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MICROWAVE ASSISTED SYNTHESIS OF PYRROLES

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ABSTRACT:- The synthesis of pyrroles by reaction of hexane-2,5-dione with primary amines has been shown to occur in less than 2 minutes under microwave activation.

In recent years, the application of microwave irradiation for the promotion of organic reactions has received increasing attention. The technique has been used to assist in transfer hydrogenations,[1] oxidations,[2] aromatic substitutions,[3] pericyclic reactions[4] and many other processes of significance to organic chemistry.[5] In addition, the technique has also found applications in the areas of inorganic and solid state synthesis.[6] The application of microwave irradiation to chemical reactions has been shown to enhance significantly the rate of many processes. In some cases, the technique has been used to promote reactions previously not observed under conventional thermal activation.[7]

The application of microwave irradiation has also been extensively applied to the synthesis of heterocyclic compounds. Reports of the assisted synthesis of indoles,[8] β-lactams,[9] thiophenes,[10] furans,[10] dihydropyidines,[11] quinazolines[12] and 2-cyanobenzothiazoles[13] have all recently appeared. As part of an ongoing programme considering the application of microwaves in organic synthesis, it was decided to study the synthesis of pyrroles *via* the Paal-Knorr route. In this note, we wish to report our preliminary findings in this area. The chemistry reported herein is the first dedicated description of a microwave assisted Paal-Knorr cyclisation although the synthesis of pyrroles by the microwave assisted dehydrogenation of pyrrolidines

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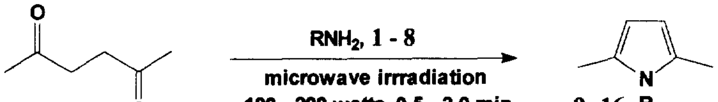
using managanese dioxide,[14] and by reaction of 1,4-diketones with ammonia and primary amines generated from ureas adsorbed on montmorillonite under microwave conditions,[15] have been described previously.

Initially the reaction between hexane-2,5-dione and aniline was studied. The neat reagents were irradiated for 30 seconds at 200 watts whereupon water droplets appeared. Addition of diethyl ether followed by magnesium sulphate and filtration through a plug of silica lead to isolation of 1-phenyl-2,5-dimethyl pyrrole as a yellow solid.



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It is notable that when this synthesis was performed under classical (thermal) conditions the reaction required at least 12 hours of prolonged heating to obtain similar yields of pyrrole to those obtained by the microwave route.[16,17] To explore the scope of this reaction a range of primary amines was reacted with hexane-2,5-dione under microwave conditions. The results from these experiments are presented in table 1.

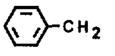
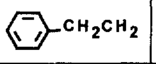
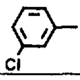
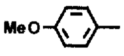
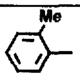
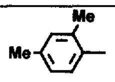
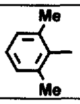
Entry	Amine	R	Time (min)	Power (Watts)	Pyrrole[*]	Yield (%)
1	1		0.5	100	9	90
2	2		0.5	100	10	90
3	3		1.0	100	11	90
4	4		1.0	100	12	80
5	5		1.0	100	13	90
6	6		2.0	200	14	85
7	7		2.0	200	15	80
8	8		2.0	200	16	75

Table 1. Synthesis of pyrroles under microwave conditions
[*] All products gave satisfactory spectroscopic and elemental data

It is of note that, for benzylamine and 2-phenylethylamine (Table 1 entries 2 and 3), only a relatively short irradiation at low power setting is required to obtain high yields of the corresponding pyrroles. This is presumably a result of the higher nucleophilic character of the aliphatic amines. When the amines are substituted in the 2-position (Table 1 entries 6, 7 and 8) higher microwave power settings and longer irradiation times are required to produce pyrroles. This observation is attributed to the greater steric interference. Previously reported procedures for the syntheses of these compounds have all reported the need for Lewis acids to activate the carbonyl groups of the 1,4-diketones.[17,18] Use of microwave irradiation for the promotion of these reactions appears to remove the need for such Lewis acids. It is of note however, that longer reaction times and higher power settings are required to obtain appreciable yields of the product pyrroles. This clearly extends the scope of the pyrrole cyclisation reaction. Also the absence of the need to activate of the carbonyl group considerably simplifies the procedure and work-up.

In conclusion, it has been shown that the synthesis of *N*–substituted pyrroles may be enhanced by utilisation of microwave conditions. The procedure is easily adapted for the synthesis of relatively hindered pyrroles where the need for carbonyl activation is removed.

The use of microwave activation for the synthesis of pyrroles from non-nucleophilic amines is currently under investigation

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19. In a typical experiment benzylamine (1.07 g, 1.0 mmol) and hexane-2,5-dione (1.14 g, 1.0 mmol) were mixed in a culture tube and the resulting mixture was irradiated at 100 watts for 0.5 min. After the mixture had cooled diethyl ether (5 ml) was added and the resulting solution was dried over magnesium sulphate. The solvent was removed under reduced pressure and the yellow mixture produced was chromatographed on silica using diethyl ether / hexane (1:5) as the eluent to yield pyrrole **9** as pale crystals (1.67 g, 90 %) after removal of the solvent. Mp. 37-38 °C; δ_H (300 MHz; $CDCl_3$) 2.09 (6H, s, 2 x CH_3), 4.93 (2H, s, CH_2Ph), 5.84 (2H, s CH) and 6.80-7.30 (5H, m, Aryl-*H*); δ_C(75 MHz; $CDCl_3$) 12.42 (2 x CH_3), 46.66 (CH_2), 105.54 (C-3 and C-4), 127.83 (C-2 and C-5), 125.63, 12.99, 128.50 and 138.60 (Ph); m/z (EI) 185 (M^+, 50 %) and 91 (100, C_7H_7).