

PMA/SiO₂ as efficient, cost-effective and recyclable catalytic system for the synthesis of highly substituted pyrroles

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Abstract

A mild and efficient method for the synthesis of highly substituted pyrroles is described using phosphomolybdic acid supported on silica gel as a reusable catalyst. The use of PMA supported on silica gel makes it quite simple, more convenient and environmentally benign. This method offers several advantages such as high conversions, short reaction times, cleaner reaction profiles and the use of inexpensive and readily available catalyst.

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Keywords: Three-component reaction; Pyrroles; Heteropoly acid; Heterogeneous catalysis

1. Introduction

The pyrrole nucleus is found in various biologically active molecules including the blockbuster drug atorvastatin as well as important anti-inflammatories, antitumor agents and immunosuppressants [1–5], and as structural components in polymers [6–8], and as intermediates in organic synthesis [9]. Therefore, considerable attention has been paid to develop efficient methods for the synthesis of pyrroles. Consequently, a large number of methods have been developed for their synthesis, which include Knorr [10], Paal–Knorr [11], and Hantzsch syntheses [12]. These methodologies typically require the preparation of the precursors prior to cyclization, which can complicate both the synthesis and structural modification of the substituted pyrroles. This has stimulated significant interest in the design of new synthetic routes to pyrroles, including several efficient multi-component reactions [13–16] and metal-catalyzed routes [17–24]. In addition, the three-component reaction of aldehyde, amine and nitroalkene has been reported previously using Sm(Oi-Pr)₃ and InCl₃/SiO₂ to synthesize substituted pyrroles [25–28]. In spite of a large number of methods reported for the synthesis of pyrroles, there is always considerable demand in exploring more milder, convenient, practical and benign reagents

for their synthesis. Therefore, the developments of simple, convenient and practical procedures for the synthesis of pyrroles continue to be a challenging endeavor in synthetic organic chemistry. Recently, a great attention has been focused on the use of phosphomolybdic acid as environmentally friendly catalyst in organic synthesis. In addition to its abundance, economical and safety reasons, phosphomolybdic acid has naturally become a substitute and an alternative environmentally benign catalyst. Phosphomolybdic acid (PMA) belongs to the class of heteropoly acids (HPA). Catalysis using HPAs and related polyoxometalate compounds is a field of growing importance [29,30]. HPAs are commercially cheap and environmentally friendly catalysts. They exhibit high activities and selectivities and allow cleaner processes than conventional catalysts. HPAs are promising solid acid bifunctional catalysts under homogeneous as well as in heterogeneous conditions. HPAs are very strong acids, approaching the super acid region, with a Bronsted acidity greatly exceeding that of ordinary mineral acids and solid acid catalysts. HPAs are several times more active than H₂SO₄, TsOH, BF₃·OEt₂ and ZnCl₂ [31]. It has been shown that in organic media, the molar catalytic activity of HPAs is often 100–1000 times higher than that of H₂SO₄ [32,33]. This makes it possible to carry out a catalytic process at low concentrations and at lower temperatures. Supported HPAs are more active than typical solid acids. Acidic or neutral substances such as silica gel [31], active carbon [34,35] or an acidic ion-exchange resin [36] are suitable supports, the more commonly used being silica gel [31]. Synthetically, various

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Table 1
PMA/SiO₂ catalyzed synthesis of alkyl pyrroles *via* a three-component reaction


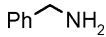
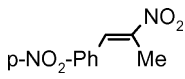
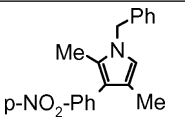
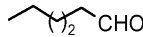
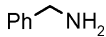
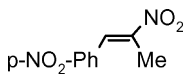
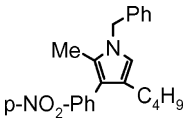

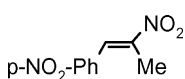
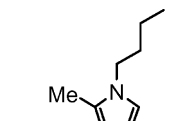

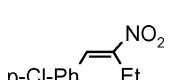
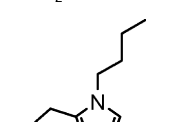
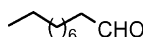
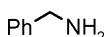
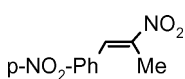
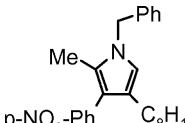
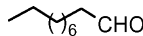
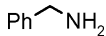
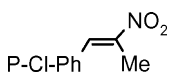
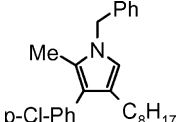
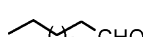
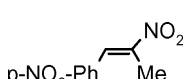
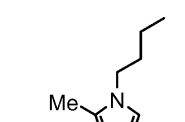

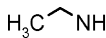
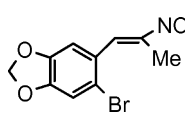
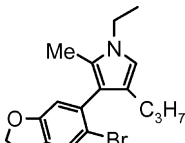
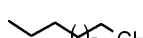

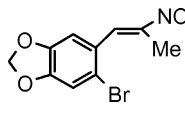
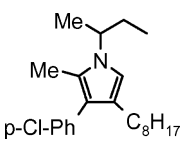
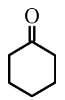

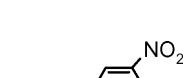
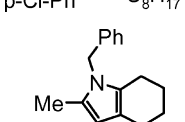
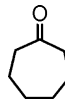

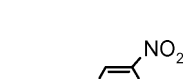
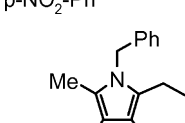

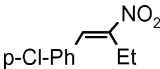
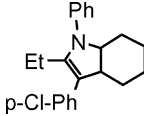

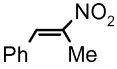
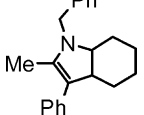
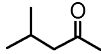
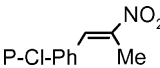
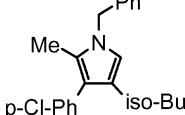
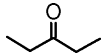
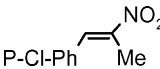
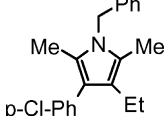
Entry	Carbonyl compound (1)	Amine (2)	Nitroalkene (3)	Product ^a (4)	Time (h)	Yield (%) ^b
a					1.5	92 [25]
b					1.5	86
c		<i>n</i> -Bu-NH ₂			1.5	90
d		<i>n</i> -Bu-NH ₂			2.0	88
e					1.5	90
f					1.5	90 [25]
g		<i>n</i> -Bu-NH ₂			1.5	86 [25]
h					2.0	85
i					2.0	78
j					1.5	90
k					1.5	89

Table 1 (Continued)

Entry	Carbonyl compound (1)	Amine (2)	Nitroalkene (3)	Product ^a (4)	Time (h)	Yield (%) ^b
l		Ph-NH ₂			2.0	80
m		Ph-CH ₂ -NH ₂			1.5	90 [25]
n		Ph-CH ₂ -NH ₂			1.5	86
o		Ph-CH ₂ -NH ₂			1.5	85

^a All products were characterized by IR, ¹H NMR and mass spectroscopy.

^b Yield refers to pure products after column chromatography.

methods have been developed and commercialized using HPAs as catalysts [37]. For example, Fries rearrangement of phenyl acetate [38], Friedel–Crafts acylation of phenols [39], oxidation of alcohols [40], regioselective ring opening of aziridines [41], chemoselective deprotection of isopropylidene acetals [42] and chemoselective hydrolysis of *tert*-butyldimethylsilyl ethers [43] have been reported using HPAs. The synthesis of glycosides using HPAs as catalysts is of great industrial importance [44]. However, there have been no reports on the use of PMA–SiO₂ for a three-component one-pot synthesis of pyrroles.

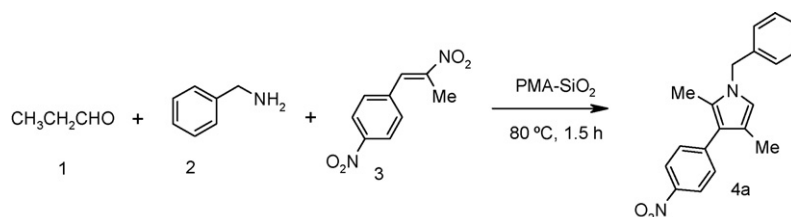
2. Results and discussion

In continuation of our efforts to explore the synthetic utility of phosphomolybdic acid supported on silica gel (PMA–SiO₂) [42,45,46], herein we report a three-component approach for the one-pot synthesis of highly substituted pyrroles using a cheap and reusable catalytic system, PMA–SiO₂ (Scheme 1).

Accordingly, treatment of propanal (1), benzyl amine (2) and 1-nitro-4-[(*E*)-2-nitro-1-propenyl]benzene (3) in the presence of PMA–SiO₂ under solvent-free conditions at 80 °C for 1.5 h gave the corresponding 1-benzyl-2,4-dimethyl-3-(4-nitrophenyl)-1*H*-pyrrole 4a in 92% yield. Encouraged by this result, we turned our attention to various substituted com-

ponents. Interestingly, several carbonyl compounds reacted smoothly with different amines and β-nitrostyrenes to furnish the corresponding alkylated pyrroles (entries a–o, Table 1). In all cases, the reactions proceeded efficiently at 80 °C under solvent-free conditions. However, in the absence of catalyst, the reaction did not proceed even at reflux temperature. Lowering the reaction temperature was detrimental to the efficiency of this procedure. The reaction conditions are mild and no side products or decomposition of the products are observed. All the products were characterized by ¹H NMR, IR and mass spectroscopy. The catalyst, i.e. PMA–SiO₂ was recovered by simple filtration and reused in subsequent runs with no decrease in activity. The possibility of recycling the catalyst, i.e. PMA–SiO₂ is one of the key advantages of this procedure, which was demonstrated using propanal (1), benzyl amine (2) and 1-nitro-4-[(*E*)-2-nitro-1-propenyl]benzene (3) as a model reaction. The recovered catalyst was recycled up to five times with no decrease in the conversion. These results clearly show the advantage of this method over existing procedures. The scope and generality of this process is illustrated with respect to various carbonyl compounds, substituted amines and β-nitrostyrenes and the results are summarized in Table 1 [47].

To know the efficiency of PMA–SiO₂, we have carried out the comparative experiments with some silica gel supported



Scheme 1.

Table 2

A comparative study of various heterogeneous catalysts for the preparation of **4a** at 80 °C

S. no.	Catalyst	Reaction time (h)	Yield (%)
a	HClO ₄ -SiO ₂	3.5	87
b	H ₂ SO ₄ -SiO ₂	4.5	83
c	PMA-SiO ₂	2.5	95
d	NaHSO ₄ -SiO ₂	6.0	79

Bronsted acids and the comparative results are summarized in Table 2.

3. Conclusion

In summary, we have described a simple, convenient and efficient protocol for the synthesis of highly substituted pyrroles using phosphomolybdic acid supported on silica gel as a reusable catalyst. The notable features of this method are mild reaction conditions, greater selectivity, simplicity in operation, cleaner reaction profiles, low cost and reusability of the catalyst, which make it an attractive and very useful process for the synthesis of alkylated pyrroles of biological importance.

4. Experimental

4.1. General remarks

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ¹H NMR spectra were recorded on Varian-unity 300 spectrometer in CDCl₃ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

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- [47] General procedure: PMA/SiO₂ catalyst was prepared following the published procedure [43]. To a mixture of the aldehyde or ketone (1 mmol), an amine (1 mmol) and a conjugated nitroalkene (1 mmol) in 1.0 g of PMA-SiO₂ (0.05 mmol) was heated at 80 °C for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC, reaction mixture was diluted with Et₂O. The catalyst, i.e. PMA-SiO₂ was recovered by simple filtration and crude product was purified by column chromatography (60–120 silica gel mesh) using EtOAc:hexane mixture to afford pure products. The filtered catalyst was reused without drying. Spectroscopic data for selected compounds. *N*-Benzyl-3-(4-nitrophenyl)-2,4-dimethylpyrrole: (**4a**): liquid; IR (KBr): ν 2925, 1593, 1510, 1339, 734 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.22 (d, J =9.0 Hz, 2H), 7.25–7.45 (m, 4H), 7.02 (d, J =6.7 Hz, 2H), 6.47 (s, 1H), 5.01 (s, 2H), 2.15 (s, 3H), 2.08 (s, 3H); LC-MS: m/z : 329 (M⁺ + Na). *N*-Benzyl-4-butyl-3-(4-nitrophenyl)-2-methyl-pyrrole: (**4b**): liquid; IR (KBr): ν 3030, 2927, 1594, 1501, 1338, 733 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 8.24 (d, J =8.7 Hz, 2H), 7.26–7.45 (m, 5H), 7.03 (d, J =8.0 Hz, 2H), 6.48 (s, 1H), 5.03 (s, 2H),

2.46 (t, $J=7.3$ Hz, 2H), 2.13 (s, 3H), 1.48–1.22 (m, 4H), 0.87 (t, $J=6.9$, 3H); LC–MS: m/z : 371 (M^+ + Na). *N*-Benzyl-3-(4-nitrophenyl)-2-methyl-4,5,6,7-tetrahydro-indole: (**4j**): liquid; IR (KBr): ν 2927, 1592, 1508, 1335, 733 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 8.21 (d, $J=8.7$ Hz, 2H),

7.26–7.46 (m, 5H), 6.92 (d, $J=7.3$, 2H), 5.03 (s, 2H), 2.51 (m, 4H), 2.23 (s, 3H), 1.8 (m, 4H). ^{13}C NMR (75 MHz CDCl_3): 144.9, 144.4, 139.0, 129.2, 128.8, 128.1, 127.2, 125.8, 125.6, 123.5, 118.4, 115.5, 46.7, 23.8, 23.2, 22.9, 22.0, 10.8. LC–MS: m/z 369 (M^+ + Na).