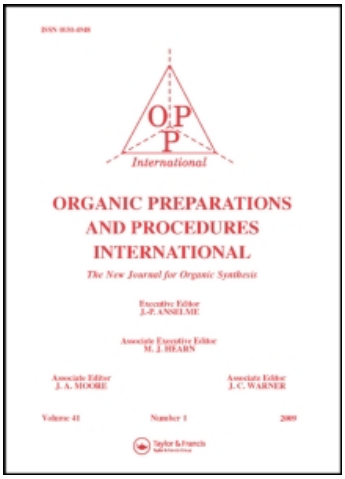

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AN EFFICIENT AND RAPID SYNTHESIS OF N-SUBSTITUTED PYRROLES BY MICROWAVE ASSISTED SOLID ACID CATALYSIS

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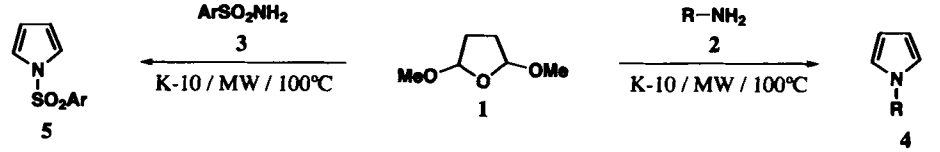
Dedicated to the late Dr. S. Y. Gadre, Abasaheb Garware College, Pune, India

Pyrroles represent an important class of heterocyclic compounds, appear as structural motif in many biologically active natural products, and serve as building blocks in the total synthesis of these compounds.[1] Accordingly, extended efforts have been made toward the synthesis of wide range of pyrrole derivatives. Most of these methods involve various cyclocondensations reactions resulting in 2,5-di- or polysubstituted pyrroles.[2] However, the environmentally benign synthesis of N-monosubstituted pyrroles is still a challenge. The commonly used traditional P_2O_5 catalysis has disadvantages such as long reaction times, low yields and difficult handling.[3] Our goal was to develop a new contemporary method that provides high yields and also satisfies recent environmental standards and safety concerns. Over the past decades solid acid catalysis[4] and microwave irradiation[5] have emerged as important tools in organic synthesis indicated by the extensive number of publications. K-10 montmorillonite is one of the most well-known and widely used solid acids in organic synthesis. Due to its strong acidity, significant surface area, and high stability, it is a catalyst of choice for both acid and bifunctional catalysis.[6] Continuing our efforts on solid acid catalyzed synthesis of organic compounds, herein we report a novel, one pot, general and rapid synthesis of N-substituted pyrroles using montmorillonite K-10 and microwave irradiation. For initial investigation, we chose a test reaction of aniline with 2,5-dimethoxytetrahydrofuran (**1**). The excellent results prompted us to extend the study. It was observed that primary amines readily underwent cyclization under K-10 catalysis and microwave irradiation to give corresponding N-substituted pyrroles *(Scheme 1)*.



Ar = a) Ph; b) *p*-CH_3Ph; c) *o*-CH_3Ph; d) *p*-NO_2Ph; e) *p*-OCH_3Ph; f) *p*-ClPh; g) Me

R = a) Ph; b) thiazol-2-yl; c) 1-biphenyl-2-yl; d) cyclohexyl; e) 2-chloro-pyridine-3-yl; f) hept-2-yl; g) 1-phenylethyl; h) 3-$CF_3C_6H_4$; i) $PhCH_2$; j) indol-3-yl-$(CH_2)_2$; k) nBu

Scheme 1

In order to illustrate the efficiency of our new method, we carried out a series of reactions with several aromatic and aliphatic primary amines. The reactions were complete within 3-6 minutes. Despite the very short reaction times, the isolated yields are excellent, indicating practically quantitative product formation with 100% selectivity and no by-product formation (*Table 1*).

Based on the excellent results obtained with amines, we carried out similar reactions with various amides and sulfonamides to study the scope and limitations of our method. It was found that although they readily underwent cyclization, amides generated multiple products including the desired pyrroles, indoles and carbazoles. Sulfonamides, however, promptly and selectively cyclized and gave practically quantitative yields of substituted pyrroles within short reaction times. (*Table 1*) It was observed that substituents did not show significant effect on rate or selectivity of the cyclization reactions (*Table 1*).

In conclusion, a new microwave assisted, solid acid catalyzed effective, economic and clean Paal-Knorr type cyclization method has been developed for the synthesis of various N-substituted pyrroles. The major advantages of our process are the excellent yield and selectivity, mild conditions and ease of product isolation. The combination of microwave irradiation and solid acid catalysis greatly reduced reaction time. The solvent-free reaction conditions also contribute to make this process ecologically friendly.

EXPERIMENTAL SECTION

All starting materials were purchased from Aldrich and used without further purification. Montmorillonite K-10 was obtained from Aldrich. $CDCl_3$ used as a solvent (99.8%) for NMR studies was also an Aldrich product. Other solvents used in synthesis with minimum purity of 99.5% were purchased from Fisher. The ^1H and ^{13}C spectra were obtained on a 300 MHz Varian NMR spectrometer. The mass spectrometric identification of the products have been carried out by an Agilent 6850 gas chromatograph-5973N mass spectrometer system (70 eV electron impact ionization) using a 30m long DB-5 type column (J&W Scientific).

General Procedure.- Amines or sulfonamides (1.0 mmol) and 2,5-dimethoxytetrahydrofuran (0.2 g, 1.5 mmol) were mixed in 3 mL of ether in a round-bottomed flask, after which then 500 mg montmorillonite K-10 was added. After 5 min stirring, the solvent was evaporated in vacuo to produce the dry mixture of reactants adsorbed on the catalyst surface. The dry mixture was transferred to a reaction tube (10 cm long and 1 cm by diameter) and irradiated in a focused microwave reactor (CEM Discover Benchmate) at standard temperature (100°C). The reaction temperature was determined and maintained by a built-in infrared temperature detector-controller. After satisfactory conversion, ether was added to the cold mixture, and the product was separated from catalyst by gravity filtration. The products were isolated as crystals or oils and purified by flash chromatography.

Table 1. Synthesis and Characterization of N-Substituted Pyrroles from Amines and Sulfonamides *via* K-10 Catalyzed Microwave Assisted Cyclization (**4a-k** and **5a-g**).[a]

Comp.	Time (min)	Yield[b] (%)	mp. (°C)	$mp_{lit.}$ (°C)	MS(EI) *m/z* (%)	^{1}H NMR / ^{13}C NMR (δ)
4a	4	90	57-59	58-60[2d]	143 (M^+, 100), 115 (90), 77 (20)	*^{1}H* 7.44 (3H, m, ArH), 7.28 (2H, m, ArH), 7.14 (2H, t, *J* = 2.4 Hz, ArH), 6.41 (2H, t, *J* = 2.4 Hz, ArH). *^{13}C* 141.0, 129.8, 125.8, 120.7, 119.5, 110.6
4b	5	91	89.5-91[c]	----	200 (M^+, 100), 173 (40), 108 (20), 66 (25)	*^{1}H* 7.86 (1H, dd, *J* = 8, 0.4 Hz, ArH), 7.76 (1H, dd, *J* = 8.0, 0.4 Hz, ArH), 7.45 (1H, dd, *J* = 1.2 Hz, ArH), 7.44 (2H, t, *J* = 2.4 Hz, ArH), 7.31 (1H, dt, *J* = 1.2 Hz, ArH), 6.37 (2H, t, *J* = 2.4 Hz, ArH). *^{13}C* 159.7, 151.3, 132.2, 126.8, 124.7, 122.3, 121.5, 120.3, 112.8
4c	3	85	oil[c]	----	218 (M^+, 100), 152 (15), 109 (30)	*^{1}H* 7.50 (1H, m, ArH), 7.44 (3H, m, ArH), 7.31 (3H, m, ArH), 7.15 (2H, m, ArH), 6.62 (2H, t, *J* = 1.2 Hz, ArH), 6.18 (2H, t, *J* = 1.2 Hz, ArH). *^{13}C* 139.2, 137.4, 131.5, 128.5, 128.4, 127.5, 126.6, 122.3, 109.2
4d	6	88	oil	----	149 (M^+, 50), 67 (100)	*^{1}H* 6.73(2H, t, *J* = 2.0 Hz, ArH), 6.12 (2H, t, *J* = 2.0 Hz, ArH), 3.81 (1H, tt, *J* = 4.0, 11.6 Hz, CH), 2.10 (2H, m, CH_2), 1.87 (2H, m, CH_2), 1.65 (2H, m, CH_2), 1.39 (2H, m, CH_2), 1.23 (2H, m, CH_2). *^{13}C* 118.6, 107.5, 58.8, 34.8, 25.95, 25.7
4e	3	90	oil	----	178 (M^+, 100), 142 (50), 115 (60), 76 (25)	*^{1}H* 8.37 (1H, dd, *J* = 4.4, 2.0 Hz, ArH), 7.66 (1H, dd, *J* = 7.6, 1.6 Hz, ArH), 7.32 (1H, dd, *J* = 7.6, 4.4 Hz, ArH), 6.92 (2H, t, *J* = 2.0 Hz, ArH), 6.36 (2H, t, *J* = 2.0 Hz, ArH) *^{13}C* 147.9, 146.8, 135.9, 123.2, 122.2, 121.4, 110.5
4f	4	92	oil	----	165 (M^+, 45), 150 (10), 136 (10), 95 (100)	*^{1}H* 6.67(2H, t, *J* = 2.0 Hz, ArH), 6.12 (2H, t, *J* = 2.0 Hz, ArH), 3.97 (1H, sextet, *J* = 6.8 Hz, CH), 1.67 (2H, m, CH_2), 1.42 (3H, d, *J* = 6.8 Hz, CH_3), 1.23 (6H, m, CH_2), 0.84 (3H, t, *J* = 7.2 Hz, CH_3). *^{13}C* 118.6, 107.5, 55.7, 38.4, 31.7, 26.2, 22.7, 22.5, 14.2
4g	6	89	oil	----	171 (M^+, 40), 105(100), 77 (45), 67 (60)	*^{1}H* 7.29 (5H, m, ArH), 6.75 (2H, t, *J* = 2.0 Hz, ArH), 6.19 (2H, t, *J* = 2.0 Hz, ArH), 5.28 (1H, q, *J* = 7.2 Hz, CH), 1.83 (3H, d, *J* = 7.2 Hz, CH_3). *^{13}C* 143.7, 128.8, 127.6, 126.0, 119.7, 108.2, 58.3, 22.3

Table 1. Continued...

Comp.	Time (min)	Yield[b] (%)	mp. (°C)	$mp_{lit.}$ (°C)	MS(EI) *m/z* (%)	^1H NMR / ^{13}C NMR (δ)
4h	3	90	oil[c]	----	211 (M^+, 100), 115 (95), 5 (10)	*^1H* 7.54 (4H, m, ArH), 7.10 (2H, t, *J* = 2.0 Hz, ArH), 6.38 (2H, t, *J* = 2.0 Hz, ArH). *^{13}C* 144.3, 141.3, 130.4, 123.6, 122.3, 119.4, 117.3, 111.5, 99.5
4i	3	88	oil	----[7]	157 (M^+, 40), 91 (100), 77 (5)	7.26 (3H, m, ArH), 7.88 (2H, m, ArH), 5.86 (2H, t, *J* = 2.3 Hz, ArH), 5.01 (2H, t, *J* = 2.3 Hz, ArH). / 138.7, 128.9, 128.2, 127.2, 125.8, 105.6, 46.9
4j	5	90	75-77	74-77[7]	210 (M^+, 60), 143 (20), 130 (100), 108 (25), 77 (15)	7.99 (1H, bs, NH), 7.60 (1H, d, *J* = 7.60 Hz, ArH), 7.37 (1H, d, *J* = 8.4 Hz, ArH), 7.21 (2H, m, ArH), 6.88 (1H, d, *J* = 2.4 Hz, ArH), 6.30 (2H, t, *J* = 2.4 Hz, ArH), 5.81 (2H, t, *J* = 2.4 Hz, ArH), 4.03 (2H, t, *J* = 7.5 Hz, CH_2), 3.06 (2H, t, *J* = 7.5 Hz, CH_2). / 136.4, 127.6, 127.4, 122.3, 122.2, 119.7, 118.7, 112.9, 111.4, 105.3, 44.5, 27.1
4k	3	92	oil	----[7]	123 (M^+, 50), 108 (100), 94 (50), 67 (15)	5.77 (2H, t, *J* = 2.4 Hz, ArH), 5.11 (2H, t, *J* = 2.4 Hz, ArH), 3.72 (2H, t, *J* = 7.6 Hz, CH_2), 1.61 (2H, quin, *J* = 7.6 Hz, CH_2), 1.38 (2H, sext, *J* = 7.6 Hz, CH_2), 0.96 (3H, t, *J* = 7.6 Hz, CH_3). / 127.5, 105.1, 43.6, 33.3, 20.3, 14.0
5a	3	93	85-87	88-89[3b]	207 (M^+, 98), 141 (85), 115 (30), 77 (100)	*^1H* 7.84 (2H, m, ArH), 7.57 (1H, m, ArH), 7.48 (2H, m, ArH), 7.15 (2H, t, *J* = 2.4 Hz, ArH), 6.28 (2H, t, *J* = 2.4 Hz, ArH). *^{13}C* 139.3, 134.0, 129.5, 126.9, 121.0, 113.8
5b	3	89	97-97.5	98-100[3b]	221 (M^+, 30), 155 (25), 91 (100), 65 (15)	*^1H* 7.61 (1H, td, *J* = 8.0, 1.2 Hz, ArH), 7.46 (1H, td, *J* = 7.6, 1.2 Hz, ArH), 7.27 (2H, m, ArH), 7.14 (2H, t, *J* = 2.0 Hz, ArH), 6.30 (2H, t, *J* = 2.0 Hz, ArH), 2.56 (3H, s, CH_3) *^{13}C* 138.1, 133.5, 128.3, 126.9, 121.8, 112.5, 20.3
5c	3	87	91-93[c]	----	221 (M^+, 30), 156 (15), 91 (100), 65 (30)	*^1H* 7.71 (2H, m, ArH), 7.27 (2H, m, ArH), 7.13 (2H, t, *J* = 2.4 Hz, ArH), 6.26 (2H, t, *J* = 2.4 Hz, ArH), 2.38 (3H, s, CH_3). *^{13}C* 145.1, 136.3, 130.1, 130.0, 127.0, 120.9, 113.7, 21.7
5d	2	90	108.5-111[c]	----	253 (M^+, 15), 222 (20), 156 (30), 99 (100)	*^1H* 7.99 (2H, m, ArH), 7.65 (2H, m, ArH), 7.05 (2H, t, *J* = 2.0 Hz, ArH), 6.55 (2H, t, *J* = 2.0 Hz, ArH). *^{13}C* 141.2, 139.8, 130.1, 119.6, 110.7, 108.3

Table 1. Continued...

Comp.	Time (min)	Yield[b] (%)	mp. (°C)	$mp_{lit.}$ (°C)	MS(EI) *m/z* (%)	^1H NMR / ^{13}C NMR (δ)
5e	3	95	99-101[c]	----	237 (M^+, 60), 171 (100), 123 (20), 77 (35)	*^1H* 7.85 (2H, m, ArH), 7.63 (2H, m, ArH), 7.08 (2H, t, *J* = 2.4 Hz, ArH), 6.13 (2H, t, *J* = 2.4 Hz, ArH), 3.85 (3H, s, CH_3). *^{13}C* 148.9, 144.3, 138.5, 125.1, 118.6, 112.9
5f	4	83	102-104	103-106[3a]	123 (M^+, 50), 108 (100), 94 (50), 67 (15)	7.82 (2H, d, *J* = 8.7 Hz, ArH), 7.50 (2H, d, *J* = 8.7 Hz, ArH), 7.17 (2H, t, *J* = 2.4 Hz, ArH), 6.34 (2H, t, *J* = 2.4 Hz, ArH).
5g	3	91	oil	----[3a]	145 (M^+, 70), 79 (20), 67 (100)	7.12 (2H, t, *J* = 2.4 Hz, ArH), 6.75 (2H, t, *J* = 2.4 Hz, ArH), 2.82 (3H, s, CH_3)

(a) at 100°C (b) Yields of isolated products after flash chromatography, (c) New compounds

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NEW AND SIMPLE SYNTHESIS OF THE PHEROMONE COMPONENT OF MALE MELON FLY

Submitted by *(07/07/06)*

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Our laboratory has been involved in the synthesis of sex pheromones and attractants.[1] We are currently investigating the pheromone component of the male melon fly (*Dacus cucurbitae Coquillett*) which is one of the most active and destructive fruit fly pests which infests more than 80 plant species.[2] Ohinata *et al.*[3] isolated and identified 5-(3*E*,6-heptadienyl)dihydro-2(3H)-furanone (**5**) as an active component of the pheromone, visible as smoke emitted at dusk during the mating period of male melon flies. Some methods for its preparation are however, cumbersome and give low overall yields. Voaden reported[4a] the synthesis of **5** from 3-(2-