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Oxonitriles: A Grignard Addition–Acylation Route to Enamides

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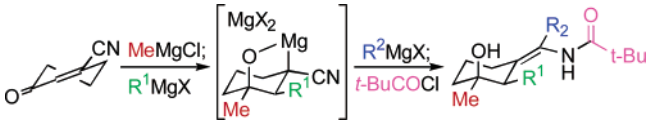
ABSTRACT

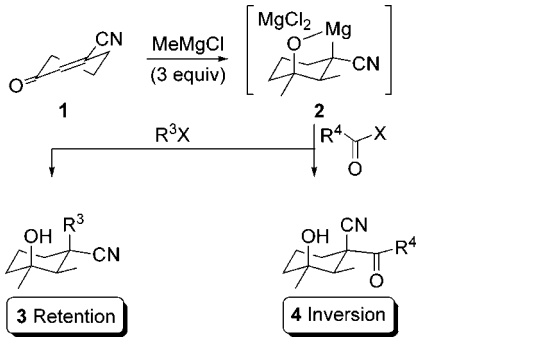


Sequential addition of three different Grignard reagents and pivaloyl chloride to 3-oxo-1-cyclohexene-1-carbonitrile installs four new bonds to generate a diverse array of cyclic enamides. Remarkably, formation of the C-magnesiated nitrile intermediate is followed by preferential acylation by pivaloyl chloride rather than consumption by an in situ Grignard reagent. Rapid N-acylation of the C-magnesiated nitrile generates an acyl ketenimine that reacts readily with Grignard reagents or a trialkylzincate, effectively assembling highly substituted, cyclic enamides.

Cyclic oxonitriles incorporate chemically distinct functionalities ideally suited for multicomponent reactions.[1] Historically, the synergistic reactivity of oxonitriles was first harnessed in regioselective Robinson annulations[2] and elegantly employed in several natural product syntheses.[3] Subsequently, zipper reactions,[4] addition−fragmentations,[5] and cycloaddition−cycloreversion[6] reactions have exploited oxonitriles in domino reaction sequences for rapidly installing high molecular complexity.

Unsaturated cyclic oxonitriles incorporate three different functionalities capable of selective deployment en route to highly substituted cyclic nitriles (Scheme 1).[7] Addition of excess methylmagnesium chloride to 3-oxo-1-cyclohexene-1-carbonitrile (**1**)[8] affords the C-magnesiated nitrile **2** that alkylates a diverse range of electrophiles. Intriguingly, alkylations of the C-magnesiated nitrile **2** are stereoelectronically controlled, with alkyl halide and sulfonate elec-

Scheme 1. Grignard Addition−Alkylations of Oxonitrile **1**



(1) Fleming, F. F.; Iyer, P. *Synthesis* **2006**, 893.

(2) For Robinson annulations with β-oxonitriles, see: (a) Ref 1. (b) Varner, M. A.; Grossman, R. B. *Tetrahedron* **1999**, *55*, 13867. (c) Gawley, R. E. *Synthesis* **1976**, 777. (d) Jung, M. E. *Tetrahedron* **1976**, *32*, 3. For Robinson annulations with γ-oxonitriles, see: (e) Sobolev, A.; Vos, M.; Zuilhof, H. T.; Sarabèr, C. E.; Jansen, B. J. M.; de Groot, A. *Arkivoc* **2005**, 39. (f) Swarts, H. J.; Verstegen-Haaksma, A. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10083. (g) Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073. (h) Inubushi, Y.; Kikuchi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K. *Chem. Pharm. Bull.* **1974**, *22*, 349. (i) Loewenthal, H. J. E. *Isr. J. Chem.* **1966**, *4*, 31.

(3) For recent examples, see: (a) Liu, H.-J.; Ly, T. W.; Tai, C.-L.; Wu, J.-D.; Liang, J.-K.; Guo, J.-C.; Tseng, N.-W.; Shia, K.-S. *Tetrahedron* **2003**, *59*, 1209. (b) Olkhovik, V.; Masalov, N.; Jansen, B. J. M.; Groot, A. de. *Tetrahedron Lett.* **2001**, *42*, 4903.

(4) (a) Ivancev, W.; Ognyanov, V. I.; Hesse, M. *Tetrahedron* **1996**, *57*, 4363. (b) Ognyanov, V. I.; Hesse, M. *Helv. Chim. Acta* **1990**, *73*, 272. (c) Ognyanov, V. I.; Hesse, M. *Helv. Chim. Acta* **1989**, *72*, 1522.

(5) Cocker, W.; Grayson, D. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1153.

(6) (a) Aundenaert, F.; Keukeleire, D. De; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593. (b) Keukeleire, D. De; Audenhove, M. Van; Hijfte, L. Van; Audenaert, F.; Vandewalle, M. *J. Photochem.* **1985**, *28*, 165.

(7) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 1126.

(8) Fleming, F. F.; Zhang, Z.; Wei, G. *Synthesis* **2005**, 3179.

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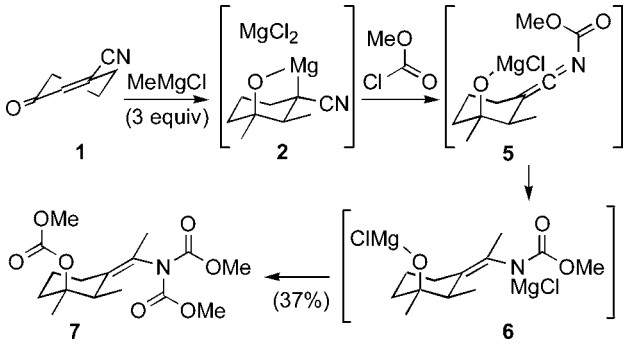
trophiles alkylating with retention of stereochemistry (**2**→**3**) and aldehyde and acyl cyanide electrophiles alkylating with inversion of stereochemistry (**2**→**4**).[9] Synthetically, the addition−alkylation installs three new stereocenters in which the stereochemistry of the nitrile-bearing carbon can be controlled through judicious choice of electrophile.

Remarkably, alkylating the C-magnesiated nitrile **2** with methyl chloroformate affords neither of the nitriles **3** or **4**. Adding excess MeMgCl to oxonitrile **1** and intercepting **2** with excess methyl chloroformate led to the incorporation of three new carbonyl functionalities and complete loss of the C≡N functionality! Spectral analysis identified the product as the enamide **7** (Scheme 2), presumably resulting

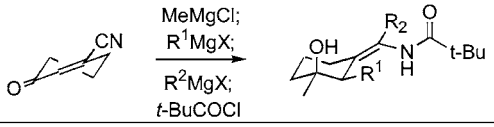
Scheme 2. Grignard Addition−Acylation of Oxonitrile **1**

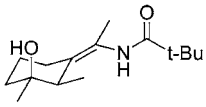
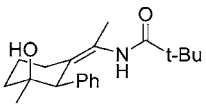
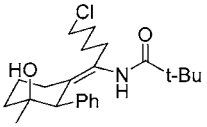
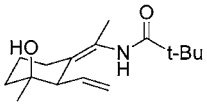
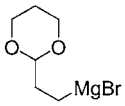
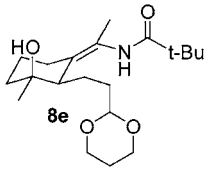
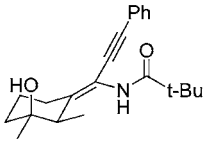
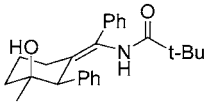
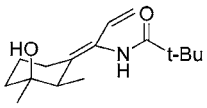
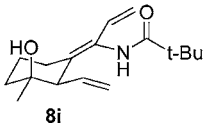


from a rare[10] N-acylation of the C-magnesiated nitrile **2**. Rapid addition of excess MeMgCl to the transient[11] acyl ketenimine[12] **5**, followed by sequential N- and O-acylation of the resulting magnesiated enamide **6**, leads to the enamide **7**. Overall, the Grignard addition−acylation sequence installs six new bonds in one synthetic operation!

Experimentally, only 2 of the 3 equiv of MeMgCl is consumed by the oxonitrile **1** prior to the addition of methyl chloroformate. Consequently, at −78 °C, methyl chloroformate must react more slowly with MeMgCl than with the metalated nitrile **2**! Armed with the speculation that methyl chloroformate might react competitively with MeMgCl and the metalated nitrile **2**, the reaction was repeated with excess pivaloyl chloride as a larger, more chemoselective electro-

Table 1. Oxonitrile Addition−Acylation Enamides Synthesis



entry	Grignard reagents R^1MgX	R^2MgX	enamide	yield(%)
1	MeMgCl	MeMgCl	 **8a**	57
2	PhMgBr	MeMgCl	 **8b**	73[a]
3	PhMgBr		 **8c**	40
4		MeMgCl	 **8d**	69
5		MeMgCl	 **8e**	69
6	MeMgCl	Ph-≡-MgCl	 **8f**	50
7	PhMgBr	PhMgBr	 **8g**	47[a,b]
8	MeMgCl		 **8h**	59
9			 **8i**	40[b]

[a] The structure was confirmed by X-ray crystallography.[16] [b] Incremental portions of the Grignard reagent and pivaloyl chloride were added at 0 °C.

(9) (a) Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2006**, *71*, 1430. (b) Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *Org. Lett.* **2005**, *7*, 447.

(10) Metalated nitriles alkylate almost exclusively on carbon with silyl[a−e] and acetyl chlorides[f] being virtually the only electrophiles with a propensity for reaction on nitrogen: (a) Kawakami, Y.; Hisada, H.; Yamashita, Y. *Tetrahedron Lett.* **1985**, *26*, 5835. (b) Differding, E.; Vandevelde, O.; Roekens, B.; Van, T. T.; Ghosez, L. *Tetrahedron Lett.* **1974**, *28*, 397. (c) Watt, D. S. *Synth. Commun.* **1974**, *4*, 127. (d) Kruger, C. R.; Rochow, E. G. *Angew. Chem., Int. Ed.* **1963**, *2*, 617. (e) Prober, M. *J. Am. Chem. Soc.* **1956**, *78*, 2274. (f) Enders, D.; Kirchhoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, *63*, 3.

(11) Attempts to detect the intermediate acyl ketenimine have not been successful, consistent with their known instability: (a) Ref 10f. (b) Finnerty, J.; Mitschke, U.; Wentrup, C. *J. Org. Chem.* **2002**, *67*, 1084. (c) Meier, S.; Wuerthwein, E. U. *Chem. Ber.* **1991**, *124*, 2339. (d) Schweng, J.; Zbiral, E. *Monatsh. Chem.* **1976**, *107*, 537.

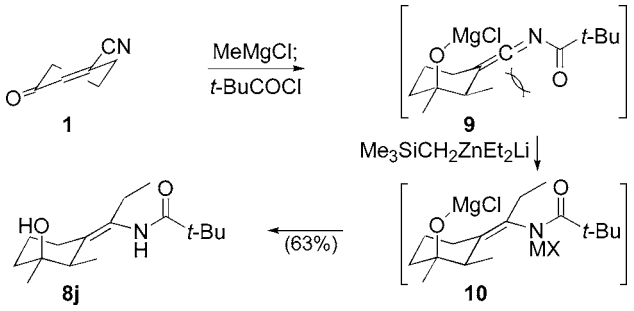
(12) Alajarín, M.; Vidal, A.; Tover, F. *Targets Heterocycl. Syst.* **2000**, *4*, 293.

phile.[13] Indeed, acylating **2** with excess pivaloyl chloride at 0 °C affords enamide **8a** considerably more efficiently (Table 1, entry 1).[14]

Sequential addition of three different Grignard reagents and pivaloyl chloride to oxonitrile **1** generates a diverse array of substituted enamides (Table 1).[15] Significant diversity is achieved through the sequential addition of three different Grignard reagents: to the carbonyl group, to the alkenenitrile, and to the acyl ketenimine. Effectively, the strategy provides excellent control over the substitution pattern simply by varying the addition order (Table 1, compare entry 4 with entry 8). Grignard reagents with sp^3 or sp^2 hybridization of the carbon−magnesium bond are required for the conjugate addition, whereas the nucleophilic attack on the reactive acyl ketenimine tolerates all hybridization types.

Nucleophilic attack on the acyl ketenimine intermediates generates highly congested enamides. X-ray crystallography[16] of **8b** and **8g** secures an enamide geometry consistent with a nucleophilic addition of Grignard reagents to the more accessible face of the acyl ketenimine intermediate **9** (Scheme 3).[17] The resulting enamides experience consider-

Scheme 3. Organozinc Addition−Acylation



able steric compression between the amide nitrogen and the allylic substituent as illustrated in the crystal structure for **8g** where the steric interaction is relieved in a chair conformation with the phenyl substituent in an axial orientation (Figure 1).[18]

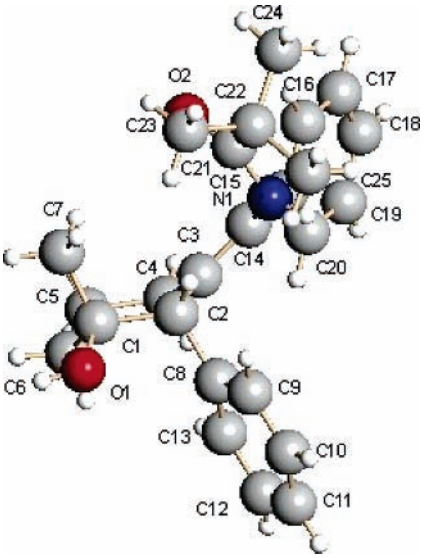


Figure 1. Crystallographic structure of enamide **8g**.

Attempts to isolate the putative acyl ketenimine **9** provided key mechanistic insight (Scheme 3). Addition of excess pivaloyl chloride in the absence of a Grignard reagent failed to afford the acyl ketenimine **9** (H = MgCl), which is consistent with the instability of this reactive species.[11] Presumably, a slow reaction of pivaloyl chloride with Grignard reagents permits rapid interception of the acyl ketenimine by the nucleophilic organomagnesium reagent immediately upon formation. In some instances, acylation of the C-magnesiated nitrile is slow, resulting in removal of the pivaloyl chloride by the Grignard reagent. In these cases (Table 1, entries 7 and 9), the portionwise addition of the Grignard reagent and pivaloyl chloride permits higher conversions.

The instability, and presumed high reactivity, of the acyl ketenimine **9** suggested intercepting this electrophile with less nucleophilic organometallics. Intercepting **9** with Et_2Zn in the presence of pivaloyl chloride affords the expected enamide **8j**, although in a disappointing 11% yield (Scheme 3). Assuming Et_2Zn to be insufficiently reactive, the portionwise addition was repeated with a mixed trialkylzincate formed by adding Me_3SiCH_2Li to Et_2Zn.[19] Selective transfer of the ethyl group led to formation of the enamide **8j** in 63% yield.

Sequential addition of three different Grignard reagents and pivaloyl chloride to 3-oxo-1-cyclohexene-1-carbonitrile (**1**) generates a diverse array of cyclic enamides. An intrinsic feature of the N-acylation is the preferential reaction of

(13) Attempts to intercept **2** with acryloyl chloride were not successful.

(14) The N-acylation of **2** with pivaloyl chloride implies that methyl chloroformate acylates first on nitrogen and then on oxygen as shown (Scheme 2).

(15) **General Grignard Addition−Acylation Procedure:** A THF solution of MeMgCl (1.05−1.1 equiv) was added to a −15 °C THF solution (0.1 M) of oxonitrile **1**. After 2 h, a THF solution of a second Grignard reagent (1.5 equiv) was added, and then the solution was allowed to warm to room temperature. After 2 h, the solution was cooled to 0 °C followed by the sequential addition of a THF solution of the third Grignard reagent (4.0 equiv) and pivaloyl chloride (6.0 equiv). After 1 h at 0 °C, the solution was warmed to room temperature and stirred for 1 h. Subsequent addition of saturated, aqueous NH_4Cl and extraction with EtOAc afforded a crude product that was washed with brine and dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford the pure enamide.

(16) X-ray crystallography of **8b** and **8g** confirmed the stereochemical assignment. The authors have deposited the crystallographic data for **8b** and **8g** with the Cambridge Crystallographic Data Center (CCDC 605398 and 605397, respectively). The supplementary crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44 1223 336033; or deposit@ccdc.cam.ac.uk.).

(17) Battaglia, A.; Cainelli, G.; Giacomini, D.; Martelli, G. Panunzio, M. *Tetrahedron Lett.* **1987**, *28*, 4347.

(18) The unit cell contains three distinct conformers: the conformer shown in Figure 1, a second similar conformer in which the phenyl group is axial, and a third conformer with a ring-flipped cyclohexane ring in which the phenyl substituent is equatorially oriented. An ORTEP diagram is provided in the Supporting Information.

(19) (a) Musser, C. A.; Richey, H. G., Jr. *J. Org. Chem.* **2000**, *65*, 7750. (b) Westerhausen, M.; Wieneke, M.; Ponikwar, W.; Nöth, H.; Schwarz, W. *Organometallics* **1998**, *17*, 1438. (c) Purdy, A. P.; George, C. F. *Organometallics* **1992**, *11*, 1955.

pivaloyl chloride with the C-magnesiated nitrile intermediate rather than with a Grignard reagent! Rapid N-acylation of the C-magnesiated nitrile generates an acyl ketenimine that reacts readily with a Grignard reagent or a trialkylzincate. Overall, the Grignard addition−acylation with pivaloyl chloride installs four new bonds and provides an effective route to highly substituted, cyclic enamides.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds and ORTEPs and CIF files for **8b** and **8g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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