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Synthesis of 3-(5-chloropyrazol-3-yl)propenals

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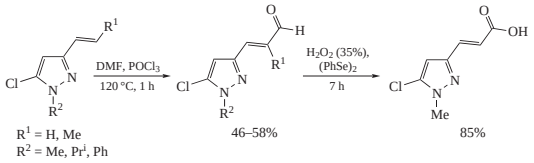
The Vielsmeier–Haack formylation of 5-chloro-3-alkenylpyrazoles proceeds at the olefinic double bond and affords (2*E*)-3-(5-chloro-1*H*-pyrazol-3-yl)prop-2-enals.



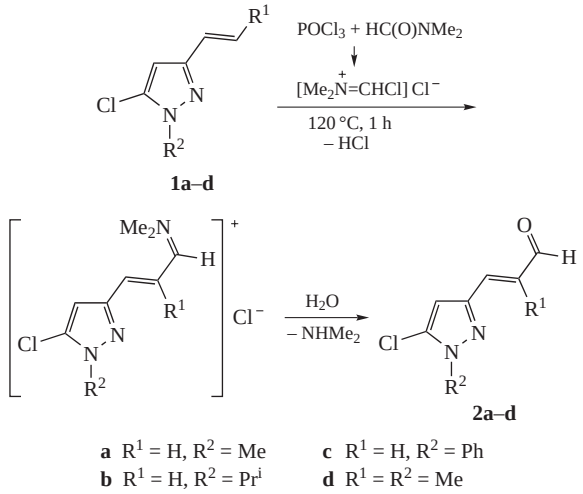
Chemistry of pyrazole and its derivatives is being studied vigorously.[1–13] State-of-the-art in the design of new pyrazole derivatives closely relates to the synthesis of multi-purpose building blocks.[14,15] In this line, 5-chloro-3-alkenylpyrazoles and 5-chloropyrazole-4-carbaldehydes attract a special attention.[8,11]

We have continued the investigations of 5-chloro-3-alkenylpyrazoles bearing two reactive sites, *i.e.* 4-position in the heterocycle and the double bond.[16–20] Unlike 1-alkenylpyrazoles,[21–23] 3-alkenyl-5-chloropyrazoles do not add electrophiles at the double bond.[16–20] At the same time, 1-alkyl-5-chloro-3-alkenylpyrazoles react with thiophenols without catalysts and solvents to deliver products of nucleophilic β-addition, 3-[2-(arylsulfanyl)alkyl]-pyrazoles, in quantitative yields.[17] Aliphatic chalcogen compounds also form β-adducts across the double bond under radical initiation.[17–19] Nucleophilic substitution of hydrogen β-atom of the exocyclic double bond in 3-alkenyl-5-chloropyrazoles was reported.[20] For instance, 1-benzyl-3-alkenyl-5-chloropyrazoles react with phosphorus pentachloride at the alkenyl groups to furnish organyltrichlorophosphonium hexachlorophosphorates, which are easily transformed to 2-(pyrazol-3-yl)alkenylphosphonic acid dichlorides.[20] Another example of substitution at the exocyclic double bond in non-chlorinated *C*-vinylpyrazoles comprised the action of a strong electrophile, ethyl *N*-(2,2,2-trichloroethylidene)carbamate.[24] Thus, the available, though limited, data indicate that β-position of the double bond in 3-alkenylpyrazoles is an active nucleophilic site.[17,20,24]

Herein, we studied formylation of 1-R-5-chloro-3-alkenylpyrazoles with the Vilsmeier–Haack reagent. Previously, it was reported that this reagent caused formylation of 4-position in 1,3-dialkylpyrazoles,[25] some pyrazolones[8,11] and 5-chloro-3-methyl-1-phenylpyrazole.[26]

Pyrazoles represent an electron-deficient heterocyclic system in which electrophilic substitution is hindered. For even more electron-deficient 5-chloropyrazoles, only nitration,[27] sulfation[28] and aroylation[29] were performed. Among numerous works on the Vilsmeier–Haack preparation of chloropyrazolecarbaldehydes, only one[26] reports direct formylation of 5-chloro-3-methyl-1-phenylpyrazole, though the data given in this paper are contradictory. The authors report that the formylation conditions are similar to those published previously,[29] when 5-oxo-4,5-dihydro-1*H*-pyrazole-4-carbaldehydes have been synthesized. In the works, where syntheses of 5(3)-chloropyrazole-4-carbaldehydes were described, pyrazolones were formylated using various conditions and solvents.[8,11,30–32] It is assumed[30–32] that formylation of pyrazolones initially involves introduction of the carbaldehyde group and only after that 4-formyl-substituted 5-pyrazolones are transformed into 4-formyl-5-halopyrazoles under the action of $POHal_3$. The attempts to synthesize 1,3-dialkyl-5-chloropyrazole-4-carbaldehydes from 5-chloropyrazoles under the reported conditions[8,11,26] and even under microwave assistance,[25] failed. Thus, formylation of 1,3-disubstituted 5-chloropyrazoles remains a challenge.

In the present work, we have found the conditions of the reaction between 1-R-5-chloro-3-alkenylpyrazoles **1a–d** and the Vilsmeier–Haack reagents (Scheme 1). The reaction proceeded chemoselectively to afford hitherto unknown (2*E*)-3-(1-R-5-chloro-1*H*-pyrazol-3-yl)prop-2-enals **2a–d** *via* substitution of the alkenyl group β-hydrogen. To achieve high yields of the products, a complex of DMF with phosphoryl chloride (in 6 : 4 ratio) should be preliminarily prepared and then used in 4-fold excess. The reaction was carried out at 120 °C for 1 h. The yields of pure products **2a–d** were 46–58%.†

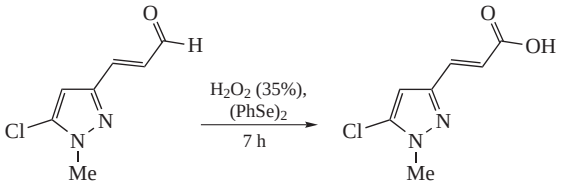


Scheme 1

† *Pyrazolylpropenals* **2** *(general procedure).* Phosphorus oxychloride (4 equiv.) was added dropwise to DMF (6 equiv.) at 0 °C. After 20 min, pyrazole **1** (1 equiv.) was added at 0 °C. The mixture was stirred at 120 °C for 1 h, then cooled to ambient temperature. Water (5 ml) was added and the mixture was neutralized with saturated solution of Na_2CO_3 to pH ~ 7. The aqueous layer was extracted with $CHCl_3$ (3×10 ml). The combined

Structure of the alkenyl group and nature of the substituent in the 1-position of the pyrazole cycle have no effect on the process (see Scheme 1). For instance, 5-chloro-1-methyl-3-(prop-1-en-1-yl)-1*H*-pyrazole **1d** was also formylated at the double bond giving rise to (2*E*)-3-(5-chloro-1-methyl-1*H*-pyrazol-3-yl)-2-methylprop-2-enal **2d**. Substitution at the 4-position of the pyrazole cycle of compounds **1a**–**d** did not occur. Obviously, owing to the effect of chlorine atom, electron density and space accessibility of the 4-position of the pyrazole cycle in substrates **1** are lower than those of β-position of the exocyclic C=C bond.

The structure of pyrazolylpropenals was further proved by oxidation of propenal **2a** to the corresponding acid **3**.‡ Among significant number of the oxidants tested,[33–35] a mixture of diphenyl diselenide with hydrogen peroxide (in 2 : 1 ratio)[35] allows one to prepare individual (2*E*)-3-(5-chloro-1-methyl-1*H*-pyrazol-3-yl)prop-2-enoic acid **3** in 85% yield (Scheme 2). Previously, it was reported that this system, upon oxidation of α,β-unsaturated aldehydes, led to the vinyl formates.[34]



2a **3**

Scheme 2

Structure of the compounds synthesized was confirmed by IR, ^{1}H, ^{13}C and ^{15}N NMR spectroscopy, chromatomass spectrometry and elemental analysis data. Alkenals **2a**–**d** and acid **3** were prepared as the *E*-isomers with characteristic spin–spin coupling constant $^3J_{HH}$ 15.9–16.2 Hz. In the ^{1}H NMR spectra of pyrazoles **2a**–**d**, signals of the aldehyde proton and proton in the 4-position of the pyrazole ring were detected in the regions of 9.67–9.87 and 6.50–6.71 ppm, respectively. For compound **3**, the H-4 signal is significantly shifted towards the low field (6.93 ppm).

The 2D ^{15}N HMBC {^{1}H–^{15}N} spectra ($CDCl_3$) of compounds **2a**–**d**, **3** contained the cross-peaks of nitrogen atoms N-1 and N-2 with protons of the pyrazole ring (H-4), protons of the methyl (**2a**,**d**) and methylene (**2b**) moieties, *ortho*-protons of the phenyl group (**2c**) with N-1, proton of the =CH fragment with N-2.

In conclusion, the discovered reaction makes it possible to efficiently access hitherto unknown 3-(5-chloropyrazol-3-yl)-propenals, precursors of promising multifunctional pyrazole derivatives being of interest in terms of biological activity and drug and pesticide design.

Spectroscopic and analytical data were obtained using instrumentation of the Baikal Analytical Center for Collective Use SB RAS.

organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by column chromatography.

For characteristics of compounds **2a**–**d**, see Online Supplementary Materials.

‡ *(2*E*)-3-(5-Chloro-1-methyl-1*H*-pyrazol-3-yl)prop-2-enoic acid* **3**. Diphenyl diselenide (0.031 g, 0.1 mmol) was treated with H_2O_2 (35 wt%, 0.05 ml, 0.5 mmol) and water (0.1 ml) and stirred at room temperature until discoloration of the reaction mixture. Then, aldehyde **2a** (0.085 g, 0.5 mmol) was added. After 7 h, the aqueous mixture was extracted with EtOAc (3×10 ml). The collected organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The solid phase was washed with $CHCl_3$ (5 ml). White powder (0.079 g, 85%), mp 163–165 °C.

For characteristics of compound **3**, see Online Supplementary Materials.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.03.024.

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