknowledges the Asahi Glass Foundation. T.I. also acknowledges the Japan Society for the Promotion of Science for Young Scientists for fellowship support.

■ REFERENCES

(1) Boulton, A. J.; McKillop, A. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Vol. 3.

(2) Synthetic protocol for chromone or quinolone derivatives. For recent reviews, see: (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Verma, A. K.; Pratap, R. *Tetrahedron* **2012**, *68*, 8523. (d) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559.

(3) For synthetic methods of thiochromones, see: (a) Willy, B.; Müller, T. J. J. *Synlett* **2009**, 1255. (b) Fuchs, F. C.; Eller, G. A.; Holzer, W. *Molecules* **2009**, *14*, 3814. (c) Usachev, B. I.; Shafeev, M. A.; Sosnovskikh, V. Ya. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 523. (d) Angel, A. J.; Finefrock, A. E.; French, K. L.; Hurst, D. R.; Williams, A. R.; Rampey, M. E.; Studer-Martinez, S. L.; Beam, C. F. *Can. J. Chem.* **1999**, *77*, 94. (e) Bossert, F. *Tetrahedron Lett.* **1968**, *41*, 4375. (f) Hawthornee, D. G.; Porter, Q. N. *Aust. J. Chem.* **1966**, *19*, 1751. (g) Kobayashi, K.; Kobayashi, A.; Ezaki, K. *Heterocycles* **2012**, *85*, 1997. (h) Kataoka, T.; Watanabe, S.; Mori, E.; Kadomoto, R.; Tanimura, S.; Kohno, M. *Bioorg. Med. Chem.* **2004**, *12*, 2397. (i) Razdan, R. K.; Bruni, R. J.; Mehta, A. C.; Weinhardt, K. K.; Papanastassiou, Z. B. *J. Med. Chem.* **1978**, *21*, 643.

(4) For biological properties of thiochromones, see: (a) Nakib, T. A.; Bezjak, V.; Meegam, M. J.; Chandy, R. *Eur. J. Med. Chem.* **1990**, *25*, 455. (b) Gotoda, S.; Takahashi, N.; Nakagawa, H.; Murakami, M.; Takechi, T.; Komura, T.; Uchida, T.; Takagi, Y. *Pestic. Sci.* **1998**, *52*, 309. (c) Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1984**, *21*, 193. (d) Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1985**, *22*, 1593. (e) Dhanak, D.; Keenen, R. M.; Burton, G.; Kaura, A.; Darcy, M. G.; Shah, D. H.; Ridgers, L. H.; Breen, A.; Lavery, P.; Tew, D. G.; West, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3677. (f) Wang, H.-K.; Bastow, K. F.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1996**, *39*, 1975. (g) Charris, J.; Dominguez, J.; Labo, G.; Riggione, F. *Pharm. Pharmacol. Commun.* **1999**, *5*, 107.

(5) For thiochromone as a photolabile protecting group, see: (a) Kitani, S.; Sugawara, K.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. *Chem. Commun.* **2008**, 2103. (b) Zhang, Y.; Tanimoto, H.; Nishiyama, Y.; Morimoto, T.; Kakiuchi, K. *Synlett* **2012**, 367. (c) Sugiura, R.; Kozaki, R.; Kitani, S.; Gosho, Y.; Tanimoto, H.; Nishiyama, Y.; Morimoto, T.; Kakiuchi, K. *Tetrahedron* **2013**, *69*, 3984.

(6) For nickel-catalyzed cycloaddition with elimination of a small molecule, see: (a) Inami, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 1912. (b) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (c) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226. (d) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2010**, *12*, 4548. (e) Inami, T.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2011**, *47*, 9711. (f) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2011**, *40*, 322. (g) Ochi, Y.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 1374.

(7) For related nickel-catalyzed cycloaddition, see: (a) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (b) Yamauchi, M.; Morimoto, M.; Miura, T.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 54. (c) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4955. (d) Miura, T.; Morimoto, M.; Yamauchi, M.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 5359.

(8) For reviews on addition of the S−X bond to carbon−carbon unsaturated bonds, see: (a) Han, L.-B.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1999**, 395. (b) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435. (c) Kuniyasu, H. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Zürich, 2001; p 217. (d) Ogawa, A. *J. Organomet. Chem.* **2000**, *611*, 463. (e) Kondo, T.; Mitudo, T. *Chem. Rev.* **2000**, *100*, 3205.

(9) For addition of the S−C(O)R bond to alkynes, see: (a) Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108. (b) Kuniyasu, H.; Kurosawa, H. *Chem.—Eur. J.* **2002**, 2660. (c) Hirai, T.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2004**, *33*, 1148. For addition of the S−C(O)R bond to alkynes, see: (d) Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108. For addition of the S−C(O)NR_2 bond to alkynes, see: (e) Toyofuku, M.; Fujiwara, S.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 9706. (f) Kuniyasu, H.; Kato, T.; Asano, S.; Ye, J.-H.; Ohmori, T.; Morita, M.; Hiraike, H.; Fujiwara, S.; Terao, J.; Kurosawa, H.; Kambe, N. *Tetrahedron Lett.* **2006**, *47*, 1141. For addition of the S−CN bond to alkynes, see: (g) Kamiya, I.; Kawakami, J.; Yano, S.; Nomoto, A.; Ogawa, A. *Organometallics* **2006**, *25*, 3562. For addition of S−allyl bond to alkynes, see: (h) Hua, R.; Takeda, H.; Onozawa, S-y.; Abe, Y.; Tanaka, M. *Org. Lett.* **2007**, *9*, 263.