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Synthesis of Mono- and Dibromo-Derivatives of 1-Phenylpyrazol-3-ol

Eglė Nedzelskytė [a], Vytas Martynaitis [a], Algirdas Šačkus [a], Gernot A. Eller [b] and Wolfgang Holzer [b, *]

a Institute of Synthetic Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, LT-50254 Kaunas, Lithuania
b Department of Drug and Natural Product Synthesis, Faculty of Life Sciences, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria
* Author to whom correspondence should be addressed. Tel: +43-1-4277-55623; E-mail: wolfgang.holzer@univie.ac.at

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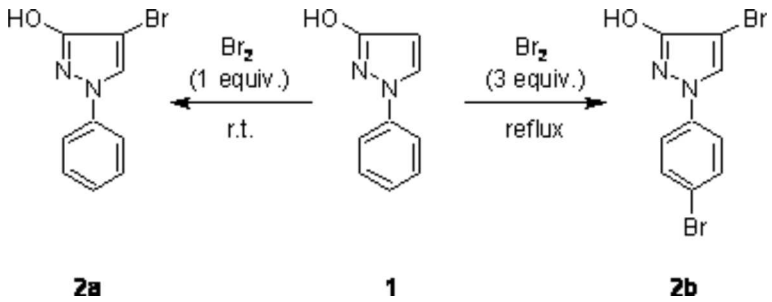
Abstract: Dependent on the reaction conditions, 1-phenylpyrazol-3-ol and bromine give either 4-bromo-1-phenylpyrazol-3-ol (2a) or 4-bromo-1-(4-bromophenyl)pyrazol-3-ol (2b). Treatment of 2a or 2b with refluxing acetic anhydride leads to the corresponding *O*-acetyl derivatives 3a and 3b, respectively. Detailed spectroscopic data (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, MS, IR) for 2b, 3a and 3b are presented.

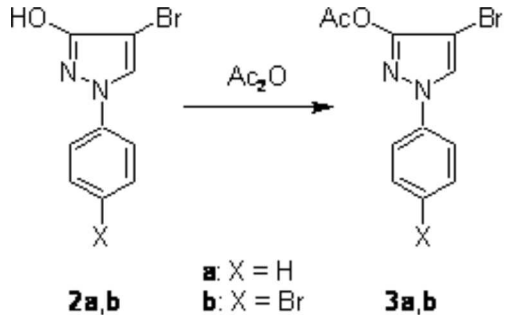
In the course of investigations regarding Pd-catalyzed cross coupling reactions with halopyrazoles [1], we prepared 4-bromo-1-phenylpyrazol-3-ol (2a) via reaction of 1-phenylpyrazol-3-ol (1) with one equivalent of bromine in high yield similarly to a previously described procedure [2]. In this respect it seemed interesting for us, if treatment of 1 with an excess of Br_2 would lead to a dibromination product (introduction of a bromo atom also into the phenyl ring) and thus to a synthon with two different targets for further C–C bond formation. Such a behaviour was reported in a related case, namely in the bromination of 1-phenylpyrazole, where the use of excess bromine together with severe reaction conditions was found to give 15% 4-bromo-1-(4-bromphenyl)pyrazole besides the main product 4-bromo-1-phenylpyrazole (65%) [3].



2a **1** **2b**

Scheme 1

We found that treatment of 1 with 3 equivalents of bromine in a solution of boiling carbon tetrachloride gave the dibromination product 2b in 82% yield (Scheme 1). The structure of 2b was unambiguously determined by spectroscopic methods (^{1}H, ^{13}C, and ^{15}N NMR, MS) and CHN analysis. Furthermore, treatment of 2a and 2b with boiling acetic anhydride afforded the corresponding *O*-acetyl products 3a and 3b in high yield (Scheme 2).



Scheme 2

4-Bromo-1-(4-bromophenyl)-1*H*-pyrazol-3-ol (2b)
To a well stirred solution of hydroxypyrazole 1 [4] (1 g, 6.25 mmol) in carbon tetrachloride (30 mL) a solution of bromine (0.32 mL, 6.25 mmol) in carbon tetrachloride (8 mL) was added dropwise during 1 h, and stirring was continued for 2 h at room temperature. Then the reaction temperature was increased to reach reflux temperature within 1 h while adding a second equivalent of bromine (0.32 mL, 6.25 mmol) in carbon tetrachloride (8 mL). After the addition was complete, stirring was continued for further 5 h at reflux temperature. Then another equivalent of bromine (0.32 mL, 6.25 mmol) in carbon tetrachloride (8 mL) was added dropwise during 1 h, and stirring was continued for further 9 h at reflux temperature. The reaction mixture was then allowed to cool to room temperature; the precipitated solid was filtered off, washed with carbon tetrachloride (15 mL), and recrystallized from aqueous ethanol to afford 1.63 g (82%) of pure 2b.

Melting point: 199–201 °C, yellowish crystals.

^{1}H NMR (300 MHz, DMSO-d_6) [6]: δ (ppm) 11.07 (s, 1H, OH), 8.54 (s, 1H, H-5), 7.62 (m, 4H, Ph H-2,3,5,6).

^{13}C NMR (75 MHz, DMSO-d_6) [6]: δ (ppm) 159.6 (C-3, ^{3}J(C-3,H-5) = 8.8 Hz), 138.5 (Ph C-1), 132.2 (Ph C-3,5), 128.7 (C-5, ^{1}J = 195.0 Hz), 118.6 (Ph C-2,6), 117.3 (Ph C-4), 82.7 (C-4, ^{2}J(C-4,H-5) = 5.0 Hz).

^{15}N NMR (50 MHz, DMSO-d_6) [7]: δ (ppm) −119.4 (N-2), −189.4 (N-1).

MS (m/z, %) [8]: 320 (M^+, 49), 318 (M^+, 100), 316 (M^+, 45), 239 (22), 237 (21), 157 (23), 157 (23), 155 (19).

Elemental Analysis: Calculated for $C_9H_6Br_2N_2O$ (317.96): C, 34.00%; H, 1.90%; N, 8.81%. Found: C, 34.24%; H, 1.95%; N, 8.64%.

4-Bromo-1-phenyl-1*H*-pyrazol-3-yl acetate (3a)
Bromopyrazole 2a (1.91 g, 8 mmol) – which had been prepared by treatment of hydroxypyrazole 1 with one equivalent of bromine at room temperature following a known procedure [2] – and excess acetic anhydride (25 mL) were heated to reflux for 30 min. Then, H_2O (15 mL) was added and the solution was stirred for further 30 min. The mixture was poured into ice-water (50 mL) and stirred for 30 min. Then the precipitate was filtered off, washed with H_2O, and dried to give 2.07 g (92%) of pure 3a.

Melting point: 82–85 °C, off-white crystals.

IR (KBr) [5]: 1758 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$) [6]: δ (ppm) 7.90 (s, 1H, H-5), 7.57 (m, 2H, Ph H-2,6), 7.43 (m, 2H, Ph H-3,5), 7.29 (m, 1H, Ph H-4), 2.38 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) [6]: δ (ppm) 167.6 (CO, ^2J(CO,CH_3) = 7.1 Hz), 154.0 (C-3, ^3J(C-3,H-5) = 9.4 Hz), 139.2 (Ph C-1), 129.5 (Ph C-3,5), 128.4 (C-5, ^1J = 194.3 Hz), 127.0 (Ph C-4), 118.5 (Ph C-2,6), 87.7 (C-4, ^2J(C-4,H-5) = 5.1 Hz), 20.4 (CH_3, ^1J = 131.0 Hz).

^{15}N NMR (50 MHz, $CDCl_3$) [7]: δ (ppm) −177.0 (N-1); N-2 not found.

MS (m/z, %) [8]: 282 (M^+, 6), 280 (M^+, 6), 240 (100), 238 (99), 104 (49), 77 (84), 51 (30), 43 (52).

Elemental Analysis: Calculated for $C_{11}H_9BrN_2O_2$ (281.11): C, 47.00%; H, 3.23%; N, 9.97%. Found: C, 46.74%; H, 3.07%; N, 9.84%.

4-Bromo-1-(4-bromophenyl)-1*H*-pyrazol-3-yl acetate (3b)
Dibromopyrazole 2b (1.27 g, 4 mmol) and excess acetic anhydride (15 mL) were refluxed for 30 min. Then H_2O (10 mL) was added and the solution was stirred for further 30 min. The mixture was poured into ice-water (50 mL) and stirred for 30 min. Then the precipitate was filtered off, washed with H_2O, and dried to give 1.17 g (81%) of pure 3b.

Melting point: 77 °C, beige powder.

IR (KBr) [5]: 1780, 1761 cm^{-1} (C=O).

^{1}H NMR (300 MHz, $CDCl_3$) [6]: δ (ppm) 7.87 (s, 1H, H-5), 7.55 (m, 2H, Ph H-3,5), 7.46 (m, 2H, Ph H-2,6), 2.38 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) [6]: δ (ppm) 167.5 (CO, ^2J(CO,CH_3) = 7.1 Hz), 154.4 (C-3, ^3J(C-3,H-5) = 9.4 Hz), 138.3 (Ph C-1), 132.6 (Ph C-3,5), 128.3 (C-5, ^1J = 194.3 Hz), 120.4 (Ph C-4), 120.0 (Ph C-2,6), 88.4 (C-4, ^2J(C-4,H-5) = 5.0 Hz), 20.4 (CH_3, ^1J = 130.7 Hz).

^{15}N NMR (50 MHz, $CDCl_3$) [7]: δ (ppm) −99.2 (N-2), −179.3 (N-1).

MS (m/z, %) [8]: 362 (M^+, 1), 360 (M^+, 3), 358 (M^+, 1), 320 (28), 318 (60), 316 (28), 157 (26), 155 (25), 76 (29), 75 (30), 43 (100).

Elemental Analysis: Calculated for $C_{11}H_8Br_2N_2O_2$ (360.00): C, 36.70%; H, 2.24%; N, 7.78%. Found: C, 36.82%; H, 2.19%; N, 7.76%.

References and Notes

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3. Finar, I.L.; Foster, T. *J. Chem. Soc. C* **1967**, 1494–1497.
4. Harries, C.; Loth G. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 513–520.
5. Obtained on a Perkin-Elmer FTIR 1605 spectrophotometer or on a Perkin-Elmer FTIR Spectrum 1000 spectrometer.
6. Obtained on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28 °C. The centre of the solvent signal was used as an internal standard which was related to TMS with δ 2.49 ppm (^{1}H NMR in DMSO-d_6), δ 7.26 ppm (^{1}H NMR in $CDCl_3$), δ 39.5 ppm (^{13}C NMR in DMSO-d_6), and δ 77.0 ppm (^{13}C NMR in $CDCl_3$).

7. Obtained on a Bruker Avance 500 spectrometer (50.68 MHz for ^{15}N) and referenced against neat, external nitromethane (coaxial capillary).
8. Obtained on a Shimadzu QP 1000 instrument (EI, 70eV).