# Nickel-Catalyzed Cycloaddition of Alkynes and Isocyanates

Hung A. Duong, Michael J. Cross, and Janis Louie*

*Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112-0850*

Received June 14, 2004;  E-mail: louie@chem.utah.edu

Transition metal-catalyzed cycloaddition reactions are a powerful strategy used for preparing heterocycles. In particular, diynes may be coupled to isocyanates to produce 2-pyridones, common heterocyclic motifs in a variety of pharmacologically valuable compounds.[1] Seminal work by Vollhardt demonstrated that Co may be used to facilitate this cycloaddition using isocyanatoalkynes and substituted alkynes, although elevated temperatures (130 °C) and high catalyst loadings (15 mol %) were necessary.[2] More recently, Itoh and co-workers discovered that 2-pyridones could be obtained from α,ω-diynes and isocyanates using a Ru-based catalyst (5 mol %, 90 °C).[3] Ni complexes are also known to oxidatively couple alkynes with isocyanates, but isolable nickelacycles are usually obtained.[4] Takahashi et al. demonstrated that this limitation could be overcome if an azazirconacyclopentenone was first transmetalated with $Ni(PPh_3)_2Cl_2$.[5] Unfortunately, this reaction is stoichiometric in both Ni and Zr.

We recently reported that the addition of N-heterocyclic carbenes (NHCs) to Ni-catalyzed[6] cycloadditions of diynes and $CO_2$ to afford 2-pyrones greatly improved the reaction's performance and substrate scope.[7] We now report that these systems may also be used for catalyzing the cycloaddition of diynes and isocyanates to produce a variety of 2-pyridones in excellent yields.
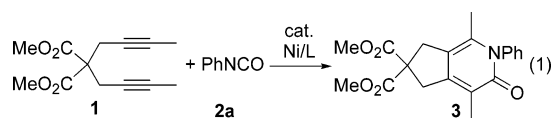


**Table 1.** Ni-Catalyzed Cycloaddition of Diynes and Isocyanates[a]

| entry | L | Ni:L | diyne 1 concn (M) | PhNCO 2 concn (M) | 1 (% conv)[b] | 3 (%)[b] (% dimer 4) |
|---|---|---|---|---|---|---|
| 1 | none | 1:2 | 0.1 | 0.1 | 48 | 3 (6) |
| 2 | $PPh_3$ | 1:2 | 0.1 | 0.1 | 100 | 58 (25) |
| 3 | $PCy_3$ | 1:2 | 0.1 | 0.1 | 88 | 13 (6) |
| 4 | $PtBu_3$ | 1:2 | 0.1 | 0.1 | 29 | 19 |
| 5 | $PnBu_3$ | 1:2 | 0.1 | 0.1 | 47 | 16 (7) |
| 6 | ICy | 1:2 | 0.1 | 0.1 | 24 | 9 (8) |
| 7 | IAd | 1:2 | 0.1 | 0.1 | 37 | 9 (4) |
| 8 | ItBu | 1:2 | 0.1 | 0.1 | 39 | 5 (8) |
| 9 | IMes | 1:2 | 0.1 | 0.1 | 100 | 12 |
| 10 | IPr | 1:2 | 0.1 | 0.1 | 100 | 97 |
| 11 | SIPr | 1:2 | 0.1 | 0.1 | 100 | 100 |
| 12 | SIPr | 1:1 | 0.2 | 0.2 | 90 | 87 |
| 13 | SIPr | 1:1 | 0.1 | 0.1 | 100 | 100 |
| 14 | **SIPr** | **1:1**[c] | **0.1** | **0.1** | **100** | **100** |

[a] Reaction conditions:  5 mol % $Ni(COD)_2$, toluene, room temperature, 30 min. [b] Determined by GC using naphthalene as an internal standard. [c] 3 mol % $Ni(COD)_2$ was employed.

As shown in Table 1, a variety of reaction conditions were screened to maximize 2-pyridone formation. $Ni(COD)_2$ was chosen as the Ni(0) precursor, and dimethyl 2,2-di-but-2-ynyl-malonate (**1**) and phenyl isocyanate (**2a**) were used as model substrates (eq 1). Various tertiary phosphines and NHCs[8] were explored as potential

**Table 2.** Ni-Catalyzed Cycloaddition of Diynes and Isocyanates[a]



| Entry | Diyne | Isocyanate | Product, % Yield[b] |
|---|---|---|---|
| 1 | **1** | **2a** R = H | **3**, 86% |
| 2 | | **2b** R = p-MeO | **5**, 84% |
| 3 | | **2c** R = p-$CF_3$ | **6**, 82%[c,d] |
| 4 | | **2d** R = 2,6-dimethyl | **7**, 82% |
| 5 | **1** | **2e** CyNCO | **8**, 91% |
| 6 | **1** | **2f** BuNCO | **9**, 92% |
| 7 | **10** R=$C(CO_2Me)_2$ | **2f** | **11**, 85%[d] |
| 8 | **12** | **2e** | **13**, 99% |
| 9 | **14** | **2a** | **15**, 78% |
| 10 | **16** | **2a** | **17**, 31% |
| 11 | **18** | **2a** | **19**, 71%[d,e,f] |
| 12 | **18** | **2e** | **20**, 77%[d,e,f] |
| 13 | **18** | **2g** BnNCO | **21**, 61%[d,e] |

[a] Reaction conditions:  0.1 M diyne, 0.1 M isocyanate, 3 mol % $Ni(COD)_2$, 3 mol % SIPr, room temperature. [b] Isolated yields (average of two runs). [c] Reaction run at 80 °C. [d] 5 mol % $Ni(COD)_2$, 5 mol % SIPr. [e] 0.05 M diyne, 0.05 M isocyanate. [f] 4 equiv of isocyanate was used.

ligands for Ni. Attention was directed toward minimizing alkyne cyclotrimerization, a known side reaction.[9] The Ni(0) precursor independently showed very little propensity to catalyze the reaction (entry 1). Although relatively high diyne conversion was observed when tertiary phosphines were included as ligands, only low to moderate yields of 2-pyridone **3** were obtained, and the product mixture contained significant amounts of diyne dimer (**4**) (entries 2–5).[10] Similarly, NHCs such as ICy, IAd, ItBu, and IMes were also relatively poor ligands for enabling Ni to catalyze the reaction

(entries 6−9). However, dramatic improvement was observed when IPr or SIPr were employed, as **3** was formed quantitatively (entries 10 and 11). Although the reaction appeared to be slightly sensitive to concentration (entry 12), the ligand-to-catalyst ratio could be lowered to 1:1 without affecting yield (entry 13).[11] Ultimately, excellent yields were obtained at room temperature using only 3 mol % catalyst (entry 14).

A variety of isocyanates and diynes were subjected to the Ni-catalyzed cycloaddition reaction under optimized conditions (Table 2). Both aryl- and alkylisocyanates were readily converted to the respective 2-pyridone. Although an arylisocyanate bearing an electron-donating group (*p*-OMe, **2b**) readily participated in the cycloaddition reaction, the analogous substrate with an electron-withdrawing group (*p*-CF₃, **2c**) required a higher temperature (80 °C) (entries 2 and 3, respectively). Sterically hindered substrates appeared to have very little affect on the reaction as excellent yields of product were obtained with bulky isocyanates and bulky diynes (entries 4 and 7). Diynes devoid of internal substitution, such as 3,9-dodecadiyne (**12**), also underwent facile cycloaddition (entry 8). The catalyst system was unaffected by a diyne containing an internal amino group (**14**), but a slightly lowered yield of product was observed with the analogous ether (**16**) (entries 9 and 10, respectively). Although dilute conditions were necessary, terminal diynes were also successfully converted to 2-pyridones (entries 11−13).

The formation of seven-membered rings is of great interest in synthetic chemistry since typical macrocyclization routes are often hampered by entropic effects. By increasing reaction temperatures (80 °C), 2,9-undecadiyne (**22**) was found to undergo smooth cycloaddition with butyl isocyanate (**2f**) and afforded 2-pyridone **23** in 36% isolated yield (eq 2). To the best of our knowledge, this is the first example of forming seven-membered rings by cyclo-adding an isocyanate with a diyne.
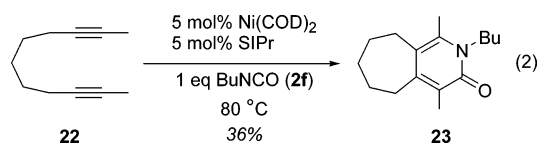


The high efficacy of the catalyst system also prompted us to investigate three-component cycloadditions. Subjecting 3-hexyne and phenyl isocyanate (2 equiv) to the optimized conditions described above (3 mol % catalyst, room temperature) afforded 2-pyridone **24** in excellent isolated yield (90%, eq 3).
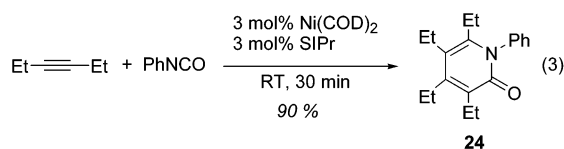


In conclusion, we have developed a mild and efficient method of preparing a wide range of 2-pyridones from diynes and isocyanates. Both intramolecular and intermolecular reactions were catalyzed by a combination of a Ni(0) precursor and an NHC ligand under mild reaction conditions. Investigations focused on expanding the scope of three component cycloadditions and understanding the mechanism of this reaction are currently underway and will be reported in due course.

**Supporting Information Available:** Detailed experimental procedures and compound characterization. This material is is available free of charge via the Internet at http://pubs.acs.org.

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(8) ICy = 1,3-dicyclohexylimidazol-2-ylidene; IAd = 1,3-diadamantylimi-dazol-2-ylidene; I*t*Bu = 1,3-di-*tert*-butylimidazol-2-ylidene; IMes = 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene; IPr = 1,3-bis-(2,6-diiso-propylphenyl)imidazol-2-ylidene; SIPr = 1,3-bis-(2,6-diisopropylphenyl)-imidazolin-2-ylidene.

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(10) In the reaction shown in eq 1, an arene product was identified to be 5-(2,2-bis-methoxycarbonyl-hex-4-ynyl)-4,6,7-trimethyl-indan-2,2-dicarboxyl-ic acid dimethyl ester **4**.
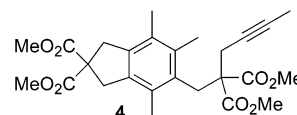


(11) An equilibrium exists between Ni(COD)₂ and SIPr; see ref 7. Thus, Ni-(COD)₂ and SIPr are allowed to stir for 6 h prior to the cycloaddition reaction.

JA046477I