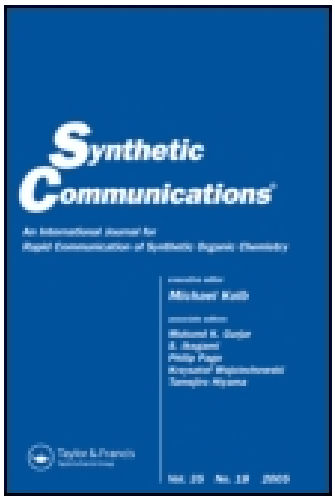

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Microwave-Assisted Synthesis of 3-(4-Pyrazolyl)propenoic Acids

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ABSTRACT

Under microwave activation, pyrazole-4-carboxaldehydes react with malonic acid in the presence of a small amount of pyridine to give 3-(4-pyrazolyl)propenoic acids in high yields.

Key Words: 3-(4-Pyrazolyl)propenoic acids; Microwave-assisted synthesis; Doebner condensation.

3-(4-Pyrazolyl)propenoic acids have attracted considerable interest due to their pronounced pharmacological activity.[1–3] In addition, they are

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employed as starting compounds in the synthesis of 4-pyrazolylacetic acids,[4] of which the most significant are 3-(4-chlorophenyl)-1-phenyl-4-pyrazolylacetic acid, the active substance of the nonsteroid antiphlogistic drug "Lonazolac,"[5] 1,3-diphenyl-4-pyrazolylacetamides displaying high hypoglycemic activity [4], and 1,5-diphenyl-3-methyl-4-pyrazolylacetonitrile applied as a nonnucleoside reverse transcriptase inhibitor of HIV-1 replication.[6,7]

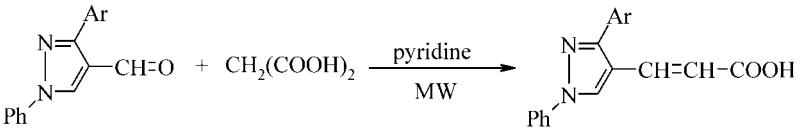
3-(1,3-Diaryl-4-pyrazolyl)propenoic acids were synthesized previously[4] by the Doebner method[8] and used to obtain the corresponding 4-pyrazolylacetamides. We reported[9] the condensation of 3-(het)aryl-1-phenylpyrazole-4-carboxaldehydes **1a–i** with malonic acid under the conditions of the Doebner reaction which furnished 3-(4-pyrazolyl)propenoic acids **2a–i** in 66–80% yields. Though affording relatively high yields of the target products, the synthesis of 3-(4-pyrazolyl)propenoic acids by the classical procedure of the Doebner condensation has two major disadvantages:

1. pyridine is used as a solvent in large amounts (to obtain 0.01 mol of the target acid, as much as 25 mL[4] or 15 mL[8] of pyridine is required);
2. the reaction needs a long time for completion (18.5 h[4] or 4.5 h[9] at 100–130°C).

In the present communication, we report the results regarding the synthesis of 3-(4-pyrazolyl)propenoic acids **2a–n** under microwave activation which enables the solvent amount and the reaction time to be reduced significantly.

It is noteworthy that the microwave method has already been applied in the preparation of chalcones and cinnamic acids.[10]

The condensation of pyrazole-4-carboxaldehydes **1a–n** with malonic acid, if run under microwave irradiation (see Sch. 1), has been found to require a 12 times lesser amount of pyridine and a radically cut (from 4.5 h to 5 min) time for completion, with significant increase of the yields of acids **2a–n** up to 88–98% (see Table 1). The procedure of the microwave activation proves particularly efficient when aldehydes **1i–n** sparingly soluble in pyridine are involved. In these instances the thermal version of the Doebner condensation allowed only 57–69% yields of the expected acids **2i–n**.



1 a-n 2 a-n

Scheme 1.

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Table 1. Comparison of yields of 3-(4-pyrazolyl)propenoic acids **2a–n** obtained under thermal and microwave conditions.

Compounds	Ar	Thermal conditions	Microwave conditions
2a	Ph	78[a]	98
2b	4-FC_6H_4	80[a]	97
2c	4-ClC_6H_4	83[a]	99
2d	4-BrC_6H_4	77[a]	96
2e	4-MeC_6H_4	71[a]	98
2f	4-$MeOC_6H_4$	69[a]	94
2g	2-thienyl	67[a]	95
2h	3-pyridyl	75[a]	98
2i	3-coumaryl	66[a]	94
2j	3-$NO_2C_6H_4$	59	88
2k	4-PhC_6H_4	61	95
2l	3-NO_2-4-$MeOC_6H_4$	58	89
2m	2-benzofuryl	69	96
2n	6-benzodioxanyl	57	90

[a]Taken from Ref.[9].

The composition and the structure of the newly synthesized products have been confirmed by elemental analysis (for C, H, N) as well as by IR and ^1H NMR spectroscopy.

In conclusion, a rapid and practical procedure for the synthesis of 3-(4-pyrazolyl)propenoic acids from pyrazole-4-carboxaldehydes and malonic acids under microwawe irradiation condition was developed.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover apparatus and are reported uncorrected. IR spectra were measured with a UR-20 spectrometer in KBr tablets. ^1H NMR spectra were recorded in $(CD_3)_2SO$ on a Varian VXR-300 instrument at 300 MHz with TMS as internal standard.

Synthesis of 3-(4-Pyrazolyl)propenoic Acids: General Procedure

1. Thermal Conditions

To a solution of pyrazole-4-carboxaldehyde **1** (0.04 mol) in pyridine (60 mL), malonic acid (8.74 g, 0.084 mol) and piperidine (1 mL) were added,

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and the reaction mixture was heated at 100°C for 0.5 h and at 130°C for another 4 h. On cooling, the reaction mixture was poured in the mixture of ice (300 g) and concentrated hydrochloric acid (40 mL). The precipitate formed was filtered off, dried, and crystallized from acetic acid.

2. Microwave Conditions

A one-neck 100-mL flask containing aldehyde **1** (0.04 mol), malonic acid (8.74 g, 0.084 mol), and pyridine (5 mL) was placed into a microwave oven (Lunik 600, 600 W, 2450 MHz) equipped with a reflux condenser and heated for 5 min. On cooling, the reaction mixture was treated as in the thermal version of the procedure. The following new compounds were obtained:

2j. m.p. 237–239°C. IR (KBr): 1645, 1720, 2580–2960. ^{1}H NMR[$(CD_3)_2SO$], δ 6.46 (d, 1H, CH═, $J = 15.9$ Hz), 7.37–7.85 (m, 10H, H–Ar + CH═), 9.22 (s, 1H, C^{5}H pyrazole), 12.25 (bs, 1H, COOH). Found: C, 62.28; H, 3.94; N, 12.57. $C_{18}H_{13}N_3O_4$. Calcd.: C, 62.48; H, 3.91; N, 12.53.

2k. m.p. 245–247°C. IR (KBr): 1650, 1715, 2600–2950. ^{1}H NMR [$(CD_3)_2SO$], δ 6.44 (d, 1H, CH═, $J = 15.9$ Hz), 7.34–7.98 (m, 15H, H–Ar + CH═), 9.18 (s, 1H, C^{5}H pyrazole), 12.15 (bs, 1H, COOH). Found: C, 78.60; H, 4.99; N, 7.55. $C_{24}H_{18}N_2O_2$. Calcd.: C, 78.67; H, 4.95; N, 7.65.

2l. m.p. 235–237°C. IR (KBr): 1650, 1725, 2590–3000. ^{1}H NMR [$(CD_3)_2SO$], δ 4.02 (s, 3H, MeO), 6.43 (d, 1H, CH═, $J = 15.6$ Hz), 7.35–8.09 (m, 9H, H–Ar + CH═), 9.16 (s, 1H, C^{5}H pyrazole), 12.06 (bs, 1H, COOH). Found: C, 62.26; H, 4.19; N, 11.57.; $C_{19}H_{15}N_3O_5$. Calcd.: C, 62.46; H, 4.14; N, 11.50.

2m. m.p. 221–222°C. IR (KBr): 1640, 1715, 2560–2970. ^{1}H NMR [$(CD_3)_2SO$], δ 6.53 (d, CH═, $J = 16.2$ Hz), 7.28–7.95 (m, 11H, H–Ar + CH═), 9.25 (s, 1H, C^{5}H pyrazole), 12.24 (bs, 1H, COOH). Found: C, 72.80; H, 4.17; N, 8.40. $C_{20}H_{14}N_2O_3$. Calcd.: C, 72.72; H, 4.27; N, 8.48.

2n. m.p. 255–257°C. IR (KBr): 1645, 1720, 2590–2960. ^{1}H NMR [$(CD_3)_2SO$], δ 4.30 [s, 2H, $(CH_2O)_2$], 6.38 (d, CH═, $J = 15.9$), 6.97–7.91 (m, 9H, H–Ar + CH═), 9.09 (s, 1H, C^{5}H pyrazole), 12.06 (bs, 1H, COOH). Found: C, 68.90; H, 4.50; N, 8.14. $C_{20}H_{16}N_2O_4$. Calcd.: C, 68.96; H, 4.63; N, 8.04.

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