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Straightforward copper-catalyzed synthesis of pyrrolopyrazoles from halogenated pyrazolecarbaldehydes ☆

Maloy Nayak, Harikrishna Batchu, Sanjay Batra *

Medicinal and Process Chemistry Division, CSIR–Central Drug Research Institute, PO Box 173, Lucknow 226001, UP, India

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ABSTRACT

Straightforward synthesis of a variety of pyrrolo-fused pyrazoles via a cascade reaction between halopyrazolecarbaldehydes and ethylisocyanoacetate in the presence of copper and a base is described.

The pyrazole ring system is considered to be of great significance because it is represented in several compounds ascribed with pharmacological and agricultural properties.[1] In recent times there has been considerable interest in the development of newer strategies to obtain substituted and annulated pyrazoles.[2] Among the strategies for preparing annulated pyrazole systems, halogenated pyrazoles are regarded as important building blocks because of their potential to undergo a variety of transition-metal based coupling reactions.[3,2c,f,1e] In a project directed toward studies related to development of strategies for generating annulated pyrazoles via transition metal-mediated coupling reactions we have achieved significant success. Whereas copper-mediated intramolecular C–N coupling in pyrazoles gives easy access to pyrazolo[4,3-*b*]pyridin-5-ones, pyrazolo[4,3-*b*]pyridines, pyrazolo-fused benzodiazepines and benzoxazoazepines, pyrazolo[4,3-*d*]pyrimidines and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones,[4] palladium mediated heteroarylation of the heteroarene C–H bond in pyrazoles leads to a variety of pyrazolo fused-azepines.[5] In continuation of our exploration related to copper mediated C–N coupling reactions in halogenated pyrazoles we envisaged that a reaction between 4-iodopyrazolecarbaldehyde and ethylisocyanoacetate would result into pyrrole-fused pyrazole derivatives. Our reasoning stemmed from the previous report of Cai et al. where they have synthesized indole-2-carboxylic acid esters using similar strategy.[6]

The pyrrole-fused pyrazoles were earlier prepared by treating the pyrazolecarbaldehyde with ethyl azoacetate followed by thermal cyclization (Fig. 1).[7] However as the copper-promoted tandem process for heterocyclic synthesis is of current interest[8] and we were interested in exploring the participation of the halogenated pyrazoles for C–N coupling we decided to proceed to investigate our strategy. We report herein straightforward synthesis of a variety of pyrrolopyrazoles via sequential condensation, coupling, and deformylation process.

We initiated the investigation by studying the reaction of 1,5-biphenyl-4-iodo-3-pyrazolecarbaldehyde **1** and ethylisocyanoacetate **2** as a model under the reported conditions. It was gratifying

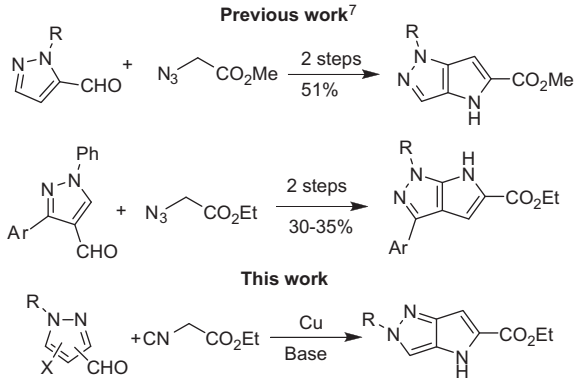

Figure 1. Strategies for the synthesis of pyrrole-fused pyrazoles.

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* Corresponding author. Tel.: +91 522 2612411 18x4234/4368; fax: +91 522 2623405.

E-mail addresses: s_batra@cdri.res.in, batra_san@yahoo.co.uk (S. Batra).

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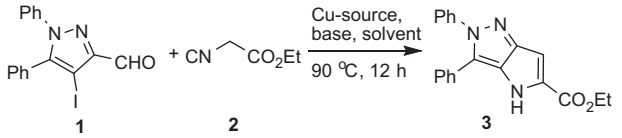
Table 1
Optimization of reaction conditions with respect to catalyst, base, and solvent[a]



1 2 3

Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	CuI	Cs_2CO_3	DMSO	70
2	CuI	Cs_2CO_3	DMF	75
3	CuI	Cs_2CO_3	Toluene	12
4	CuI	K_2CO_3	DMF	43
5	CuI	K_3PO_4	DMF	36
6	Cu_2O	Cs_2CO_3	DMF	56
7	CuCl	Cs_2CO_3	DMF	59
8	CuBr	Cs_2CO_3	DMF	62

[a] Reaction conditions: 4-iodo-3-pyrazolecarbaldehyde (0.67 mmol), ethylisocyanoacetate (0.67 mmol), Cu-source (0.13 mmol), base (1.34 mmol), solvent (4 mL), 90 °C, 12 h under nitrogen atmosphere.
[b] Isolated yields.

Table 2
Scope of the protocol[a]

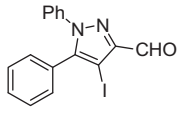
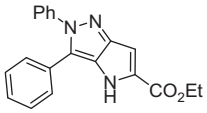
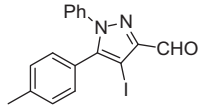
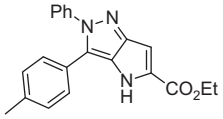
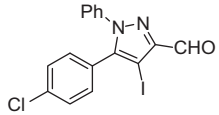
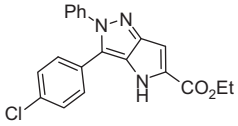
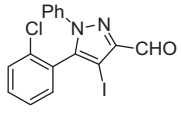
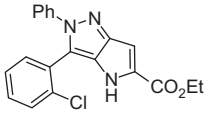
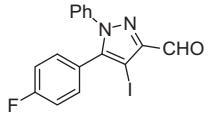
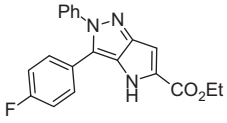
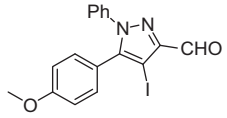
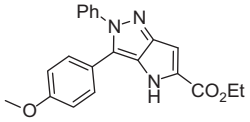
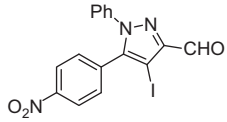
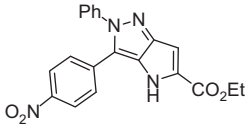
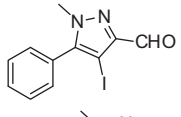
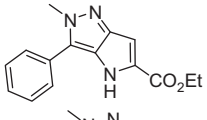
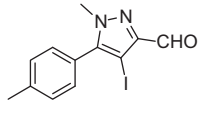
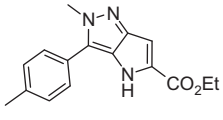
Entry	Aldehyde	Product	Yield[b] (%)
1			75
2			79
3			71
4			80
5			68
6			70
7			78
8			74
9			75

Table 2 (*continued*)

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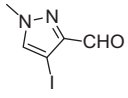
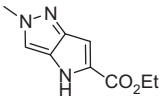
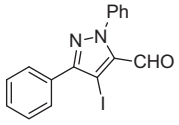
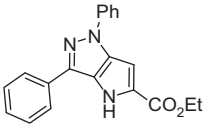
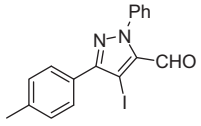
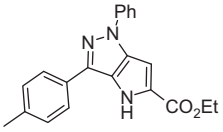
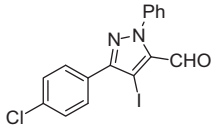
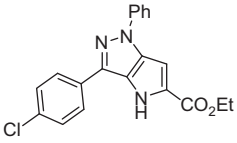
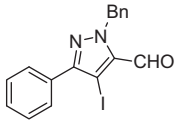
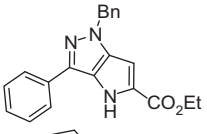
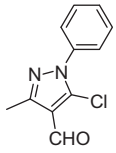
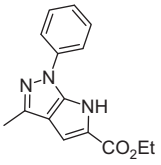
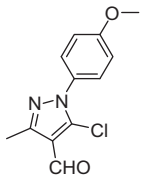
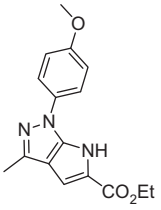
10			68
11			70
12			73
13			74
14			76
15			67
16			70

[a] Reaction conditions: halo pyrazolecarbaldehyde (1.0 mmol), ethylisocyanoacetate (1.0 mmol), Cu-source (0.2 mmol), base (2.0 mmol), solvent (4 mL), 90 °C, 12 h under nitrogen atmosphere.
[b] Isolated yields.

to note that the required product **3** was isolated in 70% yield in the presence of 10% of CuI (Table 1, entry 1). The reaction was unsuccessful in the absence of copper. Optimization with respect to solvent and base indicated that the reaction proceeded efficiently in the presence of Cs_2CO_3 as base and DMF as solvent (Table 1, entry 2). Other Cu(I) salts including Cu_2O, CuCl, and CuBr though were effective, gave inferior results (Table 1, entries 6–8). Hence the optimized reaction conditions were CuI (10 mol %), Cs_2CO_3 (2.0 equiv) in DMF at 90 °C for 12 h under nitrogen atmosphere (Table 1, entry 2).

Under these optimized conditions,[9] we set out to investigate the scope of the protocol and the results are presented in Table 2. It is noteworthy that all halogenated pyrazolecarbaldehydes undergo the reaction to afford the respective pyrrolo-fused pyrazole products. It was observed that the substitutions on the pyrazole have no bearing on the outcome of the reaction. The regioisomeric pyrazole derivatives gave comparable yields (entries 1–3 and 11–13). It was also observed that the nature of halo group (I or Cl) present on the pyrazole nucleus reacted with almost equal efficiency (for I entries 1–14, for Cl entries 15 and 16).

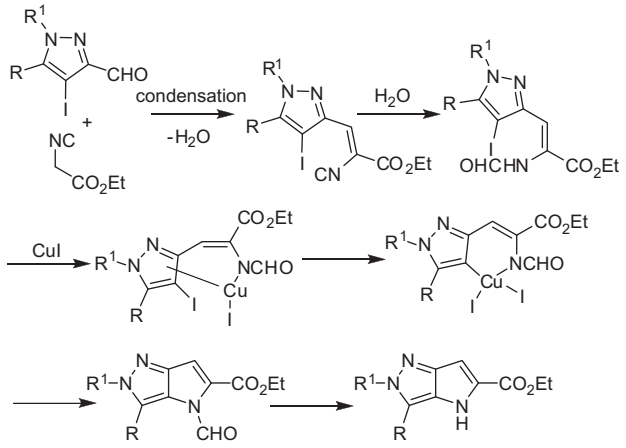


Figure 2. Plausible mechanism for the formation of pyrrolo-fused pyrazoles.

Mechanistically, first the condensation reaction between the aldehyde and ethylisocyanoacetate takes place followed by addition of water to the isonitrile moiety. Subsequent Cu-mediated C–N cross coupling and deformylation afforded the pyrrolo-fused pyrazole (Fig. 2). We presume that here too the Cu-catalyzed coupling reaction was successful because it was intramolecular in nature.

In summary, we have demonstrated the synthesis of a variety of pyrrolo-fused pyrazoles from halogenated pyrazolecarbaldehydes via a Cu-mediated cascade process in one-step. The strategy is versatile as all types of halogenated pyrazoles irrespective of substitutions and type of halogen gave products in comparable yields.

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedures, spectroscopic data of remaining compounds and copies of ^{1}H and ^{13}C NMR of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.148.

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9. *General procedure as exemplified for the synthesis of ethyl 2,3-diphenyl-2,4-dihydropyrrolo[3,2-c]pyrazole-5-carboxylate* (Table 2, entry 1): To a solution of 4-iodo-1,5-diphenyl-1*H*-3-pyrazolecarbaldehyde (250 mg, 0.67 mmol) and ethylisocyanoacetate (0.073 mL, 0.67 mmol) in DMF (4 mL), Cs_2CO_3 (434 mg, 1.34 mmol) and CuI (25 mg, 0.0134 mmol) were added and the reaction mixture was heated at 90 °C for 12 h under nitrogen atmosphere. Thereafter, water (50 mL) and EtOAc (25 mL) was added and the reaction mass was passed through a Celite bed and the layers were separated. The aqueous layer was further extracted with EtOAc (2 × 20 mL) and the collected organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Column chromatography of the crude product over silica gel furnished the pure ethyl 2,3-diphenyl-2,4-dihydropyrrolo[3,2-c]pyrazole-5-carboxylate as a white solid (EtOAc:hexanes, 1:9; yield: 166 mg, 75 %). Mp 192–194 °C; R_f = 0.61 (EtOAc:hexanes, 30:70, v/v); ν_{max} (KBr) 1699 (CO_2Et), 3067 (NH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.42 (t, 3H, J = 7.1 Hz, CH_3), 4.42 (q, 2H, J = 7.1 Hz, CH_2), 7.02 (d, 1H, J = 0.9 Hz, ArH), 7.28–7.31 (m, 2H, ArH), 7.34–7.45 (m, 8H, ArH), 8.27 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 14.5, 61.4, 100.1, 122.8, 125.9, 127.9, 128.0, 128.5, 128.6, 129.0, 129.1, 129.8, 134.4, 141.1, 149.0, 162.3; mass (ES+) m/z = 332.2; ESI-HRMS Calcd for $C_{20}H_{18}N_3O_2[MH]^+$: 332.1399. Found 332.1399.