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

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Abstract: The synthesis of a diverse array of pyrroles is reported from the cyclocondensation of 1,4-dicarbonyl compounds with magnesium nitride in methanol.

Key words: pyrroles, heterocycles, ammonia, magnesium nitride, combinatorial chemistry

Functionalised pyrroles are abundant in nature,[1] forming the characteristic subunit of heme, chlorophyll, bile pigments and vitamin B12.[2] There are also many pharmaceuticals which contain the pyrrole motif most notably the cholesterol lowering drug, Lipitor,[3] and the anti-inflammatory agent amtolmetin.[4] Consequently, a wide variety of methods have been developed to enable the synthesis of these important heterocycles.[5]

Nonetheless, the preparation of substituted pyrroles remains a challenge. Harsh acidic conditions are often required and yields can be low.[6] Pyrroles are also susceptible to chemical degradation as they are easily oxidized, which can impede their isolation and purification.[7]

Recent work from our group has demonstrated the use of commercially available magnesium nitride (Mg_3N_2) as a convenient source of ammonia. This reagent serves to generate synthetically useful solutions of ammonia in situ through its reaction with protic solvents (Equation 1).[8] So far, we have reported the amidation of esters and the Hantzsch dihydropyridine synthesis using magnesium nitride. We therefore sought to expand the scope of this reagent to include the Paal–Knorr[9] reaction: synthesis of functionalised pyrroles from the corresponding 1,4-dicarbonyl compounds.

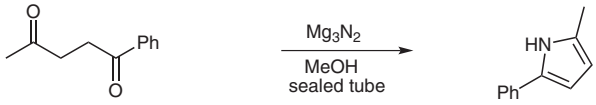
$$Mg_3N_2 + 6\ MeOH \longrightarrow 2\ NH_3 + 3\ Mg(OMe)_2$$

$$Mg_3N_2 + 6\ EtOH \longrightarrow 2\ NH_3 + 3\ Mg(OEt)_2$$

Equation 1

Preliminary investigations were carried out using phenylpentane-1,4-dione (**1**) with methanol as the solvent (Table 1). Although the desired cyclisation did proceed at ambient temperature (entries 1–4) long reaction times were necessary to achieve acceptable conversions. We therefore employed microwave heating in an attempt to reduce the reaction time and rapidly found optimal conditions which gave complete conversion to **2** after just one hour (entry 7).

Table 1 Optimisation of Reaction Conditions for the Preparation of **2**[a]



1 **2**

Entry	Mg_3N_2 (equiv)	Temp (°C)	Time	Conversion (%)[b]
1	0.5	21	24 h	21
2	2.5	21	24 h	80
3	0.5	21	7 d	62
4	2.5	21	7 d	90
5	0.5	70 (μW)	1 h	66
6	2.5	70 (μW)	1 h	90
7[c]	**2.5**	**120 (μW)**	**1 h**	**>99**

[a] Reactions were performed in a Biotage microwave vial (2–5 mL) using **1** (0.57 mmol) in MeOH at 0.1 M concentration.
[b] Calculated through analysis of crude ^{1}H NMR spectra.
[c] For precise experimental procedure see ref. 10.

These conditions were then used successfully for the synthesis of other 2,5-disubstituted pyrroles with good isolated yields obtained in all cases (Table 2, entries 2–5). However, when we attempted to prepare the 2,5-di-*tert*-butyl-1*H*-pyrrole (**7**) only 20% conversion was observed under the standard conditions. In this instance, it proved necessary both to increase the equivalents of magnesium nitride from 2.5 to 10 and to increase the reaction time to eight hours to obtain complete conversion (entry 7). It was undesirable to have such long reaction times in the microwave and so we explored the possibility of normal thermal heating to effect this transformation: pleasingly, pyrrole **7** could be obtained in near quantitative yield after 24 hours at 80 °C. All the pyrroles prepared previously could also be accessed in good yields under thermal conditions, a procedure which better lends itself to chemical library synthesis and scaleup.

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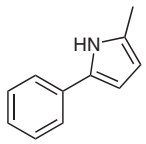
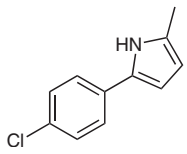
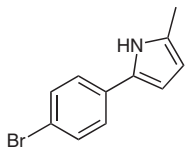
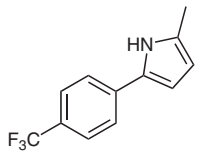
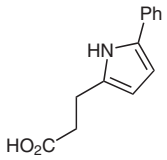
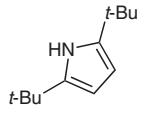
Table 2 Microwave-[a] and Thermally[b] Assisted Synthesis of Pyrroles

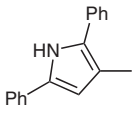
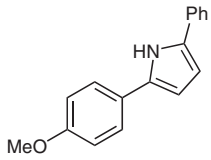
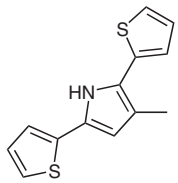
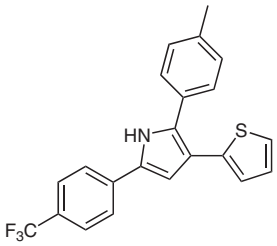
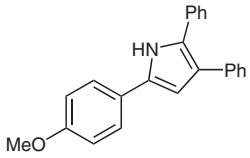
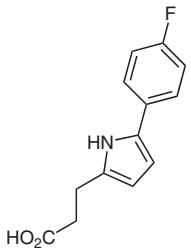
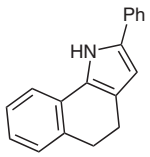
Entry	Product[10,11]	Isolated yield[c] (μw)	Isolated yield (%)[c] (heat)
1	 **2**	99	95
2	 **3**	95	87
3[12]	 **4**	92	78
4[13]	 **5**	72	91
5	 **6**	89	94
6	 **7**	95[d]	99[e]

[a] For representative experimental procedure see reference 10.
[b] For representative experimental procedure see reference 11.
[c] Isolated yield after column chromatography on SiO_2.
[d] This reaction was performed using magnesium nitride (10 equiv) for 8 h.
[e] This reaction was performed using magnesium nitride (10 equiv).

The thermal conditions employed for the preparation of **7** were then applied to a diverse set of 1,4-dicarbonyl substrates (Table 3). Both electron-rich and electron-deficient ketones provided the desired pyrroles in good yield. Furthermore, a number of densely functionalised trisubstituted pyrroles could be prepared by this method.

In summary, magnesium nitride has been used as a convenient source of ammonia in alcoholic solvents for the synthesis of 1*H*-pyrroles from 1,4-dicarbonyl compounds. The substrate scope and functional group tolerance is broad and isolated yields are good in all cases

Table 3 Thermally Assisted Synthesis of Functionalised Pyrroles[a]

Entry	Product[14]	Isolated yield (%)[b]
1	 **8**	98
2	 **9**	99
3	 **10**	79
4[15]	 **11**	85
5	 **12**	94
6	 **13**	63
7[16]	 **14**	96

Acknowledgment

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References and Notes

(1) For recent examples of the synthesis and isolation of pyrrole-containing natural products, see: (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (b) Umeyama, A.; Ito, S.; Yuasa, E.; Arihara, S.; Yamada, T. *J. Nat. Prod.* **1998**, *61*, 1433. (c) Jones, T. H.; Flournoy, R. C.; Torres, J. A.; Snelling, R. R.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **1999**, *62*, 1343. (d) Assmann, M.; Zea, S.; Köck, M. *J. Nat. Prod.* **2001**, *64*, 1593. (e) Grube, A.; Köck, M. *J. Nat. Prod.* **2006**, *69*, 1212. (f) Grube, A.; Lichte, E.; Köck, M. *J. Nat. Prod.* **2006**, *69*, 125.

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(5) For selected recent examples of pyrrole synthesis, see: (a) Binder, J. T.; Kirsch, S. F. *Org. Lett.2nt.2 1 b.867 0 T.0067 Tc0 T201.406TJ2 1 T2 0 T.01 Tc T 1 T.492.44 2.8 TIIT 1 T.067 08.0084Tc.002 2rg.4od10.2. TJ1 b.867 0 T.0067 Tc0 T201.406TJ2 1 T1.9867 0 T.01 Tc T 1 T.02.44 2.8 TIIT4 T14.89 0 T.0067 Tc.0 40 T267 T , Biee.ium110Jtride .aepau1.t7.2 2.9e7t7.2 di4. TJ1.8 1. 00T.006767 Tc.0ater.80see.8029 TMo12.6se299.ro94.9.4

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 130.5, 129.2, 127.1 (q, *J* = 31.5 Hz), 125.8 (q, *J* = 3 Hz), 124.3 (q, *J* = 270 Hz), 122.9, 108.6, 108.1, 13.2. IR (film): 3397, 2918, 2852, 1617, 1333, 1112, 844, 778 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}F_3N$: 226.0839; found: 226.0849.

(14) **General Procedure for the Thermally Assisted Synthesis of 1*H*-Pyrroles (Table 3)**: To a stirred solution of the 1,4-dicarbonyl compound (0.13 mmol) in MeOH (1.3 mL) at 0 °C was added magnesium nitride (1.3 mmol). The reaction vessel was sealed and allowed to stir for 10 min before heating to 80 °C for 24 h. After cooling to r.t., the reaction was subjected to workup and column chromatography as before. For pyrroles **10** and **11**, neutral alumina was employed for chromatography to prevent decomposition.

(15) **Physical Data for 3-(Thiophen-2-yl)-2-*p*-tolyl-5-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole (11)**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.41 (br s, 1 H), 7.59 (AB q, *J* = 8.6 Hz, 4 H), 7.44 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 7.21 (dd, *J* = 5.0, 1.0 Hz, 1 H), 6.99 (dd, *J* = 5.0, 3.5 Hz, 1 H), 6.96 (dd, *J* = 3.5, 1.0 Hz, 1 H), 6.66 (d, *J* = 2.8 Hz, 1 H), 2.38 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.0, 137.0, 136.1, 133.4, 129.7, 128.8, 128.8 (q, *J* = 33 Hz), 127.6, 127.4, 127.3, 125.6 (q, *J* = 3 Hz), 124.2 (q, *J* = 273 Hz), 124.7, 124.1, 124.0, 118.0, 109.0, 21.2. IR (film): 3427, 2919, 2849, 1616, 1324, 1164, 1121, 1068 cm^{-1}. HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{22}H_{16}NF_3S$: 383.0956; found: 383.0960.

(16) **Physical Data for 2-Phenyl-4,5-dihydro-1*H*-benzo[*g*]indole (14)**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.46 (br s, 1 H), 7.53 (d, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.6 Hz, 2 H), 7.21–7.26 (m, 4 H), 7.08 (t, *J* = 7.2 Hz, 1 H), 6.43 (d, *J* = 1.8 Hz, 1 H), 2.96 (t, *J* = 7.2 Hz, 2 H), 2.78 (t, *J* = 7.2 Hz, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 135.0, 132.6, 132.5, 129.0, 128.9, 128.4, 126.6, 126.2, 125.2, 123.7, 122.2, 118.2, 106.1, 29.9, 29.7. IR (film): 3442, 2923, 2850, 1609, 1507, 1291, 1263 cm^{-1}. HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{15}N$: 245.1205; found: 245.1192.

(17) **Physical Data for 2-(4-Fluorophenyl)-3-(4-methoxyphenyl)-5-(naphthalen-2-yl)-1*H*-pyrrole (15)**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (br s, 1 H), 7.90 (br s, 1 H), 7.81–7.87 (m, 3 H), 7.71 (dd, *J* = 8.5, 1.4 Hz, 1 H), 7.48 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.38–7.45 (m, 3 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 6.86 (dt, *J* = 9.6, 2.9 Hz, 2 H), 6.77 (d, *J* = 2.6 Hz, 1 H), 3.82 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9 (d, *J* = 245 Hz), 158.1, 133.8, 132.2, 132.1, 129.5, 129.5, 129.2, 129.2, 128.7, 128.6, 128.3, 127.8, 127.7, 126.6, 125.5, 123.7, 123.0, 121.0, 115.7 (d, *J* = 21.5 Hz), 113.9, 109.1, 55.2. IR (film): 3425, 2922, 1629, 1604, 1519, 1506, 1483 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{21}NOF$: 394.1607; found: 394.1617.

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