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Nickel-Catalyzed Cycloadditions of Thiophthalic Anhydrides with Alkynes

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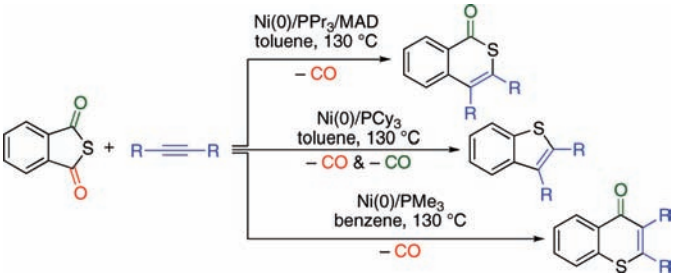
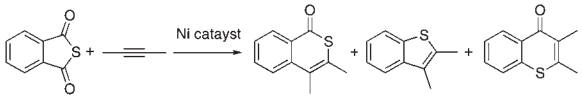
ABSTRACT



Nickel-catalyzed cycloadditions have been developed where thiophthalic anhydrides react with alkynes to afford substituted sulfur-containing heterocyclic compounds. Selective formations of thioisocoumarins, benzothiophenes, and thiochromones were accomplished with three different reaction conditions.

Recently, we have reported nickel-catalyzed cycloadditions of phthalic anhydrides with alkynes to afford isocoumarins.[1] Each reaction is supposed to proceed via oxidative addition of phthalic anhydride to nickel(0), decarbonylation, and insertion of alkyne, followed by reductive elimination. As a result, the reaction became equivalent to a substitution reaction by replacing a carbon monoxide with an alkyne in a phthalic anhydride through the catalytic process. The results prompted us to investigate the versatility of such reactions to afford heterocyclic compounds. When this method was examined with use of thiophthalic anhydride as a starting compound, a mixture of three different types of products was obtained (Scheme 1). Thus, we envisioned that we might prepare three different heterocyclic compounds selectively from a single starting heterocyclic compound by tuning the nickel catalyst. Herein, we report our results of the nickel-catalyzed selective synthesis of sulfur-containing heterocyclic compounds from a thiophthalic anhydride using such an approach.[2,3]

Scheme 1. Nickel-Catalyzed Cycloaddition of a Thiophthalic Anhydride with an Alkyne



Initially, it was found that the reaction of thiophthalic anhydride **1** with 4-octyne (**2a**) in the presence of Ni(0)/PMe$_3$ catalyst in refluxing toluene afforded thioisocoumarin **3a** in 11% yield along with benzothiophene **4a** in 11% yield and thiochromone **5a** in 26% yield (Table 1, entry 1). According to our results of decarbonylative cycloaddition of phthalic anhydrides with alkynes, in which the addition of a Lewis acid promoted the reaction process,[1] we presumed that an addition of Lewis acid to the reaction would also accelerate the formation of thioisocoumarin **3a**. Indeed, detailed examination of the reaction conditions revealed that on

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(1) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226.

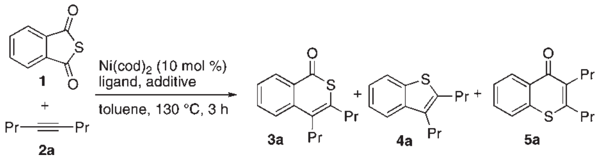
(2) Sulfur-containing heterocyclic compounds are widely distributed in nature, and their biological and physiological effects are of interest. Pharmaceutical drugs, such as Raloxifene, Zileuton, Sertaconazole, Arzoxifene, Metizoline, and Sb-271046, contain benzothiophene structures.

(3) (a) Tseng, N.-W.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 1809. (b) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *J. Org. Chem.* **2003**, *68*, 3454. (c) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (d) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (e) Leardini, R.; Franco Pedulli, G.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1390.

10.1021/ol200336c

addition of 10 mol % of Lewis acid (MAD: methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), the reaction proceeded smoothly to furnish **3a** in 99% isolated yield (entry 4). Among phosphine ligands examined, PPr_3 gave the best yield with a combination of MAD (entries 2−4). Increasing or decreasing the amount of MAD (50 mol % or 1 mol %), or replacing it with another Lewis acid, such as $B(C_6F_5)_3$ or $ZnCl_2$, gave inferior results from the points of yield and selectivity (entries 5−8).

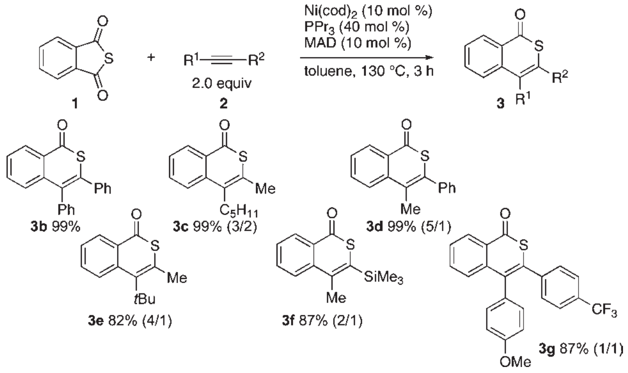
Table 1. Cycloaddition of **1** with **2a** To Form **3a**[a]



entry	ligand	additive (mol %)	yield (%) 3a	yield (%) 4a	yield (%) 5a
1	PMe_3	–	11	11	26
2	PMe_3	MAD (10)	11	<1	10
3	PCy_3	MAD (10)	15	<1	10
4	PPr_3	MAD (10)	99	<1	<1
5	PPr_3	MAD (1)	62	12	<1
6	PPr_3	MAD (50)	93	<1	<1
7	PPr_3	$B(C_6F_5)_3$ (10)	91	<1	<1
8	PPr_3	$ZnCl_2$ (10)	24	28	13

[a] All reactions were carried out with $Ni(cod)_2$ (10 mol %), ligand (40 mol %), **1** (0.2 mmol), and **2a** (0.4 mmol) at 130 °C for 3 h.

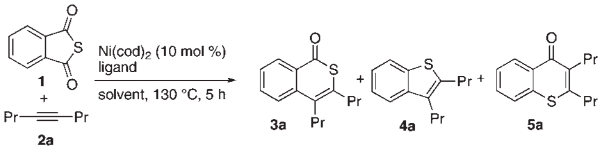
Scheme 2. Scope of Cycloaddition To Form Thioisocoumarins **3**



The cycloaddition is also compatible with aryl-substituted alkyne **2b** and afforded **3b** in 99% isolated yield (Scheme 2). The reaction of **1** with unsymmetrical alkynes such as **2c**, **2d**, **2e**, **2f**, and **2g** also gave the cycloadducts in good yields consisting of regioisomers in a range of 1/1 to 5/1 ratio. By analogy to the mechanism of the previously reported nickel-catalyzed reaction of phthalic anhydrides with alkynes to form isocoumarins,[1,4,5] it is reasonable to consider that the catalytic cycle of the present reactions should consist of oxidative addition of an anhydride S−CO bond to nickel.[6] Subsequent decarbonylation and coordination of alkyne affords five-membered nickelacycle. The alkyne would then insert into the nickelacycle, which undergoes reductive elimination to give **3** and regenerates the starting Ni(0).

We next turned our attention to the selective synthesis of benzothiophenes **4** with reactions of **1** and **2**. Thus, our initial investigation involved studying the effect of different ligands. The cycloaddition with PPr_3 as a ligand afforded **4a** in 23% yield as a major adduct (Table 2, entry 2). It was found that sterically hindered trialkylphosphine PCy_3 gave the best result with respect to both yield of **4a** and product selectivity (entry 3). In other reaction solvents, such as benzene, MeCN, and 1,4-dioxane, yields were even lower (entries 4−6). Further examination of the reaction conditions revealed that increasing the concentration of **1** in the reaction mixture improved the yield of **4a**. Consequently, benzothiophene **4a** was obtained as a sole product in 93% isolated yield when the reaction was carried out in a 0.34 M toluene solution of **1** (entry 7).

Table 2. Cycloaddition of **1** with **2a** To Form **4a**[a]



entry	ligand	solvent	yield (%) 3a	yield (%) 4a	yield (%) 5a
1	PMe_3	toluene (0.17 M)	11	11	26
2	PPr_3	toluene (0.17 M)	6	23	6
3	PCy_3	toluene (0.17 M)	<1	70	<1
4	PCy_3	benzene (0.17 M)	<1	56	<1
5	PCy_3	MeCN (0.17 M)	<1	23	<1
6	PCy_3	1,4-dioxane (0.17 M)	5	33	<1
7	PCy_3	toluene (0.34 M)	<1	93	<1

[a] All reactions were carried out with $Ni(cod)_2$ (10 mol %), ligand (40 mol %), **1** (0.2 mmol), and **2a** (0.4 mmol) at 130 °C for 5 h.

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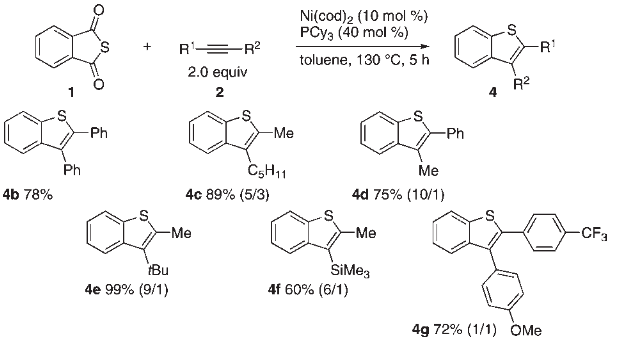
(4) (a) Trost, B. M.; Chen, F. *Tetrahedron Lett.* **1971**, *12*, 2603. (b) Sano, K.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2741. (c) Yamamoto, T.; Sano, K.; Yamamoto, A. *J. Am. Chem. Soc.* **1987**, *109*, 1092. (d) Fischer, R.; Walther, D.; Kempe, R.; Sieler, J.; Schönecker, B. *J. Organomet. Chem.* **1993**, *447*, 131.

(5) (a) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494. (b) Ooguri, A.; Nakai, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 13194.

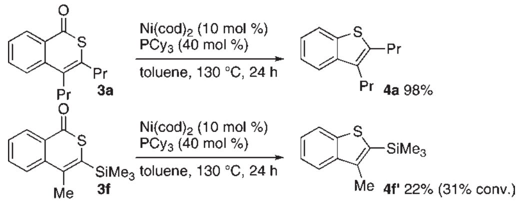
(6) For addition of the $S-CO_2R$ bond to alkynes, see: (a) Hua, R.; Takeda, H.; Onozawa, S.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* **2001**, *123*, 2899. For addition of the S−C(O)R bond to alkynes, see:(b) Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108. For addition of the $S-C(O)NR_2$ bond to alkynes, see:(c) Toyofuku, M.; Fujiwara, S.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 9706.

With the optimized reaction conditions, the scope of the reaction was briefly examined and the results are summarized in Scheme 3. The reaction of **1** to tolane (**2b**) also furnished **4b** in 78% yield as a sole product. Unsymmetrical alkynes, such as 2-octyne (**2c**) and 1-phenyl-1-propyne (**2d**), also reacted with **1** to afford the correspondingly substituted **4c** and **4b** consisting of regioisomers in a ratio of 5/3 and 10/1. The reaction of **1** to unsymmetrical alkynes, containing sterically hindered substituents such as *t*Bu and $SiMe_3$, gave adducts **4e** and **4f** in 99% and 60% yields, respectively, with good regioselectivity, while the reaction of **1** with not sterically but electronically differentiated diaryl-substituted alkyne **2g** afforded **4g** in 72% yield, consisting of regioisomers in a ratio of 1/1.

Scheme 3. Scope of Cycloaddition To Form Benzothiophenes **4**



Scheme 4. Decarbonylation of **3f**



The formation **4** can be ascribed to additional decarbonylation of **3** with Ni catalyst. In fact, the treatment of **3a** with the reaction conditions for formation of benzothiophene **4** (Ni(0)/PCy_3) afforded **4a** in 98% yield (Scheme 4). The result that decarbonylation of **3f** affords **4f′** in 22% yield suggests that **3f** is more resistant to oxidative addition of Ni(0) than the regioisomer **3f′**, leading to the observation of **4f′** as the minor product in the formation of benzothiophene **4**. Thus, a plausible reaction pathway to account for the formation of benzothiophenes **4** based on the observed results is outlined in Scheme 5. The catalytic cycle for formation of **4** may consist of the oxidative addition of thiophthalic anhydride to Ni(0). The use of bulky ligand PCy_3 inhibits insertion of alkyne to a nickelacycle **A**, and decarbonylation occurs prior to alkyne insertion. Subsequent carbonickelation of alkyne, followed by reductive elimination of **3** from nickelacycle **B** and reoxidative addition of **3**, afford intermediate **C**. Reductive elimination provides **4** and regenerates starting Ni(0) catalyst. The regioselectivity of the reaction can be rationalized as due to the direction of alkyne insertion, in which the steric repulsive interaction is minimal between the bulkier R^L substituent on alkyne and the nickel/ligand complex.

Scheme 5. Plausible Reaction Mechanism for Formation of **4**

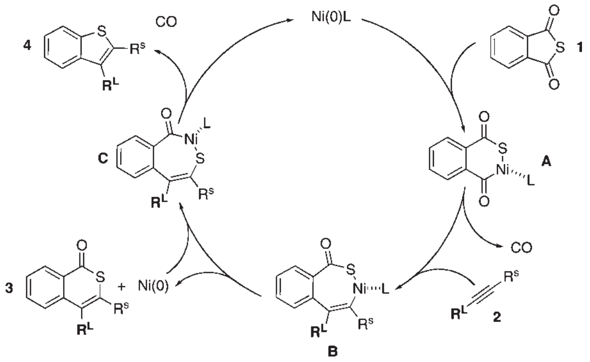
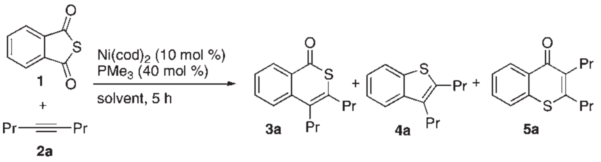


Table 3. Cycloaddition of **1** with **2a** To Form **5a**[a]

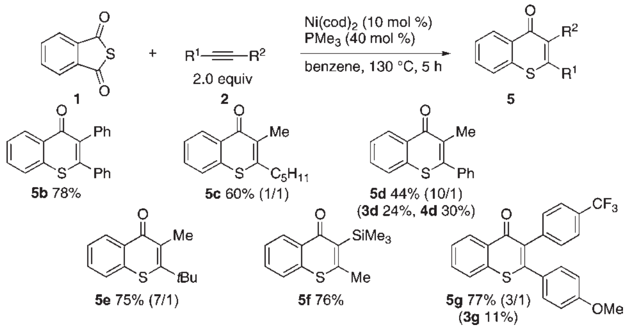


entry	solvent	reaction temp (°C)	yield (%) 3a	4a	5a
1	toluene	130	11	11	26
2	benzene	130	4	12	89
3	toluene	80	<1	<1	23
4	benzene	80	<1	<1	28
5	benzene	90	4	6	60

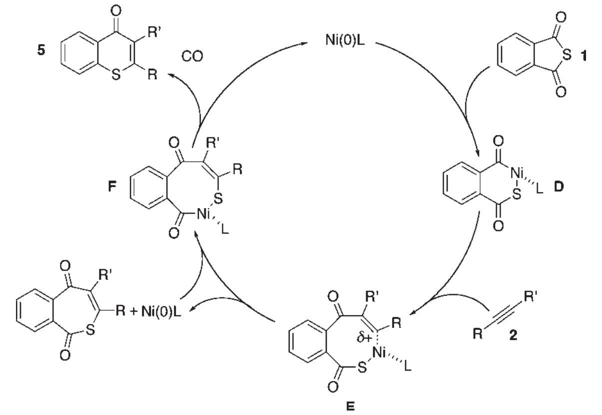
[a] All reactions were carried out with $Ni(cod)_2$ (10 mol %), ligand (40 mol %), **1** (0.2 mmol), and **2a** (0.4 mmol) for 5 h.

The results of selective synthesis of thioisocoumarins **3** and benzothiophenes **4** encouraged us to investigate the selective synthesis of thiochromones **5**. To our delight, preferential formation of **5** was accomplished by changing the reaction solvent. That is, the reaction of **1** with **2a** in benzene at 130 °C afforded **5a** as a major product in 89% yield (Table 3, entry 2). Attempts to lower the reaction temperature to improve the selectivity decreased the yield of **5a** in 28% yield (80 °C, entry 4) and 60% yield (90 °C, entry 5). We then examined the scope of the reaction to form thiochromones; the results are summarized in Scheme 6. Isolated yields ranged from 44% to 78% with aryl-, alkyl-, and trimethylsilyl-substituted alkynes.

Scheme 6. Scope of Cycloaddition To Form Thiochromones **5**



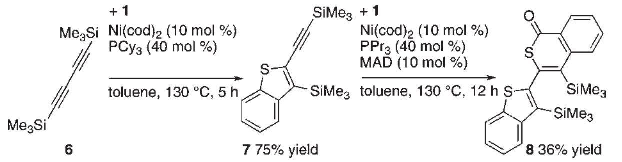
Scheme 7. Plausible Reaction Mechanism for Formation of **5**



The proposed catalytic cycle for formation of **5** is illustrated in Scheme 7. The reaction is initiated by oxidative addition of thiophthalic anhydride to Ni(0). Sterically less hindered PMe_3 ligand allowed carbonickelation of alkyne prior to decarbonylation to afford the eight-membered nickelacycle **E**. Subsequent reductive elimination and re-oxidative addition gives the eight-membered nickelacycle **F**. Following decarbonylation and reductive elimination furnishes **5**. The observed regioselectivity in the reaction is ascribed to the properties of substituted groups on alkenyl **2**; this stabilizes a developing positive charge on the alkyenyl carbon atom adjacent to nickel in nickelacycle **E**.[7] The effects of benzene as reaction solvent are not clear at the moment; however, we assumed that vigorous refluxing at 130 °C may promote exhaust of CO from the reaction system efficiently.

Lastly, we demonstrated accumulation of two different types of sulfur heterocycle in one molecule by selective stepwise reactions (Scheme 8). Thus, the reaction of **1** with 1,4-bis(trimethylsilyl)-1,3-butadiyne (**6**), which contains two conjugated carbon–carbon triple bonds, gave the corresponding benzothiophene **7** in 75% yield regioselectively with reaction conditions of Ni(0)/PCy_3. Subsequent reaction of **7** with **1** in the presence of Ni(0)/PPr_3/MAD gave the adduct **8** in 36% yield.

Scheme 8. Accumulative Reaction of **1** to 1,3-Butadiyne **8**



In conclusion, cycloadditions of thiophthalic anhydride with alkynes to afford sulfur-containing heterocyclic compounds were successfully developed by using nickel catalysts.[8] It was demonstrated that the nickel-catalyzed reaction gave three types of compounds selectively depending on the reaction conditions employed. The use of Ni(0)/PPr_3 catalyst in combination with Lewis acid afforded thioisocoumarin **3**. On the contrary, the use of Ni(0)/PCy_3 catalyst in the reaction afforded benzothiophene **4**, while the use of Ni(0)/PMe_3 catalyst furnished thiochromone **5**.

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Supporting Information Available. 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.

Note Added after ASAP Publication. Due to a production error this paper was published ASAP without the Table corrections applied. The correct version reposted March 10, 2011.

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(7) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2010**, *12*, 4548.

(8) Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reactions, presumably due to rapid oligomerization of alkynes. For an example, see: Connor, D. T.; Cetenko, W. A.; Mullican, M. D.; Sorenson, R. J.; Unangst, P. C.; Weikert, R. J.; Adolphson, R. L.; Kennedy, J. A.; Thueson, D. O. *J. Med. Chem.* **1992**, *35*, 958.