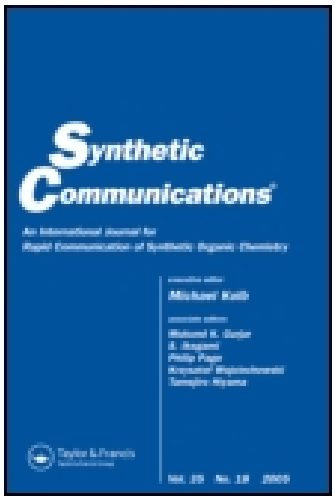

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RAPID MICROWAVE-ENHANCED SYNTHESIS OF 1-PHENYL-3-METHYL- 5-ACYLOXYPYRAZOLES UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT

The microwave-enhanced synthesis of 5-acyloxypyrazoles from 1-phenyl-3-methylpyrazole-5-one and acid chlorides under solvent-free conditions has been achieved in moderate to good yield.

Key Words: Microwave irradiation; Acylation; 1-Phenyl-3-methylpyrazole-5-one

Microwave irradiation has been employed for the synthesis of a wide variety of organic molecules. The benefit of microwave irradiation includes reduction of reaction time, higher yields, greater selectivity, cleaner reaction products and easier manipulation. Therefore, the application of microwave irradiation in organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology.[1,2]

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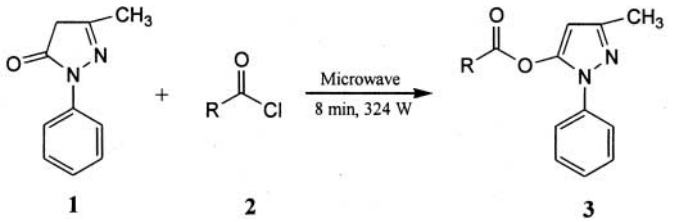
Reactions in "dry media" or under solvent-free conditions are especially appealing as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development and with the possibility of upscaling the reactions to larger scale. Solventless procedures without the use of supporting reagents are particularly eco-friendly.[3,4]

Acyl derivatives of 1-phenyl-3-methylpyrazole-5-one are very attractive compounds. Certain acyl pyrazolones as well as their complexes have biological activities, such as antiviral,[5] antiinflamatary,[6] herbicidal and growth-regulating activities.[7] Meanwhile, the 4-acylderivatives, as β-diketone reagents, are widely used as chelating agents for preparation of coordination compounds,[8] and they have been extensively studied as extractants for the actinides, lanthanides and alkali-earth metals.[9] Under normal conditions, acylation of 1-phenyl-3-methylpyrazole-5-one with 1 mol acid chlorides or anhydrides in the presence of calcium hydroxide in ethanol or dioxoane gives the 4-acylderivatives,[10,11] whereas in the absence of the solvent, 5-acyloxypyrazoles are obtained.[11] The 4-acyl-5-acyloxypyrazoles are obtained with 2 mol acid chlorides in ethyl ether.[11] The solid state reactions of 1-phenyl-3-methylpyrazole-5-one with carbonyl compounds also gave 4-substituted pyrazolone derivatives.[12]

Herein, we report the first microwave enhanced acylation of 1-phenyl-3-methylpyrazole-5-one with acid chlorides under solventless conditions. The mixture of 1-phenyl-3-methylpyrazole-5-one and acid chlorides in absence of solvent was irradiated for 8 min in an unmodified household microwave oven, the contents were cooled to room temperature and aqueous sodium hydroxide was added to decompose the unreacted acid chloride. The product precipitated from the solution. The solid material was filtered and recrystalized with ethanol or ethanol aqueous. Their m.p., IR, ^{1}H NMR and ^{13}C NMR indicated that they were 5-acyloxypyrazoles derivatives rather than 4-acylderivatives. The results for a variety of substrates are summarized in Scheme 1 and Table 1.

Optimal conditions for the synthesis were found to be 8 min reaction time using 324 W of microwave irradiation power. These optimal conditions



1 2 3

Scheme 1.

Table 1. General Synthesis of 5-Acyloxypyrazoles Produces via Scheme 1

Entry	R	Yield (%)[a]
3a	C_6H_5	87
3b	2-ClC_6H_4	79
3c	2-$NO_2C_6H_4$	40
3d	4-ClC_6H_4	81
3e	4-$NO_2C_6H_4$	86
3f	4-$CH_3OC_6H_4$	48
3g	4-$CH_3C_6H_4$	37
3h	3,5-$(NO_2)_2C_6H_3$	68

[a]All yields refer to isolated pure products.

were then applied for the synthesis of the other 5-acyloxypyrazoles. It has been found that substituted group of acid chloride has effect on the yield. When *p*-substituted group is electron-attracting group, the reaction gives higher yield than the case where substituted group is electron-donating group. When *o*-substituted group is nitro group, the yield is lower than chloro-substituted one, this effect may be interpreted with the steric hindrance of the substituted group in benzoyl chlorides. Under the same conditions, acids did not react with 1-phenyl-3-methylpyrazole-5-one. Meanwhile, the presence of excessive acid chlorides did not affect the reaction results.

In conclusion, a rapid and practical procedure for the synthesis of 5-acyloxypyrazoles from 1-phenyl-3-methylpyrazole-5-one and acid chlorides under microwave irradiation was developed, which involves solvent-free conditions. The operation simplicity, faster reaction rates, and ease of manipulation render this a useful and attractive route for the synthesis of 5-acyloxypyrazoles.

EXPERIMENTAL

All melting points are uncorrected. Yields refer to isolated products. The products were characterized by comparison of their spectral (IR, ^{1}H NMR, ^{13}C NMR and MS).

5-Acyloxypyrazoles (3d). A Typical Procedure: A mixture of 1-phenyl-3-methylpyrazole-5-one (6 mmol) and acid chloride (8 mmol) was mixed in a beaker covered with a watch glass, was placed in an unmodified household

microwave oven and irradiated for 8 min at the power of 324 W. Then, 40% aqueous sodium hydroxide was added till the pH of the solution was about 9, and boiled the solution for a few minutes until the smell of acid chloride disappeared. After cooling, the solid products were filtered, washed with cold water, dried and recrystallized from ethanol or ethanol aqueous to give crystals of the product **3d** in 81% yield (1.5 g); m.p. 95–96°C. IR (KBr): 1748, 1592, 1548, 1500, 1443, 1392, 1250, 1145, 1065, 1007, 845 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 2.36 (s, 3H, Me), 6.27 (s, 1H, H-4), 7.28–7.33 (t, 1H, phenyl), 7.40–7.46 (m, 4H, phenyl), 7.55–7.59 (d, 2H, *J* 8.4 Hz, chlorobenzoyl), 7.96–8.01 (d, 2H, *J* 8.4 Hz, chlorobenzoyl); ^{13}C NMR (400 MHz, $CDCl_3$): 14.45, 95.74, 123.17, 126.38, 127.19, 129.04, 129.19, 131.58, 138.04, 140.90, 144.19, 149.04, 160.96. MS *m*/*z*: 312, 277, 173, 139(100), 111, 77, 51.

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