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Copper-catalyzed Addition Reactions of Aromatics and Ketones to 2-Aza-2,4-cyclopentadienone: Facile and Efficient Transformation of Carbonyl-ene-nitriles to 1*H*-Pyrrolin-2(5*H*)-ones

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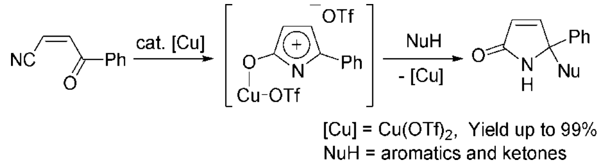
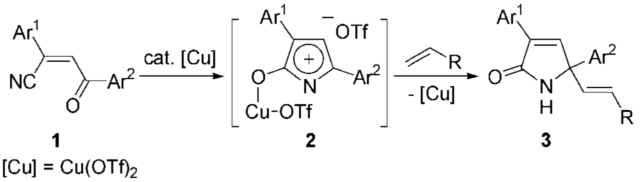
Received August 14, 2008



Copper-catalyzed reactions of carbonyl-ene-nitriles with carbon nucleophiles, such as aromatics and ketones, afforded pyrrolin-2-ones (γ-lactam) in excellent yield. The reaction mechanism involves addition reactions with a ketimine moiety of the 2-aza-2,4-cyclopentadienone intermediate, which is formed via hydration of a nitrile moiety followed by dehydrative cyclization.

Transition metal-catalyzed addition reactions of carbon nucleophiles to imines represent one of the most direct methods for the synthesis of various α-branched primary and secondary amines through the formation of new carbon−carbon bonds.[1] In contrast to the well-studied addition reactions of carbon nucleophiles with aldimines, however, reactions with ketimines are limited because of their poor electrophilicity and steric hindrance.[2,3] Therefore, most reported methods require strong nucleophiles such as organometallic species[2] and trimethylsilyl cyanide.[3] The direct addition reactions of C−H bonds of carbon nucleophiles appear to be even more difficult.[4] In particular, addition reactions of aromatics[5] and ketones to ketimines have been much less explored. To the best of our knowledge, the few existing examples are limited to the reactions of electronically activated ketimines that have electron-withdrawing groups on the imine carbon,[5a,b,d] reactions mediated by stoichiometric Brønsted or Lewis acids,[5a,c,d] or intramolecular reactions.[5d,e] Thus, the development of effective catalytic addition reactions of inactivated carbon nucleophiles to ketimines would be a significant contribution to organic synthesis.

SCHEME 1



In the course of our study on the reactivity of carbonyl-ene-nitrile compounds (**1**[6]) with alkenes, we found an unexpected copper-catalyzed formation of pyrrolin-2-ones (**3**) (Scheme 1).[7] The structure of **3** implies a reaction mechanism involving vinylation of the ketimine moiety of 2-aza-2,4-cyclopentadienone intermediate **2**, which is formed via hydration of a nitrile moiety followed by dehydrative cyclization. Although Gaviña et al. have already reported that nonsubstituted 2-aza-2,4-cyclopentadienone reacts with both enophiles and dienophiles to give the corresponding Diels−Alder adducts,[8] our report was the first example of the reaction via 2-aza-2,4-cyclopentadienone intermediate **2**[9] as an electrophile. This result encouraged us to initiate research on the catalytic addition reactions of C−H

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(3) Transition-metal catalyzed Strecker reactions of ketimines have been well-studied. For recent examples, see: (a) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500. (b) Wang, J.; Hu, X.; Jiang, J.; Gou, S.; Huang, X.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 8468. (c) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147. (d) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153. (e) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476. (f) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (g) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (h) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (i) Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. S. *Tetrahedron: Asymmetry* **1995**, *6*, 349.

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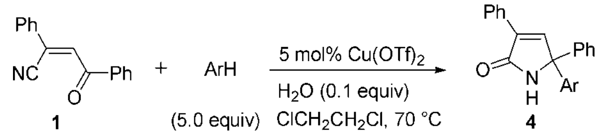
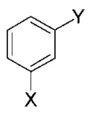
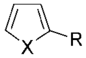
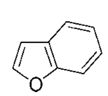
(9) 2-Aza-2,4-cyclopentadienone intermediates were proposed in nickel- and iron-catalyzed tandem cyanation, cyclization, and carboxylation of alkynylketones leading to pyrrolinone derivatives, see: (a) Rosas, N.; Sharma, P.; Arellano, I.; Ramírez, M.; Pérez, D.; Hernández, S.; Cabrera, A. *Organometallics* **2005**, *24*, 4893. (b) Arzoumanian, H.; Jean, M.; Nuel, D.; Garcia, J. L.; Rosas, N. *Organometallics* **1997**, *16*, 2726.

10.1021/jo801776v CCC: $40.75 © 2008 American Chemical Society

TABLE 1. Cu-catalyzed Arylation with Aromatics



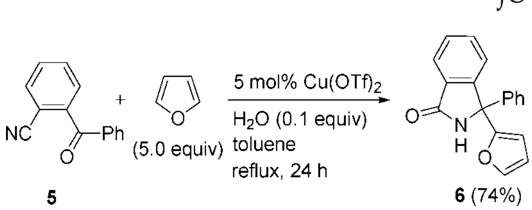
entry	ArH		time (h)	product	yield (%)[a]
1		X = OMe, Y = H	18	**4a + 4a′** [b]	84
2		X = OH, Y = H	3	**4b**	90
3		X = OMe, Y = OMe	8	**4c**	98
4[c]		X = NMe$_2$, Y = H	24	**4d**	77
5		X = O, R = H	3	**4e**	93
6[d]		X = O, R = H	6	**4e**	90
7		X = O, R = Me	3	**4f**	94
8		X = S, R = H	12	**4g**	88
9		X = S, R = Me	3	**4h**	91
10			3	**4i + 4i′** [e]	90

[a] Isolated yields. [b] **4a** (X = OMe, Y = H): **4a′** (X = H, Y = OMe) = 16:1. [c] In toluene at reflux. [d] 1 mol% of Cu(OTf)$_2$ was used. [e] **4i** (3−): **4i′** (2−) = 29:1.

bonds of various nucleophiles to intermediate **2**. We report herein copper-catalyzed addition reactions of carbon nucleophiles, such as aromatics and ketones, to a ketimine moiety of 2-aza-2,4-cyclopentadienone **2**. The resulting pyrrolin-2-ones are an important class of compounds found in a number of naturally occurring alkaloids and are applicable to the synthesis of indolizidine derivatives.

We initiated our investigation using various aromatics as carbon nucleophiles to obtain the Fridel-Crafts type arylated products. When we carried out the reaction of **1** with anisole in the presence of Cu(OTf)$_2$ (5 mol %) and H$_2$O (0.1 equiv) in ClCH$_2$CH$_2$Cl at 70 °C,[10] we obtained 84% yield of the arylated product **4a** as the major product, together with a small amount of the regio isomer **4a′** (Table 1, entry 1). Other electron-rich aromatics, such as phenol and 1,3-dimethoxybenzene, also reacted smoothly with **1** to afford **4b** and **4c** in good to excellent yields, respectively (entries 2 and 3). With *N*,*N*-dimethylaniline, the corresponding arylated product **4d** was obtained in 77% yield, although a prolonged reaction time and higher reaction temperature were required (entry 4). When the reaction of **1** with several heteroaromatic compounds, such as furan, 2-methylfuran, thiophene, 2-methylthiophene, and benzofuran were attempted, the corresponding products **4e**−**4i** were obtained in excellent yields with high regio-selectivities (entries 5−10). In addition, the reaction with furan proceeded successfully even if the catalyst loading was decreased to 1 mol % (entry 6).

The present protocol was also extended to reactions with other carbonyl-ene-nitrile compounds. For example, the reaction of 2-cyanobenzophenone **5** with furan gave the corresponding adduct **6** in 74% yield (eq 1).



(1)

In our previous report,[7] we proposed that the vinylation or ene-type reaction proceeds via the 2-aza-2,4-cyclopentadienone intermediate **2**, which is formed by hydration and dehydrative cyclization. To gain insight into the reaction mechanism, isotopic labeling experiment using the ^{18}O-labeled water (98% ^{18}O) was carried out. Treatment of **1** with furan in the presence of 3 equiv of the ^{18}O-labeled water afforded the ^{18}O-enriched product **4e** (Scheme 2). The high-resolution mass spectrum of the product **4e** showed two sharp peaks at *m*/*z* = 304.1244 (100% intensity) and 302.1168 (94% intensity), indicating 52% ^{18}O incorporation in the product.[11] This isotope-labeling experiment supports the hypothesis that the reaction proceeds via both hydration of a nitrile moiety and dehydrative cyclization between the resulting amide and an original carbonyl group.[12] Attempts to isolate 2-aza-2,4-cyclopentadienone intermediate **2** failed, probably due to its high reactivity.

SCHEME 2

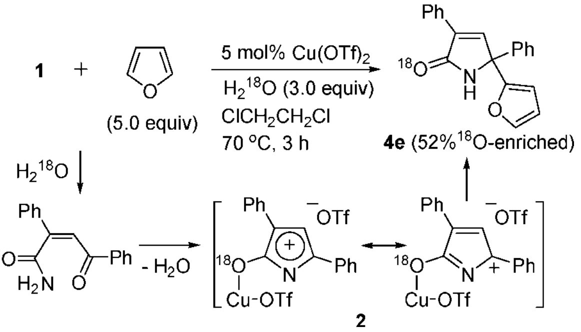
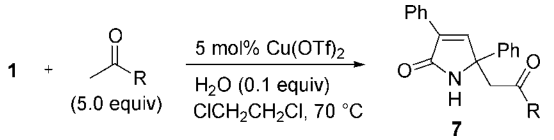


TABLE 2. Cu-catalyzed Mannich-type Reaction with Ketones



entry	R	time (h)	product	yield (%)[a]
1	Ph	24	**7a**	95
2	4-MeOC$_6$H$_4$	3	**7b**	quant
3[b]	4-CF$_3$C$_6$H$_4$	8	**7c**	97
4	Me	6	**7d**	92
5	^{t}Bu	6	**7e**	93

[a] Isolated yields. [b] 80 °C.

As demonstrated above, the ketimine moiety of the 2-aza-2,4-cyclopentadienone **2** reacted effectively with various aromatics. To demonstrate the advantages of the present transformation, we next examined the Mannich-type reaction of **1** with ketones (Table 2).[13] When the reaction of **1** with acetophenone was carried out, *β*-aminoketone **7a** was obtained in 95% yield (entry 1). Both 4-methoxy and 4-trifluoromethylacetophenone reacted with **1** to afford the corresponding products **7b** and **7c** in excellent yields, respectively (entries 2 and 3). Surprisingly,

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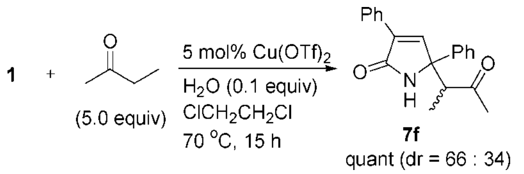
(10) Other transition metal complexes, such as Sc(OTf)$_2$, [RuCl$_2$(CO)$_3$]$_2$, PtCl$_2$, AuCl$_3$, PdCl$_2$, Cu(OTf)-benzene, CuCl, and CuCl$_2$, GaCl$_3$ were ineffective for the reaction.

(11) Theoritical percentage of ^{18}O incorporation would be 75%, when 3 equiv of H$_2$^{18}O to **1** was employed.

(12) No incorporation of ^{18}O in **4e** was observed upon admixture of **4e** with 3 equiv of H$_2$^{18}O in the presence of Cu(OTf)$_2$, which indicates the ^{18}O incorporation during the transformation of **1**.

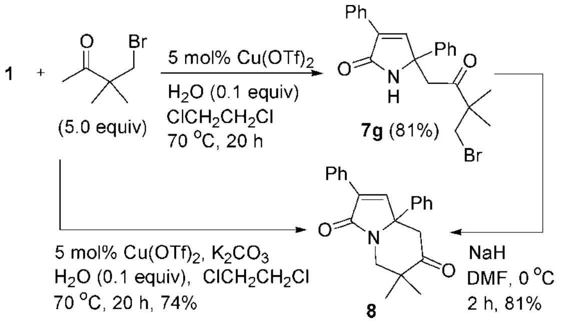
the reaction with aliphatic ketones such as acetone and *tert*-butyl methyl ketone also proceeded smoothly to give the corresponding β-aminoketone **7d** and **7e** in 92 and 93% yields, respectively (entries 4 and 5). Furthermore, **1** reacted with 2-butanone to give the single constitutional isomer **7f** quantitatively as a mixture of diastereomers (d/r = 66:34) (eq 2). The structure of **7f** suggests that 2-aza-2,4-cyclopentadienone **2** from **1** reacts selectively with a thermodynamically stable enol generated from 2-butanone.



(2)

Having established that addition reactions of aromatics and ketones to the ketimine moiety of 2-aza-2,4-cyclopentadienone intermediate lead to substituted pyrrolin-2-ones, we next demonstrated the synthetic application to azabicyclo[4.3.0]nonanone (indolizidinone), which has recently received considerable attention in view of its wide range of biological activities.[14] When the reaction of **1** with 3-bromo-2,2-dimethylbutan-2-one was attempted, the corresponding β-aminoketone was obtained in 81% yield (Scheme 3). The subsequent intramolecular cyclization of **7g** using sodium hydride afforded azabicyclo-[4.3.0]nonanone **8** in 81% yield. Furthermore, one-pot synthesis of **8** from **1** and β-bromoketone was examined in the presence of potassium carbonate as a base. We were delighted to find that **8** was obtained in 74% yield from **1** and β-bromoketone in one pot.

SCHEME 3



In conclusion, we have demonstrated $Cu(OTf)_2$-catalyzed addition reactions of C−H bonds of various aromatics and ketones to the ketimine moiety of 2-aza-2,4-cyclopentadienone intermediate. The reaction proceeds under mild conditions and provides efficient access to synthetically useful pyrrolin-2-ones. The present method might provide an efficient tool for the synthesis of various natural products containing a γ-lactam skeleton, such as salinosporamide A-C, omuralide, lactacystin, PI-091, and lucilactaene.[15] Further studies on application of these reactions to the synthesis of N-heterocycles as natural products including asymmetric transformations are now in progress.

Experimental Section

General Procedure for Copper-catalyzed Reactions of Carbonyl-ene-nitrile Compounds with Aromatics and Ketones leading to 1*H*-Pyrrolin-2(5*H*)-ones. A flame-dried Schlemk flask was charged with $Cu(OTf)_2$ (7.2 mg, 0.020 mmol), carbonyl-ene-nitrile **1** (93.3 mg, 0.40 mmol), distilled water (0.7 μL, 0.040 mmol), and furan (136 mg, 2.0 mmol) in DCE (2.0 mL), and the resulting reaction mixture was stirred at 70 °C for 3 h. The mixture was diluted with diethyl ether and filtered through a short silica gel pad. The organic solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography on silica gel (hexane/AcOEt = 7/1 to 4/1) afforded 3,5-diphenyl-5-(2-furyl)-3-pyrrolin-2-one **4e** as a white solid (112 mg, 93%): mp 141.3−142.5 °C; IR (KBr): 694, 746, 794, 894, 1076, 1153, 1236, 1361, 1446, 1491, 1599, 1687 (C=O), 2852, 3066, 3167 (N−H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.35 (s, 1H), 7.29−7.42 (m, 9H), 7.48 (s, 1H), 7.62 (br, 1H), 7.90 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.1, 107.7, 110.2, 126.1, 127.3, 128.2, 128.4, 128.7, 128.8, 130.7, 134.2, 138.8, 142.9, 143.7, 152.6, 171.8. Anal. calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02. Found: C, 80.00; H, 5.02.

One-pot Synthesis of Azabicyclo[4.3.0]nonanone (6,6-dimethyl-2,8a-diphenyl-5,6,7,8-tetrahydroindolizin-3,7-dione (8)). A flame-dried Schlemk flask was charged with $Cu(OTf)_2$ (7.2 mg, 0.020 mmol), **1** (93.3 mg, 0.40 mmol), distilled water (0.7 μL, 0.040 mmol), potassium carbonate (0.48 mmol), and 3-bromo-2,2-dimethylbutan-2-one (358 mg, 2.0 mmol) in DCE (2.0 mL), and the resulting reaction mixture was stirred at 70 °C for 20 h. The mixture was poured into water (10 mL) and then extracted with Et_2O (20 mL × 3). The combined organic layer was dried over $MgSO_4$. The organic solvent was removed under reduced pressure, and the residue was subjected to flash column chromatography on silica gel (hexane/AcOEt = 7/1 to 4/1) to afford 6,6-dimethyl-2,8a-diphenyl-5,6,7,8-tetrahydro-indolizin-3,7-dione **8** as a pale yellow viscous oil (98 mg, 0.30 mmol, 74% yield). IR (neat): 695, 789, 874, 1139, 1166, 1311, 1401, 1447, 1493, 1691 (C=O), 2867, 2929, 2969 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.22 (s, 3H), 2.71 (d, J = 13.6 Hz, 1H), 2.83 (d, J = 14.8 Hz, 1H), 3.40 (d, J = 14.8 Hz, 1H), 4.28 (d, J = 13.6 Hz, 1H), 7.21−7.28 (m, 3H), 7.30−7.44 (m, 7H), 7.98 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 25.1, 44.1, 44.5, 46.9, 67.9, 126.3, 127.2, 128.5, 128.8, 129.0, 129.3, 130.9, 133.8, 135.7, 145.7, 168.7, 210.2. HRMS (FAB, M + H^{+}): calcd for $C_{22}H_{22}NO_2$: 332.1651. Found: 332.1657.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research (B) (Grant No. 19350093) from the Japan Society for the Promotion of Science (JSPS). M. M. thanks the JSPS Research Fellowships for Young Scientists.

Supporting Information Available: General procedures and characterization of new compounds are provided as a PDF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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