Microwave-Assisted Synthesis of Ethyl 1,3-Disubstituted-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylates

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Received June 5, 2011
DOI 10.1002/jhet.1115
Published online 00 Month 2013 in Wiley Online Library (wileyonlinelibrary.com).

1 **2**

A novel series of ethyl 1,3-disubstituted-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylates can be rapidly and efficiently synthesized in excellent yields by condensing a variety of 1,3-substituted-4-formyl-5-chloropyrazole with ethyl isocyanoacetate in the presence of 1-methyl-3-butylimidazolium hydroxide under microwave irradiation. The simple experimental procedure, DMSO-free condition, short period of conversion, and excellent yields are the advantages of the present method. The structures of the novel compounds are confirmed by IR, ^{1}H NMR, ^{13}C NMR, MALDI-TOF MS, and elemental analysis.

J. Heterocyclic Chem., **00**, 00 (2013).

INTRODUCTION

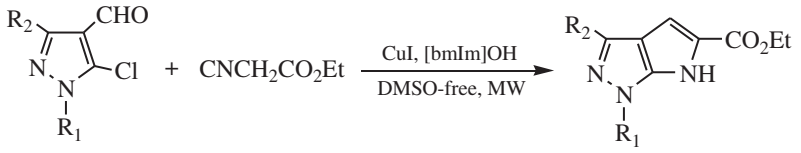
Nitrogen-containing heteroaromatic molecules and their analogs are pharmaceutically significant scaffolds, widely present in naturally occurring and synthetic biologically active molecules [1]. Among these heterocycles, pyrazole and its derivatives are important heterocyclic compounds, which show a broad spectrum of biological activities such as antimicrobial [2], herbicidal [3], antitumor [4], and anti-inflammatory activities [5]. In our design of new inhibitors of aspartyl protease [6], we were interested in differently substituted ethyl 1,3-disubstituted-1,6-dihydropyrrolo[2,3-c] pyrazole-5-carboxylates. To the best of our knowledge, only one method exists for the synthesis of these compounds. The method involves the condensation between an arylaldehyde and an azidoacetate to provide *a*-azidocinnamates, which upon heating give ethyl 1,3-disubstituted-1,6-dihydropyrrolo [2,3-c]pyrazole-5-carboxylates [7]. One problem is associated with employing high boiling solvent. In addition, the yield of the reaction is low. Therefore, it is necessary to further develop a practical method for the synthesis of such a significant scaffold.

Recently, it was reported that the reaction 2-halo aryl aldehydes or ketones with ethyl isocyanoacetate under the catalysis of CuI afforded indole-2-carboxylic acid esters [8]. According to the structure of ethyl 1,3-disubstituted-1, 6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylates, we envisioned that 1,3-substituted-4-formyl-5- chloropyrazole may be used to react with isocyanoacetate under the catalysis of CuI to synthesize such products. Although Cai [8] developed a copper-catalyzed cascade process from 2-chloro heteroaryl ketones with ethyl isocyanoacetate, the low yield and the long reaction time make it less attractive synthetically. Herein, we report a simple and efficient reaction of ethyl isocyanoacetate with 1,3-substituted-4-formyl- 5-chloropyrazole via microwave irradiation in the presence of 1-methyl-3-butylimidazolium hydroxide ([bmIm]OH). The synthetic sequence is depicted in Scheme 1.

RESULTS AND DISCUSSION

Initial studies were carried out using 1-phenyl-3-methyl-4-formyl-5-chloro-pyrazole as the substrate and isocyanoacetate as the nitrogen source in DMSO/NaOH under the catalysis of CuI (12 mol%) at 120°C for 12 h, the desired product ethyl 1-phenyl-3-methyl-1,6-dihydropyrrolo[2,3-c] pyrazole-5-carboxylate was obtained in a low yield (34%). Microwave-assisted organic synthesis has shown to be a valuable tool for reducing reaction times, improving yields, and is proving quite successful in the formation of a variety of carbon–heteroatom and carbon–carbon bonds [9]. In view of this, when the reaction under microwave irradiation is performed, high yield was reached. Encouraged by the result, we replaced DMSO/NaOH with [bmIm]OH. To our delight, substrate **1a** also successfully rendered the corresponding product in high yield (entries 2 and 3 of Table 1). Further investigations were aimed at determining the optimal conditions by changing the reaction time, as well as altering the reaction temperature. Increasing or decreasing the reaction time did not improve the yield of the desired product. It was found that 60°C was the optimal reaction temperature. Finally, the optimal condition was determined to be 12 mol % CuI at 60°C for 10 min in [bmIm]OH under microwave

Scheme 1



1 **2**

2a R_1= Ph, R_2 = Me; **2b** R_1 = p-Cl-Ph, R_2 = Me;
2c R_1= p-MeO-Ph, R_2 = Me; **2d** R_1 = p-NO_2-Ph, R_2 = Me;
2e R_1= p-Me-Ph, R_2 = Me; **2f** R_1 = Me, R_2 = Me;
2g R_1= Me, R_2 = p-Me-Ph; **2h** R_1= Me, R_2 = p-Cl-Ph

irradiation. Having these optimized reaction conditions in hand, other Cu reagents, such as CuBr or CuCl, were investigated. The results showed that replacement of CuI with CuBr slightly affected the outcome of this reaction. CuCl was less active (entries 4 and 5, Table 1). When other copper sources such as Cu_2O and $Cu(OAc)_2$ were used, no desired product was detected.

The substitution variations of substrates were then investigated. To our satisfaction, the reaction shows a wide scope for the structural variation of R_1 and R_2 groups under the optimized reaction conditions. Both electron-donating and electron-withdrawing groups allowed smooth transformation of 1,3-substituted-4-formyl-5-chloropyrazole into the corresponding products with high yields.

In conclusion, in this study, we have developed a convenient and efficient method for the synthesis of ethyl 1,3-disubstituted-1,6-dihydropyrrolo[2,3-c]pyrazole-5- carboxylates by condensation of ethyl isocyanoacetate with 1,3-substituted-4-formyl-5-chloropyrazole in the presence of [bmIm]OH under microwave irradiation. The simple experimental procedure, DMSO-free reaction conditions, and high yields are the advantages of the present method.

EXPERIMENTAL

Reagents were obtained commercially and used as received. Solvents were purified and dried by standard methods. [bmIm]OH was synthesized according to the method described in the literature [10]. 1,3-Substituted-4-formyl-5-chloropyrazole was synthesized according to Du *et al*. [11]. Microwave reactions were performed on a CEM Explorer Hybrid 12/Discover (Pynn, USA), with built in temperature/pressure probes and associated software. The melting points were determined on an XT-4 (Beijing Tech, China) micro melting point apparatus and were uncorrected. IR spectra were recorded on an EQUINOX-55 (Bruker, Germany) spectrometer on a KBr matrix. NMR spectra were recorded on an INOVA-400 (Varian, USA) NMR instrument at room temperature using TMS as internal standard. Coupling constants (J) were measured in Hz. Chemical shift values (d) are given in ppm. Elemental analyses were performed on a Vario EL III (Germany) CHNS analyzer. Electrospray mass spectra were obtained with an MALDI-TOF (Kratos, UK) mass spectrometer. For column chromatography, 200–300 mesh silica gel was used.

General procedure for the preparation of 2. An oven-dried 10-mL microwave vial was charged with CuI (0.24 mmol), [bmIm]OH (2 mL), 1,3-substituted-4-formyl-5-chloropyrazole (1 mmol) **1**, and ethyl isocyanoacetate (1.1 mmol), with an addition of a stirrer bar. The reaction vessel was sealed, evacuated, and flushed with argon three times. The mixture was irradiated by 100-W microwave at 60°C for 10 min. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography with ethyl acetate/petroleum ether as eluent on silica gel to afford the desired products.

Ethyl 1-phenyl-3-methyl-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2a). White powder, mp 102–103°C; IR (KBr) ν: 3331, 3018, 2973, 1715, 1501, 1194, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.87 (br s, 1H), 7.37–7.41 (m, 5H), 6.46 (dd, J = 2.4 Hz, 1H), 4.43 (q, J = 4.8 Hz, 2H), 2.43 (s, 3H), 1.43 (t, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 142.3, 141.7, 134.3, 130.7, 129.2, 127.1, 126.6, 109.5, 61.0, 14.9, 13.8; MALDI-TOF MS: m/z = 269 (M^+). *Anal*. Calcd for $C_{15}H_{15}N_3O_2$: C 66.90, H 5.61, N 15.60. Found: C 66.88, H 5.63, N 15.51.

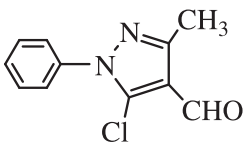
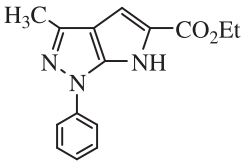
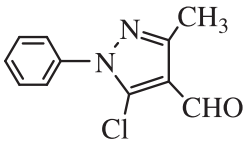
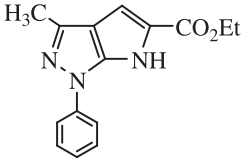
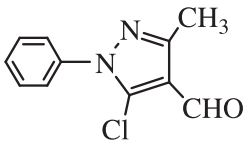
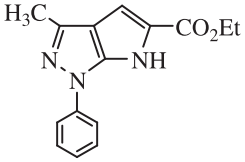
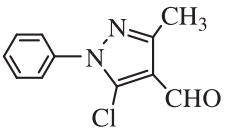
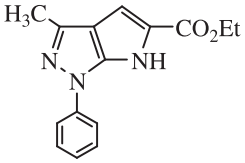
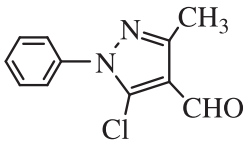
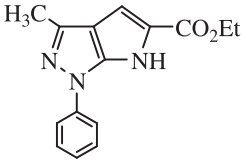
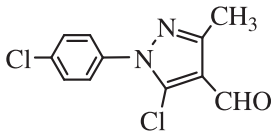
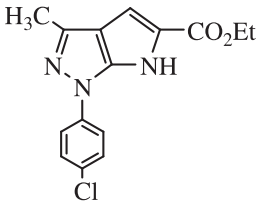
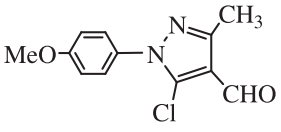
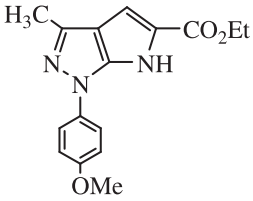
Ethyl 1-(4-chloro-phenyl)-3-methyl-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2b). White powder, mp 117–119°C; IR (KBr) ν: 3329, 3021, 2929, 1710, 1499, 1241, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.81 (br s, 1H), 7.33 (d, J = 1.6 Hz, 2H), 7.11 (d, J = 1.6 Hz, 2H), 6.41 (dd, J = 2.8 Hz, 1H), 4.47 (q, J = 4.8 Hz, 2H), 2.49 (s, 3H), 1.39 (t, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.1, 142.5, 141.2, 135.7, 133.8, 129.3, 128.9, 128.0, 127.3, 108.4, 61.5, 14.7, 13.6; MALDI-TOF MS: m/z = 303 (M^+); *Anal*. Calcd for $C_{15}H_{14}ClN_3O_2$: C 59.31, H 4.65, N 13.83. Found: C 59.33, H 4.62, N 13.86.

Ethyl 1-(4-methoxy-Phenyl)-3-methyl-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2c). White powder, mp 121–122°C; IR (KBr) ν: 3343, 3055, 2925, 1707, 1492, 1225, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.81 (br s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.49 (dd, J = 2.8 Hz, 1H), 4.39 (q, J = 4.8 Hz, 2H), 3.83 (s, 3H), 2.51 (s, 3H), 1.40 (t, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.8, 141.9, 141.0, 135.3, 133.7, 129.3 128.6, 128.1, 127.4, 109.3, 60.7, 55.1, 14.9, 13.9; MALDI-TOF MS: m/z = 299 (M^+); *Anal*. Calcd for $C_{16}H_{17}N_3O_3$: C 64.20, H 5.72, N 14.04. Found: C 64.23, H 5.69, N 14.05.

Ethyl 1-(4-nitrol-phenyl)-3-methyl-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2d). Pale yellow powder, mp 127–129°C; IR (KBr) ν: 3347, 3041, 2927, 1710, 1502, 1497,

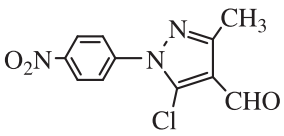
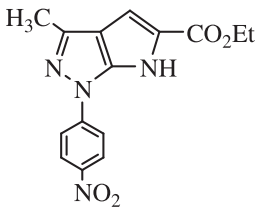
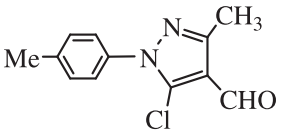
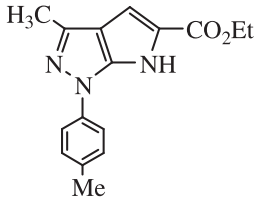
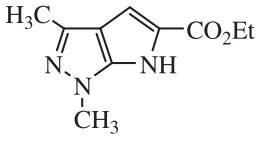
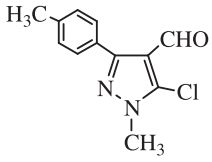
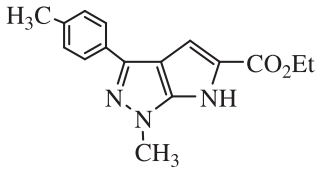
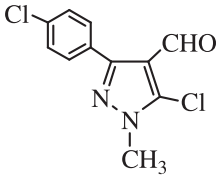
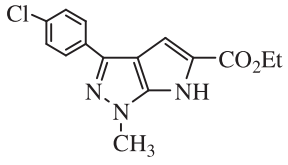
Table 1

Reactions of 1,3-substituted-4-formyl-5-chloropyrazole with ethyl isocyanoacetate.

Entry	Substrate	Product	Yield (%)[a]
1[b]			34
2[c]			89
3			90
4[d]			85
5[e]			79
6			91
7			87
8			92

(*Continued*)

Table 1
(Continued)

Entry	Substrate	Product	Yield (%)[a]
			
9			89
10			89
11			89
12			91

Reaction conditions: CuI (0.24 mmol), [bmIm]OH (2 mL), 4-formyl-5-chloropyrazole (1 mmol), ethyl isocyanoacetate (1.1 mmol), Ar atmosphere, microwave irradiation, 60°C, 10 min.
[a]Isolated yields.
[b]CuI (0.24 mmol), DMSO (1 mL), NaOH (3.0 mmol), 4-formyl-5-chloropyrazole (1 mmol), ethyl isocyanoacetate (1.1 mmol), 100°C, 12 h, Ar atmosphere.
[c]CuI (0.24 mmol), DMSO (1 mL), NaOH (3.0 mmol), 4-formyl-5-chloropyrazole (1 mmol), ethyl isocyanoacetate (1.1 mmol), microwave irradiation, 60°C, 10 min, Ar atmosphere.
[d]CuBr as catalyst.
[e]CuCl as catalyst.

1341, 1229, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.93 (br s, 1H), 7.91 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 7.2 Hz, 2H), 6.54 (dd, J = 2.8 Hz, 1H), 4.41 (q, J = 4.0 Hz, 2H), 2.37 (s, 3H), 1.44 (t, J = 4.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5, 143.6, 141.7, 141.4, 134.1, 130.2, 129.4, 129.1, 127.8, 109.5, 60.9, 15.1, 14.0; MALDI-TOF MS: m/z = 314 (M^+); *Anal*. Calcd for $C_{15}H_{14}N_4O_4$: C 57.32, H 4.49, N 17.83. Found: C 57.34, H 4.46, N 17.81.

Ethyl 1-(4-methyl-phenyl)-3-methyl-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2e). White powder, mp 107–109°C; IR (KBr) ν: 3347, 3031, 2927, 1711, 1497, 1223, 829 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.89 (br s, 1H), 7.19 (d, J = 7.2 Hz, 2H), 6.96 (d, J = 7.2 Hz, 2H), 6.44 (dd, J = 2.0 Hz, 1H), 4.45 (q, J = 4.8 Hz, 2H), 2.39 (s, 3H), 2.17 (s, 3H),1.40 (t, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4, 141.5, 141.1, 135.3, 133.3, 130.7, 129.6, 128.9, 127.5,

108.7, 60.3, 20.9, 15.3, 14.1; MALDI-TOF MS: $m/z = 283$ (M^+); *Anal*. Calcd for $C_{16}H_{17}N_3O_2$: C 67.83, H 6.05, N 14.83. Found: C 67.77, H 6.11, N 14.81.

Ethyl 1,3-dimethyl-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2f). White powder, mp 95–97°C; IR (KBr) ν: 3340, 2925, 1707, 1223, 925 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.77 (br s, 1H), 6.37 (dd, $J = 2.8$ Hz, 1H), 4.36 (q, $J = 5.6$ Hz, 2H), 2.91 (s, 3H), 2.21 (s, 3H),1.33 (t, $J = 5.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.1, 140.7, 140.2, 128.8, 127.3, 108.1, 60.4, 40.5, 14.8, 13.9; MALDI-TOF MS: $m/z = 207$ (M^+); *Anal*. Calcd for $C_{10}H_{13}N_3O_2$: C 57.96, H 6.32, N 20.28. Found: C 57.93, H 6.29, N 20.24.

Ethyl 1-methyl-3-(4-methyl-phenyl)-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2g). White powder, mp 114–116°C; IR (KBr) ν: 3353, 3039, 2931, 1703, 1503, 1227, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.85 (br s, 1H), 7.32 (d, $J = 9.0$ Hz, 2H), 7.08 (d, $J = 9.0$ Hz, 2H), 6.53 (dd, $J = 3.0$ Hz, 1H), 4.42 (q, $J = 7.2$ Hz, 2H), 2.93 (s, 3H), 2.10 (s, 3H),1.36 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 142.9, 141.7, 136.4, 135.2, 131.1, 130.9, 129.6, 128.4, 127.3, 60.1, 40.3, 20.2, 13.9; MALDI-TOF MS: $m/z = 306$ $[M + Na]^+$; *Anal*. Calcd for $C_{16}H_{17}N_3O_2$: C 67.83, H 6.05, N 14.83. Found: C 67.89, H 6.03, N 14.79.

Ethyl 1-methyl-3-(4-chloro-phenyl)-1,6-dihydropyrrolo[2,3-c]pyrazole-5-carboxylate (2h). White powder, mp 111–113°C; IR (KBr) ν: 3353, 3047, 2931, 1713, 1503, 1227, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.78 (br s, 1H), 7.36 (d, $J = 2.4$ Hz, 2H), 7.17 (d, $J = 2.4$ Hz, 2H), 6.58 (dd, $J = 2.8$ Hz, 1H), 4.33 (q, $J = 4.8$ Hz, 2H), 3.03 (s, 3H), 1.42 (t, $J = 4.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 142.3, 141.4, 135.8, 134.6, 131.3, 130.6, 129.1, 127.8, 126.9, 60.4, 40.8, 14.0; MALDI-TOF MS: $m/z = 303$ (M^+); *Anal*. Calcd for $C_{15}H_{14}ClN_3O_2$: C 59.31, H 4.65, N 13.83. Found: C 59.29, H 4.67, N 13.80.

Acknowledgment. The authors thank the Youth Fund of Yunnan University of Nationalities (no. 09QN04) for the financial support.

REFERENCES AND NOTES

[1] Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. Chem Rev 2008, 108, 264.

[2] Velaparthi, S.; Brunsteiner, M.; Uddin, R.; Wan, B.; Franzblau,S. G.; Petukhov, P. A. J Med Chem 2008, 51, 1999.

[3] Vicentini, C. B.; Guccione, S.; Giurato, L.; Ciaccio, R.; Mares, D.; Forlani, G. J Agric Food Chem 2005, 53, 3848.

[4] Magedov, I. V.; Manpadi, M.; Van slambrouck, S.; Steelant, W. F. A.; Rozhkova, E.; Przheval'skii, N. M.; Rogelj, S.; Kornienko, A. J Med Chem 2007, 50, 5183.

[5] Rovnyak, G. C.; Millonig, R. C.; Schwartz, J.; Shu, V. J Med Chem 1982, 25, 1482.

[6] (a) Gu, L. J.; Liu, F. L.; Li, X. G.; Gao, B.; Yang, B. Q. Synth Commun 2010, 40, 242; (b) Gu, L. J.; Liu, F. L.; Yang, B. Q. J Braz Chem Soc 2010, 21, 58.

[7] El-Saied, A. A.; El-Borai, M. A.; Barren, M. A. Chem Abstr 2004, 142, 261453

[8] Cai, Q.; Li, Z. Q.; Wei, J. J.; Ha, C. Y.; Pei, D. Q.; Ding, K. Chem Commun 2009, 46, 7581.

[9] Varma, R. S. J Heterocycl Chem 1999, 36, 1565.

[10] Ranu, B. C.; Banerjee, S. Org Lett 2005, 7, 3049.

[11] Du, H. T.; Ouyang, G. P.; Du, H. J.; Shi, D. B.; Jin, L. H. Chin J Org Chem 2006, 26, 383.