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Magnesium Nitride as a Convenient Source of Ammonia: Preparation of Dihydropyridines

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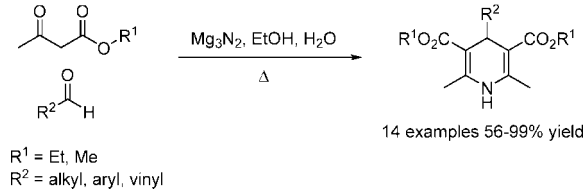
ABSTRACT



Magnesium nitride (Mg_3N_2) has been investigated for the preparation of dihydropyridines. This is a commercially available, bench-stable solid that generates ammonia upon treatment with protic solvents. The main features of the process are the facile reaction setup and good yields obtained in the majority of cases.

Dihydropyridines (DHPs) represent an important class of biologically active molecules, several of which have found use in the treatment of cardiovascular disease and hypertension.[1] In addition, the dihydropyridine unit has been widely employed as a hydride source for reductive amination:[2] an enantioselective variant of this reaction has recently been developed, in which an H-bonding catalyst acts as an enzyme analogue and a dihydropyridine as an NADH analogue.[3]

The preparation of dihydropyridines was first reported by Hantzsch via the condensation of ethyl acetoacetate and acetaldehyde with ammonia in refluxing alcohol or acetic acid.[4] Owing to the modest yield reported, numerous improvements on this method have since been developed, including the use of catalysts such as boronic acids,[5] metal triflates,[6] molecular iodine,[7] TMS iodide,[8] Bu_4NHSO_4,[9] bakers' yeast,[10] ceric ammonium nitrate,[11] in situ generated HCl,[12] and silica-supported acids.[13] Solvent free[14] and microwave irradiation[15] conditions have also been reported. Nonetheless, the synthesis of dihydropyridines remains of interest, due to their prevalence in pharmaceutical agents.

(1) Bossert, F.; Meyer, H.; Wehinger, H. *Angew Chem., Int. Ed.* **1981**, *20*, 762–769. Nakayama, H.; Kasoaka, Y. *Heterocycles* **1996**, *42*, 901–909. Gordeev, M. F.; Patel, D.; Gordon, E. M. *J. Org. Chem.* **1996**, *26*, 924–928. Shan, R.; Velaskez, C.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 254–261.

(2) Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, *60*, 6649–6655.

(3) Hoffman, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424–7427. Rueping, M.; Suiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781–3783. Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86.

(4) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1–82.

(5) Sridhar, R.; Perumal, P. T. *Tetrahedron* **2005**, *61*, 2465–2470. Debache, A.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Synlett* **2008**, 509–512.

(6) Wang, L.-M.; Sheng, J.; Zhang, L.; Han, J.-W.; Fan, Z.-Y.; Tian, H.; Qian, C.-T. *Tetrahedron* **2005**, *61*, 1539–1543.

(7) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, 46.

(8) Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129–4131.

(9) Tewari, N.; Dwivedi, N.; Tripathi, R. P. *Tetrahedron Lett.* **2004**, *45*, 9011–9014.

(10) Lee, J. H. *Tetrahedron Lett.* **2005**, *46*, 7329–7330.

(11) Ko, S.; Yao, C.-F. *Tetrahedron* **2006**, *62*, 7293–7299.

(12) Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Krishna, P. R. *Synthesis* **2006**, 55–58.

(13) Maheswara, M.; Siddaiah, V.; Rao, Y. K.; Tzeng, Y.; Sridhar, C. *J. Mol Catal. A. Chem* **2006**, *17*, 9–180. Gupta, R.; Gupta, R.; Paul, S.; Loupy, A. *Synthesis* **2007**, 2835–2838.

(14) Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827–828.

(15) Ösberg, L.; Westman, J. *Synlett* **2001**, *129*, 6–1298. Salehi, H.; Guo, Q. *Synth. Commun.* **2004**, *34*, 4349–4357.

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We have recently discovered that magnesium nitride (Mg_3N_2)[16] releases ammonia upon treatment with methanol or ethanol along with the corresponding magnesium salt (Figure 1).[17] It was anticipated that this reagent could serve

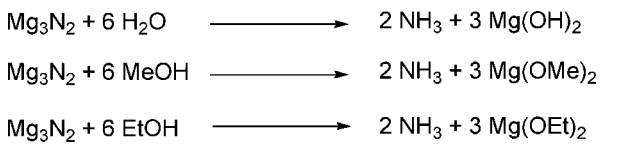
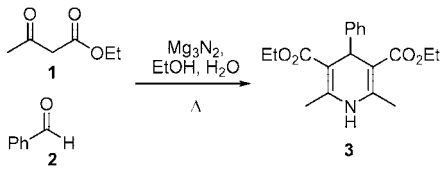


Figure 1. Reactivity of magnesium nitride.

a dual role in the Hantzsch reaction as it releases ammonia in situ while generating a magnesium salt with the potential to act as a catalyst.

Ethyl acetoacetate **1** and benzaldehyde **2** were selected for initial optimization studies, and we were pleased to isolate 70% of dihydropyridine **3** using magnesium nitride and water in ethanol[18] (Table 1, entry 1).[19] However, the ^{1}H NMR

Table 1. Optimization Studies



entry[a]	Mg_3N_2 (equiv)	benzaldehyde (equiv)	water (equiv)	yield[b] (%)
1	1	2	6.5	70[c]
2	**1**	**3.2**	**6.5**	**99(93)[d]**
3	2	3.2	6.5	81
4	1	3.2	0	65
5[e]	1	3.2	6.5	0

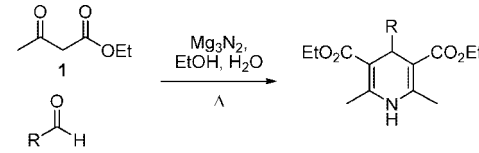
[a] Reactions performed at 0.9 M ammonia concentration using 4.5 equiv of β-ketoester, heated at 80 °C for 16 h in a sealed microwave vial. [b] ^{1}H NMR conversion. [c] Enaminoester intermediate present. [d] Isolated yield in parentheses. [e] Reaction performed at 0.1 M.

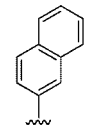
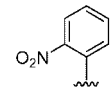
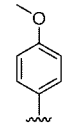
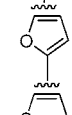
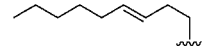
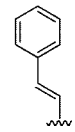
spectrum of the crude reaction mixture in this case indicated that the enaminoester intermediate had not been fully consumed. An excess of benzaldehyde was employed to avoid this, which increased the conversion to 99% (entry 2). After purification, dihydropyridine **3** was isolated in 93% yield. There was no evidence of amidation, highlighting the versatility of this reagent.

Increasing the equivalents of magnesium nitride did not improve the conversion (entry 3), and in the absence of water, a drop in yield was observed (entry 4). It is noteworthy that changing the concentration from 0.9 to 0.1 M shut down the desired reaction pathway (entry 5).

The optimized conditions were then applied to a range of aldehyde substrates (Table 2, entries 2−12). Both electron-poor and electron-rich aldehydes were well tolerated (entries 3−5). The reaction of heteroaromatic aldehydes proceeded in high yield (entries 6−8), and linear aldehydes afforded

Table 2. Substrate Scope



entry[a]	R		yield[b]
1		**3**	93
2		**4**	76
3		**5**	88
4		**6**	83
5		**7**	95
6		**8**	58
7		**9**	96
8		**10**	99
9		**11**	56
10		**12**	66
11		**13**	93
12		**14**	82

[a] All reactions performed with ethyl acetoacetate (4.5 equiv), aldehyde (3.2 equiv), magnesium nitride (1 equiv), and water (6.5 equiv) in ethanol (0.9 M ammonia concentration) and heated at 80 °C in a sealed microwave vial. [b] Isolated yields.

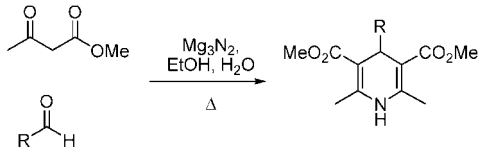
(16) Sigma-Aldrich catalog no. 415111. Price $2.34/g.

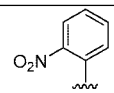
(17) Veitch, G. E.; Bridgwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623–3626.

(18) Both methanol and ethanol were tested for the Hantzsch reaction but ethanol proved superior.

(19) It should be noted that as with any ammonia reaction a pressure buildup will occur and it is important to contain this in an appropriately sealed vessel.

Table 3. Altering the β-Ketoester Substituent



entry[a]	R		yield[b]
1		**15**	84
2		**16**	93

[a] All reactions performed with ethyl acetoacetate (4.5 equiv), aldehyde (3.2 equiv), magnesium nitride (1 equiv), and water (6.5 equiv) in ethanol (0.9 M ammonia concentration) and heated at 80 °C in a sealed microwave vial. [b] Isolated yields.

the corresponding dihydropyridines, albeit in reduced yield (entries 9 and 10). Cyclopropane aldehyde and cinnamaldehyde gave **13** and **14**, respectively, in very good yield (entries 11 and 12).

Methyl acetoacetate was also employed for the Hantzsch reaction in place of ethyl acetoacetate and afforded dihydropyridines **15** and **16** in good yield, with no evidence of transesterification (Table 3).

In summary, we have demonstrated the utility of magnesium nitride in the Hantzsch dihydropyridine reaction. This reagent obviates the need for an additional catalyst and has allowed the preparation of a range of dihydropyridines in good to excellent yields (56−99%). The experimental procedure is simple[20] and represents an attractive alternative to existing methods. It is noteworthy that acidic conditions are not used, extending the functional group tolerance of the Hantzsch reaction. Further uses of this reagent will be reported in due course.

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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.

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(20) See the Supporting Information for more details.