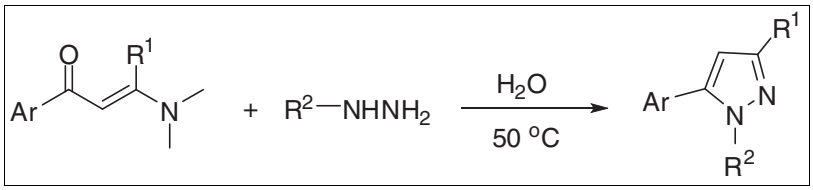
Pan Xu, Yu-Kun Xi, Hui Chen, and Da-Qing Shi*

Key Laboratory of Organic Synthesis of Jiangsu Province, Soochow University, Suzhou 215123, People's Republic of China
*E-mail: dqshi@suda.edu.cn
Received May 9, 2012
DOI 10.1002/jhet.2056
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



A series of 5-aryl-1*H*-pyrazole derivatives were synthesized via the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-one with hydrazine in aqueous media without using any catalyst. This method has the advantages of easier work-up, mild reaction condition, high yields, and an environmentally benign procedure.

J. Heterocyclic Chem., **00,** 00 (2014).

INTRODUCTION

The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods [1]. One of the most promising approaches uses water as the reaction medium [2]. Breslow [3], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic reactions in the 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions [4]. The aqueous medium with respect to organic solvent is less expensive, less dangerous, and environmentally friendly. Many important types of heterocyclic compounds, such as triazines, acridines, quinolines, pyridines, indoles, pyrazines, furans, and pyrimidines [5], have been synthesized in aqueous media. The synthesis of new and important type of heterocyclic compounds in water continues to attract wide attention among synthetic chemists.

Pyrazole and its derivatives are shown to possess important biological and pharmaceutical activities [6] such as antimicrobial [7], antiviral [8], antitumor [9], anti-inflammatory [10], antifungal [11], and antidepressant [12] activities. They are also useful intermediates for many industrial products [13]. Many syntheses of pyrazoles have been developed [14]. However, these syntheses are usually carried out in organic solvents. As part of our current studies on the development of new routes to heterocyclic systems in aqueous media [15], we now report an efficient and clean synthetic route to pyrazole and isoxazole derivatives via the reaction of 3-(dimethylamino)-1-arylprop-2-en-1-one with hydrazine or hydroxylamine in aqueous media.

RESULTS AND DISCUSSION

When an equivalent mixture of 3-(dimethylamino)-1-arylprop-2-en-1-one derivatives **1** and hydrazine **2** was stirred at 50°C in aqueous media, 5-aryl-1*H*-pyrazole derivatives **3** were obtained in good yields (Scheme 1). The results are summarized in Table 1.

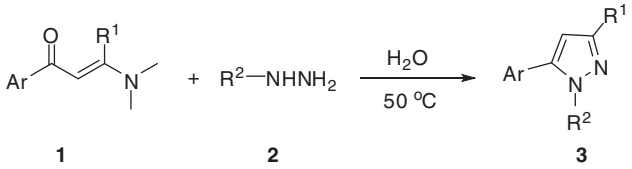
As shown in Table 1, this protocol could be applied to the 3-(dimethylamino)-1-arylprop-2-en-1-ones with both electron-withdrawing groups (such as halide groups) and electron-donating groups (such as methoxyl group). Polysubstituted 3-(dimethylamino)-1-arylprop-2-en-1-ones could also be used in this synthesis. We concluded that the electronic nature of the substituent on the aromatic ring of 3-(dimethylamino)-1-arylprop-2-en-1-ones had no significant effect on this reaction.

This synthesis was confirmed to follow the group-assistant chemistry [16] process, which can avoid traditional chromatography and recrystallization purification; that is, all the pure products can be simply obtained by washing the crude products with water.

The structures of the compounds **3** were identified by their spectroscopy analysis. Thus, the IR spectra of compounds **3a–g** measured as potassium bromide pellets show one band of the stretching vibrations of the NH group at 3123–3461 cm^{-1}. In the ^1H NMR spectra of compounds **3** measured in DMSO-d_6 or $CDCl_3$solution, the CH_3 proton signals were observed at 2.24–2.31 ppm, and the C_4–H proton signals at 6.23–6.74 ppm.

Although the detailed mechanism of the aforementioned reaction remains to be fully clarified, the formation of 5-aryl-1*H*-pyrazoles **3** could be explained by a reaction sequence presented in Scheme 2. We proposed that the reaction proceeded via a reaction sequence of Michael addition, elimination, cyclization, and dehydration. First, the Michael addition of 3-(dimethylamino)-

Scheme 1. The synthesis of 5-aryl-1*H*-pyrazole derivatives in aqueous media.



1 2 3

Table 1

The synthesis of 5-aryl-1*H*-pyrazole derivatives **3** in aqueous media.

Entry	Ar	R^1	R^2	Isolated yield (%)
3a	4-ClC_6H_4	H	H	86
3b	4-$CH_3OC_6H_4$	H	H	89
3c	4-ClC_6H_4	CH_3	H	88
3d	C_6H_5	CH_3	H	81
3e	2,4-$Cl_2C_6H_3$	CH_3	H	78
3f	Thiophen-2-yl	CH_3	H	82
3g	4-BrC_6H_4	CH_3	H	92
3h	4-$CH_3OC_6H_4$	H	4-$CH_3OC_6H_4$	88
3i	4-ClC_6H_4	CH_3	C_6H_5	82
3j	C_6H_5	CH_3	C_6H_5	85
3k	2,4-$Cl_2C_6H_3$	CH_3	C_6H_5	80

1-arylprop-2-en-1-ones **1** and hydrazine **2** gave the intermediate product **4**. The intermediate **4** eliminated one molecule dimethylamine to give the intermediate product **5**, which upon intramolecular cyclization and dehydration, gave rise to product **3**.

In conclusion, we have developed a simple and clean synthesis of 5-aryl-1*H*-pyrazole derivatives in aqueous media without using any catalyst. This method has the advantages of easier work-up, mild reaction condition, high yields, and an environmentally benign procedure.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Varian F-1000 spectrometer (Varian Inc., Palo Alto, CA) in KBr with absorptions in cm^{-1}. ^1H NMR spectra were determined on Varian-400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS.

General procedure for the synthesis of 5-aryl-1*H*-pyrazole derivatives 3 in aqueous media. 3-(Dimethylamino)-1-arylprop-2-en-1-ones **1** (1 mmol) and hydrazine **2** (1 mmol) were added to a 25-mL round-bottom flask containing 5 mL water. The mixture was then stirred at 50°C for 2 h. After completion of the reaction, the precipitate was collected by suction to give products **3** without further purified.

5-(4-Chlorophenyl)-1H-pyrazole (3a). This compound was obtained as solid with mp 94–96°C (lit. [17] 98.5–99°C); IR (potassium bromide): 3168, 2942, 1644, 1447, 1091, 941, 829, 764 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.74 (s, 1H, CH), 7.45 (d, *J* = 7.2 Hz, 2H, ArH), 7.83 (d, *J* = 7.2 Hz, 3H, ArH and CH), 12.98 (s, 1H, NH).

5-(4-Methoxyphenyl)-1H-pyrazole (3b). This compound was obtained as solid with mp 122–123°C (lit. [18] 129°C); IR (potassium bromide): 3123, 2910, 1612, 1517, 1440, 1249, 1177, 1100, 1022, 835 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.77 (s, 3H, CH_3O), 6.60 (s, 1H, CH), 6.97 (d, *J* = 7.6 Hz, 2H, ArH), 7.49–7.73 (m, 3H, ArH and CH), 12.76 (s, 1H, NH).

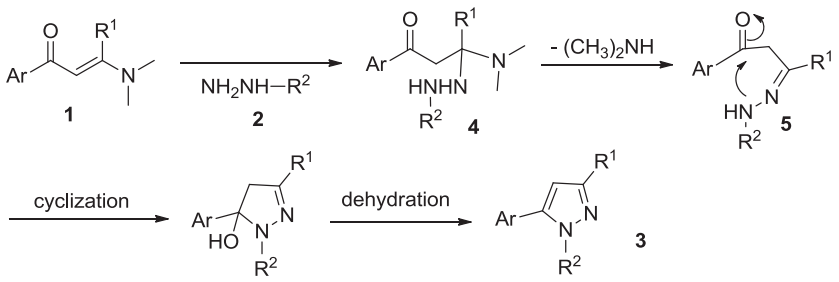
3-(4-Chlorophenyl)-5-methyl-1H-pyrazole (3c). This compound was obtained as solid with mp 143–144°C (lit. [19] 147–148°C); IR (potassium bromide): 3458, 3198, 2853, 1579, 1433, 1420, 1198, 1093, 1017, 834 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 6.45 (s, 1H, CH), 7.42 (d, *J* = 7.2 Hz, 2H, ArH), 7.76 (d, *J* = 7.6 Hz, 2H, ArH), 12.63 (s, 1H, NH).

5-Methyl-3-phenyl-1H-pyrazole (3d). This compound was obtained as solid with mp 94–95°C (lit. [20] 98–100°C); IR (potassium bromide): 3190, 3084, 2960, 2846, 1579, 1459, 1277, 1201, 1067, 960, 875, 759, 683 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.24 (s, 3H, CH_3), 6.43 (s, 1H, CH), 7.27 (t, *J* = 7.2 Hz, 1H, ArH), 7.38 (t, *J* = 7.2 Hz, 2H, ArH), 7.74 (d, *J* = 7.6 Hz, 2H, ArH), 12.58 (s, 1H, NH).

5-(2,4-Dichlorophenyl)-3-methyl-1H-pyrazole (3e). This compound was obtained as oil; IR (potassium bromide): 3396, 3073, 1591, 1442, 1290, 1099, 1032, 962, 809 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 6.50 (s, 1H, CH), 7.45 (d, *J* = 8.0 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.79 (d, *J* = 5.6 Hz, 1H, ArH), 12.83 (s, 1H, NH).

3-Methyl-5-(thiophen-2-yl)-1H-pyrazole (3f). This compound was obtained as solid with mp 115–117°C (lit. [21] 118–123°C); IR (potassium bromide): 3461, 3054, 2962, 1591, 1412, 1265, 1093, 1026, 792 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 6.31 (s, 1H, CH), 7.04 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.38 (d, *J* = 3.2 Hz, 1H, ArH), 12.51 (s, 1H, NH).

Scheme 2. The proposed mechanism for the synthesis of 5-aryl-1*H*-pyrazole derivatives.



1 2 4 5 3

5-(4-Bromophenyl)-3-methyl-1H-pyrazole (3g). This compound was obtained as solid with mp 128–130°C; IR (potassium bromide): 3443, 3086, 2856, 1584, 1433, 1288, 1074, 827 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 6.48 (s, 1H, CH), 7.60 (d, $J = 8.0$ Hz, 4H, ArH), 12.80 (s, 1H, NH).

1,5-Di(4-methoxyphenyl)-1H-pyrazole (3h). This compound was obtained as solid with mp 78–79°C; IR (potassium bromide): 3080, 2934, 2837, 1606, 1511, 1250, 1173, 1022, 828 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.42 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 6.53 (s, 1H, CH), 6.88–6.96 (m, 4H, ArH), 7.12–7.19 (m, 4H, ArH), 7.66 (s, 1H, CH).

5-(4-Chlorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3i). This compound was obtained as solid with mp 66–67°C; IR (potassium bromide): 3057, 2925, 1590, 1491, 1432, 1185, 1082, 1015, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 6.23 (s, 1H, CH), 7.05–7.07 (m, 2H, ArH), 7.17–7.28 (m, 7H, ArH).

3-Methyl-1,5-diphenyl-1H-pyrazole (3j). This compound was obtained as solid with mp 119–121°C (lit. [22] 124°C); IR (potassium bromide): 3058, 2926, 1596, 1498, 1370, 1183, 1018, 920 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 6.44 (s, 1H, CH), 7.19–7.22 (m, 4H, ArH), 7.32–7.39 (m, 6H, ArH).

5-(2,4-Dichlorophenyl)-3-methyl-1-phenyl-1H-pyrazole (3k). This compound was obtained as solid with mp 59–60°C; IR (potassium bromide): 3086, 2935, 1594, 1495, 1420, 1088, 811, 753, 676 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.29 (s, 3H, CH_3), 6.42 (s, 1H, CH), 7.15 (d, $J = 7.6$ Hz, 2H, ArH), 7.26 (t, $J = 7.2$ Hz, 1H, ArH), 7.33 (t, $J = 7.2$ Hz, 2H, ArH), 7.42–7.49 (m, 2H, ArH), 7.67 (s, 1H, ArH).

Acknowledgments. The authors are grateful to the National Natural Science Foundation of China (21072144), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 10KJA150049), A Project Funded by the Priority Academic Project Development of Jiangsu Higher Education Institutions and the Foundation of Key Laboratory of Organic Synthesis of Jiangsu Province (No. JSK0812), and the Key Project in Science and Technology Innovation Cultivation Program of Soochow University for their financial support.

REFERENCES AND NOTES

[1] (a) Amato, J. Science 1993, 259, 1538; (b) Illman, D. L. Chem Eng News 1993, 71, 5; (c) Illman, D. L. Chem Eng News 1994, 72, 22.

[2] (a) Li, C. J.; Chang, T. H. Organic Reactions in Aqueous Media; Wiley: New York, 1997; (b) Fringuell, F., Piematti, O., Pizzo, F., Vaccaro, L. Eur J Org Chem 2001, 439; (c) Stinson, S. C. Chem Eng News 1996, 74, 39.

[3] (a) Breslow, R.; Rideout, D. C. J Am Chem Soc 1980, 102, 7816; (b) Breslow, R. Acc Chem Res 1991, 24, 59.

[4] (a) Li, C. J. Chem Rev 1993, 93, 2023; (b) Li, C. J. Chem Rev 2005, 105, 1273.

[5] (a) Dandia, A.; Arya, K.; Sati, M.; Sarangi, P. J Fluorine Chem 2004, 125, 1273; (b) Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. Tetrahedron Lett 2005, 46, 7169; (c) Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T. J.; Shim, S. C.; Yoon, N. S. Tetrahedron 2000, 56, 7747; (d) Khadikar, B. M.; Gaikar, V. G.; Chitnavis, A. A. Tetrahedron Lett 1995, 36, 8083; (e) Cho, C. S.; Kim, J. H.; Shim, S. C. Tetrahedron Lett 2000, 41, 1811; (f) Totlani, V. M.; Peterson, D. G. J Agric Food Chem 2005, 53, 4130; (g) Wnorowski, A.; Yaylayan, V. A. J Agric Food Chem 2000, 48, 3549; (h) Bose, D. S.; Fatima, L.; Mereyala, H. B. J Org Chem 2003, 68, 587.

[6] (a) Behr, L. C.; Fusco, R.; Jarboe, C. H. in Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings; Wiley, R. H., Ed.; Interscience Publishers: New York, 1967; (b) Elguero, J. in Comprehensive Heterocyclic Chemistry; Katritaky, A. R.; Rees, C. W., Ed.; Pergamon: Oxford, 1984; Vol 5, p 167; (c) Elguero, J. in Comprehensive Heterocyclic Chemistry II; Katritaky, A. R.; Rees, C. W.; Scriven, E. F., Ed.; Pergamon: Oxford, 1996; Vol. 3, p 1.

[7] Mahajan, R. N.; Havaldar, F. H.; Fernandes, P. S. J Indian Chem Soc 1991, 68, 245.

[8] Janus, S. L.; Magdif, A. Z.; Erik, B. P.; Claus, N. Monatsh Chem 1999, 130, 1167.

[9] (a) Hatheway, G. J.; Hansch, C.; Kim, K. H.; Milstein, S. R.; Schimidt, C. L.; Smith, R. N.; Quin, F. R. J Med Chem 1978, 21, 563; (b) Katayama, H.; Oshiyama, T. Can J Chem 1997, 75, 913.

[10] Badawey, E.; El-Ashmawey, I. M. Eur J Med Chem 1998, 33, 349.

[11] Chen, H. S.; Li, Z. M. Chem J Chin Univ 1998, 19, 572.

[12] Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. J Med Chem 1985, 28, 256.

[13] (a) Cativiela, C.; Serrano, J. L.; Zurbano, M. M. J Org Chem 1995, 60, 3074; (b) Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K.; Hori, M.; Fujimura, H. J Med Chem 1977, 20, 80.

[14] Katritzky, A. R. Handbook of Heterocyclic Chemistry, Pergamon: New York, 1985, p 416.

[15] (a) Shi, D. Q.; Niu, L. H.; Shi, J. W.; Wang, X. S.; Ji, S. J. J Heterocyclic Chem 2007, 44, 1083; (b) Shi, D. Q.; Yao, H.; Shi, J. W. Synth Commun 2008, 38, 1662; (c) Shi, D. Q.; Mou, J.; Zhuang, Q. Y.; Niu, L. H.; Wu, N.; Wang, X. S. Synth Commun 2004, 34, 4557.

[16] (a) Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. Chem Commun 2010, 4330; (b) Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. J Org Chem 2010, 75, 5144; (c) Kaur, P.; Wever, W.; Pindi, S.; Milles, R.; Gu, P.; Shi, M.; Li, G. Green Chem 2011, 13, 1288.

[17] Kazumasa, T.; Yuko, U.; Katsuyuki, O.; Hirotada, I. Synthesis 1985, 690.

[18] Susann, B.; Gotthelf, W.; Harald, K.; Werner, T. R. Inorg Chim Acta 2008, 361, 2059.

[19] Jose, B.; Laudina, M.; Jose, L. M.; Vicente, G. J Chem Soc Perkin Trans 1, 1984, 611.

[20] Wang, Z. X.; Qin, H. L. Green Chem 2004, 6, 90.

[21] Valerio, P. Ann Chim 1957, 47, 929.

[22] Barry, W. J.; Flnar, I. L.; Simmonds, A. B. J Chem Soc 1956, 4974.