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Amidation of esters assisted by $Mg(OCH_3)_2$ or $CaCl_2$

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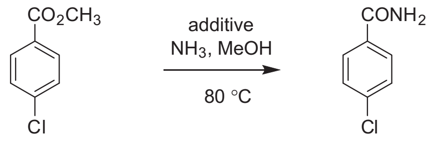
ABSTRACT

Magnesium methoxide ($Mg(OCH_3)_2$) and calcium chloride have been shown to facilitate the direct aminolysis of esters by ammonia to primary amides. Methyl, ethyl, isopropyl, and *tert*-butyl esters were converted to the corresponding carboxamides in good yields. Reactions have been run on a larger scale and without the safety liability inherent in the use of magnesium nitride (Mg_3N_2). Ammonium chloride and amine hydrochlorides have been used successfully in the place of ammonia with magnesium methoxide.

The transformation of carboxylic esters to carboxamides is a transformation that is frequently undertaken in organic synthesis. The direct aminolysis of esters with amines is attractive for its simplicity and economy, yet this transformation frequently performs poorly in practice, attended by incomplete conversion and long reaction times. As a result, numerous methods have been reported to effect this transformation in high yield and with short reaction times.[1] Recently, magnesium nitride (Mg_3N_2) has been reported as a commercially available, convenient source of ammonia to effect the transformation of carboxylic esters to primary amides.[2] The reported procedure utilized excess Mg_3N_2 in methanol in a sealed vial at 80 °C. Notably, the procedure using Mg_3N_2 was shown to proceed in higher yield than a control experiment in which a commercially available solution of ammonia in methanol was used.[3] In these experiments, the reaction of Mg_3N_2 with methanol generated ammonia and magnesium methoxide in an exothermic reaction[4] within the sealed reaction vessel.[5] This exotherm presents an inherent safety liability that has resulted in overpressurization and explosion of the sealed reaction vessel.[6] We sought to develop conditions for this useful transformation that remedied the inherent safety defect involved with the use of Mg_3N_2, and which could be applied at larger reaction scales,[7] using commercially available ammonia in methanol solution. Clearly Mg_3N_2 served as more than a source of ammonia, because amidation was incomplete in its absence. Transesterification of ethyl and higher esters to methyl esters had been shown to occur under the reaction conditions reported, and the methyl ester could reasonably be expected to undergo amidation more rapidly than an isopropyl or *tert*-butyl ester. However, it appeared to us that the magnesium ion present may also function as a Lewis acid which could activate the ester carbonyl to nucleophilic attack by ammonia. We therefore conducted a parallel screen of potential Lewis acids[8] using methyl 4-chlorobenzoate (**1**) as a model ester (Table 1).

From this effort, $Mg(OCH_3)_2$, $MgCl_2$, $CaCl_2$, and $CeCl_3$ appeared to offer the best conversion. Preparative experiments on a larger (3 mmol) scale showed that $Mg(OCH_3)_2$ and $CaCl_2$ afforded the highest isolated yields of **2**.[9] Anhydrous $CeCl_3$ and $MgCl_2$ also gave acceptable yields as anticipated.[10] Anhydrous $CaCl_2$ is much more readily available in most laboratories, and less expensive than

Table 1
Screening of Lewis acid assisted amidation of **1**



1 **2**

Additive	Ratio **1**:**2**, 2 h[a]	Ratio **1**:**2**, 6 h	Ratio **1**:**2**, 18 h	Yield[b]
$Al(OEt)_3$	95:3	92:6	86:11	N.D.
$BF_3{\cdot}Et_2O$	96:3	88:10	72:25	N.D.
$CaCl_2$	44:50	15:85	6:93	93
$CeCl_3$	75:25	33:66	15:85	71
$InCl_3$	98:0	95:3	90:9	N.D.
LiCl	86:12	71:27	51:47	52
$Mg(OCH_3)_2$	76:23	65:34	17:81	87
$MgCl_2$	90:9	64:35	38:60	72
NH_4Cl	96:4	96:4	95:4	N.D.
None	95:4	86:12	70:28	40
$Ti(OCH_3)_4$	95:5	83:16	72:27	N.D.
$ZnCl_2$	91:8	73:25	50:45	33

[a] Experiments were conducted in 8 mL screw cap vials using 1.4 mmol of **1**, 1.4 mmol of additive, 2 mL (14 mmol, 10 equiv) of 7 M NH_3 in MeOH and 2 mL of MeOH at 80 °C. Aliquots were taken at 2, 6, and 18 h time points. Ratio of **1**:**2** determined by integration of peak areas on UPLC. Ratio sums may not equal 100 if minor impurities were detected. All additives were commercial anhydrous grades.
[b] Isolated yield of **2** on 3 mmol scale after 24 h (N.D.: not determined).

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Table 2
Amidation of esters with $Mg(OCH_3)_2/NH_3$ or $CaCl_2/NH_3$[a]

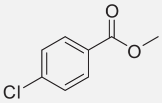
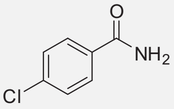
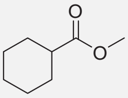
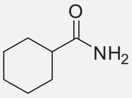
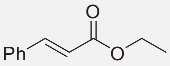
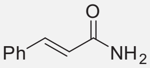
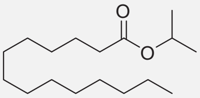
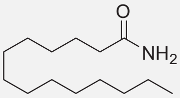
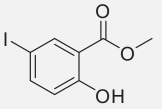
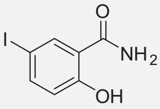
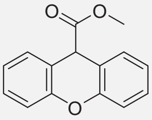
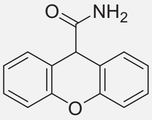
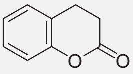
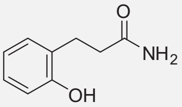
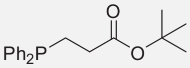
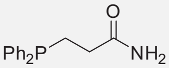
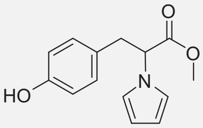
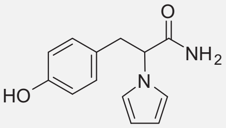
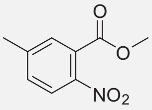
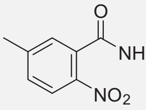
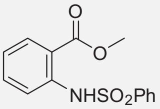
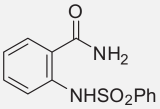
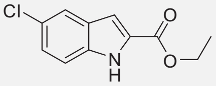
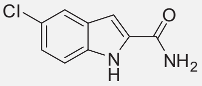
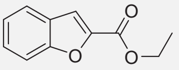
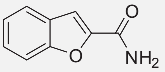
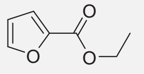
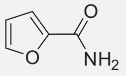
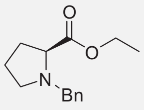
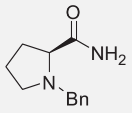
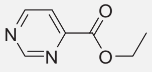
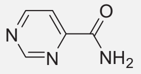
Entry	Ester	Amide	Yield[b]	Yield[c]
1	 **1**	 **2**	87 (83)	93
2	 **3**	 **4**	78 (85)	72
3	 **5**	 **6**	71 (99)	85
4	 **7**	 **8**	99 (79)	94
5	 **9**	 **10**	97[d] (75)	93
6	 **11**	 **12**	81	93
7	 **13**	 **14**	38[d] (82)	62
8	 **15**	 **16**	87 (93)	92
9	 **17**	 **18**	88[d]	90
10	 **19**	 **20**	84	83
11	 **21**	 **22**	95	45[e]
12	 **23**	 **24**	72	98
13	 **25**	 **26**	80	88

Table 2 (*continued*)

Entry	Ester	Amide	Yield[b]	Yield[c]
14	 **27**	 **28**	6	45
15	 **29**	 **30**	90	82
16	 **31**	 **32**	95	86

[a] Reactions were conducted with 3 mmol of ester, 10 equiv of 7 M NH_3 in MeOH, and 1 equiv of 0.6 M $Mg(OCH_3)_2$ in MeOH in screw cap sealed tubes at 80 °C for 24 h.

[b] Isolated yields of pure products using $Mg(OCH_3)_2$. Yields in parentheses are those reported in Ref. 2.

[c] Isolated yields of pure products using $CaCl_2$.

[d] 3 Equiv of 2.1 M $Mg(OCH_3)_2$ in MeOH were used.

[e] Remainder recovered starting ester.

anhydrous $MgCl_2$ or $CeCl_3$. These conditions were then applied to a set of esters including several previously published examples[2] (Table 2).

Our results generally compare favorably with those previously reported for the use of Mg_3N_2. In the case of the lactone **13** and the furan **27**, complete conversion to the amides **14** and **28** was observed but recovery of the products from the aqueous solution during workup was inefficient.[11] Some esters containing (latent) acidic functional groups (**9**, **13**, and **17**) gave incomplete conversion with 1 equiv of $Mg(OCH_3)_2$ but afforded complete conversion when 3 equiv of $Mg(OCH_3)_2$ was used.[12] The sulfonamide **21** was the only substrate examined that performed poorly with $CaCl_2$. In this case the reaction was only 45% complete after 24 h at 80 °C. Indole and benzofuran substrates were successful with both $Mg(OCH_3)_2/NH_3$ and $CaCl_2/NH_3$. By contrast, ethyl 2-furoate was decomposed by $Mg(OCH_3)_2/NH_3$ with the formation of resinous by-products, but underwent reaction successfully with $CaCl_2/NH_3$. However, in none of these cases did a pressure excursion occur.[13] An extractive workup was not necessary in most cases, making product isolation easier on a larger scale.[14] Exposure of a substrate with a chiral center (**29**, 96% ee) afforded the primary amide product with partial epimerization (65% ee) in the case of $Mg(OCH_3)_2/NH_3$ and significantly less epimerization (91% ee) when $CaCl_2/NH_3$ was employed. As a control experiment, treatment of **1** under the conditions employed in Table 2 in the absence of $Mg(OCH_3)_2$ or $CaCl_2$ returned a 40% isolated yield of **2** after 24 h.[15,16]

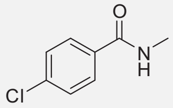
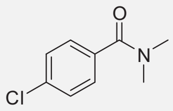
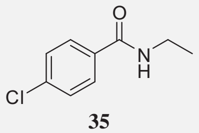
Importantly, and in contrast to Mg_3N_2, there was no noticeable exotherm upon mixing of these reagents. Although our method does utilize a closed system to contain the ammonia, the internal pressure at the reaction temperature of 80 °C was measured at about 170 kPa.[17] This pressure is low enough to permit the use of standard sealed tube techniques with appropriate safety precautions, including shielding of the reaction tube with a blast shield.

It should be noted that $Mg(OCH_3)_2$ is commercially available as a 6–10% solution in methanol,[18] however it may be very easily prepared from magnesium turnings and methanol.[19] We have found that solutions of ammonia in methanol can occasionally lose ammonia in an unpredictable manner and therefore the concentration of ammonia should be confirmed periodically.[20]

Many laboratories may not have convenient access to ammonia gas or its solutions in methanol. We were therefore pleased to find that a mixture of NH_4Cl and $Mg(OCH_3)_2$ also afforded good yields of primary amides from esters. Other amines that are gases at room temperature and pressure could also be used under these conditions, in the form of their hydrochloride salts (Table 3).[21,22]

The role of $Mg(OCH_3)_2$ in this transformation is not fully understood.[23] Clearly transesterification of higher alkyl esters to kinetically more reactive methyl esters occurs, as the methyl ester has been isolated as an intermediate in these cases. However, we believe that magnesium or calcium ion may coordinate to the ester carbonyl and predispose the ester to nucleophilic attack by the product amide to yield an intermediate imide that undergoes aminolysis more rapidly than the ester starting material. A similar mechanism was proposed in 1965 for the amidation of esters by formamide catalyzed by sodium methoxide.[24] The intermediacy of an imide in these reactions is supported by the isolation of a sample of the imide **36** in 2% yield from the reaction of **23** with $Mg(OCH_3)_2$ and NH_3.[25,26] Thus the reaction in the presence of

Table 3
Amidation with amine HCl salts[a]

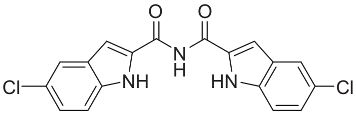
Entry	Ester	Amide	Yield[b]
1	**1**	**2**	67
2	**5**	**6**	87
3	**1**	 **33**	93
4	**1**	 **34**	94[c]
5	**1**	 **35**	95

[a] Reactions were conducted with 3 mmol of ester, 10 equiv of amine HCl, and 6 equiv of 2.1 M $Mg(OCH_3)_2$ in MeOH in screw cap sealed tubes at 80 °C for 24 h.

[b] Isolated yields of pure products.

[c] Heated for 72 h.

$Mg(OCH_3)_2$ or $CaCl_2$ is autocatalytic, as any amide that is formed spontaneously from the ester and NH_3 can undergo reaction with additional ester to form imide, which may then undergo aminolysis to form additional amide.



36

The formation of a precipitate in all reactions employing $Mg(OCH_3)_2/NH_3$, particularly reactions such as with ester **1**, in which all reactants and products are completely soluble in the hot reaction mixture, provides evidence that residual water has been consumed by reaction with $Mg(OCH_3)_2$ with the formation of insoluble $Mg(OH)_2$.

In summary, we present a method for the amidation of esters by ammonia and amines, or their hydrochloride salts that uses inexpensive commercial reagents.[27] The method affords good yields with the convenient reaction times associated with Mg_3N_2 but without the safety liability inherent in the use of Mg_3N_2.

Acknowledgments

The authors wish to thank colleagues Robert Maguire, David Hepworth, John Humphrey, and Joel Hawkins for their support and valuable discussions.

References and notes

1. (a) Larock, R.C. Comprehensive Organic Transformations A Guide to Functional Group Preparations, 2nd ed., John Wiley& Sons, Inc., New York, NY, 1999.; In particular, the use of dialkylaluminum amides described by Weinreb has gained popularity, see: (b) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4174; (c) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993; A modification of this procedure uses DABCO·Me_3Al complex, see: (d) Novak, A.; Humphreys, L. D.; Walker, M. D.; Woodward, S. *Tetrahedron Lett.* **2006**, *47*, 5767–5769; It should be noted that the DABCO·Me_3Al complex is not commercially available and may be pyrophoric in air if not prepared and isolated properly, see; (e) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2232–2234.
2. Veitch, G. E.; Bridgwood, K. L.; Ley, S. V. *Org. Lett.* **2008**, *10*, 3623–3625.
3. See Table 3 in Ref. 2.
4. The reaction of $Mg_3N_2$with water or methanol is highly exothermic, estimated at 165 kcal/mol. If uncontrolled, this may be sufficient to raise the pressure of the mixture to between 30 and 60 atmospheres. See: Buske, G. *Chem. Eng. News* **2009**, *87*, 2.
5. The nature and extent of the exotherm were not elaborated upon in the Letter or Supplementary data and some subsequent workers may have been unaware of the need to control it.
6. (a) Crane, S. *Chem. Eng. News* **2009**, *87*, 2; (b) Ley, S. V. *Chem. Eng. News* **2009**, *87*, 4. These accidents may have resulted either from failure to control the exotherm, or from attempts to use the reagent on a larger scale than first reported.
7. The reactions described in Ref. 2 were carried out on 0.7 mmol scale.
8. Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491–3494.
9. Preparative yields were generally slightly higher than screening yields, except in the cases of $CeCl_3$ and $ZnCl_2$, presumably due to losses of NH_3 in screening due to multiple septum punctures during sampling of screening reactions.
10. The amidation of esters using $MgCl_2/NHR_1R_2$ in THF has been reported: Guo, Z.; Dowdy, E. D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* **2001**, *42*, 1843–1845.
11. We believe that the aqueous solubility of these products is increased by the magnesium or calcium salts present.
12. The 2.1 M solution of $Mg(OCH_3)_2$ was used in these experiments.
13. Ley and coworkers noted (Ref. 6b) that the reaction proceeded uneventfully for a large number of esters, but that upon investigation of furan and indole esters explosions occurred despite measures to control the exothermic reaction of Mg_3N_2 with MeOH.
14. Amide **12** was prepared in 81% yield on a 24 mmol scale by linear scale up of these conditions.
15. A reaction time of 6 days was required to attain 90% conversion of **1** to **2** under the conditions of Table 2 in the absence of $Mg(OCH_3)_2$.
16. Treatment of **1** with 1 equiv $BnNH_2$ under the conditions of Table 2 returned a <10% yield of *N*-benzyl 4-chlorobenzamide, suggesting that an excess of amine is required to secure complete consumption of the ester.
17. This corresponds to about 1.7 bar or about 25 psig.
18. Commercially available from Sigma–Aldrich and Alfa/Aesar. These solutions typically contain about 0.6 M $Mg(OCH_3)_2$ as determined by quenching with 1.00 M H_2SO_4 and back-titration with 1.00 M NaOH to a phenolphthalein endpoint.
19. Baumgarten, H. E.; Petersen, J. M. *Org. Synth.* **1961**, *41*, 82–90. We have typically used about 4 g of Mg turnings per 100 mL of MeOH; this affords a solution that is approximately 2.1 M $Mg(OCH_3)_2$..
20. Ammonia concentrations were determined by titration with 1.00 M H_2SO_4 to a methyl red endpoint.
21. Amine HCl salts are preferred because the by-product $MgCl_2$ is soluble in the reaction mixture at 80 °C.
22. Substitution of CaO or MgO for $Mg(OCH_3)_2$ in amidations of **1** with NH_4Cl returned **2** significantly contaminated by 4-chlorobenzoic acid.
23. The authors of Ref. 2 attempted to use $Mg(OCH_3)_2$ with ammonia in methanol with low yield (23%). It is unclear to us why this attempt was not more successful. See Ref. 2, footnote 12.
24. A modification of these conditions was subsequently published, see: Allred, E. L.; Hurwitz, M. D. *J. Org. Chem.* **1965**, *30*, 2376–2381; Jagdmann, G. E., Jr.; Munsun, H. R., Jr.; Gero, T. W. *Synth. Commun.* **1990**, *20*, 1203–1208.
25. In this case, the relatively low solubility of the reactants and products in the reaction mixture may have facilitated the recovery of the imide **36** from this experiment.
26. *Characterization of* **36**: ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.29 (dd, $J = 8.78$, 2.15 Hz, 2H) 7.50 (d, $J = 8.97$ Hz, 2H) 7.56 (d, $J = 1.37$ Hz, 2H) 7.80 (d, $J = 1.95$ Hz, 2H) 11.17 (s, 1H) 12.12 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 106.97, 114.22, 121.27, 124.71, 125.01, 127.62, 131.54, 135.88, 159.79. IR (film): 3304, 2955, 1725, 1673 cm^{-1}. API MS 372, 374, 376 (MH^+, 2Cl isotope pattern). Mp 293–296 °C (decomposes). Anal. Calcd for $C_{18}H_{11}Cl_2N_3O_2$: C, 58.09; H, 2.98. Found: C, 58.21; H, 2.90.
27. *Representative procedure*: To the reaction vessel[28] equipped with a magnetic stir bar under N_2 are added the substrate ester (3 mmol), $Mg(OCH_3)_2$ in MeOH (6–10%, about 0.6 M, 4.5 mL, about 3 mmol),[29] and 7 N NH_3 in MeOH (4.5 mL, about 30 mmol). The reaction vessel is sealed and heated at 80 °C for 24 h. Workup may be accomplished using either of the two methods. (a) For reaction products that may be expected to be solids, the reaction mixture is concentrated and the residue is treated with saturated NH_4Cl solution (1 mL per mmol substrate) and H_2O (3 mL per mmol substrate). The resulting mixture is adjusted to pH 5 with HCl, and the mixture is stirred for 20 min to dissolve Mg or Ca salts, after which the precipitated amide is filtered, washed with H_2O, and dried. (b) For small scale reactions, or for amide products that are not solids, the reaction mixture is concentrated and the residue is treated with saturated NH_4Cl solution as described above. The mixture is then extracted with a suitable solvent. If the reaction product is not soluble in dilute acid, the residue may be treated with dilute HCl instead of NH_4Cl, which permits a more rapid removal of Mg or Ca salts from the product.
28. Both 15 mL heavy walled pressure tubes (Chemglass CG-1880-01) and 20 mL Biotage microwave vials are satisfactory.
29. When $CaCl_2$ was used, the $Mg(OMe)_2$ solution was replaced with anhydrous $CaCl_2$ (3 mmol) and 4.5 mL of MeOH.