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Magnesium Nitride as a Convenient Source of Ammonia: Preparation of Primary Amides

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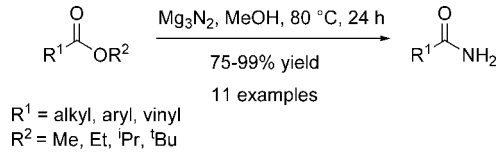
ABSTRACT



The use of magnesium nitride (Mg_3N_2) as a convenient source of ammonia has been explored for the direct transformation of esters to primary amides. Methyl, ethyl, isopropyl, and *tert*-butyl esters are converted to the corresponding carboxamides in good yields (75−99%).

Ammonia is often employed as a source of nitrogen in organic chemistry, yet its use can be hampered by handling issues, particularly on a small scale. With this in mind, we sought to explore new methods for the generation of ammonia in situ and were attracted by magnesium nitride, a commercially available,[1] bench-stable solid that has been largely ignored by the synthetic community to date. Magnesium nitride is known to release ammonia upon reaction with water,[2] yet its only application in organic synthesis has been as a source of magnesium ions for the preparation of phthalocyanines[3] and as a source of ND_3.[4]

Early studies were directed toward the release of ammonia from magnesium nitride using proton sources other than water. It was found that methanol and ethanol were particularly successful in this regard, while the more sterically hindered 2-propanol proved unreactive (Figure 1).

The release of ammonia from magnesium nitride with protic solvents was accompanied by a distinctive color change from brown to white, which indicated the formation of magnesium salts (Figure 2).[5]

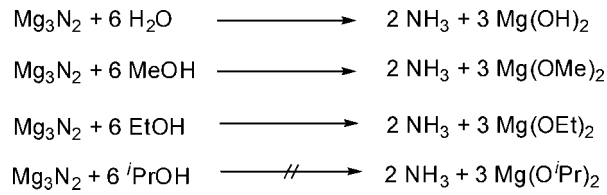


Figure 1. Reaction of Mg_3N_2 with various proton sources.

Following these preliminary observations, the preparation of primary amides from the corresponding esters was investigated. This application was selected as we had experienced difficulties in this deceptively simple transformation during our synthesis of Sildenafil, where it was necessary to prepare a saturated solution of ammonia in methanol using a gas cylinder.[6] Indeed, others have reported similar cumbersome procedures to effect this reaction.[7] The use of magnesium nitride was therefore viewed as a practical solution to some of the problems encountered. Moreover,

(1) Sigma-Aldrich catalog no. 415111. Price $2.34/g.
(2) Moser, L.; Herzner, R. *Monatsh. Chem.* **1923**, *44*, 115–122.
(3) Toku, K.; Saibi, S.; Kotatsu, K.; Eisho, R.; Jukun, L.; Meika, R.; Shunei, C. Feb 21, 2003, JP2003048892.
(4) Ley, S. V.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 6670–6679.
(5) It should be noted that as with any ammonia reaction a pressure build-up will occur and it is important to contain this in an appropriately sealed vessel.
(6) Baxendale, I. R.; Ley, S. V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1983–1986.

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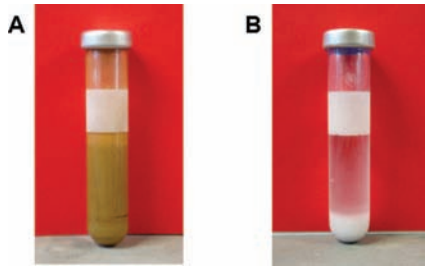
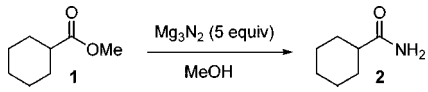


Figure 2. Initial appearance of Mg_3N_2 in MeOH (A) and after 1 h stirring in a water bath at ambient temperature (B).

since the primary amide motif occurs widely in natural products[8] and drug-like substances[9] we saw this as a desirable transformation worthy of further study.

The results of our optimization studies using cyclohexane methyl ester **1** are summarized in Table 1. Treatment of **1** with 5 equiv of magnesium nitride under microwave irradiation afforded the corresponding carboxamide (**2**), albeit in low yield (entry 1). As primary amide **2** was the only product isolated following aqueous workup, it is proposed that any unreacted starting material was hydrolyzed during this process. In order to improve the conversion, we next investigated thermal heating for extended periods of time (entries 2−6). Ultimately, optimal conditions were identified, which provided **2** in good yield and purity (entry 5).

Table 1. Optimization Studies in the Synthesis of **2**[a]

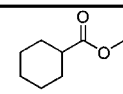
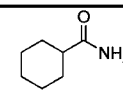
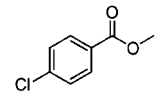
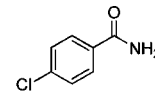
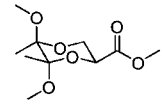
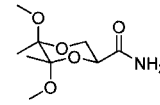
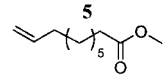
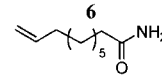
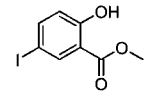
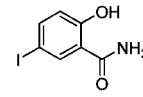
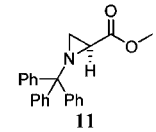
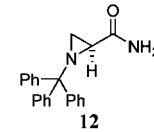
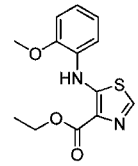
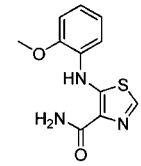
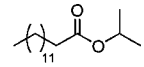
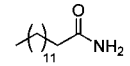
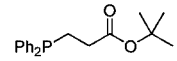
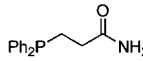
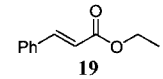
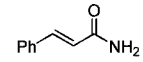
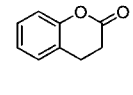
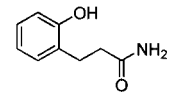
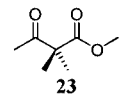
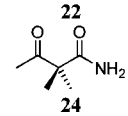


entry	ammonia concn (M)	T (°C)	time (h)	yield[b] (%)
1	1.3	80	1	10
2	1.3	80	24	50
3	1.3	120	24	40
4	3.1	80	48	70
5	**3.1**	**80**	**24**	**85**
6	3.1	120	24	40

[a] Reactions conducted with 0.7 mmol of cyclohexane methyl ester and 3.5 mmol of magnesium nitride in methanol in a new sealed biotage microwave vial. [b] Isolated yield of pure product.

The optimized conditions were then applied to a range of methyl ester substrates and we were pleased to obtain very good yields in all cases (Table 2, entries 1−6). We next investigated more hindered esters such as ethyl (entry 7), isopropyl (entry 8), and *tert*-butyl (entry 9) and, again, obtained satisfactory results. Although the direct conversion of a *tert*-butyl ester to the corresponding carboxamide has been described previously in liquid ammonia, only a modest yield was reported.[10] Indeed, it is more common to proceed

Table 2. Scope of Primary Amide Synthesis[a]

entry	starting ester	primary amide	yield[c] [%]
1	 **1**	 **2**	85
2	 **3**	 **4**	83
3	 **5**	 **6**	94
4	 **7**	 **8**	99
5	 **9**	 **10**	75
6	 **11**	 **12**	90
7	 **13**	 **14**	99
8	 **15**	 **16**	79
9	 **17**	 **18**	93
10	 **19**	 **20**	99
11	 **21**	 **22**	82
12	 **23**	 **24**	0[c]

[a] Reactions conducted with 0.7 mmol of ester and 3.5 mmol of magnesium nitride in methanol (2.25 mL) in a new sealed microwave vial. [b] Isolated yield of product. [c] The only products isolated were acetamide and isobutyramide.

(7) Patino-Molina, R.; Cubero-Lajo, I.; Perez de Vega, M. J.; Garcia-Lopez, M. T.; Gonzalez-Muniz, R. *Tetrahedron Lett.* **2007**, *48*, 3613–3616. (a) Fukuyama, T.; Li, L.; Laird, A. A.; Frank, K. R. *J. Am. Chem. Soc.* **1987**, *109*, 1587–1589.

(8) A Beilstein search displayed 1226 hits for natural products containing primary amides.

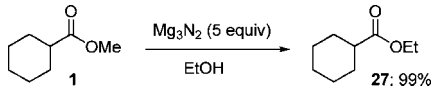
(9) Sugiyama, H.; Yoshida, M.; Mori, K.; Kawamoto, T.; Sogabe, S.; Takagi, T.; Oki, H.; Tanaka, T.; Kimura, H.; Ikeura, Y. *Chem. Pharm. Bull.* **2007**, *55*, 613–624. Fish, P. V.; Allan, G. A.; Bailey, S.; Blagg, J.; Butt, R.; Collis, M. G.; Greiling, D.; James, K.; Kendall, J.; McElroy, A.; McCleverty, D.; Reed, C.; Webster, R.; Whitlock, G. A. *J. Med. Chem.* **2007**, *50*, 3442–3456.

via a laborious three step sequence, namely ester hydrolysis, formation of an activated ester and finally, aminolysis.[7] The use of magnesium nitride therefore represents a significant simplification of exisiting procedures.

We proceeded to test more challenging substrates including conjugated ester **19** and lactone **21**, both of which afforded the desired amides **20** and **22** in good yield (entries 10 and 11). The only substrate in this study that presented any difficulties was β-ketoester **23** (entry 12). In this case, a retro-Claisen reaction was, not unexpectedly, observed in addition to aminolysis, to cleanly yield acetamide and isobutyramide.

It is noteworthy that the reaction of esters **13**, **15**, and **17** likely proceed via transesterification to the corresponding methyl ester, which is then able to undergo aminolysis. The methyl ester of isopropyl myristate was isolated as a byproduct of the reaction, which lends support to this hypothesis. Furthermore, when **1** was subjected to magnesium nitride in ethanol, cyclohexane ethyl ester **27** was isolated as the sole product (Scheme 1).

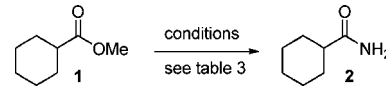
Scheme 1. Treatment of **1** with Magnesium Nitride in Ethanol[a]



[a]Reaction performed in a sealed tube at 80 °C for 24 h.

We were interested to see how a commercially available solution of ammonia in methanol would compare to magnesium nitride. Accordingly, **1** was treated with a 2 M solution of ammonia in methanol[11] which afforded amide **2** in poor yield (table 3, entry 2). This suggests that other factors play a role in assisting the reaction pathway with magnesium nitride as the experiments performed in this paper gave higher yields at both lower (entry 1) and higher (entry 3) concentrations.[12]

Table 3. Comparison of Commercially Available Ammonia in Solution to Magnesium Nitride



entry[a]	ammonia source	ammonia concn (M)	yield[b] (%)
1	Mg_3N_2	1.3	50
2	commercial solution	2	20
3	Mg_3N_2	3.1	85

[a] Reactions performed in methanol in a sealed tube at 80 °C for 24 h. [b] Isolated yield of pure product.

In summary, we have described the first application of magnesium nitride as a convenient source of ammonia to effect the conversion of a range of ester substrates to primary amides. Noteworthy features of this procedure include the facile reaction setup as magnesium nitride is a bench-stable solid, the ease of reaction workup,[13] and the excellent yields observed in the majority of cases. It is anticipated that magnesium nitride will find further application within the field of organic synthesis.

Acknowledgment. We gratefully acknowledge the EPSRC for funding (G.E.V. and K.L.B.) and Pfizer Global Research and Development (Sandwich) for additional support (S.V.L.).

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801398Z

(10) Hellberg, M. R.; Conrow, R. E.; Sharif, N. A.; McLaughlin, M. A.; Bishop, J. E.; Crider, J. Y.; Dean, W. D.; DeWolf, K. A.; Pierce, D. R.; Sallee, V. L.; Selliah, R. D.; Severns, B. S.; Sproull, S. J.; Williams, G. W.; Zinke, P. W.; Klimko, P. G. *Bioorg. Med. Chem.* **2002**, *10*, 2031–2049.

(11) Sigma-Aldrich catalog no. 341428.

(12) In an attempt to recreate the reaction medium generated with magnesium nitride, cyclohexane methyl ester **1** was treated with 2 M ammonia in methanol and additional magnesium methoxide. However, the desired amide **2** was still isolated in low yield (23%). Further studies are currently underway to ascertain the precise mechanism of action of this reagent.

(13) See the Supporting Information for full experimental details.