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Short Note

4-Bromo-3-methoxy-1-phenyl-1*H*-pyrazole

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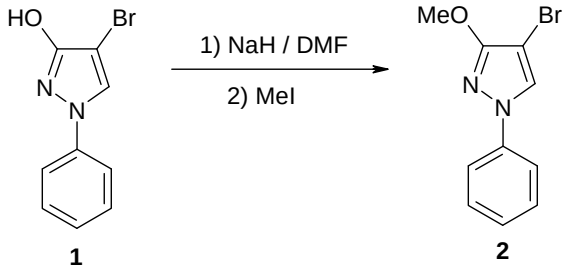
Abstract: The title compound was prepared by treatment of 4-bromo-1-phenyl-1*H*-pyrazol-3-ol with sodium hydride/methyl iodide in good yield. Detailed spectroscopic data (^{1}H NMR, ^{13}C NMR, ^{15}N NMR, IR, MS) are presented.

Keywords: pyrazole; 1*H*-pyrazol-3-ol; methylation; NMR

Bromo(hetero)arenes are valuable starting materials for further functionalization, for instance *via* metalation reactions (halogen-metal exchange) [1] or transition-metal-catalyzed cross coupling reactions [2–4]. With an OH- or OR function in *ortho*-position to the bromo atom, such (hetero)arenes can be considered as potential precursors for condensed systems involving a ring-oxygen atom (condensed furans, pyranes) [5]. However, for some of the above mentioned functionalization reactions, free hydroxy groups are unfavourable, for instance in metalation reactions [6] or in Suzuki-type cross couplings [7]. In such cases, the OH group has to be masked. In this regard, a possible option is to transform the OH into the very stable OMe group. The O–Me bond then can be cleaved in the course of the cyclization reaction into the *O*-containing ring system employing, for instance, pyridine hydrochloride as the reagent [8].

We here present the synthesis of 4-bromo-3-methoxy-1-phenyl-1*H*-pyrazole (**2**), with a protected OH-group in position 3 and a bromo substituent in position 4 of the pyrazole nucleus, which can be considered as a desirable starting compound for further transformation. The preparation of **2** was carried out according to a standard method for *O*-alkylation, namely by reaction of 4-bromo-1-phenyl-1*H*-pyrazol-3-ol (**1**) [9] with methyl iodide in alkaline medium, which afforded the title compound in 88% yield after column chromatograpy (Scheme 1).

Scheme 1.



1 **2**

Although compound **2** is reported in a patent application, neither an experimental procedure for its preparation nor spectroscopic/physical data, was provided [10]. Thus, a detailed characterization of **2** including IR, MS and NMR (^{1}H, ^{13}C, ^{15}N) spectral data as well as microanalytical data is given in the Experimental.

Experimental

The melting point was determined on a Mel-Temp (Capillary Melting point Apparatus) and is uncorrected. Mass spectrum was recorded on a Waters ZQ 2000 instrument (APCI+, 20 V) and IR spectrum on a Perkin Elmer Spectrum GX FT-IR System instrument (KBr-disc). The elemental analysis was performed with an Exeter Analytical CE-440 Elemental Analyzer. All NMR spectra were recorded from $CDCl_3$ solutions on a Bruker Avance 500 instrument with a 'directly' detecting broadband observe probe (BBFO) at 298 K (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, 50.68 MHz for ^{15}N). The centre of the solvent signal was used as an internal standard which was related to TMS with δ = 7.26 ppm (^{1}H in $CDCl_3$) and δ = 77.0 ppm (^{13}C in $CDCl_3$). The digital resolutions were 0.2 Hz/data point in the ^{1}H and 0.4 Hz/data point in the ^{1}H-coupled ^{13}C-NMR spectra (gated decoupling). The ^{15}N NMR spectrum (gradient-selected ^{15}N, ^{1}H-HMBC) was referenced against external nitromethane.

*4-Bromo-3-methoxy-1-phenyl-1*H*-pyrazole* (**2**)

A solution of 4-bromo-1-phenyl-1*H*-pyrazol-3-ol (**1**) (3.825 g, 16.0 mmol) in dry DMF (20 mL) was cooled to 0 °C under an inert atmosphere and NaH (60% dispersion in mineral oil, 640 mg, 16.0 mmol) was added portionwise. After stirring for 15 min, methyl iodide (1.2 mL, 19.2 mmol) was added dropwise at 0 ºC. The mixture was warmed to r.t. and stirred at 60 ºC for 1 h (TLC control, eluent: ethyl acetate–*n*-hexane, 1:10). Then, 10 mL of water were added and the mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, eluent: ethyl acetate–*n*-hexane, 1:20) to give pure **2** as colorless crystals, m.p. 24.5–25.5 ºC. Yield: 3.56 g (88%).

IR (KBr) ν (cm^{-1}): 2947, 1554, 1502, 1099, 749, 686.

MS (EI, 70 eV): (*m/z*, %) 253/255 (M^+, 100/99), 175 ($[M–Br+H]^+$, 47), 174 ($[M–Br]^+$, 75).

^{1}H NMR ($CDCl_3$): δ (ppm) 4.05 (s, 3H, Me), 7.23 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H-3,5), 7.56 (m, 2H, Ph H-2,6), 7.78 (s, 1H, H-5).

^{13}C NMR ($CDCl_3$): δ (ppm) 56.8 (OCH_3, ^{1}J = 146.2 Hz), 82.0 (C-4, ^{2}J(C4,H5) = 5.2 Hz), 117.6 (Ph C-2,6), 125.8 (Ph C-4), 127.8 (C-5, ^{1}J = 191.7 Hz), 129.4 (Ph C-3,5), 139.7 (Ph C-1), 161.2 (C-3, ^{3}J(C3,H5) = 8.8 Hz, ^{3}J(C3,OCH_3) = 3.7 Hz).

^{15}N NMR ($CDCl_3$): δ (ppm) –187.8 (N-1), –119.9 (N-2).

Anal. Calcd for $C_5H_9BrN_2O$: C, 47.46%; H, 3.58%; N, 11.07%. Found: C, 47.08%; H, 3.42%; N 10.72%.

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