# Unsaturated Nitriles: Conjugate Addition−Silylation with Grignard Reagents

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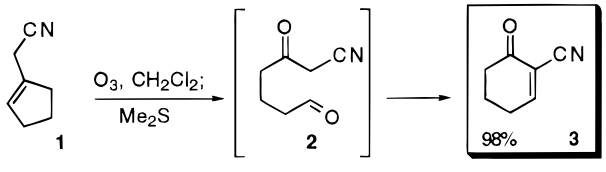
## Introduction

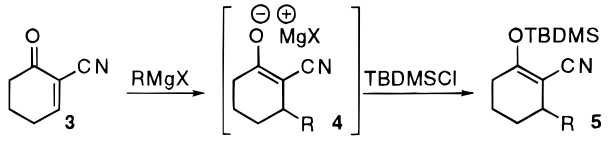
Conjugate addition reactions have occupied a central position in carbon−carbon bond construction for almost 100 years.[1] The first conjugate additions of nonstabilized anions were restricted to reactions of Grignard reagents with activated alkenes bearing multiple aromatic substituents.[2] These limitations have been largely overcome with excellent advances in cuprate chemistry,[3] so that the reaction of nonstabilized anions with conjugated olefins is now relatively routine.[4]

The *uncatalyzed* conjugate addition reactions of organometallics are generating renewed interest. Two potential advantages are stereoselective conjugate additions directed by heteroatoms and improved addition−alkylation sequences that are sometimes problematic with cuprates.[5] Recent examples of uncatalyzed conjugate additions include the use of organolithium,[6] organozinc,[7] and Grignard reagents.[8] The uncatalyzed conjugate addition of Grignard reagents has received the most attention, possibly since Grignard reagents with $sp^3$−Mg bonds are generally easier to prepare than the corresponding organolithium reagents.[9] Grignard reagents have the added advantage that alkoxide-directed additions to enones are highly stereoselective.[10]

Grignard reagents are reported to react conjugately[11] with unsaturated amides, aldimines, malonates, esters,[12] sulfoxides, acids,[13] ketones,[14] and a few nitriles.[15] These reactions fall into two catagories: unsaturated carbonyl compounds with unique stereochemical constraints that prevent 1,2-addition[16] and doubly activated alkenes containing two electron-withdrawing groups on the α-carbon.[17] Our continuing interest in conjugate additions to α,β-unsaturated nitriles[18] led us to prepare several 1-oxo-2-cycloalkene-2-carbonitriles[19] by a highly efficient, one-pot procedure (**1** → **3**). These oxonitriles are extremely reactive Michael acceptors,[20] and in this context we report the conjugate addition of Grignard reagents to the cyclic oxonitrile **3**.




**Scheme 1**




## Results and Discussion

Oxonitrile **3** reacts with Grignard reagents affording good to excellent yields of the corresponding conjugate addition products. For example, methylmagnesium bromide reacts with **3** affording the conjugate adduct in 83% yield (entry 1, Table 1). $^1$H NMR analysis of the crude reaction mixture indicates that the reaction procedes without any competitive 1,2-addition. Protonation of the intermediate enolate **4** (R = Me) generates a diastereomeric mixture of ketonitriles, and therefore the intermediate enolates are silylated to provide the more easily characterized unsaturated nitriles **5** (Scheme 1).

The reaction of Grignard reagents with **3** is highly regioselective. Only in the case of *tert*-butylmagnesium bromide have we observed any 1,2-addition products in the crude reaction mixture. The ability to *conjugately* transfer a *tert*-butyl group from a Grignard reagent is highly unusual, and this is, to the best of our knowledge, the first report of an uncatalyzed conjugate addition with *tert*-butylmagnesium bromide. Both $sp^2$- and $sp^3$-hybridized Grignards react with equal efficacy (compare entries 1 and 2), and the reaction is effective with both aromatic and aliphatic Grignard reagents.

The reaction efficiency exhibits a dependence on the size of the Grignard reagent (compare entries 1 and 2 with entries 3−6). The lower yields may result from a

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(6) (a) Cooke, M. P., Jr. *J. Org. Chem.* **1993**, *58*, 6833. (b) Hunt, D. A. *Org. Prep. Proc. Int.* **1989**, *21*, 705.

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(14) Grignard reagents usually react in a 1,2-sense although the proportions of 1,2- and 1,4-addition are dependent upon solvent basicity: Gocmen, M.; Soussan, G. *J. Organomet. Chem.* **1974**, *80*, 303.

(15) (a) Kruger, D.; Sopchik, A. E.; Kingsbury, C. A. *J. Org. Chem.* **1984**, *49*, 778. (b) Gupte, S. D.; Sunthankar, S. V. *J. Org. Chem.* **1959**, *24*, 1334.

(16) (a) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131. (b) Modi, S. P.; Gardner, J. O.; Milowsky, A.; Wierzba, M.; Forgione, L.; Mazur, P.; Solo, A. J.; Daux, W. L.; Galdecki, Z.; Grochulski, P.; Wawrzak, Z. *J. Org. Chem.* **1989**, *54*, 2317. (c) Ireland, R. E.; Baldwin, S. W.; Welch, S. C. *J. Am. Chem. Soc.* **1972**, *94*, 2056. (d) Ireland, R. E.; Baldwin, S. W.; Dawson, D. J.; Dawson, M. I.; Dolfini, J. E.; Newbould, J.; Johnson, W. S.; Brown, M.; Crawford, R. J.; Hudrlik, P. F.; Rasmussen, G. H.; Schmiegel, K. K. *J. Am. Chem. Soc.* **1970**, *92*, 5743. See also ref 11, pp 72−99.

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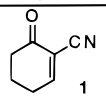
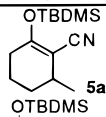
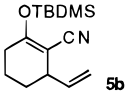
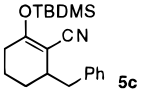
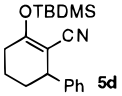
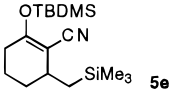
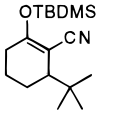
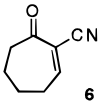
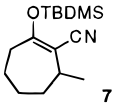
S0022-3263(97)00543-4 CCC: $14.00 

**Table 1. Conjugate Addition−Enolate Silylation of Unsaturated Ketonitriles**

| Entry | Substrate | RMgX | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **1** | MeMgBr |  **5a** | 83 |
| 2 | **1** | $CH_2CHMgBr$ |  **5b** | 84 |
| 3 | **1** | BnMgCl |  **5c** | 61 |
| 4 | **1** | PhMgBr |  **5d** | 55 |
| 5 | **1** | $Me_3SiCH_2MgCl$ |  **5e** | 59 |
| 6 | **1** | *t*-BuMgBr |  **5f** | 65 |
| 7 |  **6** | MeMgBr |  **7** | 23 |

slower conjugate addition allowing the intermediate enolate **4** to accumulate before all of the oxonitrile **3** is consumed. A subsequent Michael condensation between **4** and **3** will afford oligomers as has been observed in related systems[21] and in the reaction of methylmagnesium bromide with **6**[19] (Table 1, entry 7).

## Conclusion

1-Oxo-2-cyclohexene-2-carbonitrile (**3**) reacts conjugately with a variety of Grignard reagents. The reaction is rapid and efficient, and the intermediate enolates are readily silylated. The overall procedure exploits the high reactivity of oxonitriles and represents a new and expediant method for preparing cyclic unsaturated nitriles.

## Experimental Section

General experimental details are the same as those previously reported.[18b] $^1$H NMR spectra were recorded at 300 MHz, while $^{13}$C NMR spectra were recorded at 75 MHz.

**General Procedure.** A THF or ether solution of the Grignard reagent (1.2 equiv) was added, by syringe, to a cold (−78 °C) THF solution of **3** (1 equiv). After 30 min TBDMSCl (1.5 equiv) was added, and then the resultant solution was allowed to warm to room temperature overnight. Saturated, aqueous ammonium chloride was then added to the reaction mixture, the aqueous phase was extracted with EtOAc (3 × 10 mL), and the extracts were combined and then dried over anhydrous sodium sulfate. The crude material was concentrated under reduced pressure and purified by radial chromatography.

**2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-1-cyclohexene-1-carbonitrile (5a).** The general procedure was employed with **3** (51.2 mg, 0.43 mmol), methylmagnesium bromide (1 M solution in ether, 0.52 mmol), and TBDMSCl (97.2 mg, 0.64 mmol) in 2 mL of THF. Chromatography of the crude reaction mixture (1 mm plate, 2:3 EtOAc:hexane) provided 87.9 mg (83%) of **5a** as an oil: IR (film) 2210, 1626 cm$^{-1}$; $^1$H NMR $\delta$ 0.23 (s, 6H), 0.98 (s, 9H), 1.16 (d, $J$ = 6.9 Hz, 3H), 1.19−1.35 (m, 1H), 1.56−1.81 (m, 3H), 2.11−2.15 (m, 2H), 2.41−2.47 (m, 1H); $^{13}$C NMR $\delta$ −3.8, 18.1, 20.0, 20.7, 25.5, 30.1, 30.3, 30.9, 96.5, 118.3, 165.0.

**2-[(*tert*-Butyldimethylsilyl)oxy]-6-vinyl-1-cyclohexene-1-carbonitrile (5b).** The general procedure was employed with **3** (54.4 mg, 0.45 mmol), vinylmagnesium bromide (1 M solution in THF, 0.54 mmol), and TBDMSCl (101.1 mg, 0.67 mmol) in 2 mL of THF. Chromatography of the crude reaction mixture (1 mm plate, 1:19 EtOAc:hexane) provided 98.9 mg (84%) of **5b** as an oil: IR (film) 3082, 2210, 1626 cm$^{-1}$; $^1$H NMR $\delta$ 0.24 (s, 6H), 0.98 (s, 9H), 1.43−1.81 (m, 4H), 2.15 (bt, $J$ = 5 Hz, 2H), 3.02 (bs, 1H), 5.11−5.17 (m, 2H), 5.75 (bddd, $J$ = 16, 11, 7.2 Hz, 1H); $^{13}$C NMR $\delta$ −3.7, 18.1, 19.0, 25.5, 27.7, 30.8, 39.8, 93.3, 116.3, 118.3, 165.9.

**6-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]-1-cyclohexene-1-carbonitrile (5c).** The general procedure was employed with **3** (57.7 mg, 0.47 mmol), benzylmagnesium chloride (1 M solution in ether, 0.57 mmol), and TBDMSCl (107.3 mg, 0.71 mmol). Chromatography of the crude reaction mixture (1 mm plate, hexane, 1:49 and 1:19 EtOAc:hexane) provided 95.2 mg (61%) of **5c** as an oil: IR (film) 3021, 2208, 1633, 1595 cm$^{-1}$; $^1$H NMR $\delta$ 0.19 (s, 3H), 0.20 (s, 3H), 0.95 (s, 9H), 1.15−1.26 (m, 1H), 1.41−1.58 (m, 2H), 1.64−1.74 (m, 1H), 2.09 (btd, $J$ = 6, 1.6 Hz, 2H), 2.43 (dd, $J$ = 13, 10.6 Hz, 1H), 2.49−2.57 (m, 1H), 3.14 (dd, $J$ = 13.0, 3.2 Hz, 1H), 7.12−7.27 (m, 5H); $^{13}$C NMR $\delta$ −3.8, 18.0, 19.4, 25.5, 25.8, 31.0, 37.2, 40.6, 95.3, 118.4, 126.2, 128.3, 129.2, 139.4, 166.0; MS *m/e* 312 (M − $CH_3$).

**2-[(*tert*-Butyldimethylsilyl)oxy]-6-phenyl-1-cyclohexene-1-carbonitrile (5d).** The general procedure was employed with **3** (49.4 mg, 0.41 mmol), phenylmagnesium bromide (1 M solution in THF, 0.49 mmol), and TBDMSCl (91.8 mg, 0.61 mmol). Chromatography of the crude reaction mixture (1 mm plate, 1:49 EtOAc:hexane) provided 70.0 mg (55%) of **5d** as a white, crystalline[22] solid (mp 76.5−77.5 °C): IR (KBr) 3068, 3035, 2207, 1622 cm$^{-1}$; $^1$H NMR $\delta$ 0.28 (s, 3H), 0.29 (s, 3H), 1.00 (s, 9H), 1.56−1.77 (m, 3H), 1.92−1.98 (m, 1H), 2.22−2.27 (m, 2H), 3.63−3.68 (m, 1H), 7.18−7.35 (m, 5H); $^{13}$C NMR $\delta$ −3.7, −3.6, 18.2, 19.3, 25.6, 31.0, 42.4, 94.0, 118.2, 126.9, 127.8, 128.6, 143.0, 166.6; MS *m/e* 314 (M + H), 256 (M − *t*-Bu).

**2-[(*tert*-Butyldimethylsilyl)oxy]-6-[(trimethylsilyl)methyl]-1-cyclohexene-1-carbonitrile (5e).** The general procedure was employed with **3** (46.5 mg, 0.38 mmol), [(trimethylsilyl)-methyl]magnesium chloride (1 M solution in ether, 0.46 mmol), and TBDMSCl (86.4 mg, 0.57 mmol). Chromatography of the crude reaction mixture (1 mm plate, 1:49, 1:19, and 1:9 EtOAc: hexane) provided 73.3 mg (59%) of **5e** as an oil: IR (film) 2207, 1626, 837 cm$^{-1}$; $^1$H NMR $\delta$ 0.04 (s, 9H), 0.22 (s, 3H), 0.23 (s, 3H), 0.58 (dd, $J$ = 14.7, 11.7 Hz, 1H), 0.97 (s, 9H), 1.14 (bdd, $J$ = 15, 3.1 Hz, 1H), 1.17−1.25 (m, 1H), 1.47−1.62 (m, 1H), 1.76−1.84 (m, 2H), 2.09−2.14 (m, 2H), 2.40−2.45 (m, 1H); $^{13}$C NMR $\delta$ −3.8, −0.6, 18.1, 20.3, 23.2, 25.5, 29.8, 30.8, 32.2, 98.8, 118.7, 164.3; MS *m/e* 250 (M − $SiMe_3$).

**6-*tert*-Butyl-2-[(*tert*-butyldimethylsilyl)oxy]-1-cyclohexene-1-carbonitrile (5f).** The general procedure was employed with **3** (33.0 mg, 0.27 mmol), *tert*-butylmagnesium chloride (1 M solution in THF, 0.33 mmol), and TBDMSCl (61.4 mg, 0.41 mmol). Chromatography of the crude reaction mixture (1 mm plate, 1:19 and 1:9 EtOAc:hexane) provided 51.7 mg (65%) of **5f** as an oil: IR (film) 2207, 1607, 829 cm$^{-1}$; $^1$H NMR $\delta$ 0.22 (s, 3H), 0.25 (s, 3H), 0.98 (s, 9H), 1.03 (s, 9H), 1.25−1.86 (m, 4H), 2.11−2.14 (m, 2H), 2.24 (bt, $J$ = 7 Hz, 1H); $^{13}$C NMR $\delta$ −3.7, 18.2, 21.0, 24.5, 25.6, 28.6, 31.2, 34.8, 45.2, 93.5, 120.4, 168.3; MS *m/e* 294 (M + H).

**2-[(*tert*-Butyldimethylsilyl)oxy]-7-methyl-1-cycloheptene-1-carbonitrile (7).** The general procedure was employed with 1-oxo-2-cycloheptene-2-carbonitrile (**6**)[19] (101.1 mg, 0.75 mmol), methylmagnesium bromide (1 M solution in ether, 0.90 mmol), and TBDMSCl (168.6 mg, 1.12 mmol) in 2 mL of THF. Chromatography of the crude reaction mixture (1 mm plate, 2:3 EtOAc:hexane) provided 45.8 mg (23%) of **7** as an oil: IR (film) 2203, 1614 cm$^{-1}$; $^1$H NMR $\delta$ 0.23 (s, 6H), 0.97 (s, 9H), 1.19 (d, $J$ = 7.2 Hz, 3H), 1.37−1.70 (m, 5H), 1.86−1.91 (m, 1H), 2.21−2.29 (m, 1H), 2.42−2.54 (m, 2H); $^{13}$C NMR $\delta$ −3.3, 18.5, 21.4, 24.4, 26.0, 29.6, 32.2, 35.4, 36.2, 100.5, 119.1, 170.9; MS *m/e* 266 (M + H).

(21) Munch-Petersen, J. *J. Org. Chem.* **1957**, *22*, 170.

(22) Fleming, F. F.; Pu, Y.; Norman, R. E.; Chang, S.-C. *Acta Crystallogr.*, submitted for publication.

**Acknowledgment.** Financial support from the Jacob and Frieda Hunkele Charitable Foundation and the Kresge Foundation is gratefully acknowledged.

**Supporting Information Available:** $^{1}H$ and $^{13}C$ NMR spectra of all new compounds (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9705430

# *Additions and Corrections*

Vol. 61, 1996

**Yoko Nakajima Yamakoshi, Takeshi Yagami, Shoko Sueyoshi, and Naoki Miyata*.** Acridine Adduct of [60]Fullerene with Enhanced DNA-Cleaving Activity.

Page 7237. The last sentence in the left column, "The previously reported ...", and ref 20 should be changed as follows:

Recently DNA-cleaving activities of several $C_{60}$ derivatives have been reported,[20] and we examined the enhancement of DNA-cleaving activity of compound **4** compared with $C_{60}$.

(20) (a) Tokuyama, H.; Yamago, S.; Nakamura, E.; Shiraki, T.; Sugiura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 7918−7919. (b) Boutorine, A. S.; Tokuyama, H.; Takasugi, M.; Isobe, H.; Nakamura, E.; Hélène C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2462−2465. (c) An, Y.-Z.; Chen, C.-H. B.; Anderson, J. L.; Sigman, D. S.; Foote, C. S.; Rubin, Y. *Tetrahedron* **1996**, *52*, 5179−5189.

JO974003E

Vol. 61, 1996

**Okiko Miyata, Tomoko Koizumi, Ichiya Ninomiya, and Takeaki Naito*.** New Imino-Wittig Rearrangement of Benzyl and Allyl Hydroximates.

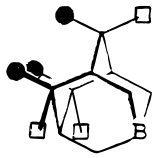
Page 9078, column 1, 8th line. With respect to the sentence "However, migration of an imino group ($R^1$: RC═NR) to a negatively charged carbon has not been reported so far.", we regret our failure to cite an earlier study in which the first imino-Wittig rearrangement had previously been reported: Katritzky, A. R.; Ponkshe, N. K. *Tetrahedron Lett.* **1981**, *22*, 1215−1216.

JO974007J

Vol. 61, 1996

**Elena M. Gonikberg, Francis Picart, and William J. le Noble*.** Enhanced Stereoselectivity in the Capture of a 5-Substituted 2-Adamantyl Radical by Substitution of C-5 by Negative Boron.

Page 9589. The structure shown in Figure 1 should be replaced by




In the caption of Figure 2, the words "top" and "bottom" should be interchanged. The conclusions are not affected. The authors are indebted to Professor William Adcock for alerting them to the need for these changes.

JO974006R

Vol. 62, 1997

**Michael Harmata* and Darin E. Jones.** Vinyl Oxocarbenium Ions in Intermolecular [4 + 3] Cycloaddition Reactions.

Page 1578. The pioneering studies by Lee and coworkers on functionalized allylsilanes were inadvertantly not acknowledged. The relevant references are given below:

(1) Lee, T. V.; Porter, J. R. *Org. Synth.* **1993**, *72*, 189.
(2) Lee, T. V.; Boucher, R. J.; Porter, J. R.; Taylor, D. A. *Tetrahedron* **1988**, *44*, 4233.
(3) Lee, T. V.; Porter, J. R.; Roden, F. S. *Tetrahedron Lett.* **1988**, *29*, 5009.
(4) Lee, T. V.; Richardson, K. A.; Taylor, D. A. *Tetrahedron Lett.* **1986**, *27*, 5021.

JO9740094