



α,β -Unsaturated nitriles: preparative MgO elimination

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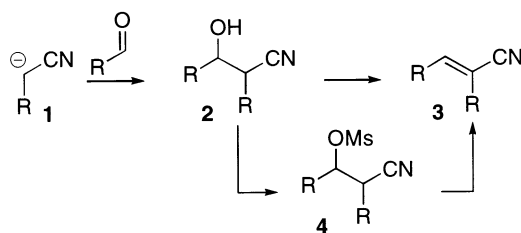
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Abstract

Double deprotonation of β -hydroxynitriles with MeMgCl (2.1 equiv.) generates a dianion that ejects MgO to provide the corresponding α,β -unsaturated nitriles. Structurally diverse β -hydroxynitriles readily eliminate MgO providing an expedient route to highly substituted α,β -unsaturated nitriles. © 2000 Published by Elsevier Science Ltd.

α,β -Unsaturated nitriles are versatile synthetic intermediates¹ being readily transformed into an array of carbocycles² and heterocycles.³ Conjugate additions⁴ to α,β -unsaturated nitriles provide substituted nitriles that are equally valuable synthetic intermediates. The use of nitriles in synthesis,⁵ combined with the increasing isolation of nitrile-containing natural products,⁶ provides a strong impetus for new, efficient syntheses of α,β -unsaturated nitriles.

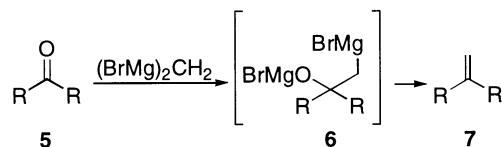
The versatility of α,β -unsaturated nitriles has stimulated numerous syntheses of this functionality.⁷ Typically, α,β -unsaturated nitriles are synthesized by condensing nitrile anions (**1**) with aldehydes and ketones to generate β -hydroxynitriles⁸ (**2**) that are subsequently dehydrated (Scheme 1). This strategy is particularly effective for condensing aromatic acetonitriles with aryl aldehydes and ketones since the dehydration is facilitated by the aromatic substituents.⁹ Aliphatic β -hydroxy nitriles dehydrate less readily¹⁰ requiring conversion to the corresponding mesylate (**4**) for elimination to the α,β -unsaturated nitrile (**3**).¹¹



Scheme 1.

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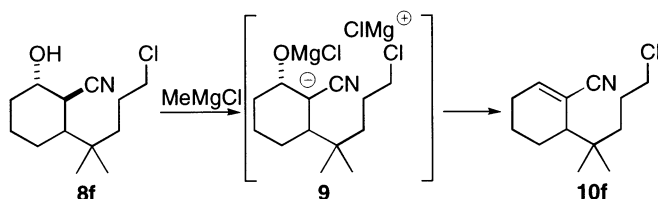
Conceptually the elimination of hydroxide, or a metal oxide, represents the most direct conversion of β -hydroxy nitriles to α,β -unsaturated nitriles. Metal oxide eliminations generally require elevated temperatures and strong bases.¹² The elimination of MgO is anomalous in occurring at significantly lower temperatures,¹³ reflecting the highly covalent character of the MgO bond.¹⁴ In fact, the elimination of MgO from dianions, such as **6**, occurs readily under mild conditions providing a facile methylenation of ketones (Scheme 2).¹⁵



Scheme 2.

The facile MgO eliminations with Grignard reagents provide a strong precedent for the elimination of MgO from β -hydroxy nitriles—providing the potential addition to the nitrile group is avoided. Encouraged by the low proclivity of several Grignard reagents to add to nitriles,¹⁶ the reaction of β -hydroxynitriles with Grignard reagents was investigated and found to provide a very efficient route to α,β -unsaturated nitriles.

The elimination of MgO was first established with the β -hydroxynitrile **8f** (Scheme 3). Addition of MeMgCl (2.1 equiv.) initially generates a magnesium alkoxide that is further deprotonated adjacent to the nitrile to form the dianion **9**.² Formation of the dianion **9**, at -78°C , followed by warming to room temperature, initiates the elimination of MgO to provide **10f** in 92% yield.

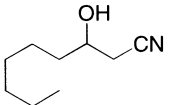
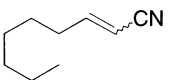
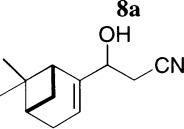
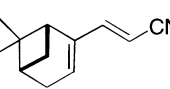
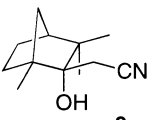
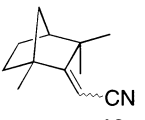
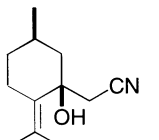
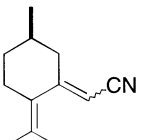
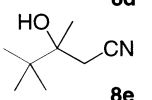
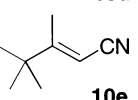
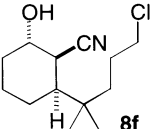
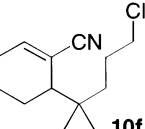
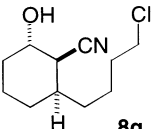
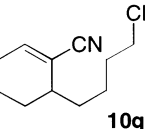
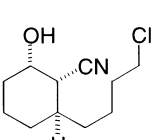
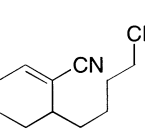


Scheme 3.

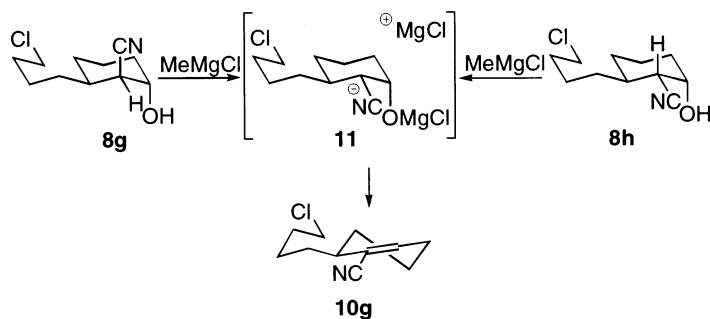
The elimination of MgO from β -hydroxynitriles¹⁷ is remarkably facile (Table 1). Elimination of MgO is equally efficient with secondary (**a–b**), tertiary (**c–e**), and allylic alcohols (**b**, **d**) and tolerates acyclic (**a–b**), exocyclic (**c–d**), and endocyclic hydroxylation (**f–h**). A diverse range of di- and tri-substituted unsaturated nitriles are obtained as virtually exclusive products (71–92% yield), even in the presence of pendant alkyl chlorides (Table 1, entries 6–8).^{18–20}

Formation of the unsaturated nitrile **10c** illustrates the inherent advantage of this MgO elimination method (Table 1, entry 3). The two-step addition of lithiated acetonitrile to hindered ketones (84–93% for **8a–8e**) and subsequent MgO elimination provides an efficient synthesis of highly substituted α,β -unsaturated nitriles that are otherwise difficult to access. Furthermore, the reaction displays an intriguing stereoselectivity with highly substituted β -hydroxynitriles (Table 1, entries 2, 3, and 5), while the sterically unbiased β -hydroxynitrile **8a** exhibits a stereoselectivity comparable to that obtained in Wittig olefinations.²¹

Table 1
MgO eliminations from β -hydroxynitriles

Entry	β -Hydroxynitrile	Product	Yield (%)
1			71 1:1 E:Z
2			84
3			91 5:1 E:Z
4			87 2:1 E:Z
5			81
6			92
7			90
8			87

MgO elimination from the stereoisomeric β -hydroxynitriles **8g** and **8h** provide insight into the reaction mechanism (Scheme 4). Nitriles **8g** and **8h** react under identical conditions in virtually the same yield, implying the intermediacy of a common dianion intermediate. Formation of the dianion is an integral requirement since the addition of less than 2 equiv. of MeMgCl does not provide the unsaturated nitrile **10g**,²² indicating that MgO, and not hydroxide, is the leaving group.



Scheme 4.

α,β -Unsaturated nitriles are readily synthesized from β -hydroxynitriles by deprotonation with an excess of MeMgCl. Deprotonation generates a dianion intermediate that ejects MgO providing an efficient synthesis of a diverse array of α,β -unsaturated nitriles.

Acknowledgements

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17. The β -hydroxynitriles **a–e** were prepared by the addition of lithioacetonitrile to the corresponding aldehyde or ketone. The β -hydroxynitriles **a** and **e** have been prepared previously by this method. For **a** see: Barhdadi, R.; Gal, J.; Heintz, M.; Troupel, M.; Périchon, J. *Tetrahedron* **1993**, *49*, 5091. For **e** see: Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613.
18. The procedure for **8e** is representative: A THF solution of MeMgCl (2.00 mmol) was added to a rt, THF solution (5 mL) of **8e** (134 mg, 0.95 mmol). The solution was stirred at rt for 10 h and then saturated, aqueous NH₄Cl was added. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts dried (Na₂SO₄), and concentrated. The crude material was purified by radial chromatography (1 mm plate, 1:9 EtOAc:hexanes) to afford 95 mg (81%) of **10e**: IR (film): 2219, 1613 cm⁻¹; ¹H NMR δ 1.09 (s, 9H), 2.06 (d, $J=0.7$ Hz, 3H), 5.17 (br s, 1H); ¹³C NMR δ 17.8, 28.3, 37.4, 93.4, 117.8, 172.8; MS m/e 124 (M+H). All new compounds exhibited satisfactory ¹H NMR, ¹³C NMR, MS, and IR spectra.
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22. Nitrile **8h** is completely recovered precluding the formation of any 'retro nitrile-aldol' product.