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Synthesis of Quinolones by Nickel-Catalyzed Cycloaddition via Elimination of Nitrile

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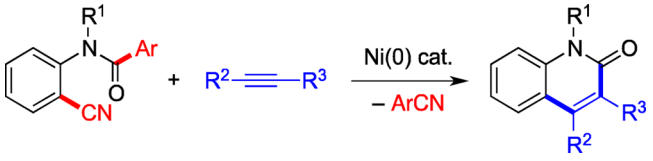
ABSTRACT



Substituted quinolones were efficiently synthesized via the nickel-catalyzed cycloaddition of *o*-cyanophenylbenzamide derivatives with alkynes. The reaction involves elimination of a nitrile group by cleavage of the two independent aryl–cyano and aryl–carbonyl C–C bonds of the amides.

A number of *N*-heterocycles containing carbonyl groups have been recognized as biologically active agents, quinolones[1] and isoquinolones[2] being among the most representative examples of such heterocycles. Because of their functionality, development of synthetic routes and methods for the functionalization of these compounds is of great significance.[3] From this perspective, we have developed cycloaddition reactions of heterocycles with alkynes to generate such benzopyridones via the elimination of CO[4a] (Scheme 1, eq 1) or CO_2[4b] (eq 2). We further attempted to synthesize 2-quinolone from *o*-cyanophenylbenzamides and alkynes via the elimination of nitrile, using a nickel catalyst (eq 3).[5]

The initial treatment of *o*-cyanophenylbenzamide derivative **1a** and 4-octyne **2a** in the presence of a nickel catalyst (prepared *in situ* from $Ni(cod)_2$ and $P(CH_2Ph)_3$ using methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) as a cocatalyst by treatment in toluene at 120 °C for 12 h) generated quinolone **3aa** in 36% yield (Table 1, entry 1).

(1) For selected examples, see: (a) Hamann, L. G.; Higuchi, R. I.; Zhi, L.; Edwards, J. P.; Wang, X.-N.; Marschke, K. B.; Kong, J. W.; Farmer, L. J.; Jones, T. K. *J. Med. Chem.* **1998**, *41*, 623. (b) Naito, Y.; Yoshikawa, T.; Tanigawa, T.; Sakurai, K.; Yamasaki, K.; Uchida, M.; Kondo, M. *Free Radical Biol. Med.* **1995**, *18*, 117. (c) Joseph, B.; Darro, F.; Béhard, A.; Lesur, B.; Collignon, F.; Decaestecker, C.; Frydman, A.; Guillaumet, G.; Kiss, R. *J. Med. Chem.* **2002**, *45*, 2543. (d) Kraus, J. M.; Verlinde, C. L. M. J.; Karimi, M.; Lepesheva, G. I.; Gelb, M. H.; Buckner, F. S. *J. Med. Chem.* **2009**, *52*, 1639.

(2) For selected examples, see: (a) Krane, B. D.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 377. (b) Calogero, A. E.; Kamilaris, T. C.; Bernardini, R.; Johnson, E. O.; Chrousos, G. P.; Gold, P. W. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 729. (c) Ikeura, Y.; Tanaka, T.; Kiyota, Y.; Morimoto, S.; Ogino, M.; Ishimaru, T.; Kamo, I.; Doi, T.; Natsugari, H. *Chem. Pharm. Bull.* **1997**, *45*, 1642. (d) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085. (e) Maezaki, H.; Banno, Y.; Miyamoto, Y.; Moritou, Y.; Asakawa, T.; Kataoka, O.; Takeuchi, K.; Suzuki, N.; Ikedo, K.; Kosaka, T.; Sasaki, M.; Tsubotani, S.; Tani, A.; Funami, M.; Yamamoto, Y.; Tawada, M.; Aertgeerts, K.; Yano, J.; Oi, S. *Bioorg. Med. Chem.* **2011**, *19*, 4482. (f) Du, J.; Xi, L.; Lei, B.; Liu, H.; Yao, X. *Chem. Biol. Drug Des.* **2011**, *77*, 248.

(3) For selected examples of transition-metal-catalyzed syntheses and functionalizations of 2-quinolone, see: (a) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem.* **2003**, *687*, 425. (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772. (c) Battistuzzi, G.; Bernini, R.; Cacchi, S.; de Salve, I. *Adv. Synth. Catal.* **2007**, *349*, 297. (d) Queiroz, M. J. R. P.; Abreu, A. S.; Calhelha, R. C.; Carvalho, M. S. D.; Ferreira, P. M. T.; Fabrizi, G. *Tetrahedron* **2008**, *64*, 5139. (e) Tadd, A. C.; Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583. (f) Tang, D.-J.; Tang, B.-X.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 6749. (g) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900. (h) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 9602. (i) Fu, L.; Huang, X.; Wang, D.; Zhao, P.; Ding, K. *Synthesis* **2011**, 1547. (j) Kato, H.; Ishigame, T.; Oshima, N.; Hoshiya, N.; Shimawaki, K.; Arisawa, M.; Shuto, S. *Adv. Synth. Catal.* **2011**, *353*, 2676. (k) Tang, B.-X.; Song, R.-J.; Wu, C.-Y.; Wang, Z.-Q.; Liu, Y.; Huang, X.-C.; Xiea, Y.-X.; Li, J.-H. *Chem. Sci.* **2011**, *2*, 2131. (l) Borhade, S. R.; Waghmode, S. B. *Can. J. Chem.* **2011**, *89*, 1355.

(4) (a) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (b) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494.

(5) We recently reported a new method for generating coumarins from *o*-arylcarboxybenzonitriles and alkynes via elimination of nitrile in the presence of a nickel catalyst; see: Nakai, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 11066.

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Scheme 1. Synthetic Approaches toward All of the Structural Isomers of Benzopyridones

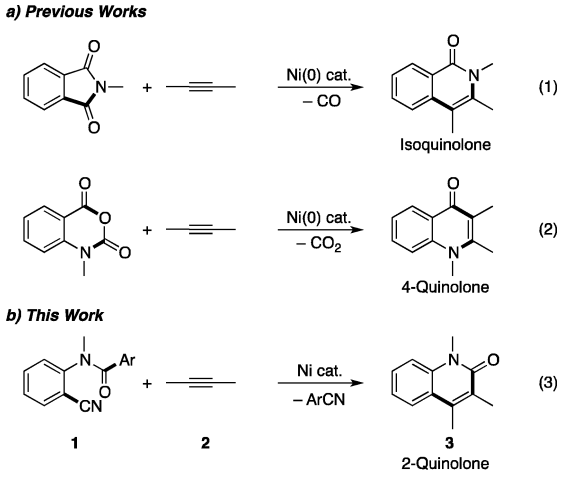
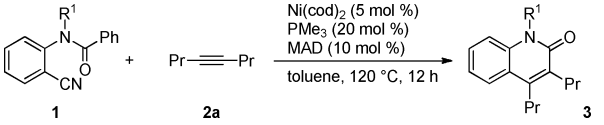
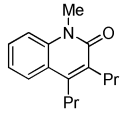
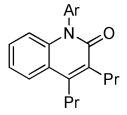
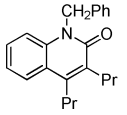


Table 1. Scope of the Cycloaddition[a]



entry	product		yield (%)[b]
1		**3aa**	36[c]
2			80
3		Ar = Ph (**3ba**)	99
4		*p*-MeOC$_6$H$_4$ (**3ca**)	94
5		*p*-CF$_3$C$_6$H$_4$(**3da**)	63
6		**3ea**	80

[a] Reactions were carried out using Ni(cod)$_2$ (5 mol %), PMe$_3$ (20 mol %), MAD (10 mol %), **1** (0.5 mmol), and **2a** (1.5 mmol) in 3 mL of toluene at 120 °C for 12 h in a sealed tube. [b] Isolated yields are given. [c] Using Ni(cod)$_2$ (5 mol %), P(CH$_2$Ph)$_3$ (10 mol %), MAD (10 mol %); see ref 5.

In order to promote oxidative addition of the Ar–CN bond, a more electron-rich nickel(0) catalyst prepared from Ni(cod)$_2$/PMe$_3$/MAD was used, which increased the reaction efficiency. Eventually, it was found that the use of Ni(cod)$_2$ (5 mol %), PMe$_3$ (20 mol %), and MAD (10 mol %) generated **3aa** in 80% yield (entry 2). PCy$_3$, PPh$_3$, IPr, and other ligands were less reactive in this case. The cycloaddition reactions of several amides and **2a** were carried out under the optimized conditions. Amides substituted with electron-donating or -deficient aryl groups on the nitrogen atom gave the corresponding quinolones **3ba**, **3ca**, and **3da** in good-to-excellent yields (entries 3–5). A substrate possessing a benzyl group (**1e**) also gave the corresponding product **3ea** in high yield (entry 6).

To extend the applicability of this protocol, various alkynes were evaluated (Table 2). It was found that 2-octyne and 1-methoxy-3-heptyne were also well suited for this reaction (entries 1, 2). 4-Methyl-2-pentyne gave the corresponding adduct **3bd** in low yield under the same conditions mentioned above (entry 3). However, a slight modification of the conditions (using PMe$_2$Ph instead of PMe$_3$ and twice the amount of MAD) increased the yield to 96% (entry 4). Bulkier alkynes (**2e**, **2f**) also reacted with substrate **1b** to afford the relevant cycloadducts in high yields, although a slightly larger quantity of the Lewis acid (20–30 mol %) was required (entries 5, 6). The molecular structures of the major cycloadducts **3bd** and **3be** were determined via X-ray crystal structure analysis (see Supporting Information). Under the conditions listed in entry 4, diphenylacetylene **2g** afforded the corresponding product in 86% yield (entry 7). The monoaryl-substituted internal alkyne **2h** also reacted with **1b** to afford **1bh** in 99% yield (entry 8). Enyne **2i** and diyne **2j** participated in the reaction with **1b** to afford the desired products, **3bi** and **3bj**, in respective yields of 99% and 59% without any evidence of oligomerization of the alkynes (entries 9, 10). Almost all of these examinations were performed without high regioselectivity, except in the case of alkynes possessing the trimethylsilyl group, which may be attributed to the electronic nature of the silyl group. Terminal alkynes such as 1-octyne or phenylacetylene failed to participate in the reaction, because of the rapid oligomerization of the alkynes.

The proposed mechanism for this reaction, shown in Scheme 2, involves the initial oxidative addition of substrate **1** to nickel(0) to form complex **A**.[6–8] Subsequent *ipso*-electrophilic attack of the leaving aryl group affords the seven-membered intermediate **B**.[9] Ensuing elimination

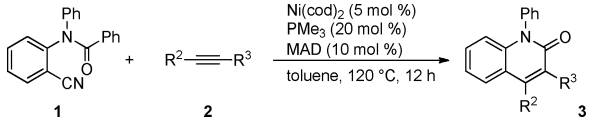
(6) For studies on an oxidative addition of C–CN bond to nickel(0), see: (a) Atesin, T. A.; Li, T.; Lachaize, S.; García, J. J.; Jones, W. D. *Organometallics* **2008**, *27*, 3811. (b) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627. (c) García, J. J.; Arévalo, A.; Brunkan, N. M.; Jones, W. D. *Organometallics* **2004**, *23*, 3997. (d) García, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547. (e) Favero, G.; Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1983**, *241*, 251. (f) Abla, M.; Yamamoto, T. *J. Organomet. Chem.* **1997**, *532*, 267. (g) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360. (h) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1981**, *208*, 103.

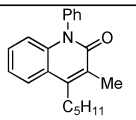
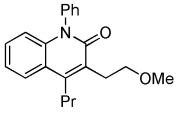
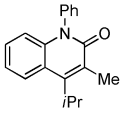
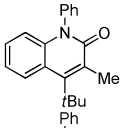
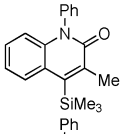
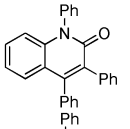
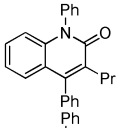
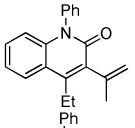
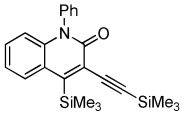
(7) For examples of nickel-catalyzed C–CN bond activation in coupling reactions with organometallic reagents, see: (a) Miller, J. A.; Dankwardt, J. W. *Tetrahedron Lett.* **2003**, *44*, 1907. (b) Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991. (c) Sun, M.; Zhang, H.-Y.; Han, Q.; Yang, K.; Yang, S.-D. *Chem.—Eur. J.* **2011**, *17*, 9566. (d) Liu, N.; Wang, Z.-X. *Adv. Synth. Catal.* **2012**, *354*, 1641. (e) Yu, D.-G.; Yu, M.; Guan, B.-T.; Li, B.-J.; Zheng, Y.; Wu, Z.-H.; Shi, Z.-J. *Org. Lett.* **2009**, *11*, 3374.

(8) For examples of nickel-catalyzed C–CN bond activation in insertion reactions with carbon–carbon unsaturated compounds, see: (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (b) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428. (c) Nakao, Y.; Yukawa, T.; Hirata, Y.; Oda, S.; Satoh, J.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7116. (d) Hirata, Y.; Yukawa, T.; Kashihara, N.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 10964.

(9) A reaction via the same type of *ipso*-electrophilic attack has already been known as the Hayashi rearrangement; see: (a) Hayashi, M. *J. Chem. Soc.* **1927**, 2516. (b) Sandin, R. B.; Melby, R.; Crawford, R.; McGreer, D. *J. Am. Chem. Soc.* **1956**, *78*, 3817.

Table 2. Cycloaddition with Various Alkynes[a]



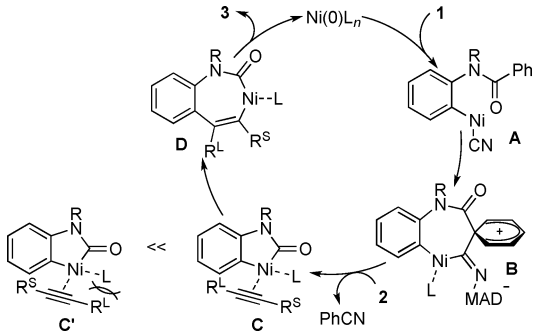
entry	product		yield (%)[b]
1		**3bb**	95 (1/1[e])
2		**3bc**	82 (1/1[e])
3		**3bd**	32 (3/1[e])
4			96[c] (3/1[e])
5		**3be**	71[d] (2/1[e])
6		**3bf**	71[c] (>20/1[e])
7		**3bg**	86[c]
8		**3bh**	99[c] (1/1[e])
9		**3bi**	99[c] (1/1[e])
10		**3bj**	59[c] (>20/1[e])

[a] Reactions were carried out using $Ni(cod)_2$ (5 mol %), PMe_3 (20 mol %), MAD (10 mol %), **1b** (0.5 mmol), and **2** (1.5 mmol) in 3 mL of toluene at 120 °C for 12 h in a sealed tube. [b] Isolated yields are given. [c] Using PMe_2Ph instead of PMe_3, MAD 20 mol %. [d] Using PMe_2Ph instead of PMe_3, MAD 30 mol %. [e] Ratio of regioisomers.

of the nitrile and coordination of alkyne **2** give the five-membered nickelacycle **C**. Finally, the seven-membered nickelacycle **D** is generated after alkyne insertion, and reductive elimination gives quinolone **3** with regeneration of the nickel(0) catalyst. The regioselectivity of the reaction can be rationalized in terms of the direction of alkyne insertion, in which the repulsive steric interaction is minimal between the bulkier R^L group and the ligand (a phosphine or an eliminated nitrile) on the nickel atom, to give the nickel(II) intermediate **C**.

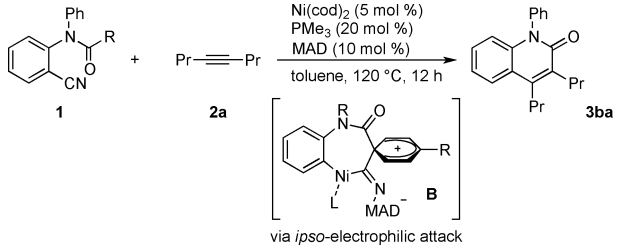
The formation of **B** is consistent with the electron-rich aryl being a stronger leaving group than the

Scheme 2. Proposed Reaction Mechanism



electron-deficient group. The substrate possessing an electron-rich aryl group (**1f**) gave quinolone **3ba** in 82% yield (Table 3, entry 1), whereas the substrates having relatively electron-deficient aryl groups (**1b**, **1g**) afforded **3ba** in lower yields (entries 2, 3). Furthermore, substrates with alkyl groups (**1h**) remained intact under the present nickel-catalyzed reaction conditions.

Table 3. Effect of the Leaving Group[a]



entry	R	yield (%)[b]
1	*p*-$MeOC_6H_4$ (**1f**)	82
2	Ph (**1b**)	80
3	*p*-$CF_3C_6H_4$ (**1g**)	39
4	Me (**1h**)	<1

[a] Reactions were carried out using $Ni(cod)_2$ (5 mol %), PMe_3 (20 mol %), MAD (10 mol %), **1** (0.5 mmol), and **2a** (1.5 mmol) in 3 mL of toluene at 120 °C for 12 h in a sealed tube. [b] Isolated yields.

In conclusion, we have illustrated the efficacy of a new nickel-catalyzed reaction based on carbon−carbon bond cleavage of amides for the synthesis of quinolones. This technique should prove useful for the synthesis of a variety of complicated quinolones from simple substrates. Current efforts are directed toward further clarifying the reaction mechanism and discovering new catalytic processes triggered by carbon−carbon bond activation.

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Supporting Information Available. Experimental procedures including spectroscopic and analytical data of new compounds (PDF) and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.