ORGANIC
LETTERS

2006
Vol. 8, No. 8
1557−1559

Alkenenitriles: Zn–Cu Promoted Conjugate Additions of Alkyl Iodides in Water

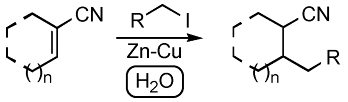
Fraser F. Fleming* and Subrahmanyam Gudipati

Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania 15282-1530

flemingf@duq.edu

Received January 3, 2006

ABSTRACT

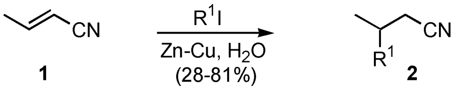


A new silica-supported zinc–copper matrix dramatically promotes conjugate additions of alkyl iodides to alkenenitriles *in water*. Acyclic and cyclic nitriles react with functionalized alkyl iodides, overcoming the previous difficulty of performing conjugate additions to disubstituted alkenenitriles with nonstabilized carbon nucleophiles. Conjugate additions with ω-chloroalkyl iodides generate cyclic nitriles primed for cyclization, collectively providing one of the few annulation methods for cyclic alkenenitriles.

Conjugate additions to alkenenitriles are notoriously difficult.[1] Organometallic conjugate additions are particularly challenging because the powerful electron withdrawal of the nitrile group[2] polarizes the α-carbon more than the β-carbon,[3] often redirecting nucleophilic attack to the nitrile group.[1] Intramolecular conjugate additions with highly nucleophilic organometallic reagents,[4] particularly through temporary chelation,[5] overcome the recalcitrance of alkenenitriles toward conjugate addition and simultaneously identify key features required for intermolecular conjugate addition.

Currently, the most successful *intermolecular* conjugate addition to alkenenitriles involves sonicating zerovalent zinc with alkyl iodides in water−ethanol solutions (Scheme 1).[6]

Scheme 1. Zn−Cu Conjugate Additions to Alkenenitriles[6]



The reaction is remarkably tolerant of functionality in the nitrile and the iodide,[1] which likely reflects the intermediacy of surface-adsorbed radicals as the reactive intermediates.[7] The most pressing challenge for the Zn−Cu method lies in overcoming the steric and electronic deactivation[8] of additional alkyl substitution which prevents conjugate addition to substituted alkenenitriles.[9]

The difficulty of conjugate additions to increasingly substituted alkenenitriles has prevented alkyl additions to

---

(1) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.

(2) (a) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715. (b) Bradamante, S.; Pagani, G. A. *Adv. Carbanion Chem.* **1996**, *2*, 189. (c) Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035. (d) Dayal, S. K.; Ehrenson, S.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 9113.

(3) Reddy, G. S.; Mandell, L.; Goldstein, J. H. *J. Am. Chem. Soc.* **1961**, *83*, 3, 1300.

(4) (a) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353. (b) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305. (c) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165.

(5) (a) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1126. (b) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 7646. (c) Fleming, F. F.; Gudipati, V.; Steward, O. W. *Tetrahedron* **2003**, *59*, 5585.

(6) (a) Dupuy, C.; Petrier, C.; Sarandeses, L. A.; Luche, J. L. *Synth. Commun.* **1991**, *21*, 643. (b) Shono, T.; Nishiguchi, I.; Sasaki, M. *J. Am. Chem. Soc.* **1978**, *100*, 4314.

(7) Sarandeses, L. A.; Mouriño, A.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1992**, 798.

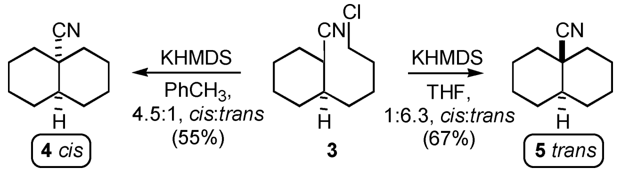
(8) Zhao, M. M.; Qu, C.; Lynch, J. E. *J. Org. Chem.* **2005**, *70*, 6944.

(9) An exception is conjugate additions to alkenenitriles conjugated with additional electron-withdrawing groups which are particularly facile: (a) Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem.* **1997**, *62*, 4883. (b) Wallenfels, K.; Friedrich, K.; Reiser, J.; Ertel, W.; Thieme, H. K. *Angew. Chem., Int. Ed.* **1976**, *15*, 261.

10.1021/ol060010q CCC: $33.50

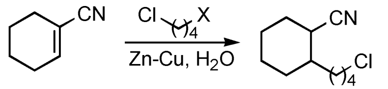
cyclic alkenenitriles, which necessarily have two-ring carbon substituents.[10] Conceptually, conjugate additions of ω-chloroiodoalkanes to cyclic alkenenitriles are particularly attractive because the resulting cyclic nitriles are readily cyclized to ubiquitous ring systems.[11] For example, nitrile **3** is selectively cyclized to the *cis*-decalin **4** in toluene or to the *trans*-decalin **5** simply by judiciously employing THF as the solvent (Scheme 2).[12]

Scheme 2. Solvent-Selective Cyclizations to *cis*- and *trans*-Decalins

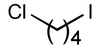
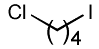
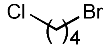
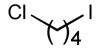


The unique cyclizations of cyclic nitriles stimulated developing conjugate additions of ω-chloroiodoalkanes to cyclic alkenenitriles. Exploratory forays with 1-chloro-4-iodobutane, cyclohexenecarbonitrile (**6c**), and zinc−copper matrix, under standard conditions,[6a] afforded the conjugate addition product **7d** in 4% yield (Table 1, entry 1). An intensive screening of solvent,[6] temperature, stoichiometry, ultrasonic irradiation,[13] matrix,[14] and additives[15] identified ambient water as the best medium. Closely monitoring the reaction revealed a rapid initial consumption of 1-chloro-4-iodobutane accompanied by significant formation of 1,8-dichlorooctane, presumably formed by radical−radical coupling. This suggested generating the surface radical over an extended time period leading to seven sequential additions of the iodide at 1 h intervals[16] with two additional infusions of zinc−copper matrix at 3 h intervals (Table 1, entry 2). The 10-fold increase in yield is consistent with the continuous formation of adsorbed radicals and the diminished efficiency of 1-chloro-4-bromobutane as a radical precursor (Table 1, entry 3).

Table 1. Conjugate Additions to Cyclohexenecarbonitrile (**6c**)



6c **7d**

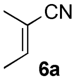
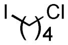
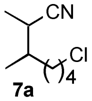
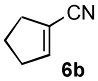
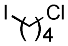
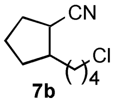
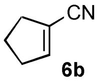
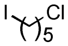
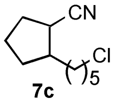
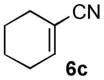
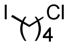
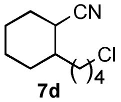
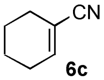
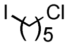
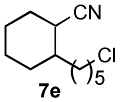
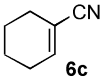
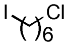
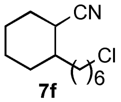
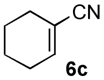
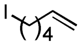
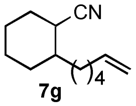
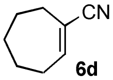
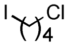
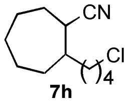
entry	alkyl halide (equivalents)	conditions	yield
1	 (3)	Zn-Cu^a	4%
2	 (8)	Zn-Cu^b	43%
3	 (8)	Zn-Cu^b	33%
4	 (8)	SiO_2-Zn-Cu^c	64%

[a] Standard conditions for Zn−Cu promoted additions except with 3 equiv of iodide with pure water as the solvent.[6a] [b] Using the general procedure without silica gel.[17] [c] Using the general procedure.[17]

Further optimization focused on improving the poor mass recovery in these remarkably clean reactions. Suspecting that the diminished mass balance is due to radical polymerization, the zinc−copper matrix was adsorbed onto silica gel prior to the introduction of nitrile **6c** and 1-chloro-4-iodobutane. The silica-supported zinc−copper matrix dramatically improves the conjugate addition, providing the nitrile **7d** in 64% yield (Table 1, entry 4).

The dramatic effect of the silica-supported zinc−copper matrix is clearly evident from comparative conjugate additions with unmodified zinc−copper matrix (Table 2, compare columns b and a, respectively). In all cases, the silica-supported zinc−copper matrix is significantly more effective in promoting the conjugate addition of alkyl iodides to

Table 2. Alkenenitrile Conjugate Additions with Zn−Cu and Alkyliodides

entry	alkenenitrile	alkyl iodide	alkanenitrile	yield (%)^a	
				a	b
1	 **6a**		 **7a**	17	72
2	 **6b**		 **7b**	45	78
3	 **6b**		 **7c**	36	82
4	 **6c**		 **7d**	43	64
5	 **6c**		 **7e**	56	73
6	 **6c**		 **7f**	64	76
7	 **6c**		 **7g**	-	80
8	 **6d**		 **7h**	-	80

[a] Zinc−copper matrix in water. [b] Silica-supported zinc−copper matrix.

---

(10) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747.

(11) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.

(12) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.

(13) Ultrasonic irradiation was deleterious in contrast to reactions with less highly substituted enones: Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373.

(14) (a) Takai, K.; Ueda, T.; Ikeda, N.; Ishiyama, T.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 347. (b) Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990.

(15) (a) Shukla, P.; Hsu, Y.-C.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 655. (b) Blanchard, P.; Da Silva, A. D.; El Kortbi, M. S.; Fourrey, J.-L.; Machado, A. S.; Robert-Gero, M. *J. Org. Chem.* **1993**, *58*, 6517.

alkenenitriles.[17] The effect is particularly pronounced with the nitrile **6a** (Table 2, entry 1) where the reduced steric demand of the planar, acyclic alkenenitrile likely emanates in a more facile radical polymerization. The silica-supported zinc−copper matrix uniformly promotes conjugate additions to acyclic and cyclic five- to seven-membered nitriles with roughly equal efficacy. *This represents the first general method for the conjugate addition of nonstabilized alkyl groups to disubstituted acyclic and cyclic alkenenitriles.*

Mechanistically, the reaction likely involves the conjugate addition of surface-generated radicals to alkenenitriles.[7] The unique efficacy of the modified matrix (Figure 1) in water may stem from an increased concentration of the organic reagents at the metal surface,[18] localizing the intermediate radical proximal to the alkenenitrile. In this scenario, hydrogen bonding between the nitrile[19] and the silica support may position the β-carbon of the alkenenitrile in close proximity to an alkyl radical adsorbed on an adjacent metal surface. The resulting nitrile-stabilized radical must be rapidly reduced[20] because no cyclization[21] onto the pendant olefin occurs for nitrile **7g** (Table 2, entry 7).

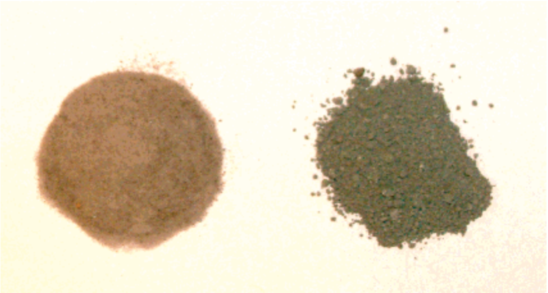
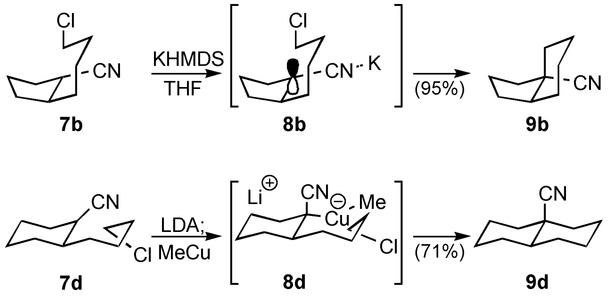


Figure 1. Slica-supported zinc−copper matrix (left) and the conventional matrix (right).

Selective reduction of the carbon−iodine bond enables formation of cyclic chloroalkanenitriles ideally poised for anionic cyclization. Deprotonating **7b** with KHMDS readily generates the *cis*-hydrindane **9b** presumably via the N-potassiated nitrile **8b** (Scheme 2).[11] The centrality of bioactive *trans*-decalins stimulated a new cyclization of **7d** via the putative C-cuprated nitrile **8d** (Scheme 3).[22] Deprotonating **7d** with LDA, transmetallating[22] with methylcopper, and warming the metalated nitrile to room temperature trigger cyclization to the *trans*-decalin **9d**. Exclusive[23] formation of *trans*-decalin **9d** implies a distinctly different mechanism from the cyclizations with amide bases and strongly suggests an equatorially oriented Cu(III) intermediate as the reactive species.[24]

Scheme 3. Hydrindane and Decalin Cyclizations of ω-Halonitriles



Depositing a mixture of zinc dust and copper iodide on silica generates a highly efficient matrix for promoting the conjugate addition of alkyl iodides to alkenenitriles in water. The silica-supported zinc−copper matrix effectively permits the conjugate addition of alkyl iodides to disubstituted alkenenitriles and overcomes the long-standing difficulty of conjugate addition to *cyclic* alkenenitriles. Chloroalkyl iodides are excellent substrates for the conjugate addition, generating functionalized nitriles that are readily cyclized to hydrindane and decalin ring systems.

Acknowledgment. Financial support from the National Science Foundation (CHE 0515715) is gratefully acknowledged.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060010Q

---

[16] The portionwise addition was significantly more effective than a constant addition using a syringe pump.

[17] General Procedure: Water (192 equiv) was added to a stirred mixture of Zn dust (3 equiv, 100 mesh) and powdered CuI (0.5 equiv). After 10 min, silica gel (27 equiv, 230−400 mesh) was added, followed by additional water (192 equiv) and the alkenenitrile (1 equiv). After 15 min, the alkyliodide (1 equiv) was added, followed by seven sequential additions of the iodide (1 equiv) at 1 h intervals. Two additional infusions of Zn (3 equiv) and CuI (0.5 equiv) were added after 3 and 6 h with additional water (192 equiv) added during the last addition. The resulting mixture was stirred overnight and filtered through a glass fritted funnel, and then the crude product was extracted with EtOAc, dried (Na_2SO_4), concentrated, and purified by radial chromatography (1:20 EtOAc/hexanes) to afford analytically pure material.

[18] Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.

[19] Le Questel, J.-Y.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2000**, *13*, 347.

[20] Hydrogen-atom abstraction may occur from a zinc iodide−water complex analogous to trialkylborane reductions in water: Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513.

[21] Newcomb, M.; Horner, J. H.; Filipkowshi, M. A.; Ha, C.; Park, S.-U. *J. Am. Chem. Soc.* **1995**, *117*, 3674.

[22] Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200.

[23] No *cis*-decalin was observed, either in the crude reaction mixture or after purification.

[24] Analogous Cu(III) species were verified as key intermediates during coupling of lithium dimethyl cuprate with halobenzenes,[a] although the lifetime of this intermediate may be short because a Cu(III) intermediate was not detected by ^{13}C NMR during the reaction of Me_2CuLi with 1-bromocyclooctene.[b] (a) Spanenburg, W. J.; Snell, B. E.; Su, M.-C. *Microchem. J.* **1993**, *47*, 79. (b) Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 12264.