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Synthesis of Polyfunctional Pyridazine Derivatives Using a Solvent-Free Microwave Assisted Method

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SYNTHESIS OF POLYFUNCTIONAL PYRIDAZINE DERIVATIVES USING A SOLVENT-FREE MICROWAVE ASSISTED METHOD

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Abstract: The synthesis of several polyfunctional pyridazine derivatives has been carried out very efficiently under microwave irradiation and solvent-free conditions allowing short reaction times and high yields. Non thermal effects induced by microwave were observed.

For more than one decade there has been considerable interest in the chemistry and biological activity of pyridazine derivatives.[1-4] In connection with our program to investigate synthetic approaches directed to obtain polyfunctional substituted pyridazines as starting material for the synthesis of new heterocyclic compounds and potential biodegradable agrochemicals, we developed an efficient and quick method to prepare the key intermediates ethyl-5-cyano-1,6-dihydro-4-methyl-6-oxo-1-(4-X-phenyl)-pyridazine-3-carboxylate (**2a-d**) using microwave irradiation. These compounds have been previously prepared by reaction of the hydrazones (**1**)

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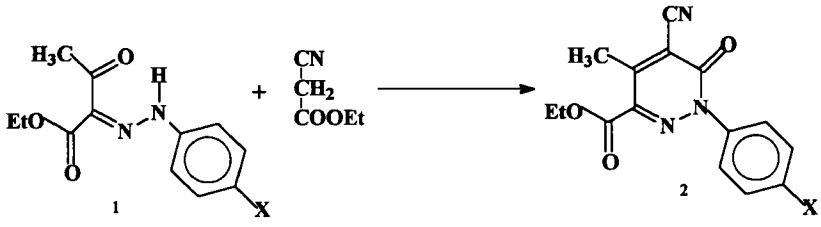
with ethyl cyanoacetate using a mixture of acetic acid-ammonium acetate as a catalyst, refluxing in a Dean-Stark apparatus for several hours.[5-10]



a) X= CH_3 b) X= H c) X= Cl d) X= NO_2

The results obtained in the cyclocondensation of hydrazones **1a-d** (Table 2) showed short reaction times and almost quantitative yields in the corresponding ethyl-5-cyano-1,6-dihydro-4-methyl-6-oxo-1-(4-X-phenyl) pyridazine-3-carboxylates (**2a-d**).

We report in Table 1 several sets of conditions finally allowing the isolation of **2a** in 97% yield. The use of a catalyst mixture constituted from acetic acid and ammonium acetate,[5-10] as in the traditional method, increases the yields in the substituted pyridazinone by activation of the Knoevenagel condensation,[11] this effect being not observed for the molar ratio (Table 1). These results were extended to obtain **2b-d** in good yields and purity (Table 2).

Table 1 Synthesis of **2a** under microwave irradiation (power =385W).

Run	Molar ratio[a]	Catalyst	Reaction time (sec.)	Yield (%)
1	1:1	-	240	10
2	1:2	-	240	15
3	1:1	b	50	97
4	1:2	b	50	97

a) Hydrazone **1a**: ethyl cyanoacetate b) Acetic acid + ammonium acetate.

In order to discern the possible intervention of specific effects (*i.e.* non thermal) of microwave irradiation we carried out the reaction using conventional heating mode (oil bath) at the same final temperature and reaction times as measured in the microwave experiments. In all cases no reaction was detected neither by tlc or gc, revealing thus a very important specific influence of microwave exposure in relation with a lot of previous analogous observations in the literature.[12-17]

Table 2 Synthesis of Pyridazinones (**2 a-d**) under microwave irradiation (power = 385W). molar ratio = 1:1 catalyst = acetic acid + ammonium acetate

Compound	X	Reaction time (sec)	Temp. (°C)[a]	Yield (%)
2a	CH_3	50	75	97
2b	H	56	70	98
2c	Cl	55	68	97
2d	NO_2	60	70	97

a) Temperatures were measured immediately after the reaction using a glass thermometer.

The results were very satisfactory taking into account the decrease in reaction times and the increase in pyridazine yields. Extending these advantages, the simple procedure and easier work-up by use of irradiation in a domestic microwave oven as activation mode allow us to propose this method as an efficient way to obtain the key intermediates **2a-d**.

EXPERIMENTAL PART

The starting hydrazones were obtained using reported procedures.[18] Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. Reactions were carried out in a Sanyo domestic microwave oven that allows the selection of output power up to 800 Watts. Tlc analyses were run on 60 F_{254} silicagel chromatoplates from Merck in chloroform as an eluent. Gc analyses were performed on an apparatus from Shimadzu fitted with flame ionization detector. All the solvents used for chromatographic analyses were HPLC grade from BDH. Ir. spectra were recorded on a Philips Analytical PU 9600 FTIR Spectrometer. ^{1}H-Nmr. spectra were recorded on a Bruker AC 250 using TMS as standard internal reference and $CDCl_3$ as a solvent, chemicals shifts are given in the δ scale. Mass spectra were determined in a TRIO 1000 Instrument 70 eV.

General Procedure. An equimolar mixture (4 mmol) of ethyl cyanoacetate, ammonium acetate and acetic acid and the corresponding hydrazone was placed into a Pyrex-glass open vessel and irradiated in a domestic microwave oven. When the irradiation was stopped, the final temperature attained in the reaction was measured by introducing a glass thermometer into the reaction mixture and homogenizing it, in order to obtain a temperature value representative of the whole mass. The reaction product was washed with cold water, filtered off and recrystallized from ethanol.

Ethyl-5-cyano-1,6-dihydro-4-methyl-6-oxo-1-(4-tolyl)-3-pyridazinecarboxylate (2a)

m.p. 165°C (EtOH); ν_{max} (KBr)/cm^{-1}: 2220, 1700, 1730; ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.39 (t, 3H),

2.42 (s, 3H), 2.75 (s, 3H), 4.42 (q, 2H), 7.30-7.50 (q, 4H); MS (m/z): 297 M^+ (98%), 269 (10), 252 (15), 241 (70), 224 (70), 210 (15), 132 (20), 105 (90), 91 (100), 78 (45), 65 (60).

Ethyl-5-cyano-1,6-dihydro-4-methyl-6-oxo-1-phenyl-3-pyridazinecarboxylate (2b).
m.p. 152-154 °C, lit.[5] 152 °C (EtOH); ν_{max} (KBr)/cm^{-1}: 2223, 1690; ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.30 (t, 3H), 2.77 (s, 3H), 4.36 (q, 2H), 7.45-7.61 (m, 5H); MS (m/z): 283 M^+ (5 %), 269 (98), 238 (30), 210 (30), 143 (20), 108 (22), 105 (42), 92 (90), 91 (100), 77 (95), 64 (50), 51 (52).

Ethyl-1-(4-chlorophenyl)-5-cyano-1,6-dihydro-4-methyl-6-oxopyridazine-3-carboxylate (2c)
m.p. 191° C, lit. [5] 190°C (EtOH); ν_{max} (KBr)/cm^{-1}: 2225, 1696, 1715; ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.40 (t, 3H), 2.75 (s, 3H), 4.42 (q, 2H), 7.52-7.61(q, 4H); MS (m/z): 319 M+1 (25 %), 317 M^+ (77), 272 (12), 263 (16), 261 (55), 189 (10), 153 (12), 139 (28), 125 (95), 111 (100), 90 (25), 75 (25), 63 (10).

Ethyl-1,6-dihydro-1-(4-nitrophenyl)-5-cyano-4-methyl-6-oxopyridazine-3-carboxylate (2d)
m.p. 170-172 °C (EtOH); ν_{max} (KBr)/cm^{-1}: 2220, 1700, 1720; ^{1}H-nmr ($CDCl_3$) δ (ppm): 1.30 (t, 3H), 2.70 (s, 3H), 4.36 (q, 2H), 7.70-8.42 (q, 4H); MS (m/z): 328 M^+ (95%), 312 (12), 300 (15), 282 (68), 272 (100), 255 (50), 242 (17), 209 (15), 150 (13), 122 (95), 90 (19), 76 (22), 63 (25).

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