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An efficient synthesis of N-substituted pyrroles catalyzed by MgI_2 etherate

Abstract: We describe a convenient and useful procedure for the synthesis of various 2,5-dimethyl-N-substituted pyrrole derivatives by the addition of 2,5-hexadione with aromatic amines, heteroaromatic amines and aliphatic amines catalyzed by MgI_2 etherate ($MgI_2{\cdot}(OEt_2)_n$) in good to excellent yields.

Keywords: amines; 2,5-hexadione; MgI_2 etherate; Paal-Knorr condensation; pyrrole.

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Introduction

Pyrroles are important heterocyclic compounds displaying remarkable pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antitumoral and antioxidant activities (Fürstner et al., 1998; Jacobi et al., 2000; Fürstner, 2003). Furthermore, pyrroles are also considered to be important building blocks in many naturally occurring compounds such as heme, chlorophyll and vitamin B_{12} (Santo et al., 1998; Ragno et al., 2000; Hoffmann and Lindel, 2003; Bellina and Rossi, 2006). In view of their important significance, preparation of pyrroles has attracted considerable attention of chemists in recent years. Many methodologies have been developed for the construction of the pyrrole moiety regarded as skeleton (Fang et al., 2012; Heugebaert et al., 2012). Among them, the Paal-Knorr synthesis remains the most useful preparative method for generating pyrroles (Aghapoor et al., 2012; Balme, 2012; Rahmatpour, 2012).

Recently, many methods for the synthesis of pyrroles, such as Paal-Knorr cyclization of primary amines and 1,4-diketones, have been developed in the presence of various Lewis acid catalysts, such as $Ti(O^iPr)_4$ (Yu and Quesne, 1995), $ZrOCl_2{\cdot}8H_2O$ (Rahmatpour, 2011), $Sc(OTf)_3$ (Chen et al., 2006), $Bi(NO_3)_3{\cdot}5H_2O$ (Banik et al., 2004), $UO_2(NO_3)_2{\cdot}6H_2O$ (Satyanarayana and Sivakumar, 2011), $BiCl_3/SiO_2$ (Aghapoor et al., 2012), $InCl_3$ (Shanthi and Perumal, 2009) and $FeCl_3$ (Azizi et al., 2009). Some of the synthetic protocols suffer from disadvantages, such as the use of stoichiometric and even excess amounts of catalyst, harsh reaction conditions, prolonged reaction time, expensive reagents and low yield of the products. From the above viewpoints, the development of less expensive, environmentally benign and easily handled promoters for the synthesis of N-substituted pyrroles by Paal-Knorr condensation under neutral, mild and convenient condition is still highly desirable.

MgI_2 etherate is easily preparative, inexpensive and easier to be handled than other metal halides such as $Ti(O^iPr)_4$, $InCl_3$ and $Sc(OTf)_3$. To the best of our knowledge, there is no report of the use of MgI_2 etherate as a mild catalyst for the Paal-Knorr reaction. In the continuation of our research field, herein, we will wish to report a simple and efficient procedure for the Paal-Knorr pyrrole condensation of primary amines with 2,5-hexadione catalyzed by MgI_2 etherate under mild reaction conditions in good to excellent yields (Scheme 1).

Results and discussion

We initiated our studies by carrying out the Paal-Knorr condensation of aniline with 2,5-hexadione in the presence of 3 mol% of MgI_2 etherate (1.0 M in Et_2O/benzene 1:2) in CH_2Cl_2 at room temperature. After stirring for 2.0 h, the desired 2,5-dimethyl-*N*-phenyl pyrrole (**2a**) was afforded in 93% yield. In order to evaluate the generality of this process, a variety of diversified examples illustrating the present method for the synthesis of 2,5-dimethyl-N-substituted pyrroles (**2b**–**2o**) were studied. The results are listed in Table 1. The reaction of 2,5-hexadione with a series of aromatic substituted primary amines bearing either electron-donating (Table 1, entries 2–5) or electron-withdrawing (Table 1, entries 6–9) groups on the aromatic ring was carried out

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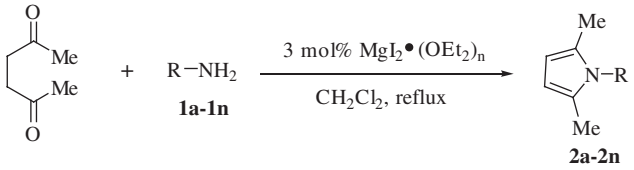
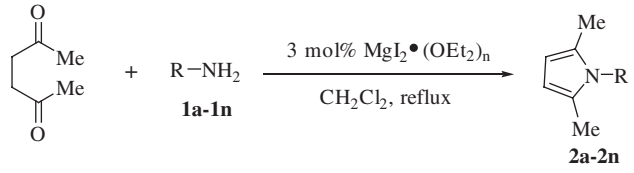
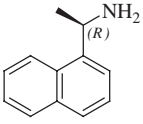
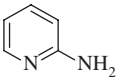
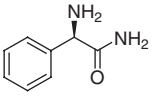


Scheme 1 MgI_2 etherate catalyzed Paal-Knorr condensation.

Table 1 Paal-Knorr condensation of 2,5-hexadione catalyzed by MgI_2 etherate[a].



Entry	Amine	*t* (h)	Product[b]	Yield (%)[c]
1	$C_6H_5NH_2$	2	**2a**	93
2	3-$MeOC_6H_4NH_2$	4	**2b**	80
3	3,4-$(MeO)_2C_6H_3NH_2$	2	**2c**	95
4	4-$EtOC_6H_4NH_2$	2	**2d**	92
5	2,6-$(^iPr)_2C_6H_3NH_2$	8	**2e**	76
6	2-$FC_6H_4NH_2$	6	**2f**	74
7	3,5-$F_2C_6H_3NH_2$	4	**2g**	73
8	3-$ClC_6H_4NH_2$	2	**2h**	86
9	4-$NO_2C_6H_4NH_2$	10	**2i**	78
10	4-$CH_3OC_6H_4CH_2NH_2$	2	**2j**	90
11	4-$ClC_6H_4(CH_2)_2NH_2$	2	**2k**	97
12		2	**2l**	78
13		2	**2m**	92
14		8	**2n**	70

[a]The reaction was carried out by the condensation of 2,5-hexadione (6 mmol) with primary amine (5 mmol) catalyzed by 3 mol% of MgI_2 etherate.

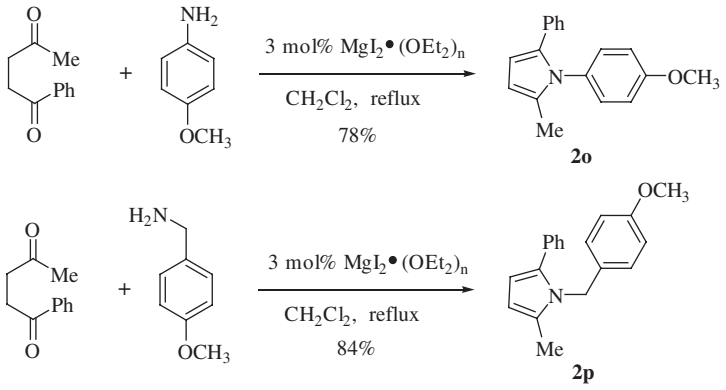
[b]All products were identified by their ^1H NMR spectra.

[c]Yields of products isolated by column chromatography.

as catalyzed by 3 mol% of MgI_2 etherate under mild conditions. As shown in Table 1, the reaction proceeded smoothly in Dichloromethane (DCM) at reflux and provided a single product without any side products in good to excellent yields. Furthermore, the substitution group on the phenyl ring could affect the yield and reaction rate in the Paal-Knorr reaction. We have observed the reactivity of anilines bearing an electron-donating group (i.e., -OMe, -OEt) reacted *much faster* than aniline-bearing electron-withdrawing group (i.e. -Cl, -F, $-NO_2$) and provided the corresponding products in excellent yields. The Paal-Knorr condensation of 2,6-diisopropylaniline with 2,5-hexadione also gave a good yield although it has a more sterically hindered effect (Table 1, entry 5). Furthermore, we have examined the Paal-Knorr reaction of aliphatic amines with 2,5-hexadione (Table 1, entries 10 and 11). Also, the corresponding products were obtained with excellent yields. Unfortunately, no reaction of *tert*-butylamine with 2,5-hexadione was observed under the same conditions, due to its higher steric hindrance. Under further observation, it is observed that the reaction of chiral amine such as (*R*)-(+)-1-(1-naphthyl)ethylamine **1l** with 2,5-hexadione provided the optically pyrrole derivative without racemization. Moreover, we examined the reactivity of heterocyclic amines with 2,5-hexadione in the presence of MgI_2 etherate. Thus, using 3 mol% of MgI_2 etherate the Paal-Knorr reaction of heterocyclic amine such as 2-aminopyridine (**1m)** affords 2-(2,5-dimethyl-1H-pyrrol-1-yl)pyridine (**2m**) in 92% yield (Table 1, entry 13). Therefore, heterocyclic amines exhibited analogous behavior to that of aromatic amines and aliphatic amines. Interestingly, the condensation of (*R*)-2-amino-2-phenylacetamide, which has two amino groups, exclusively gave (*R*)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-2-phenylacetamide (**2n**) with the retention of absolute configuration.

The reaction using MgI_2 etherate as a catalyst has shown an important feature, that is, the ability to tolerate various amines including aliphatic, aromatic and heterocyclic amines. To extend the scope of MgI_2 etherate-catalyzed Paal-Knorr condensation for the synthesis of N-substituted pyrrole derivatives, other substituted diketones such as 1,4-diphenylbutane-1,4-dione and 1-phenylpentane-1,4-dione were investigated. Unfortunately, no reaction of 1,4-diphenylbutane-1,4-dione with *p*-methoxyaniline occurred. The condensation of 1-phenylpentane-1,4-dione with *p*-methoxyaniline or *p*-methoxybenzyl amine resulted in good yields (Scheme 2).

The high coordinating ability of magnesium (II) towards oxygen atoms of the carbonyl moiety is presumably responsible for the effective activation of ketonic carbonyl. To examine the halide anion effect, halogen analogs of MgI_2 etherate, $MgCl_2$ etherate and $MgBr_2$ etherate were compared under parallel reaction conditions (3 mol% of catalyst) in the Paal-Knorr condensation of aniline with 2,5-hexadione. $MgCl_2$ etherate and $MgBr_2$ etherate are less effective in terms of substrate conversion yield and provide the moderate yields. Apparently, the unique reactivity of MgI_2 etherate is attributed to the dissociative character of iodide counterion and a more Lewis acidic cationic $[MgI]^+$ species.



Scheme 2 Paal-Knorr condensation with 1-phenylpentane-1,4-dione catalyzed by MgI_2 etherate.

In conclusion, we have demonstrated the unique reactivity of MgI_2 etherate in the Paal-Knorr reaction for the synthesis of N-substituted pyrroles. Compared to previously reported methodologies, the present protocol features simple operation, mild condition and good to excellent yield. Exploitation of this protocol for generation of novel multicyclic structures is actively pursued in our lab.

Experimental section

General methods

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90°C) were used. ^{1}H NMR spectra were taken on a Bruker Avance III 500 MHz spectrometer (Switzerland) with Tetramethylsilane (TMS) as an internal standard and $CDCl_3$ as solvent. The reaction monitoring was accomplished by thin layer chromatography (TLC) on silica gel polygram SILG/UV 254 plates. FT-IR spectra were recorded with a Nicolet 6700 spectrophotometer with NaCl optics (Thermo Company, USA). Melting points were measured on BUCHI B-540. High resolution mass spectroscopy (HRMS) were determined on a Waters GCT Premier spectrometer (Waters Company, USA). Elemental analysis was performed on a VarioEL-3 instrument (Elementar, Germany). All compounds were identified by ^{1}H NMR and are in good agreement with those reported. All starting materials and reagents are purchased from the Sigma-Aldrich company.

General procedure for the synthesis of N-substituted pyrroles

To a mixture of amine (5 mmol) and 2,5-hexadione (6 mmol, 1.1 equiv) in 5 mL dichloromethane was added 3 mol% freshly prepared MgI_2 etherate (Arkley et al., 1962). The mixture was stirred at reflux for the appropriate time. The progress of the reaction was monitored by TLC. After reaction, the mixture was concentrated and the residue was purified on silica gel with petroleum ether/ethyl acetate as eluent.

1-Phenyl-2,5-dimethyl-1*H*-pyrrole(2a) (Satyanarayana and Sivakumar, 2011): light yellow solid. R_f=0.67 (100% PE). m.p. 49–50°C (lit. 48–50°C). ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.11 (s, 6H), 5.98 (s, 2H), 7.27–7.29 (m, 2H), 7.44–7.47 (m, 1H), 7.50–7.54 (m, 2H).

1-(3-Methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (2b) (Lee and Kim, 2013): light yellow liquid. R_f=0.42 (100% PE), ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.18 (s, 6H), 3.92 (s, 3H), 6.01(s, 2H), 6.88 (d, *J*=2.2 Hz, 1H), 6.89–6.94 (m, 1H), 7.05–7.7.07 (m, 1H), 7.46 (t, *J*=8.0 Hz, 1H).

1-(3,4-Dimethoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (2c) (Noberini et al., 2008): pale yellow liquid. R_f=0.18 (100% PE). ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.09 (s, 6H), 3.90 (s, 3H), 3.97 (s, 3H), 5.93 (s, 2H), 6.78 (d, *J*= 2.3 Hz, 1H), 6.83 (dd, *J*=2.3, 8.4 Hz, 1H), 6.97 (d, *J*=8.4 Hz, 1H).

1-(4-Ethoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (2d) (Hazlewood et al., 1937): white solid. R_f=0.33 (100% PE). m.p. 59–61°C (lit. 63°C), FT-IR (KBr) υ (cm^{-1}): 2983, 1514, 1475, 1404, 1290, 1246, 1169, 1052, 845, 768. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.55 (t, *J*=7.0 Hz, 3H), 2.12 (s, 6H), 4.16 (dd, *J*=5.0, 10.0 Hz, 2H), 5.98 (s, 2H), 7.03–7.07 (m, 2H), 7.19–7.23 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.01, 14.90, 63.56, 105.06, 114.45, 128.72, 128.94, 131.31, 157.94. EI-MS-215 ($[M]^+$, 100), 186 (62), 172 (10), 145 (14), 117 (12), 77 (5). Elemental analyses: calculated (%) for $C_{16}H_{21}NO$ (243.16 g/mol): C 78.97; H 8.70; N 5.76, found: C 78.85, H 8.58, N 5.65.

1-(2,6-Diisopropylphenyl)-2,5-dimethyl-1*H*-pyrrole (2e) (Chen et al., 2009): white solid. R_f=0.73 (PE:EA=10:1). m.p. 56–57°C (lit. 56–58°C). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.16 (d, *J*=6.9, 12H), 1.95 (s, 6H), 2.0–2.1 (m, 2H), 5.98 (s, 2H), 7.28 (d, *J*=7.7 Hz, 2H), 7.44 (t, *J*=7.7 Hz, 1H).

1-(2-Fluorophenyl)-2,5-dimethyl-1*H*-pyrrole (2f) (Chen et al., 2009): yellow liquid. R_f=0.62 (PE:EA=10:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.95 (s, 6H), 5.94 (s, 2H), 7.29 (t, *J*=7.8 Hz, 1H), 7.61 (t, *J*=7.8 Hz, 1H), 7.69 (t, *J*=7.6 Hz, 1H), 7.84–7.86 (m, 1H).

1-(3,5-Difluorophenyl)-2,5-dimethyl-1*H*-pyrrole (2g) (Thomas et al., 2004): white solid. R_f=0.68 (PE:EA=10:1). m.p. 54.8–55.3°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.09 (s, 6H), 5.93 (s, 2H), 6.81 (dd, J_1= 2.2, 7.4 Hz, 2H), 6.88–6.92 (m, 1H).

1-(3-Chlorophenyl)-2,5-dimethyl-1*H*-pyrrole (2h) (Jafari et al., 2012): white solid. R_f=0.43 (100% PE). m.p. 48–49°C (lit. 47–49°C). ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.07 (s, 6H), 5.93 (s, 2H), 7.13–7.16 (m, 1H), 7.25–7.28 (m, 1H), 7.40–7.44 (m, 2H).

1-(4-Nitrophenyl)-2,5-dimethyl-1*H*-pyrrole (2i) (Satyanarayana and Sivakumar, 2011): yellow solid. R_f=0.35 (PE:EA=10:1). m.p. 142–143°C (lit. 143–144°C). ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.10 (s, 6H), 5.98 (s, 2H), 7.39–7.43 (m, 2H), 8.35–8.38 (m, 2H).

1-(4-Methoxybenzyl)-2,5-dimethyl-1*H*-pyrrole (2j) (Chen et al., 2009): white solid. R_f=0.23 (100% PE). m.p. 75–76°C (lit. 76–77°C). ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.20 (s, 6H), 3.82 (s, 3H), 5.00 (s, 2H), 5.90 (s, 2H), 6.85–6.90 (m, 4H).

1-(4-Chlorophenethyl)-2,5-dimethyl-1H-pyrrole (2k) White solid. R_f=0.29 (100% PE). m.p. 64–66°C. FT-IR (KBr) υ (cm^{-1}): 2970, 1518, 1492, 1411, 1298, 1094, 1017, 811, 715. ^{1}H NMR (500 MHz, $CDC1_3$): δ=2.16 (s, 6H), 2.90 (t, *J*=7.5 Hz, 2H), 3.97 (t, *J*=7.4 Hz, 2H), 5.82 (s, 2H), 7.01–7.03 (m, 2H), 7.27–7.30 (m, 2H). ^{13}C NMR (125 MHz, $CDC1_3$): δ=12.44, 36.80, 44.92, 105.18, 127.05, 128.42, 130.03, 132.20, 136.68. EI-MS: 233 ([M]$^+$, 20), 235 ([M+2]$^+$, 7), 215 (8), 108 (100), 92 (16), 77 (18). Elemental analyses: calculated (%) for $C_{14}H_{16}ClN$ (233.10 g/mol): C 71.94, H 6.90, N 5.99, found: C 71.85, H 6.78, N 5.87.

(*R*)-1-(1-(Naphthalen-1-yl)ethyl)-2,5-dimethyl-1H-pyrrole (2l) Yellow liquid, R_f=0.31 (PE:EA=10:1). FT-IR (KBr) υ (cm^{-1}): 2978, 1566, 1516, 1448, 1420, 1245, 1212, 1060, 760. ^{1}H NMR (500 MHz, $CDC1_3$): δ=2.05 (d, *J*=7.1 Hz, 3H), 2.19 (s, 6H), 5.91 (s, 2H), 6.10 (q, *J*=7.1 Hz, 1H), 7.53-7.57 (m, 3H), 7.77-7.79 (m, 1H), 7.90-7.95 (m, 1H), 7.95–7.96 (m, 1H). ^{13}C NMR (125 MHz, $CDC1_3$): δ=14.2, 20.5, 51.7, 106.5, 123.2, 123.4, 124.4, 126.7, 128.0, 128.4, 128.8, 129.4, 132.3, 135.3, 137.0. EI-MS: 249.1 (10), 155.2 (100), 149.2 (31), 95.2 (43), 81.2 (23). Elemental analyses: calculated (%) for $C_{18}H_{19}N$ (249.15 g/mol): C 86.70, H 7.68, N 5.62, found: C 86.79, H 7.58, N 5.70.

2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)pyridine (2m) (Chen et al., 2006): yellow liquid. R_f=0.54 (PE:EA=5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.15(s, 6H), 5.93(s, 2H), 7.23–7.28 (m, 1H), 7.30–7.33 (m, 1H), 7.82–7.86 (m, 1H), 8.62–8.64 (m, 1H).

(*S*)-2-(2,5-Dimethyl-1H-pyrrol-1-yl)-2-phenylacetamide (2n) Yellow solid. R_f=0.4 (PE:EA=3:1). m.p. 102.7–105.2°C. FT-IR (KBr) υ (cm^{-1}): 2983, 1693, 1564, 1513, 1444, 1230, 1074, 840, 765. ^{1}H NMR (500 MHz, $CDC1_3$): δ=2.07 (s, 6H), 5.70 (s, 1H), 5.89 (s, 2H), 5.98 (s, 1H), 6.85 (s, 1H), 7.25–7.28 (m, 2H), 7.30 (s, 1H), 7.31–7.36 (m, 2H). ^{13}C NMR (125 MHz, $CDC1_3$): δ=13.6, 61.1, 107.7, 127.8, 128.1, 128.4, 128.8, 135.4, 171.6. EI-MS: 228.1 (7), 185.4 (11), 184.3 (43), 94.7 (100), 106.4 (10). Elemental analyses: calculated (%) for $C_{14}H_{16}N_2O$ (228.13 g/mol): C 73.66, H 7.06, N 12.27, found: C 73.78, H 6.96, N 12.36.

1-(4-Methoxyphenyl)-2-methyl-5-phenyl-1H-pyrrole (2o) (Lee and Kim, 2013): yellow solid. R_f=0.49 (PE:EA=10:1). m.p. 104–106°C. ^{1}H NMR (500 MHz, $CDC1_3$): δ=2.19 (s, 3H), 3.86 (s, 3H), 6.15 (d, *J*=3.0 Hz, 1H), 6.42 (d, *J*=3.4 Hz, 1H), 6.94 (d, *J*=8.8 Hz, 2H), 7.12–7.16 (m, 5H), 7.20 (t, *J*=7.6 Hz, 2H).

1-(4-Methoxybenzyl)-2-methyl-5-phenyl-1H-pyrrole (2p) Yellow solid. R_f=0.68 (PE:EA=10:1). m.p. 91–92°C. FT-IR (KBr) υ (cm^{-1}): 2930, 1550, 1510, 1444, 1403, 1240, 1170, 1033, 820. ^{1}H NMR (500 MHz, $CDC1_3$): δ=2.28 (s, 3H), 3.87 (s, 3H), 5.20 (s, 2H), 6.18 (d, *J*=3.0 Hz, 1H), 6.37 (d, *J*=3.3 Hz, 1H), 6.97 (dd, *J*=5.2, 8.9 Hz, 4H), 7.27–7.36 (m, 1H), 7.40–7.46 (m, 4H). ^{13}C NMR (125 MHz, $CDC1_3$): δ=12.5, 47.0, 55.1, 107.2, 107.9, 114.0, 126.5, 126.7, 128.3, 128.5, 130.3, 130.9, 133.8, 134.5, 158.1. EI-MS: 277.1 (8), 156.2 (2), 121.2 (100), 91.4 (11), 77.3 (13); elemental analyses: calculated (%) for $C_{19}H_{19}NO$ (277.15 g/mol): C 82.28, H 6.90, N 5.05, found: C 82.41, H 6.79, N 5.15.

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