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*Short Note*

# 3-(2-Chloroethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde

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**Abstract:** Herein, we describe the synthesis of 3-(2-chloroethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde via the Vilsmeier-Haack reaction. The structure of this previously unreported compound is thoroughly elucidated through NMR, FT-IR spectroscopy and HRMS spectrometry.

**Keywords:** Vilsmeier-Haack reaction; pyrazole; aldehyde; dual functionalization



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## 1. Introduction

The Vilsmeier-Haack reaction is a useful tool for the formylation of aromatic and heterocyclic compounds, such as pyrroles, imidazoles, pyrazoles, etc. [1]. It has been shown that variously substituted pyrazole derivatives can be transformed into condensed pyrazolo[3,4-*b*]pyridines, pyrazolo[1,5-*a*]-, and pyrazolo[3,4-*d*]pyrimidines through the Vilsmeier-Haack reaction [2,3]. Our group has successfully employed the Vilsmeier-Haack formylation reaction to obtain various pyrazole-4-carbaldehydes from commercially available 1-phenyl-1*H*-pyrazol-3-ol and utilized them to prepare fluorescent sensors [4] and biologically active compounds [5–7]. Additionally, it has been reported that the products of the Vilsmeier-Haack formylation reaction could be versatile scaffolds in the synthesis of materials for solar cells [8,9], organic light-emitting diodes [10,11], and natural products [12–14].

Usually, dimethylformamide and phosphorus trichloride are utilized to form the Vilsmeier reagent [15]. The latter was shown to participate in chlorination as well as chloroformylation reactions [16]. Compounds containing a 2-chloroethoxy chain are of particular interest, as they can be readily modified through a nucleophilic substitution reaction with various amines to furnish aminoalkoxy-functionalized potential anti-cancer, neuroprotective, or biological imaging agents [17–19]. 2-Amino-6-(2-chloroethoxy)benzothiazole was used in the preparation of cationic azo dyes [20], while 2-chloroethoxyacetaldehyde has been revealed to participate in an organocatalytic asymmetric direct cross-aldol reaction with aromatic aldehydes to yield chiral dioxanes and morpholines, which often possess various biological activities [21].

In this work, we employ the Vilsmeier-Haack reaction to achieve dual functionalization of 3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole (**1**), giving rise to 3-(2-chloroethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**2**). The structure of the newly synthesized compound **2** was elucidated through NMR, FT-IR spectroscopy, and HRMS spectrometry.

## 2. Results and Discussion

Examples of structural modifications leading to the formation of haloalkoxy chains are relatively scarce in the scientific literature. The 2-ethoxyethanol groups can be converted to the more reactive 2-bromoethoxy chains using phosphorus bromide in toluene [22].

Meanwhile, the 2-chloroethoxy chain can be inserted through the palladium-catalysed chloroethoxylation reaction of aryl chlorides with tetrakis(2-chloroethoxy)borate, with good tolerance towards different existing functional groups in the molecule, including formyl [23]. Another method for introducing a chloroethoxy group entails reacting phenols with 1,2-dichloroethane in the presence of potassium carbonate as a base [24]. The possibility of the methoxy group cleavage and simultaneous replacement with a chlorine atom in a methoxyethoxy chain, in the presence of pyridine and phosphorus oxychloride, or phosphorus oxychloride/diethylamine in toluene, has been only briefly described in the synthesis of quinazoline-based pharmaceuticals [25,26].

Since phosphorus oxychloride is also known to participate in the Vilsmeier-Haack formylation reaction in conjunction with dimethylformamide, we ought to perform a dual functionalization, namely, to simultaneously formylate, and chlorinate 3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole (**1**) to obtain a (2-chloroethoxysubstituted)pyrazole carbaldehyde **2**. The starting material **1** was readily prepared from 1-(4-methoxyphenyl)-3-hydroxy-1*H*-pyrazole adopting a previously published synthetic method [27]. It was then subjected to the reaction with the Vilsmeier reagent, which has been pre-formed from equimolar amounts of phosphorus oxychloride and dimethylformamide at −10 °C, and then the reaction mixture was heated to 70 °C and stirred for 24 h. After column chromatography, the target compound **2** (Figure 1) was obtained in a moderate yield of 48%.

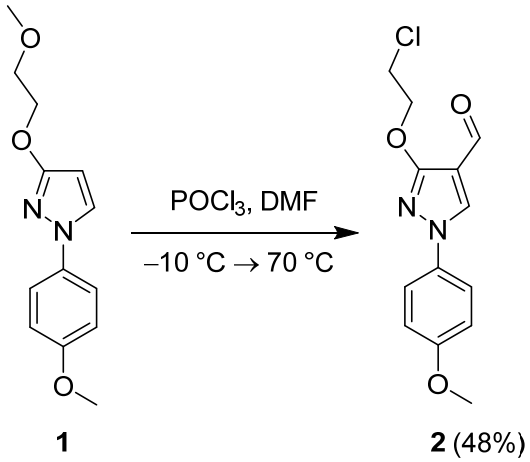


**Figure 1.** Synthesis of compound **2**.

The structure of compound **2** was thoroughly elucidated through NMR spectroscopy (Figure 2). In the $^{1}$H NMR spectrum of compound **2** (Figure S1), only one singlet of methoxy group protons appeared at δ 3.85 ppm. Then, according to the $^{1}$H-$^{13}$C heteronuclear single quantum coherence (HSQC) spectrum, these protons had a one-bond correlation with the carbon, which resonated at δ 55.6 ppm. Furthermore, the $^{1}$H-$^{13}$C heteronuclear multiple bond correlation (HMBC) spectrum revealed a correlation between these methoxy group protons and the quaternary carbon at δ 158.9 ppm (phenyl C-4′). The $^{1}$H-$^{1}$H NOESY spectral data revealed that the methoxy group protons exhibited NOEs with the neighboring phenyl group 3′(5′)-H protons (δ 6.95−7.00 ppm), confirming their proximity in space (Figure S3). Thus, it was concluded that only a cleavage of the methoxy group in the 2-methoxyethoxy chain had occurred. The DEPT-135 spectrum clearly showed the negative -$\underline{C}H_2$ peaks at δ 68.9 and 41.5 ppm (Figure S4); the latter was significantly upfield due to the absence of a neighboring methoxy group. Finally, the most downfield $^{1}$H and $^{13}$C NMR signals were easily attributed to the formyl moiety via $^{1}$H-$^{13}$C HSQC and HMBC spectral data (Figure S5). The $^{15}$N NMR data were obtained through the $^{1}$H-$^{15}$N HMBC experiment where the pyrazole 5-H proton (singlet, δ 8.15 ppm) exhibited long-range correlations with neighboring N-1 “pyrrole-like” (δ −179.0 ppm) and N-2 “pyridine-like” (δ −117.0 ppm) nitrogen atoms (Figure S6).

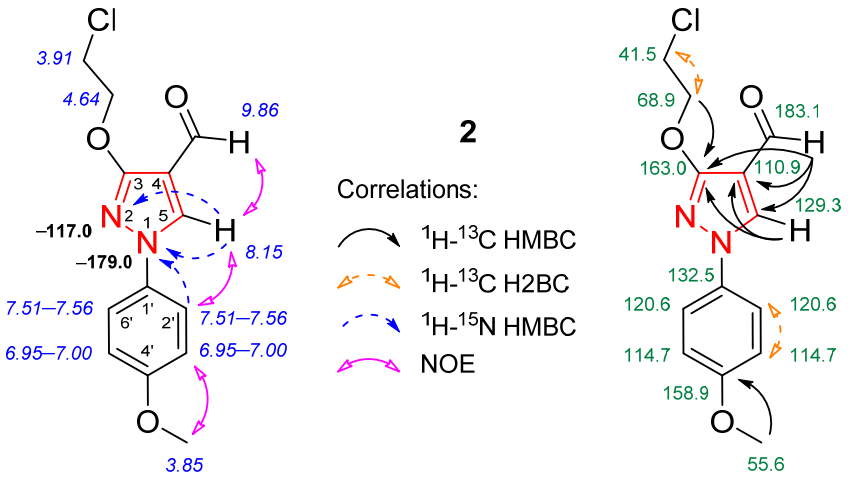


**Figure 2.** Relevant $^1$H-$^{13}$C HMBC, $^1$H-$^{13}$C H2BC, $^1$H-$^{15}$N HMBC, and $^1$H-$^1$H NOESY correlations, as well as $^1$H NMR (in italics), $^{15}$N NMR (in bold), and $^{13}$C NMR chemical shifts of compound **2**.

The replacement of the methoxy group in the methoxyethoxy chain with a chlorine atom was confirmed by high-resolution mass spectrometry (HRMS) data, as the HRMS spectrum showed a molecular ion $[M + H]^+$ at $m/z$ 281.0691 (calculated for $C_{13}H_{14}ClN_2O_3$, 281.0687) and the predominant sodium adduct $[M + Na]^+$ at $m/z$ 303.0508 (see Figure S7). A characteristic, intense formyl group peak in the FT-IR spectrum of compound **2** is situated at 1667 $cm^{-1}$.

## 3. Materials and Methods

All chemicals and solvents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded in $CDCl_3$ solutions at 25 °C on a Bruker Avance III 700 (700 MHz for $^1$H, 176 MHz for $^{13}$C, 71 MHz for $^{15}$N) spectrometer equipped with a 5 mm TCI $^1$H-$^{13}$C/$^{15}$N/D z-gradient cryoprobe (Bruker BioSpin AG, Fällanden, Switzerland) and processed using TopSpin 3.6.4 and MestReNova 11.0 software. The chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). The $^{15}$N NMR ($^1$H-$^{15}$N HMBC) spectrum was referenced to neat, external nitromethane (coaxial capillary). FT-IR spectrum was collected using the ATR method on a Bruker Vertex 70v spectrometer (Bruker Optik GmbH, Ettlingen, Germany) with an integrated Platinum ATR accessory and processed using OPUS 7.2 software. The melting point was determined in an open capillary tube with a Buchi M-565 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and was uncorrected (temperature gradient—2 °C/min). High-resolution mass spectrometry (HRMS) spectrum was obtained in ESI mode with a Bruker MicrOTOF-Q III spectrometer (Bruker Daltonik GmbH, Bremen, Germany) and processed with Bruker Compass DataAnalysis 4.1 software. Reaction progress was monitored by TLC analysis on Macherey-Nagel™ ALUGRAM® Xtra SIL G/UV254 plates (Macherey-Nagel GmbH & Co., Düren, Germany). TLC plates were visualized with UV light (wavelengths 254 and 365 nm). Compounds were purified by flash chromatography in a glass column (stationary phase—silica gel 60, 0.063–0.200 mm, 70–230 mesh ASTM, Merck KGaA, Darmstadt, Germany).

Synthesis of 3-(2-chloroethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**2**): Phosphorus oxychloride (40 mmol, 2.5 mL, 4 eq.) was added dropwise into dry dimethylformamide (40 mmol, 2.1 mL, 4 eq.) under Ar at −10 °C. The mixture was stirred at −10 °C until the viscous, white Vilsmeier reagent was formed. Then, 3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole (**1**) (6.7 mmol, 1680 mg, 1 eq.) was dissolved in dry dimethylformamide (5 mL) and added dropwise into the Vilsmeier reagent at r.t. The reaction temperature was subsequently raised to 70 °C and maintained for 24 h. Subsequently, the reaction mixture was chilled, poured into ice water (200 mL), and basified with solid $Na_2CO_3$ and NaOH (pH > 10). The resulting precipitate was filtered and purified by column chromatography on silica gel (eluent—EtOAc/Hex 1/3 to 1/1 *v*/*v*) to give **2** ($R_f$ = 0.22,

EtOAc/Hex 3/1 *v*/*v*) as a white solid (907 mg, 48% yield). m.p. = 106–107 °C; IR (neat) $\nu_{max}$ 3127, 3101, 2940, 2826, 2748 ($CH_{arom}$, $CH_{aliph}$), 1667 (C=O), 1560, 1516, 1499, 1367, 1304, 1246, 1228, 1177, 1024, 944, 825 (C=C, $CH_3$, $CH_2$ bending, C-O, C-N, C-$H_{arom}$ oop bending) $cm^{-1}$; $^1H$ NMR (700 MHz, $CDCl_3$): δ 9.86 (s, 1H, -C<u>H</u>O), 8.15 (s, 1H, Pyr 5-H), 7.56–7.51 (m, 2H, Ph 2,6-H), 7.00–6.95 (m, 2H, Ph 3,5-H), 4.64 (t, *J* = 5.9 Hz, 2H, -OC<u>H</u>$_2$CH$_2$Cl), 3.91 (t, *J* = 5.9 Hz, 2H, -OCH$_2$C<u>H</u>$_2$Cl), 3.85 (s, 3H, -OC<u>H</u>$_3$). $^{13}C$ NMR (176 MHz, $CDCl_3$): δ 183.1 (-<u>C</u>HO), 163.0 (Pyr C-3), 158.9 (Ph C-4), 132.5 (Ph <u>C</u>-1), 129.3 (Pyr C-5), 120.6 (Ph C-2,6), 114.7 (Ph C-3,5), 110.9 (Pyr C-4), 68.9 (-O<u>C</u>H$_2$CH$_2$Cl), 55.6 (-O<u>C</u>H$_3$), 41.5 (-OCH$_2$<u>C</u>H$_2$Cl). $^{15}N$ NMR (71 MHz, $CDCl_3$): δ −179.0 (N-1), −117.0 (N-2). HRMS (ESI-TOF) for $C_{13}H_{13}ClN_2NaO_3$ ($[M + Na]^+$): calcd. 303.0507; found 303.0508, Δ = −0.3 ppm.

**Supplementary Materials:** 2D MDL molfile of Compound **2**, Figure S1: $^1H$ NMR spectrum of compound **2**; Figure S2: $^{13}C$ NMR spectrum of compound **2**; Figure S3: $^1H$-$^1H$ NOESY spectrum of compound **2**; Figure S4: $^{13}C$ NMR/DEPT 135 spectra of compound **2**; Figure S5: The overlaid $^1H$-$^{13}C$ HSQC/HMBC NMR spectra of compound **2**; Figure S6: $^1H$-$^{15}N$ HMBC spectrum of compound **2**; Figure S7: FT-IR spectrum of compound **2**; Figure S8: HRMS spectrum of compound **2**.

**Author Contributions:** Conceptualization, A.B. and A.Š.; methodology, A.B. and A.Š.; formal analysis, G.V.; investigation, G.V. and A.B.; resources, A.Š.; data curation, A.B.; writing—original draft preparation, G.V.; writing—review and editing, A.Ž., N.K., A.B. and A.Š.; visualization, G.V. and A.B.; supervision, N.K.; project administration, A.Š.; funding acquisition, A.Š. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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