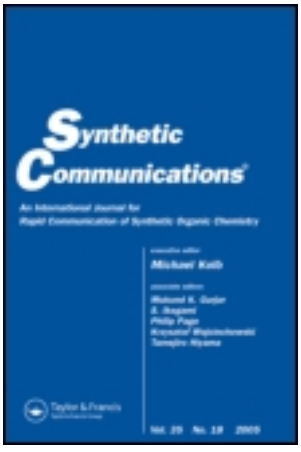

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Facile Synthesis of Pyrano[2,3-c]pyrazol-6-one Derivatives Under Microwave Irradiation in Solvent-Free Conditions

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Abstract: A series of substituted 1H,6H-pyrano[2,3-c]pyrazol-6-one derivatives were synthesized from one-pot cyclocondensation of hydrazine derivatives or 1H-pyrazol-5-one derivatives with various β-keto esters under solvent-free conditions using microwave irradiation in short time with good to excellent yields.

Keywords: Cyclocondensation, microwave irradiation, pyrano[2,3-c]pyrazol-6-one, solvent-free conditions

Pyranopyrazolone and their derivatives are a group of compounds possessing a wide spectrum of biological activity. They exhibit analgesic, antiinflammatory activities and act as vasodilators and hypotensive and hypoglycemic agents.[1–3] There are few general routes to obtain pyranopyrazolone, and most of these methods are based on the reaction of hydrazine derivatives or 1H-pyrazol-5-one with malononitrile,[4] dimethyl acetylenedicarboxylate,[3] or a β-keto ester in an oil bath at high temperature (130–170°C).[5–9] Recently, Stanovnik et al. reported the preparation of this heterocyclic ring from the reaction of 1H-pyrazol-5-one with substituted 3-dimethylaminopropenoate in a solvent under reflux conditions for a long reaction time.[10–12]

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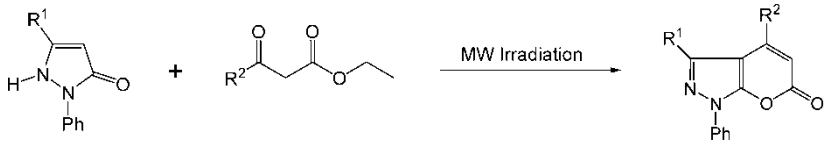
There have been growing interest in applying microwave irradiation to enhancement of organic synthesis in solvent-free systems.[13,14] The effects usually observed are decreasing reaction time and in some cases cleaner reactions with easier workup.[15]

In view of these findings and as a further stage of our work on the synthesis of 1H-pyrazol-5-one,[16] here we describe the synthesis of 1H,6H-pyrano[2,3-c]pyrazol-6-one derivatives from condensation of hydrazine derivatives or 1H-pyrazol-5-one derivatives with various β-keto esters under solvent-free conditions using microwave irradiation in short time with good to excellent yields. When 1H-pyrazol-5-one **1** was treated with 1.0 equivalent of β-keto ester **2** under microwave irradiation, without any solvent, the coupling reaction was completed after 3–5 min with the elimination of water and ethanol molecules and led to 1H,6H-pyrano[2,3-c]pyrazol-6-one **3**(**a**–**f**) (Scheme 1).

In another method, derivatives of 1H,6H-pyrano[2,3-c]pyrazol-6-one **5** were prepared from the reaction of a mixture of hydrazine derivative **4** with 2.0 equivalents of β-keto ester **2** by microwave irradiation after 3–4:30 min (Scheme 2). Water was added to the reaction mixture, the solid product was removed by filtration, and the product was recrystallized from an ethanol–water mixture.

In contrast, condensation of phenyl hydrazine and 2 equivalents of ethyl acetoacetate by the use of classical heating in an oil bath (140°C) gave a low yield (62%) of 3,4-dimethyl-1-phenyl-1H,6H-pyrano[2,3-c]pyrazol-6-one after 4 h. The reaction of phenyl hydrazine with 2 equivalents of ethyl benzoylacetate or ethy β-oxo-2-furanpropionate, however, did not give the desired products. To examine relatively large-scale synthesis, we irradiated 100 mmol of phenyl hydrazine and ethyl acetoacetate in a conventional microwave oven for 6 min; **5a** was obtained in 80% isolated yield.

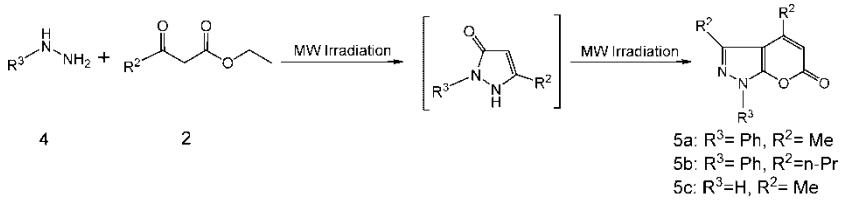
In conclusion, we report a rapid and efficient method for the preparation of substituted pyrano[2,3-c]pyrazol-6-one from condensation of hydrazine derivatives or 1H-pyrazol-5-one derivatives with various β-keto esters under microwave irradiation in a short time with high yields without any solvent.



1 2

3a: R^1= n-Pr, R^2= Me; 3b: R^1= Ph, R^2= Me
3c: R^1= Me, R^2=Ph; 3d: R^1= n-Pr, R^2= Ph
3e: R^1= Me, R^2=2-Furyl; 3f: R^1= Me, R^2=n-Pr

Scheme 1.



Scheme 2.

EXPERIMENTAL

A conventional microwave oven (900 W) was used for the irradiation of the reaction mixture. All reported yields are isolated yields. Melting points were determined with a Buchi melting-point apparatus without any correction. IR spectra were recorded on a FT-IR Bruker model Vector 22 spectrophotometer in KBr pellets; ^{1}H NMR spectra were recorded on FT-NMR Bruker Ac 80 (80 MHz) in DMSO-d_6 and $CDCl_3$ with TMS as internal reference. Mass spectra were recorded on Fisons 8000 Trio instrument at an ionization potential of 70 eV.

General Procedure for the Preparation of Pyranopyrazolone Derivatives

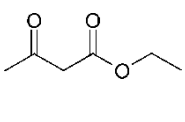
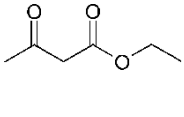
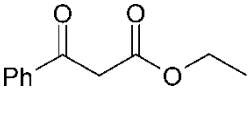
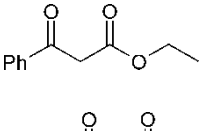
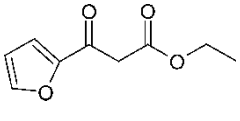
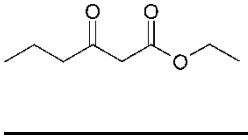
Method A

A mixture of phenyl hydrazine (2 mmol, 0.22 g) and ethyl butyrylacetate (4 mmol, 0.63 g) were placed in a Pyrex test tube, which was placed into a microwave oven (900 W). The mixture was irradiated for the length of time indicated in Table 1 by the pulsed irradiation technique (1 min with 29-s intervals). After completion of the reaction, which was monitored by TLC using hexane/ethyl acetate (8 : 2), the reaction mixture was poured into ice water (10 mL). The precipitate was collected by filtration and recrystallized using EtOH/H_2O, affording the pure product.

Method B

A mixture of 1-phenyl-3-propyl-5-pyrazolone (2 mmol, 0.22 g) and ethyl butyrylacetate (2 mmol, 0.32 g) were placed in a Pyrex test tube. The mixture was exposed to microwave irradiatied for the time given in Table 2, using the pulsed irradiation technique (1 min with 29-s intervals). After cooling, the reaction mixture was poured into ice water (10 mL). The precipitate was collected by filtration and recrystallized using EtOH/H_2O, affording the pure product.

Table 1. Preparation of substituted pyrano[2,3-c]pyrazol-6-one under microwave irradiation (method A)

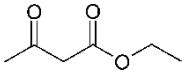
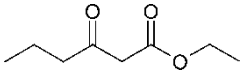
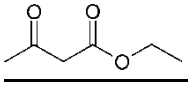
Starting materials	Products	Time (min)	Yield (%)
	**3a**	4	95
	**3b**	5	88
	**3c**	3	90
	**3d**	4	90
	**3e**	3	86
	**3f**	3:40	92

The structure of the products was approved by the comparison of their IR, ^{1}H NMR, ^{13}C NMR, and MS spectra and their melting points with those reported in the literature.

3a: Yellow solid, mp 80°C; ^{1}H NMR (DMSO-d_6): δ 1.10 (t, 3H, $J = 7.2$ Hz), 1.70–2.00 (m, 2H), 2.60 (d, 3H, $J = 1.2$ Hz), 2.95 (t, 2H, $J = 8.0$ Hz), 6.05 (d, 1H, $J = 1.2$ Hz), 7.50–8.00 (m, 5H) ppm; ^{13}C NMR (DMSO-d_6): δ 18.1, 24.3, 27.2, 35.5, 106.2, 110.1, 125.6, 131.2, 133.5, 134.4, 142.2, 153.1, 159.8, 165.5 ppm; IR (KBr): υ 1747, 1546, 1455, 829, 765 cm^{-1}; MS (70 eV): m/z = 268 (M^+), 240, 77.

3b: Yellow solid, mp 210°C (211°C lit.[6]); ^{1}H NMR (DMSO-d_6): δ 2.25 (d, 3H, 1.2 Hz), 6.12 (q, 1H, 1.2 Hz), 7.50–8.10 (m, 10H) ppm; ^{13}C NMR (DMSO-d_6): δ 25.4, 111.6, 118.5, 120.2, 127.2, 127.6, 129.4, 133.0, 133.3,

Table 2. Preparation of substituted pyrano[2,3-c]pyrazol-6-one under microwave irradiation (method B)

Starting materials		Products	Time (min)	Yield (%)
	$PhNHNH_2$	**5a**	4:30	83
	$PhNHNH_2$	**5b**	4	86
	NH_2NH_2	**5c**	3	88

133.4, 133.7, 134.5, 150.2, 152.7, 161.1 ppm; IR (KBr): υ 1734, 1595, 1534, 1179, 760, 690 cm^{-1}; MS (70 eV): m/z = 302 (M^+), 139, 115, 77.

3c: Yellow solid, mp 135°C (140°C lit.[6]); ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H), 5.90 (s, 1H), 7.30–7.95 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$): δ 15.2, 105.3, 110.9, 121.5, 126.7, 126.8, 127.0, 127.5, 128.4, 128.5, 129.1, 129.6, 148.1, 155.4, 162.1 ppm; IR (KBr): υ 1734, 1534, 1164, 1074, 843, 775, 707 cm^{-1}; MS (70 eV): m/z = 302 (M^+), 115, 77.

3d: Yellow solid, mp 110°C; ^1H NMR ($CDCl_3$): δ 0.62 (t, 3H, 7.2 Hz), 1.10–1.50 (m, 2H), 2.30–2.50 (t, 2H, 7.2 Hz), 5.87 (s, 1H), 7.30–7.95 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.1, 21.3, 31.2, 106.7, 118.7, 120.6, 126.6, 126.8, 127.0, 127.1, 128.4, 128.5, 129.1, 129.6, 151.6, 155.4, 160.8 ppm; IR (KBr): υ 1734, 1595, 1572, 1164, 1074, 775 cm^{-1}; MS (70 eV): m/z = 330 (M^+), 301, 77.

3e: Brown solid, mp 164°C; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H), 6.14 (s, 1H), 6.51–6.65 (m, 1H), 7.05–7.92 (m, 7H) ppm; ^{13}C NMR ($CDCl_3$): δ 16.4, 100.2, 112.4, 114.1, 120.8, 126.1, 126.8, 127.1, 127.5, 129.0, 145.9, 155.3, 158.1, 160.2 ppm; IR (KBr): υ 1739, 1547, 1488, 791, 751 cm^{-1}; MS (70 eV): m/z = 292 (M^+), 187, 159, 77.

3f: Red solid, mp 80°C; ^1H NMR ($CDCl_3$): δ 1.00 (t, 3H, J = 7.2 Hz), 1.50–1.90 (m, 2H), 2.49 (s, 3H), 2.40–2.80 (m, 2H), 5.76 (t, 1H, J = 1 Hz), 7.20–7.92 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.5, 14.6, 21.5, 34.6, 103.9, 120.4, 122.1, 126.6, 129.1, 129.5, 145.1, 152.6, 154.8, 160.0 ppm; IR (KBr): υ 1751, 1548, 823, 763 cm^{-1}; MS (70 eV): m/z = 268 (M^+), 225, 77.

5a: Yellow solid, mp 143°C (145°C lit.[6]); ^1H NMR ($CDCl_3$): δ 2.32 (d, 3H, J = 1.2 Hz), 2.40 (s, 3H), 5.75 (q, 1H, 1.2 Hz), 7.25–7.90 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$): δ 14.2, 20.5, 105.3, 118.5, 120.2, 126.1, 128.1, 129.0, 145.3, 152.1, 154.5, 160.7 ppm; IR (KBr): υ 1760, 1614, 1550, 1513, 1430, 1381, 1100, 830, 748 cm^{-1}; MS (70 eV): m/z = 240 (M^+), 77.

5b: Yellow solid, mp 95°C; ^1H NMR ($CDCl_3$): δ 1.10 (t, 6H, J = 7.2 Hz), 1.50–1.90 (m, 4H), 2.55–2.90 (m, 4H), 5.80 (t, 1H, J = 1 Hz), 7.25–7.90

(m, 5H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.5, 14.4, 21.2, 21.5, 31.8, 34.6, 103.6, 110.8, 121.2, 122.0, 126.1, 129.7, 145.2, 152.1, 154.5, 160.2 ppm; IR (KBr): υ 1742, 1605, 1542, 1457, 822, 681 cm^{-1}; MS (70 eV): $m/z = 296$ (M^+), 253, 240, 225, 91, 77.

5c: Yellow solid, mp 239°C (245°C lit.[6]); ^{1}H NMR (DMSO): δ 2.42 (d, 3H, $J = 1.2$ Hz), 2.53 (s, 3H), 5.90 (d, 1H), 12.50–13.50 (br, 1H) ppm; ^{13}C NMR (DMSO): δ 14.4, 20.8, 106.2, 118.4, 129.7, 152.9, 154.5, 161.2 ppm; IR (KBr): υ 3250, 1720, 1610, 1520, 1200, 1120, 1100, 930, 760 cm^{-1}; MS (70 eV): $m/z = 164$ (M^+), 136, 107, 77.

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REFERENCES

1. Kuo, S. C.; Huang, L. J.; Nakamura, H. Synthesis and analgesic and antiinflammatory activities of 3,4-dimethylpyrano[2,3-c]pyrazol-6-one derivatives. *J. Med. Chem.* **1984**, *27*, 539–554.
2. Huang, L.-J.; Hour, M.-J.; Teng, C.-M.; Kuo, S.-C. Synthesis and antiplatelet activities of n-arylmethyl-3,4-dimethylpyrano[2,3-c]pyrazol-6-one derivatives. *Chem. Pharm. Bull.* **1992**, *40*, 2547–2551.
3. Ueda, T.; Mase, H.; Oda, N.; Ito, I. Synthesis of pyrazolone derivatives. Synthesis and analgesic activity of pyrano[2,3-c]pyrazoles. *Chem. Pharm. Bull.* **1981**, *29*, 3522–3528.
4. Zhou, J. F.; Tu, S. J.; Zhu, H. Q.; Zhi, S. J. A facile one-pot synthesis of pyrano[2,3-c]pyrazole derivatives under microwave irradiation. *Synth. Commun.* **2002**, *32* (21), 3363–3366.
5. Abdel-Megeed, M. F. Studies on the pyridylpyrazolone system: Part V—cyclocondensation of 1-phenyl-3-(3′-pyridyl)-2-pyrazolin-5-one with ethyl acetoacetate and related compounds. *Indian J. Chem.* **1987**, *26B*, 827–831.
6. Khan, M. A.; Cosenza, A. G.; Ellis, G. P. Pyranopyrazoles. 2. Synthesis and reactions of 1H,6H-pyrano[2,3-c]pyrazol-6-ones. *J. Heterocycl. Chem.* **1982**, *19*, 1077–1085.
7. Kumar, D.; Kaushik, C. P.; Singh, S. P. Synthesis and NMR (^{1}H, ^{13}C) spectral studies of isomeric pyranopyrazoles. *Indian J. Chem.* **1999**, *38B*, 1377–1380.
8. Kikukawa, H.; Nishiwaki, T. 2-Pyridones and pyrano[2,3-c]pyrazol-6(1H)-one bearing a trifluoromethyl group. *J. Chem. Res.* **1995**, *11*, 476–477.
9. Nam, N. L.; Grandberg, I. I. Condensation of 3-methyl-1-phenylpyrazole-5-thione with acetoacetic ester. *Chem. Heterocycl. Compounds* **2003**, *8*, 1115–1116.
10. Smodis, J.; Stanovnik, B. The synthesis and transformations of substituted 2-hydroxy-3-dimethylaminopropenoates. The preparation of condensed 3-hydroxypyran-2-ones. *Tetrahedron* **1998**, *54*, 9799–9810.
11. Stanovnik, B.; Svete, J.; Tisler, M. Methyl 2-benzoylamino-3-dimethylaminopropenoate in the synthesis of heterocyclic systems. The synthesis of

benzoylamino substituted 7H-pyrano[2,3-d]pyramide, 1H,6H-pyrano[2,3-c]pyrazole and 2H-1-benzopyran derivatives. *J. Heterocycl. Chem.* **1989**, *26*, 1273–1275.
12. Toplak, R.; Svete, J.; Gradadolnik, G.; Stanovnik, B.; Grdadolnik, S. G. The synthesis of methyl 2-(benzyloxycarbonyl)amino-3-dimethylaminopropenoate. The synthesis of trisubstituted pyrroles, 3-amino-2H-pyran-2-ones, fused 2H-pyran-2-ones and 4H-pyridin-4-ones. *J. Heterocycl. Chem.* **1999**, *36*, 225–235.
13. Loupy, A. Microwaves in Organic Synthesis. Wiley-VCH Verlag: Weinheim, 2002; pp. 253–290.
14. Tamaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH Verlag: Weinheim, 2003.
15. Mojtahedi, M. M.; Sharifi, A.; Kaamyabi, S.; Saidi, M. R. Efficient and practical solvent-free oxidation of alcohols using microwave irradiation. *J. Chem. Res.* **2002**, *6*, 286–287.
16. Mojtahedi, M. M.; Jalali, M. R.; Bolourtchian, M. Microwave-assisted preparation of substituted pyrazolones under solvent-free conditions. *Monatsh Chem.* (*submitted*).