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A simple method for the preparation and selective functionalization of 4,5-diaminopyrazoles

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Abstract—A simple procedure for the synthesis and further functionalization of 4,5-diaminopyrazoles using mild conditions is reported herein. The desired products were obtained in good yield, and the structures have been confirmed by X-ray crystallography. © 2003 Published by Elsevier Science Ltd.

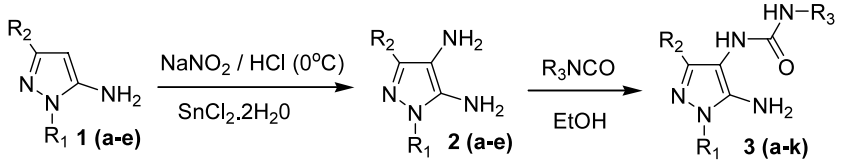
Aromatic amines, particularly diamines, are widely used as intermediates in the preparation of important materials such as pharmaceuticals, agricultural chemicals, and dyes. We have recently become interested in 4,5-diaminopyrazoles, as they, and their derivatives, have been shown to possess a wide range of interesting biological properties including PAF-antagonism, anticancer, anti-HIV, antiasthmatic and anti-inflammatory activity.[1] Various 4,5-diaminopyrazole derivatives have been reported as intermediates in the preparation of 1,2,4-triazoles[2], imidazo[4,5-c]pyrazoles[3], and benzodiazepines[4], an important class of psychotherapeutic compounds. In addition, this class of compounds has found wide use in the hair dye industry.[5] There have been a limited number of synthetic approaches to 4,5-diaminopyrazoles reported in the literature, including preparation from azopyrazole with the application of sodium dithionite.[6] Palladium catalyzed reduction of nitrosopyrazole derivatives with both hydrazine and hydrogen has also been reported.[7]

We wish to report a mild procedure for the synthesis of various 4,5-diaminopyrazoles and their simple conversion to 5-amino-4-pyrazolyl ureas. Thus, commercially available 5-aminopyrazoles (**1a–e**) were oxidized with sodium nitrite in the presence of dilute hydrochloric acid at 0°C, and the resulting nitroso intermediates were subsequently reduced in situ with stannous chloride dihydrate to provide the desired 4,5-diaminopyrazoles in fair to excellent yield (**2a–e**, Scheme 1, Table 1).

Further functionalization of **2a–e** was then easily accomplished by condensation with an isocyanate in ethanol to provide the corresponding urea derivative **3** (Table 2). Surprisingly, the reactions were highly selective, as only one of the two possible urea regioisomers

Table 1. Formation of 4,5-diaminopyrazoles[8]

Entry	R_1	R_2	Yield (%)
2a	Ph	Me	90
2b	*p*-Tolyl	*t*-Butyl	94
2c	Ph	Ph	50
2d	Me	Ph	86
2e	Me	Me	50



Scheme 1.

Keywords: 4,5-diaminopyrazoles; nitrosation; urea derivatives.
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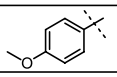
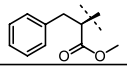
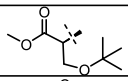
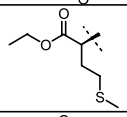
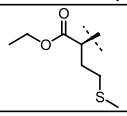
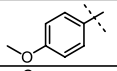
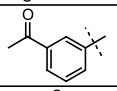
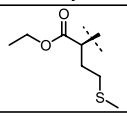
Table 2. Functionalization of 4,5-diaminopyrazoles[9]

Entry	R_1	R_2	R_3	Isolated Yield (%)
3a	Ph	Me	Ph	50
3b	Ph	Me		78
3c	Ph	Me		71
3d	Ph	Me	n-Bu	70
3e	Ph	Me		63
3f	Ph	Me		61
3g	p-Tolyl	t-Butyl		56
3h	p-Tolyl	t-Butyl		67
3i	Ph	Ph		51
3j	Me	Ph		90
3k	Me	Me	n-Bu	53

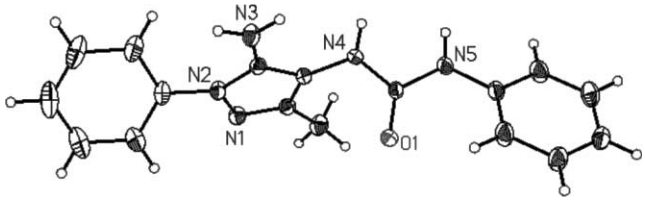


Figure 1. X-Ray crystal structure of **3a**.

was observed. Condensation of the isocyanate with the 4-amino group dominates the reaction as indicated by X-ray crystal structure, Figure 1. This is most likely due to the decreased nucleophilicity of the 5-amino substituent of the amino pyrazole.

In summary, we have developed an efficient and simple procedure for the preparation of 4,5-diaminopyrazoles and their selective conversion to the corresponding mono-urea derivatives in good yield.

References

1. (a) Fray, M. J.; Bull, D. J.; Cooper, K.; Parry, M. J.; Stefaniak, M. H. *J. Med. Chem.* **1995**, *38*, 3524–3535; (b) Makarov, Y. 14th International Symposium on Medicinal Chemistry, Maastricht, The Netherlands, 8–12 September 1996; (c) Daidone, G.; Maggio, B.; Raffa, D.; Plescia, S. Schillaci 1st Italian–Swiss Meeting on Medicinal Chemistry, Turin, Italy, 23–26 September 1997; (d) Namiki, T.; Yuasa, M.; Takakuwa, T.; Ichinomiya, S.; Kawasu, Y.; Kishii, K. WO9833799 A1, 1998.
2. Moderhack, D. *Liebigs Ann.* **1996**, 777–779.
3. Vicentini, C. B.; Veronese, A. C.; Giori, M. G. *Tetrahedron Lett.* **1998**, *29*, 6171–6172.
4. Braulio, I. O.; Henry, I. I.; Jairo, Q. P. *J. Heterocyclic Chem.* **1999**, *36*, 635–638.
5. (a) Goettel, O.; Pirrello, A.; Hayoz, A.; Morand, E. EP 1236460 A1, 2002; (b) Braun, H. J. DE 19643059 A1, 1998; (c) Malle, G.; Vidal, L.; Samain, H. EP 796850 A1, 1997; (d) Weinges, A.; Balzer, W. R.; Gerstung, S.; Gerstung, S. D. DE 4422603 A1, 1996; (e) Jean, C. WO 0251373 A1, 2002; (f) Javet, M.; Dousse, C.; Le, C. D. DE 10109806 A1, 2002.
6. Eid, E. E.; Bonner, T. G.; Lewis, D. *J. Heterocyclic Chem.* **1983**, *20*, 1501–1503.
7. (a) Vicentini, C. B.; Ferretti, V.; Veronese, A. C.; Guarneri, M.; Manfrini, M.; Giori, P. *Heterocycles* **1995**, *41*, 497–506; (b) Fray, M.; Bull, D. J.; Kinns, M. *J. Chem. Res. Synop.* **1992**, *1*, 10–11.
8. Typical procedure (**2b**): A solution of $NaNO_2$ (260 mg, 3.77 mmol) in water (2.5 mL) was added drop wise to a solution of 5-amino-3-tert-butyl-1-*p*-tolyl pyrazole (HCl salt, 1.0 g, 3.77 mmol) in aqueous 0.8 N HCl (50 mL) at 0°C. The solution was stirred at 0°C for 10 minutes and then a solution of stannous chloride dihydrate (3.40 g, 15.1 mmol) in conc. HCl (20 mL) was added slowly. The resultant reaction mixture was allowed to warm slowly to room temperature and stirred for 15 minutes. The solution was then basified with NaOH and extracted with EtOAc

(3×100 mL). The combined extracts were dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the desired product **2b** (868 mg, 94%). The product obtained could be carried to the next step without purification. Spectral data for Table 1. Entry **2a** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 2.23 (s, 3H), 7.42–7.58 (m, 5H). (M^+H) 189. Entry **2b** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.31 (s, 3H), 7.26–7.46 (m, 4H). (M^+H) 245. Entry **2c** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 7.55–7.72 (m, 6H), 7.81 (d, $J=7.30$ Hz, 2H), 7.98 (d, $J=7.10$ Hz, 2H). (M^+H) 251. Entry **2d** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 3.63 (s, 3H), 7.27 (m, 2H), 7.37 (t, $J=5.5$ Hz, 1H), 7.68 (d, $J=7.0$ Hz, 2H). (M^+H) 189. Entry **2e** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 3.71 (s, 3H). (M^+H) 127.

9. Typical procedure (**3a**): 4,5-Diamino-3-methyl-1-phenyl pyrazole **2a** (100 mg, 0.53 mmol) was dissolved in EtOH (20 mL) followed by the addition of phenyl isocyanate (63.13 mg, 0.53 mmol). The resulting reaction mixture was stirred at room temperature for 2 hours. Solvent was evaporated and the crude residue was purified over preparative HPLC affording **3a** in 50% yield (Rf 0.30, 5% MeOH-DCM). Spectral data for Table 2. Entry **3a** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 2.60 (s, 3H), 6.80–7.55 (m, 10H). (M^+H) 308. Entry **3b** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.79 (s, 3H), 6.83 (d, $J=8.5$ Hz, 2H), 7.23 (d, $J=8.5$ Hz, 2H), 7.50–7.60 (m, 5H). (M^+H) 338. Entry **3c** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 2.10 (s, 3H), 3.13 (dd, $J=5.5$ Hz each, 2H), 3.71 (s, 3H), 4.65 (br s, 1H), 7.12 (d, $J=6.67$ Hz, 2H), 7.38–7.50 (m, 8H). (M^+H) 394. Entry **3d** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 0.95 (t, $J=7.20$ Hz, 3H), 1.29 (m, 2H), 1.45 (m, 2H), 2.23 (s, 3H), 3.17 (t, $J=7.0$ Hz, 2H), 7.50–7.62 (m, 5H). (M^+H) 288. Entry **3e** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 1.11 (s, 9H), 2.21 (s, 3H), 3.71 (s, 3H), 3.84 (dd, $J=3.0$ Hz each, 2H), 4.52 (br s, 1H), 7.44–7.56 (m, 5H). (M^+H) 390. Entry **3f** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 1.28 (t, $J=7.13$ Hz, 3H), 2.09 (s, 3H), 2.21 (s, 3H), 2.54 (m, 2H), 2.73 (m, 2H), 4.15 (q, $J=7.0$ Hz, 2H), 4.49 (m, 1H), 7.34–7.53 (m, 5H). (M^+H) 392. Entry **3g** (^{1}H NMR, 300 MHz, $CDCl_3$): δ 1.13 (m, 3H), 1.23 (s, 9H), 1.92 (s, 3H), 1.98 (m, 2H), 2.26 (s, 3H), 2.37 (m, 2H), 4.06 (m, 2H), 4.45 (m, 1H), 7.10–7.30 (m, 4H). (M^+H) 448. Entry **3h** (^{1}H NMR, 300 MHz, MeOD): δ 1.42 (s, 9H), 2.46 (s, 3H), 3.76 (s, 3H), 6.83–6.90 (m, 2H), 7.29–7.35 (m, 6H). (M^+H) 394. Entry **3i** (^{1}H NMR, 300 MHz, MeOD): δ 2.47 (s, 3H), 7.15–7.50 (m, 11H), 7.60 (d, $J=7.87$ Hz, 1H), 7.68 (t, $J=6.55$ Hz, 1H), 7.90 (s, 1H). (M^+H) 412. Entry **3j** (^{1}H NMR, 300 MHz, MeOD): δ 1.27 (t, $J=7.13$ Hz, 3H), 2.05 (s, 3H), 2.12 (m, 2H), 2.48 (m, 2H), 3.72 (s, 3H), 4.20 (q, $J=7.12$ Hz, 2H), 4.30 (t, $J=2.20$ Hz, 1H), 7.36–7.53 (m, 5H). (M^+H) 392. Entry **3k** (^{1}H NMR, 300 MHz, MeOD): δ 0.96 (t, $J=7.30$ Hz, 3H), 1.35 (m, 2H), 1.56 (m, 2H), 2.30 (s, 3H), 3.19 (t, $J=7.0$ Hz, 2H), 3.73 (s, 3H). (M^+H) 226.