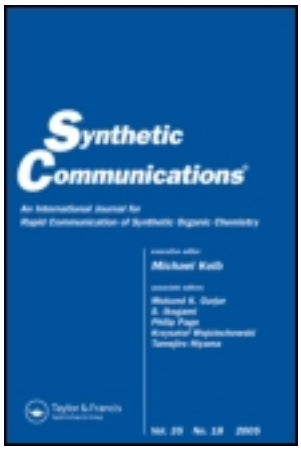

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Synthesis of Novel 1-*H*-Pyrazole-4-carboxylic Acid Esters by Conventional and Microwave Assisted Vilsmeier Cyclization of Hydrazones

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ABSTRACT

A convenient method for the synthesis of 1*H*-pyrazole-4-carboxylic acid esters is described. A comparison between the conventional and microwave assisted Vilsmeier reaction is carried out.

Key Words: Hydrazones; Vilsmeier cyclization; Microwave assistance; Pyrazole.

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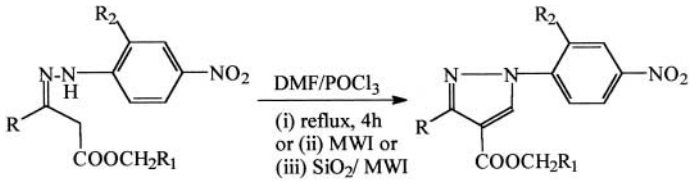
Pyrazoles find a wide range of applications in medicine. Steroids containing pyrazole moiety are of interest as psychopharmacological agents.[1] Pyrimidinopyrazoles are being studied in the fight against cancer.[2] Pyrazole derivatives have been found to have antimalarial activity[3] and antihyperglycemic activity.[4] Some alkyl and aryl substituted pyrazoles have a sharply pronounced sedative action on the central nervous system.[5] Certain alkyl pyrazoles show significant bacteriostatic, bacteriocidal and fungicidal, analgesic and antipyretic activities.[6] The versatile pollen formation inhibitor activity,[7] herbicidal and insecticidal activity[8] of 1*H*-pyrazole-4-carboxylic acid esters prompted us to synthesize these compounds in high yields through Vilsmeier reaction.

Hydrazones of aliphatic and aromatic methyl ketones yield pyrazole-4-carboxaldehyde upon diformylation on treatment with Vilsmeier reagent.[9] Hydrazones of aromatic ethyl and propyl ketones yield methyl and ethyl pyrazoles respectively without undergoing diformylation.[10]

Our interest was to study the reactivity hydrazones of β-keto esters towards the Vilsmeier reagent, to target the title compound, both in conventional and microwave methods, and to compare their yields.

Hydrazones of β-keto esters when treated with Vilsmeier reagent yield upon neutralization with aqueous NaOH a pale yellow solid pyrazoles (Sch. 1). The NMR spectrum of the recrystallized sample showed the disappearance of the methylene proton signal and N–N–H signal. The proton signal for the newly formed pyrazole appears at δ 8.2 ppm, leaving the other proton signals almost unchanged. This confirmed the formation of the target molecule, which was also characterized by mass spectral and elemental analysis. Similar results were obtained when the reaction mixture was subjected to microwave irradiation, however, the yield was increased considerably, with the reaction completed after a short duration of time. Even better yields were noticed upon microwave irradiation of the reaction mixture on SiO_2 support.



Where R = CH_3, C_6H_5, p-chlorophenyl; R_1 = H, CH_3 and R_2 = H, NO_2

Scheme 1. Synthesis of 1*H*-pyrazole-4-carboxylic acid esters.

The chloromethyleniminium ion attacks selectively the active methylene carbon and no side products were obtained. No further addition of the Vilsmeier complex occurs even when excess of reagent is employed (8 equiv. of $POCl_3$ and 12 equiv. of DMF).

We have provided an efficient methodology for the preparation of 1*H*-pyrazole-4-carboxylic acid esters in high yield, both by conventional and by microwave irradiation methods. Results obtained are tabulated in the Table 1. The uniqueness of the application of microwave irradiation lies not only in the reduction of reaction time but also in the increase of product yield.

EXPERIMENTAL

All the reagents were distilled prior to use from an appropriate drying agent. Infrared spectra were recorded as KBr pellets on a Perkin Elmer FT-IR instrument. Nuclear Magnetic Resonance spectra recorded on a Brucker Spectrometer, at 300 MHz (PMR) and at 75 MHz (^{13}C NMR). Mass spectra were obtained on a Perkin Elmer Mass Spectrometer.

General Procedure for the Preparation of 1*H*-Pyrazole-4-carboxylic Acid Esters

Method I

Four point six zero grams of $POCl_3$ (0.003 mol) was added dropwise to an ice-cold stirred solution of hydrazone (0.001 mol) in 4 mL dry DMF. The reaction mixture was allowed to attain room temperature and then refluxed at 70–80°C for about 4 h. The resulting mixture was poured onto crushed ice, neutralized with dilute sodium hydroxide and left standing overnight. The pale yellow precipitate obtained was purified by Silica gel (60–120 mesh) column chromatography with ethyl acetate–petroleum ether mixture (15:85) to yield the product.

Method II

Four point six zero grams of $POCl_3$ (0.003 mol) was added dropwise to a stirred, ice-cold solution of hydrazone (0.001 mol) in 4 mL dry DMF.

Table 1. Comparison between conventional Vilsmeier reaction (method I) and the microwave-assisted methods (methods II and III).

Entry[a]	R	R_1	R_2	M.p.[b] (°C)	Method I		Method II		Method III	
					Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1	CH_3	H	H	89	4	70	3	83	3	87
2	CH_3	H	NO_2	114	4	78	3	86	3	89
3	CH_3	CH_3	H	98	4	75	3	83	3	88
4	CH_3	CH_3	NO_2	122	4	80	3	87	3	90
5	C_6H_5	CH_3	H	118	4	78	3	84	3	87
6	C_6H_5	CH_3	NO_2	138	4	83	3	88	3	90
7	*p*-ClC_6H_4	CH_3	H	148	4	82	3	90	3	93
8	*p*-ClC_6H_4	CH_3	NO_2	169	4	88	3	92	3	94

[a]All the products were duly characterized by ^{1}H NMR, ^{13}C NMR, Mass, IR, elemental analysis.
[b]Melting points found were uncorrected.

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The reaction mixture was then allowed to attain room temperature and subjected to microwave irradiation in a domestic microwave oven (BPL microwave cooking system model BMO-7007) for about 3 min with a pulse of 20 s each at 70% power corresponding to 210 Watts. Then, the reaction mixture was poured onto crushed ice, neutralized, filtered and column chromatographed to afford pure product as described above.

Method III

After dropwise addition of $POCl_3$ (0.003 mol) to an ice-cold solution of 0.001 mol of hydrazone in 4 mL of dry DMF, the reaction mixture was slurried with SiO_2 (60–120 mesh). The slurry was subjected to microwave irradiation as described above. Finally, the slurry was washed with ice-cold water, allowed to settle and the supernatent washings are collected. The process is repeated 3 to 4 times and the combined water washings is filtered to get the crude pyrazole which was filtered and recrystallized with chloroform to yield the pure product.

Methyl 1-(2,4-dinitrophenyl)-3-methyl-1*H*-pyrazole-4-carboxylate 2: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.73 (d, $J = 2.4$ Hz, 1H), 8.55 (dd, $J = 2.4$ Hz, $J = 8.7$ Hz, 1H), 8.21 (s, 1H), 7.85 (d, $J = 8.7$ Hz, 1H), 3.87 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162, 154, 146, 143, 137, 134, 128, 126, 121, 115, 52, 13; IR (KBr) cm^{-1}: 3090, 1725, 1690, 1546, 1353, 1267; MS (m/z): 306 (M^+); Anal. calcd. for $C_{12}H_{10}N_4O_6$: C, 47.06; H, 3.27; N, 18.30; Found: C, 47.45; H, 3.36; N, 18.51.

Ethyl 1-(2,4-dinitrophenyl)-3-methyl-1*H*-pyrazole-4-carboxylate 4: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70 (d, $J = 2.4$ Hz, 1H), 8.50 (dd, $J = 2.4$ Hz, $J = 8.7$ Hz, 1H), 8.20 (s, 1H), 7.83 (d, $J = 8.7$ Hz, 1H), 4.35 (q, $J = 7.1$ Hz, 2H), 2.49 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163, 155, 147, 144, 137, 135, 128, 126, 122, 117, 61, 15, 14; IR (KBr) cm^{-1}: 3074, 1722, 1693, 1550, 1349, 1276; MS (m/z): 320 (M^+); Anal. calcd. for $C_{13}H_{12}N_4O_6$: C, 48.75; H, 3.75; N, 17.50; Found: C, 48.82; H, 3.81; N, 17.46.

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