

GRINDING SOLVENT-FREE PAAL-KNORR PYRROLE SYNTHESIS ON SMECTITES AS RECYCLABLE AND GREEN CATALYSTS

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ABSTRACT. An environmentally benign method for the synthesis of *N*-substituted pyrroles from one-pot solvent-free condensation reaction of 2,5-hexanedione with various primary amines (Paal-Knorr pyrrole synthesis) on smectite clays as green and reusable heterogeneous Lewis acid catalysts is presented. The use of nontoxic, inexpensive, easily available and reusable catalysts under solvent-free conditions make this protocol practical, environmentally friendly and economically attractive.

KEY WORDS: Paal-Knorr, Smectites, Pyrrole, Solvent-free, Grinding

INTRODUCTION

Paal-Knorr condensation has experienced a rekindled interest in the synthetic chemistry for preparation of pyrrole, pyrazoles, and their derivatives, as important heterocyclic compounds displaying remarkable pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antitumoral, and antioxidant activities [1]. The pyrrole moiety is found in many naturally occurring compounds such as heme, chlorophyll, and vitamin B₁₂ [2]. Pyrroles are also present in various bioactive drug molecules such as atorvastatin, anti-inflammatory and antitumor agents, and immunosuppressants [3, 4].

This reaction remains one of the most significant and simple methods which consists the cyclocondensation of primary amines with 1,4-dicarbonyl compounds to produce *N*-substituted pyrroles. Several catalysts have been used to promote this reaction including HCl [5a], *p*-TSA [5b], H₂SO₄ [5c], Sc(OTf)₃ [5d], Bi(NO₃)₃·5H₂O [5e], SnCl₂·2H₂O [5f], Ti(O*i*Pr)₄ [5g], RuCl₃ [5h], InCl₃, InBr₃, In(OTf)₃ [5i], zeolite [5j], Al₂O₃ [5k], MgI₂ etherate [5l], ZrOCl₂·8H₂O [5m], ZrCl₄ [5n], montmorillonite K10 [6a], silica sulfuric acid [6b], layered zirconium phosphate and phosphonate [6c], Fe³⁺-montmorillonite [6d], montmorillonite KSF-clay and I₂ [6e]. Additionally, the above cyclocondensation process could proceed in ionic liquid [6f] or ultrasonic and microwave irradiation [6g].

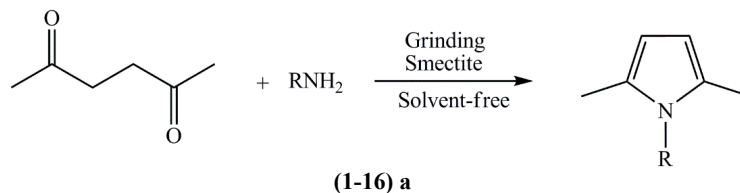
Many of these procedures involve the use of expensive reagents, metal triflates, and extended reaction times and produce a huge amount of corrosive, toxic waste products and tedious workup and the use of extra energy source, such as high-power microwave irradiation or ultrasound. So, a milder, nonhazardous, recyclable, and ecofriendly organic catalyst is still in demand [7].

Natural aluminosilicates, such as zeolites and clays, are solid acids that could act as an efficient alternative to liquid acids. Natural and modified clays have attracted attention due to their extremely versatile properties and high potential in green chemistry [8]. Many clay based catalysts such as K-10 and KSF montmorillonites, hectorite, bentonite, kaolin, envirocat, etc. are commercially available and two most common clays applied in organic synthesis are K-10 and KSF clays. Though the physicochemical properties of the clays are similar their BET surface areas differ.

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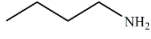
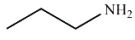
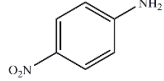
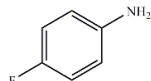
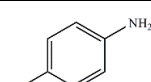
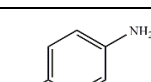
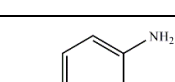
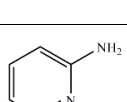
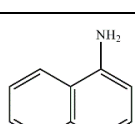
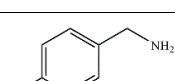
In continuation of ongoing investigations exploring the use of solid supports in organic synthesis [9], this paper reports a simple, efficient, inexpensive and solvent free procedure for the Paal-Knorr synthesis of *N*-substituted pyrroles on smectite clays as efficient heterogeneous, green and recyclable catalysts employing grindstone technique (Scheme 1). The solid clays can be recovered later and reused in the subsequent reactions. Details of recyclability of the recovered solid clays have been shown in the Table 1.



Scheme 1. Solvent-free grinding synthesis of *N*-substituted pyrroles on smectites.

Table 1. The yields and reaction times for smectite supported solvent-free grinding Paal–Knorr synthesis of *N*-substituted pyrroles.

Entry	Amine	Product	Yield ^a , % KSF/ Bentonite Hectorite/ K10	Time, min KSF/ Bentonite Hectorite/ K10
1		1a	96(93)/98(96) 95(92)/94(92)	3/2 4/4
2		2a	95(91)/98(95) 96(92)/96(94)	4/2 3/3
3		3a	97(94)/98(95) 93(90)/93(92)	3/2 3/4
4		4a	97(93)/98(94) 94(92)/97(92)	4/3 3/4
5		5a	98(96)/98(95) 95(92)/96(93)	4/3 5/4
6		6a	95(91)/98(95) 93(90)/94(91)	4/3 4/4

7		7a	96(93)/98(95) 94(92)/95(92)	4/2 3/4
8		8a	96(92)/97(95) 93(85)/94(92)	4/3 4/5
9		9a	93(89)/94(91) 91(87)/92(88)	5/5 5/6
10		10a	92(88)/95(92) 90(85)/90(86)	5/4 5/5
11		11a	91(89)/93(89) 89(86)/90(87)	5/3 4/5
12		12a	94(88)/95(90) 88(84)/91(86)	5/3 5/5
13		13a	90(86)/93(87) 89(85)/89(83)	4/2 3/4
14		14a	95(91)/98(95) 90(88)/90(84)	5/4 5/5
15		15a	95(91)/97(95) 90(88)/94(93)	5/3 5/4
16		16a	92(87)/95(90) 91(90)/94(89)	4/2 3/3

*Isolated yields after recrystallization. The yields indicated in the parenthesis correspond to those reactions which the recovered clays were used (1st run).

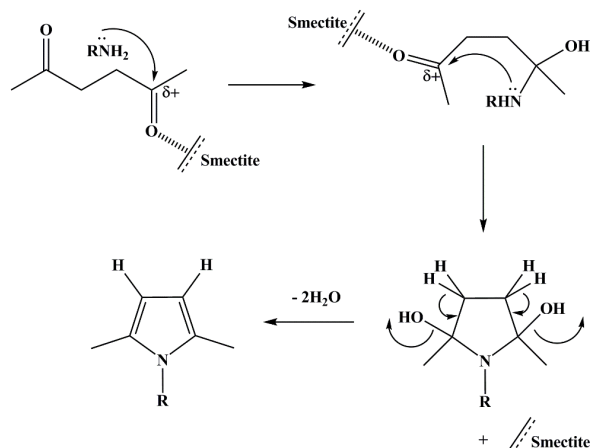
RESULTS AND DISCUSSION

The clay supported grinding synthesis of *N*-substituted pyrroles were through the reaction of hexane-2,5-dione with primary amines (Scheme 1) under solvent-free conditions. Results summarized in the Table 1 indicate the scope and generality of the reaction with respect to the various primary amines. The nature of the substituents on the aromatic ring of primary amines has different influences. The presence of the electron donating groups such as methyl and ethyl give high yields of products compared to aniline (entries 4a, 5a and 6a).

The catalysts studied were smectite-type laminar silicates. The structure of an elementary sheet of these materials consists of an octahedral layer of $\text{Al}[\text{O}_4(\text{OH})_2]$ (for montmorillonites KSF, K-10, and bentonite) or $\text{Mg}[\text{O}_4(\text{OH})_2]$ (for hectorite) sandwiched between two tetrahedral layers of SiO_4 tetrahedral. The total concentration of acid sites on the catalyst surface was determined by NH_3 adsorption [10a] and the surface area by the BET method [10b]. The key factor for the reaction is the acidity of the clay, while the surface area seems to play a less important role. Indeed, all clays display activity in the reaction, but of all the catalysts examined, the bentonite, which shows the greatest overall acidity, is the most efficient catalyst [11]. Chemical composition, surface area and surface acidity of the applied clays are shown in Table 2. In this method, the reaction time has been shortened and the synthesis of these compounds has the feature of rapid reaction, convenient operation, high yield, and clean. The use of the solid clay catalyst in this method offers high yields of products compared to conventional procedures. From the other advantages of our method is the recyclability of solid clay. The used clay catalysts in the first cycle were recovered by filtration, washed with methanol and reused.

Table 2. Chemical composition, surface area and surface acidity of applied smectites.

Clay	Surface area (m^2/g)	Surface acidity (meq. H^+/g)	SiO_2 (%)	Al_2O_3 (%)	Fe_2O_3 (%)	CaO (%)	MgO (%)	Na_2O (%)	K_2O (%)
KSF Clay	15±10	0.70	54.0	17.0	5.2	1.5	2.5	0.4	1.5
K-10 Clay	200±10	0.65	73.0	14.0	2.7	0.2	1.1	0.6	1.9
Bentonite	205 ± 10	0.77	70.9	20.1	0.2	1.2	2.5	0.4	0.5
Hectorite	63 ± 10	0.21	34.7	0.7	0.3(FeO)	23.4	15.3	1.3	0.1



Scheme 2. Possible mechanism for smectite supported grinding solvent-free synthesis of *N*-substituted pyrroles.

Reusability of the catalyst

The feasibility of repeated use of smectite clay was also examined. Recovery of the catalyst was very easy. After completion of the reaction and extraction of the product, smectite clay was filtered and washed with ethanol (50 mL) in a beaker under stirring for 10 min at room temperature. The catalyst is insoluble in ethanol and was simply filtered. The recycled catalyst was washed with ethanol once more, filtered off and dried at 100 °C for 1 h. The reused catalyst was stable under the reaction conditions, and its activity in terms of yields was slightly decreased with an increasing number of reaction cycles. Hence, the loss of catalytic activity for reused catalyst one after five cycles was negligible. Recyclability of the bentonite smectite for the synthesis of 1-phenyl-2,5-dimethyl-1*H*-pyrrole (**1a**) for five runs is shown in Figure 1.

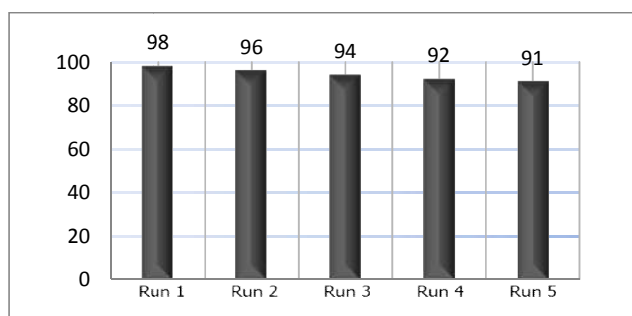


Figure 1. Recyclability of the bentonite for the synthesis of **1a**.

EXPERIMENTAL

Chemicals were purchased from Aldrich and Merck chemical companies and used without further purification. Commercially available heterogeneous clays, montmorillonites KSF and K10 (Fluka), hectorite [SHCa-118 (Clay Source)] and bentonite [Bieliaea (Rudex)] were tested in this method.

Melting points were measured on an Electro thermal 9100 apparatus. ¹H NMR spectra were recorded by a FTNMR Bruker DRX 500 Avance spectrometer (500 MHz). Chemical shifts were measured in ppm from TMS. CDCl₃ was used as solvent as well as the internal standard. The IR spectra were recorded on a Perkin Elmer FT-IR GX instrument in KBr discs.

General procedure

2,5-hexanedione (10 mmol) and 1 g smectite clay was ground together in a mortar using pestle for 2 min. Amine (10 mmol) was added to this mixture and grinding was continued at room temperature for the time presented in Table 1 to complete the reaction (monitored by TLC, n-hexane/ ethyl acetate, 1/3). After completing the reaction the product was extracted with CH₂Cl₂ (2×15 mL) and the clay filtered off. The organic layer after washing with water, was dried over MgSO₄, filtered and the solvent was evaporated under vacuum to afford the product. The products were isolated as low melting crystals or oils. The solid pyrroles were washed thoroughly with water, dried, and then recrystallized from methanol. The oily products were purified by column chromatography using hexane and ethyl acetate as the eluent. The solid clay portion was washed with ethanol and dried at 100 °C under a reduced pressure to be reused in the subsequent reactions which showed the gradual decrease in the activity (Table 1). Isolated

products were characterized by the melting points, IR, ¹H NMR spectrometric data and were compared with the literature or authentic samples.

1-Phenyl-2,5-dimethyl-1H-pyrrole (1a). M.p. 52-54 °C (reported m.p. 50-51 °C [12a]); $\nu_{\max}/\text{cm}^{-1}$ 3051, 2925, 1609, 1527, 1488, 1412, 1318; δ_{H} (500 MHz, CDCl₃): 2.09 (s, 6H, CH₃), 5.69 (s, 2H, pyrrole ring), 7.13-7.29 (2H, m, Ar H), 7.45-7.53 (3H, m, ArH).

1-Benzyl-2,5-dimethyl-1H-pyrrole (2a). Oily solid (reported m.p. 40-41 °C [6d]; $\nu_{\max}/\text{cm}^{-1}$ 3059, 2928, 2849, 1568, 1522, 1493, 1401, 1323; δ_{H} (500 MHz, CDCl₃): 2.11 (6H, s, CH₃), 4.98 (2H, s, CH₂), 5.93 (2H, s, pyrrole ring), 6.88-6.94 (2H, m, Ar H), 7.25-7.39 (3H, m, Ar H).

1-(2-Phenylethyl)-2,5-dimethyl-1H-pyrrole (3a). Oil (reported as oil [12b]); δ_{H} (500 MHz, CDCl₃): 2.31 (6H, s, CH₃), 3.12 (t, $J = 7.5$ Hz, 2H), 4.18 (t, $J = 7.5$ Hz, 2H), 5.95 (2H, s, pyrrole ring), 6.81-6.88 (2H, m, Ar H), 7.42-7.50 (3H, m, Ar H).

1-(p-Tolyl)-2,5-dimethyl-1H-pyrrole (4a): Oil (reported as oil [12b]); δ_{H} (500 MHz, CDCl₃): 2.23 (6H, s, CH₃), 2.34 (3H, s, CH₃), 5.87 (2H, s, pyrrole ring), 6.69 (d, $J = 9$ Hz, 2H), 7.31 (d, $J = 9.0$ Hz, 2H).

1-(p-Ethylphenyl)-2,5-dimethyl-1H-pyrrole (5a). Oil (reported as oil [12b]); δ_{H} (500 MHz, CDCl₃): 2.10 (6H, s, CH₃), 2.72 (q, $J = 7.5$ Hz, 2H), 5.90 (s, 2H, pyrrole ring), 1.35 (t, $J = 7.5$ Hz, 3H); 7.19 (d, $J = 8.8$ Hz, 2H), 7.33 (d, $J = 8.8$ Hz, 2H).

1-(m-Tolyl)-2,5-dimethyl-1H-pyrrole (6a). Oil (reported as oil [12b]); δ_{H} (500 MHz, CDCl₃): 2.09 (6H, s, CH₃), 2.37 (3H, s, CH₃), 5.85 (2H, s, pyrrole ring), 7.02-7.29 (m, 4H, Ar).

1-Butyl-2,5-dimethyl-1H-pyrrole (7a). Oil (reported as oil [12b]); δ_{H} (500 MHz, CDCl₃): 0.91 (t, $J = 7.2$ Hz, 3H), 1.32 (m, 2H), 1.65 (m, 2H), 2.21 (s, 6H, CH₃), 3.71 (t, $J = 7.2$ Hz, 2H), 5.86 (s, 2H, pyrrole ring).

1-Propyl-2,5-dimethyl-1H-pyrrole (8a). Oil (reported as oil [12b]); $\nu_{\max}/\text{cm}^{-1}$ 3100, 2965, 2932, 2875, 1519, 1348, δ_{H} (500 MHz, CDCl₃): 1.02 (t, $J = 7.4$ Hz, 3H), 1.65 (m, 2H), 2.34 (s, 6H, CH₃), 3.78 (t, $J = 7.5$ Hz, 2H), 5.83 (s, 2H, pyrrole ring).

1-(4-Nitrophenyl)-2,5-dimethyl-1H-pyrrole (9a). M.p. 145-147 °C (reported m.p. 143-144 °C, [12b]); δ_{H} (500 MHz, CDCl₃): 2.12 (s, 6H), 5.96 (s, 2H, pyrrole ring), 6.92 (d, $J = 8.7$ Hz, 2H, Ar), 7.74 (d, $J = 8.7$ Hz, 2H, Ar).

1-(4-Fluorophenyl)-2,5-dimethyl-1H-pyrrole (10a). Oil (reported as oil [12b]); δ_{H} (500 MHz, CDCl₃): 2.01 (s, 6H, CH₃); 5.88 (s, 2H, pyrrole ring), 7.17 (d, $J = 9.0$ Hz, 2H, Ar), 7.31 (d, $J = 9.0$ Hz, 2H, Ar).

1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrole (11a). M.p. 77-79 °C (reported m.p. 75 °C, [12b]); δ_{H} (500 MHz, CDCl₃): 2.07 (s, 6H, CH₃); 5.64 (s, 2H, pyrrole ring), 7.19 (d, $J = 8.8$ Hz, 2H, Ar), 7.68 (d, $J = 8.8$ Hz, 2H, Ar).

1-(4-Bromophenyl)-2,5-dimethyl-1H-pyrrole (12a). M.p. 75-77 °C (reported m.p. 75 °C, [12b]); δ_{H} (500 MHz, CDCl₃): 2.05 (s, 6H, CH₃); 5.73 (s, 2H, pyrrole ring), 7.15 (d, $J = 8.8$ Hz, 2H, Ar), 7.71 (d, $J = 8.8$ Hz, 2H, Ar).

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole (13a). M.p. 60-63 °C (reported m.p. 59-60 °C, [11]); δ_{H} (500 MHz, CDCl₃): 1.98 (s, 6H, CH₃); 3.82 (OCH₃, s, 3H), 5.81 (s, 2H, pyrrole ring), 6.92 (d, $J = 8.5$ Hz, 2H, Ar), 7.24 (d, $J = 8.5$ Hz, 2H, Ar).

2-(2,5-Dimethyl-1H-pyrrol-1-yl) pyridine (**14a**). Oil (reported as oil [12b]); δ_{H} (500 MHz, CDCl_3): 2.08 (s, 6H, CH_3), 5.91 (s, 2H, pyrrole ring), 7.25-7.38 (Ar, m, 2H), 7.73-7.86 (Ar, m, 1H), 8.68-8.75 (Ar, m, 1H).

1-(Naphthalene-1-yl)-2,5-Dimethyl-1H-pyrrole (**15a**). M.p. 123-126 °C (reported m.p. 120-121 °C, reported [12b]); δ_{H} (500 MHz, CDCl_3): 1.95 (s, 6H, CH_3), 6.12 (s, 2H, pyrrole ring), 7.18 (d, $J = 8.6$ Hz, 1H, Ar), 7.30-7.48 (m, 4H, Ar), 7.91 (d, $J = 8.6$ Hz, 2H, Ar).

1-(4-Methylbenzyl)-2,5-dimethyl-1H-pyrrole (**16a**). M.p. 48-50 °C (reported m.p. 44-47 °C, [12b]); δ_{H} (500 MHz, CDCl_3): 2.08 (s, 6H, CH_3), 2.41 (CH_3 , s, 3H), 4.98 (s, 2H, CH_2 , benzylic), 5.94 (s, 2H, pyrrole ring), 6.95 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 8.7$ Hz, 2H).

CONCLUSION

In conclusion, a simple and efficient procedure for the synthesis of *N*-substituted pyrroles was established. This present method is superior since it is eco-friendly, advantageous over previously described methods in yield, requires no special apparatus, there is simplicity of operation, and is non-hazardous, simple and convenient. In addition, the simple experimental and product isolation procedures combined with the easy recovery and reuse of these worthwhile natural smectite clays play an important role in development of the clean and environmentally friendly strategy in this new and benign method.

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