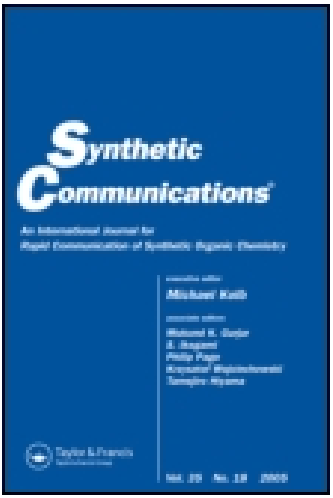


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Microwave-Assisted Synthesis of Pyrazoline Derivatives on Soluble Polymer

Min Xia [a] & Xue-jie Pan [a]
[a] Department of Applied Chemistry , Zhejiang Institute of Science and Technology , Hangzhou, 310033, P.R. China
Published online: 10 Jan 2011.

To cite this article: Min Xia & Xue-jie Pan (2004) Microwave-Assisted Synthesis of Pyrazoline Derivatives on Soluble Polymer, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:19, 3521-3528, DOI: 10.1081/SCC-200030984

To link to this article: http://dx.doi.org/10.1081/SCC-200030984

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 19, pp. 3521–3528, 2004

Microwave-Assisted Synthesis of Pyrazoline Derivatives on Soluble Polymer

Min Xia* and Xue-jie Pan

Department of Applied Chemistry, Zhejiang Institute of Science and Technology, Hangzhou 310033, P.R. China

ABSTRACT

1-Phenyl-3-substituted-2-pyrazolinyl-5-carboxylates could be synthesized rapidly and regioselectively in good yield through the protocol of 1,3-dipolar cycloaddition of polyethylene glycol supported acrylic acid with aldehyde phenylhydrazones under microwave irradiation.

Key Words: Liquid-phase synthesis; Polyethelene glycol; Pyrazoline derivatives; Microwave.

It is known that pyrazoline derivatives are significant compounds, not only as intermediates and agricultural pesticides, but as effective luminescent and fluorescent substances as well.[1] There exist various approaches to their

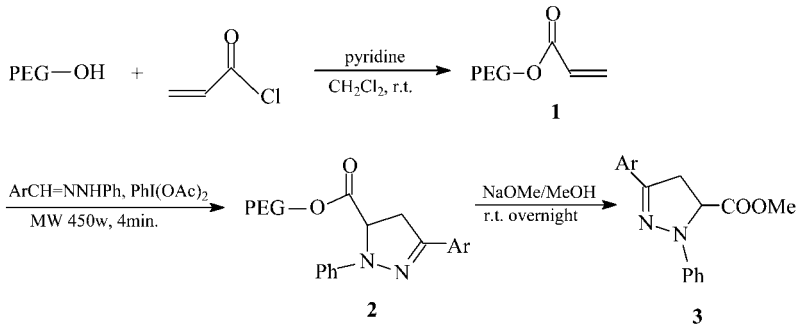
*Correspondence: Min Xia, Department of Applied Chemistry, Zhejiang Institute of Science and Technology, Hangzhou 310033, P.R. China; E-mail: xiamin@hxcnc.com.

DOI: 10.1081/SCC-200030984 0039-7911 (Print); 1532-2432 (Online)

synthesis; however, 1,3-dipolar cycloaddition through nitrilimines generated in situ is the most powerful and versatile route to construct the five-member heterocycles.[2] A number of methods have been reported for the generation in situ of nitrilimines, e.g., the base-induced dehydrochlorination of the hydrazonyl halides,[3] the thermal decomposition of 2,5-disubstituted tetrazoles[4] or the sodium salt of 2-nitrohydrazones,[5] the photolysis of 3,4-disubstituted sydones[6] or 2,5-disubstituted tetrazoles,[7] and the oxidation of aldehyde arylhydrazones with lead tetraacetate.[8] Nevertheless, all of them have shortcomings such as troubles with operation, harsh conditions, difficulty in preparation of starting substrates, low yields of nitrilimines, or the use of toxic reagents. (Diacetoxy)iodobenzene is the most useful and promising reagent among the hypervalent iodine compounds, which can be prepared readily without any toxicity and is an effective oxidant, especially for the oxidation of the compounds containing N atoms in good yields under mild conditions.[9]

In recent years, the application of microwave (MW) irradiation in organic synthesis has been the focus of considerable attention and is becoming an increasingly popular technology.[10] The prominent features of the microwave approach are the rapid reactions, clean reaction conditions, and ease of manipulation. 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. In the literature, there exist many reports that 1,3-dipolar cycloadditions can be effectively promoted through microwave irradiation,[11] thus affording the rapid and convenient routines to the construction of five-member heterocycles.

Currently, organic synthesis of small molecular compounds on soluble polymers, i.e., liquid-phase chemistry, has increasingly become an attractive field.[12] It couples the advantages of homogeneous solution-phase chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis without the cleavage-and-check procedure) with those of solid-phase chemistry (use of excessive reagents, easy isolation and purification of products). Besides, owing to the homogeneity of liquid-phase reactions, reaction conditions can be readily shifted from solution-phase systems without many changes, and the amount of excessive reagents is less than that in solid-phase reactions. Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising. Due to the low melting point (mp) of PEG ($\sim$51°C), it can be readily melted to turn liquid under microwave heating. Therefore, synthesis of small organic molecules on PEG by microwave heating has the advantage in that PEG plays the roles of polymer support and liquid solvent as well.[13] In connection with our work on the synthesis of small molecular compounds on soluble polymer,[14] herein we report the microwave-promoted synthesis of pyrazoline derivatives through 1,3-



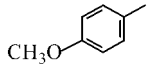
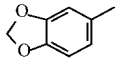
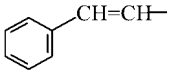
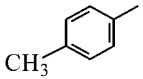
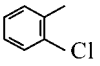
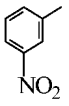
Scheme 1.

cycloaddition of aryldehyde phenylhydrazones with PEG-bound acrylate (Sch. 1).

We selected PEG 4000 as the polymeric support due to its good compromise of crystallization and loading capacity. The terminal hydroxyl groups were active enough to be esterified by acryloyl chloride in the presence of pyridine at room temperature overnight. The conversion of terminal hydroxyl groups was quantitative, which could be determined by ^{1}H NMR to check that the signal of hydroxyl groups on PEG at 4.58 ppm disappeared. The PEG-linked acrylate (**1**) was taken as the dipolarophile to react with the nitrilimines generated in situ by the oxidation of aldehyde phenylhydrazones with (diacetoxy)iodobenzene. The 1,3-dipolar cycloaddition was carried out smoothly and rapidly under microwave heating within 4 minutes to form the PEG loaded pyrazoline intermediates (**2**). During microwave irradiation, the PEG-bound acrylate (**1**) was melted into a liquid, in which substrates were ensured to react with each other in homogeneity. The PEG 4000 in our case acted simultaneously as a polymeric support and as a solvent as well under MW irradiation, transporting energy and diffusing the chemicals in the reaction system. The target products of 1-phenyl-3-substituted-2-pyrazolinyl-5-carboxylates (**3**) were completely released from the support [checked by thin-layer chromatography (TLC)] in the media of 1 N NaOMe/MeOH solution at room temperature overnight. Owing to the excellent precipitation of PEG in ether, the PEG-bound pyrazoline intermediates (**2**) could be obtained in excellent purities after simple filtration and washing, avoiding the complicated isolation and separation procedure. The target products could be obtained without further chromatography.

The results are shown in Table 1, indicating that the 1,3-dipolar cycloaddition had obvious electronic effects. When the aldehydes had electron-donating groups, the yields were excellent. However, when there existed

Table 1. 1,3-Dipolar cycloaddition of nitrilimines with PEG-bound acrylate under microwave irradition.[a]

Entry	Ar	Yield (%)	Entry	Ar	Yield (%)
3a		84	3e		88
3b		92	3f		94
3c		86	3g		61
3d		74	3h		0

[a]The yields were determined by loading capacity of terminal hydroxyl groups on PEG 4000 with 0.5 mmol/g.

electron-withdrawing groups, the yields were low, especially for the strongly electron-withdrawing NO_2 group where the expected product could not be obtained. Not only aromatic hydrazones but also heterocyclic and α, β-unsaturated hydrazones were efficient substrates.

It was found that PEG-supported 1,3-dipolar cycloaddition was completely regioselective,[15] since only the 1-phenyl-3-substituted-2-pyrazolinyl-5-carboxylates (**3**) were provided. The regioselectivity was determined by ^{1}H NMR that the chemical shifts of C_5-H were at 4.8 ppm, at relatively low field.

In conclusion, we herein report the rapid and readily microwave-assisted 1,3-dipolar cycloaddition for pyrazoline derivatives on PEG support, utilizing (diacetoxy)iodobenzene to generate nitrilimines in situ. The PEG-supported synthesis of pyrazoline derivatives could give the products in good yields and excellent purities with complete regioselectivity, avoiding the complicated isolation and separation procedure of intermediates. Therefore, the protocol described was an effective and easy approach to the pyrazoline derivatives.

EXPERIMENTAL SECTION

1. General procedure for the preparation of PEG 4000-supported acrylate (**1**): At 0°C, the acryoyl chloride (3 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to the mixture of PEG 4000 (1 mmol,

2 g) and pyridine (5 mmol) in anhydrous CH_2Cl_2 (15 mL) over 1 hour; the resultant mixture was stirred at room temperature overnight. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL), and cold ether (70 mL) was poured to precipitate the white solid, which was washed by cold ether three times (3 × 20 mL). After drying under reduced pressure, the PEG 4000-bound acrylate (1) was obtained as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.53 ∼ 3.84 (m, PEG backbone, OCH_2CH_2O), 4.33 (t, J = 4.8 Hz, 2 H, PEG-OCH_2CH_2OCO), 5.88 (dd, J = 10 Hz, J = 2 Hz, 1 H), 6.20 (dd, J = 16.5 Hz, J = 10 Hz, 1 H), 6.43 (dd, J = 16.5 Hz, J = 2 Hz, 1 H).

2. General procedure for the preparation of PEG 4000-supported pyrazoline intermediates (**2**): At room temperature, the well-ground mixture of PEG 4000-bound acrylate (**1**) (0.5 mmol, 1 g), (diacetoxy) iodobenzene (1 mmol), and aldehyde phenylhydrazone (1 mmol) was put in an open vessel and irradiated for 4 minutes at 450 w (irradiated for 2 minutes and cooled for 1 minute, cycled for two times) in a domestic microwave oven. After the mixture was cooled to room temperature, CH_2Cl_2 (10 mL) was added and the resultant mixture was filtrated. The filtrate was poured with ether (70 mL) and stirred to precipitate the white solid, which was filtrated and washed with ether three times (3 × 20 mL). After drying under reduced pressure, the PEG 4000-bound pyrazoline intermediate (**2**) was obtained as a white powder.
3. General procedure for the preparation of 1-phenyl-3-substituted-2-pyrazolinyl-5-carboxylates (**3**): The PEG 4000-loaded pyrazoline intermediate (**2**) was dissolved in a solution of 1 N NaOMe/MeOH (15 mL). The resultant solution was stirred at room temperature overnight. By pouring with water (30 mL), the solution was extracted with ether (3 × 10 mL). After drying over anhydrous $MgSO_4$, the organic solvent was removed to give the target products without further chromatography.

Compound **3a**: mp 105 ∼ 106°C (Lit.[15] 106 ∼ 107°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.42 (dd, J = 17 Hz, J = 6.5 Hz, 1 H), 3.68 (dd, J = 17 Hz, J = 12.5 Hz, 1 H), 3.75(s, 3 H), 4.83(dd, J = 12.5 Hz, J = 6.5 Hz, 1 H), 6.88(t, J = 7 Hz, 1 H), 7.12 (d, J = 8 Hz, 2 H), 7.25 ∼ 7.41 (m, 5 H), 7.72 (d, J = 7 Hz, 2 H); FT-IR (KBr) υ (cm^{-1}) 3029, 2952, 1737, 1596, 1504, 1493, 1397, 1336, 1263, 1135, 1016, 889, 745, 686; MS m/z (%) 280 (M^+, 33.34), 221 (100), 118 (14.79), 104 (18.45), 91 (28.05), 77 (53.97), 51 (30.91).

Compound **3b**: mp 135°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.38 (dd, J = 7 Hz, J = 17 Hz, 1 H), 3.62 (dd, J = 13 Hz, J = 17 Hz, 1 H), 3.75 (s, 3 H), 4.78 (dd, J = 7 Hz, J = 13 Hz, 1 H), 5.99 (s, 2 H), 6.80 (d, J = 8 Hz, 1 H), 6.86 (t, J = 7 Hz, 1 H), 7.02 (dd, J = 1.5 Hz, J = 8 Hz, 1 H), 7.09 (d, J = 8 Hz, 2 H), 7.25 ~ 7.29 (m, 2 H) 7.38 (d, J = 1.5 Hz, 1 H); FT-IR (KBr) υ (cm^{-1}) 3042, 2921, 1732, 1599, 1500, 1454, 1351, 1318, 1220, 1039, 936, 876, 812, 747, 694, 669, 619; MS m/z (%) 324 (M^+, 51.86), 265 (100), 235 (10.85), 207 (24.05), 104 (9.44), 91 (9.86), 77 (34.16), 51 (16.19).

Compound **3c**: mp 103 ~ 104°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.37 (s, 3 H), 3.40 (dd, J = 17 Hz, J = 7 Hz, 1 H), 3.67 (dd, J = 13 Hz, J = 17 Hz, 1 H), 3.75 (s, 3 H), 4.81 (dd, J = 13 Hz, J = 7 Hz, 1 H), 6.87 (t, J = 7.5 Hz, 1 H), 7.11 (d, J = 8 Hz, 2 H), 7.20 (t, J = 8 Hz, 2 H), 7.25 ~ 7.30 (m, 2 H), 7.60 (d, J = 8 Hz, 2 H); FT-IR (KBr) υ (cm^{-1}) 3027, 2950, 1740, 1597, 1497, 1378, 1321, 1268, 1200, 1122, 1031, 880, 821, 753, 692; MS m/z (%) 294 (M^+, 38.29), 235 (100), 117 (10.44), 104 (9.56), 91 (22.54), 77 (28.18), 51 (13.71).

Compound **3d**: mp 84 ~ 85°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.39 (dd, J = 6.5 Hz, J = 17 Hz, 1 H), 3.62 (dd, J = 13 Hz, J = 17 Hz, 1 H), 3.73 (s, 3 H), 4.81 (dd, J = 13 Hz, J = 6.5 Hz, 1 H), 6.48 (dd, J = 2 Hz, J = 3.5 Hz, 1 H), 6.63 (d, J = 3.5 Hz, 1 H), 6.87 (t, J = 7 Hz, 1 H), 7.09 (d, J = 8 Hz, 2 H), 7.25 ~ 7.29 (m, 2 H), 7.49 (d, J = 2 Hz, 1 H); FT-IR (KBr) υ (cm^{-1}) 3136, 2954, 1735, 1595, 1503, 1373, 1264, 1133, 1002, 922, 887, 804, 746, 690; MS m/z (%) 270 (M^+, 58.45), 211 (100), 183 (18.37), 117 (8.83), 104 (8.89), 91 (13.05), 77 (42.28), 51 (27.00).

Compound **3e**: mp 115 ~ 117°C (Lit.[15] 114 ~ 115°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.38 (dd, J = 7 Hz, J = 17 Hz, 1 H), 3.64 (dd, J = 17 Hz, J = 13 Hz, 1 H), 3.74 (s, 3 H), 3.83 (s, 3 H), 4.79 (dd, J = 13 Hz, J = 7 Hz, 1 H), 6.86 (t, J = 7.5 Hz, 1 H), 6.92 (d, J = 9 Hz, 2 H), 7.10 (d, J = 8 Hz, 2 H), 7.25 ~ 7.3 (m, 2 H), 7.66 (d, J = 8.5 Hz, 2 H); FT-IR (KBr) υ (cm^{-1}) 3043, 2958, 1735, 1596, 1501, 1392, 1250, 1132, 1034, 879, 826, 743, 691; MS m/z (%) 310 (M^+, 48.45), 251 (100), 162 (18.10), 135 (25.33), 117 (14.70), 104 (14.23), 91 (68.32), 77 (61.24), 57 (33.13), 51 (27.65), 43 (33.31).

Compound **3f**: mp 123 ~ 124°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.32 (dd, J = 6.5 Hz, J = 17 Hz, 1 H), 3.56 (dd, J = 13 Hz, J = 17 Hz, 1 H), 3.75 (s, 3 H), 4.82 (dd, J = 6.5 Hz, J = 13 Hz, 1 H), 6.62 (d, J = 16.5 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H), 7.06 (d, J = 7.5 Hz, 2 H), 7.19 (d, J = 16.5 Hz, 1 H), 7.26 ~ 7.30 (m, 3 H), 7.36 (t, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.5 Hz, 2 H); FT-IR (KBr) υ (cm^{-1}) 2950, 1741, 1599, 1501, 1324, 1200, 1122, 1038, 958, 882, 748, 691; MS m/z (%) 306 (M^+, 58.42), 247 (100), 115 (15.11), 104 (17.99), 91 (19.36), 77 (76.95), 51 (33.04).

Compound **3g**: mp 143 ~ 144°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.63 (dd, J = 6.5 Hz, J = 17 Hz, 1 H), 3.74 (s, 3 H), 3.92 (dd, J = 13 Hz, J = 17 Hz, 1 H), 4.84 (dd, J = 6.5 Hz, J = 13 Hz, 1 H), 6.89 (t, J = 7 Hz, 1 H), 7.11 (d, J = 8 Hz, 2 H), 7.25 ~ 7.30 (m, 4 H), 7.38 ~ 7.40 (m, 1 H), 7.84 ~ 7.86 (m, 1 H); FT-IR (KBr) υ (cm^{-1}) 3064, 2952, 1739, 1599, 1502, 1435, 1389, 1322, 1265, 1204, 1141, 1036, 879, 750, 691, 666; MS m/z (%) 314 (M^+, 41.92), 255 (100), 117 (13.83), 104 (9.31), 91 (23.88), 77 (49.44), 51 (27.25).

ACKNOWLEDGMENT

We are grateful for the financial support of the Natural Science Fund of Zhejiang Province (202031).

REFERENCES

1. Kost, A.N.; Grandberg, I.I. In *Advances in Heterocyclic Chemistry*; Katritzky, A.R., Boulton, A.J., Eds.; Academic Press: New York and London, 1966; 347.
2. (a) Shawli, A.S. Reaction of heterocyclic compounds with nitrilimines and their precursors. Chem. Rev. **1993**, *93*, 2731–2777; (b) Bertrand, G.; Wentrup, C. Nitrilimines: from characterization in the matrix to stable compounds. Angew. Chem. Int. Ed. Engl. **1994**, *33*, 527–545.
3. Clovis, J.S.; Eckell, A.; Huisgen, R.; Sustamann, R. 1,3-Dipolar cycloaddition XXVIII: diphenylinitrilimines and aryl-conjugated alkenes. Chem. Ber. **1967**, *100*, 1593–1600.
4. Padwa, A.; Nahm, S.; Satu, E. Intramolecular 1,3-dipolar cycloaddition reactions of alkenyl-substituted nitrile imines. J. Org. Chem. **1978**, *43*, 1664–1668.
5. Hassaneen, H.M.; Shawli, A.S. Thermal reaction of sodium salts of α-nitrohydrazones with arylidenemalononitriles and α,β-unsaturated ketones. Indian J. Chem. **1989**, *28B*, 133–135.
6. Haneda, A.; Imagawa, T.; Kawanish, M. Double 1,3-diploar cycloaddition reaction of 3-phenylsydone with 1,3-dienes. Bull. Chem. Soc. Jpn. **1976**, *49*, 748–749.
7. Scheiner, P.; Dina, J.F. Product formation in tetrazole photolysis. Tetrahedron **1970**, *26*, 2619–2627.
8. Gladstone, W.A.F.; Ayiward, J.B.; Norman, R.O.C. Reaction of lead tetraacetate XVIII: oxidation of aldehyde hydrazones: new methods for the generation of nitrilimines. J. Chem. Soc. **1969**, 2587–2589.

9. Chen, D.W.; Chen, Z.C. Hypervalent iodine in synthesis XIX: oxidation of aldehyde hydrazones with phenyliodine diacetate: a new method for the generation of nitrilimines. Synth. Commun. **1995**, *25*, 1617–1626.
10. (a) Varma, R.S. Solvent-free organic synthesis. Green Chem. **1999**, 43–55; (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. New solvent-free organic synthesis using focused microwaves. Synthesis **1998**, 1213–1234.
11. (a) Rigolet, S.; Goncalo, P.; Melot, J.M.; Vebrel, J. The 1,3-dipolar cycloaddition of 3-methylene-N-substituted isoindolones and nitrones by classical and microwave techniques: reactivity and stereochemical studies. J. Chem. Res. (S) **1998**, 686–687; (b) Diaz-Ortiz, A.; Diaz-Barra, E.; Hoz, A.; Prieto, P.; Moreno, A. Cycloaddition of ketene acetals under microwave irradiation in solvent-free conditions. Perkin Trans. I **1994**, 3595–3598; (c) Syassi, B.J.; Bougrin, K.; Soufiaour, M. Addition dipolaire-1,3 des arylnitriloxydes avec quelques dipolarophiles olfiniques sur alumine en milieu sec et sous micro-ondes. Tetrahedron Lett. **1997**, *38*, 8855–8858.
12. (a) Gravert, D.J.; Janda, K.D. Organic synthesis on soluble polymer supports: liquid-phase methodologies. Chem. Rev. **1997**, *97*, 489–510; (b) Toy, P.H.; Janda, K.D. Soluble polymer-supported organic synthesis. Acc. Chem. Res. **2000**, *33*, 546–554; (c) Wentworth, P.; Janda, K.D. Liquid-phase chemistry: recent advances in soluble polymer-supported catalysts, reagents and synthesis. Chem. Commun. **1999**, 1917–1924.
13. (a) Xia, M.; Wang, Y.G. A Novel microwave-activated Sonogashira coupling reaction and cleavage using polyethylene glycol as phase-transfer catalyst and polymer support. J. Chem. Res. (S) **2002**, 173–175; (b) Sauvagnet, B.; Lamaty, F.; Lazaro, R.; Martinez, J. Polyethylene glycol (PEG) as polymeric support and phase-transfer catalyst in the soluble polymer liquid-phase synthesis of α-aminoesters. Tetrahedron Lett. **1998**, *39*, 821–823.
14. Xia, M.; Wang, Y.G. An efficient protocol for the liquid-phase synthesis of methyl 3,4-dihydropyrimidin-2(1H)-one-5-carboxylate derivatives. Synthesis **2003**, 262–266.
15. Kanemasa, S.; Kobayashi, S. Lewis acid coordinated nitrile oxide and nitrile imine 1,3-dipoles. *syn*-selective cycloadditions to 2-(1-hydroxyalkyl)acrylates. Bull. Chem. Soc. Jpn. **1993**, *66*, 2685–2693.

Received in Japan April 22, 2004