Short Note

(*Z*)-1-(3,5-dichloro-2H-pyrrol-2-ylidene)-*N*,*N*-dimethylmethanamine

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(*Z*)-1-(3,5-dichloro-2H-pyrrol-2-ylidene)-*N*,*N*-dimethylmethanamine

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Abstract: The Vilsmeier-Haack reaction is a convenient method for the formylation of electron-rich aromatic compounds. However, this interaction sometimes gives specific side products. We report the isolation and structural characterization of a novel compond (*Z*)-1-(3,5-dichloro-2-pyrrolidin)-*N*,*N*-dimethylmethanamine obtained as a side product during the formylation of 2-chloropyrrole. The product was characterized using NMR spectroscopy and X-ray crystallography.

Keywords: Vilsmeier-Haack reaction; side products; formylation; halogenated pyrroles

1. Introduction

The Vilsmeier-Haack reaction (VHR) plays a crucial role in modern organic synthesis [1, 2]. It facilitates the introduction of a formyl group into the core of electron-rich aromatic molecules such as phenols, pyrrole [3], pyrazoles [4] and other [5]. Additionally, Vilsmeier reagent (VR) could interact with nonaromatic compound like alkenes, ketones, aldehydes and heterocycles [6]. Formylopyrroles are important intermediates in the synthesis of pyrrole-containing molecules, *e.g.* difluoroboron dyes like BODIPY, BOPHY, *etc* [7]. Using halogenated 2-formylopyrroles enables the preparation of halogenated pyrrole-containing intermediates. Commonly, halogenated 2-formylopyrroles could be obtained by formylation of 2-halopyrroles with VR [8]. However, yields of this reaction are often low. It is well known, that VHR can lead to the formation of different unexpected products, depending on substrate and reaction conditions. Herein we report the isolation and characterization of (*Z*)-1-(3,5-dichloro-2-pyrrolidin)-*N*,*N*-dimethylmethanamine from the reaction mixture of 2-chloropyrrole VHR.

2. Results

2.1. Synthesis of (Z)-1-(3,5-dichloro-2-pyrrolidin)-N,N-dimethylmethanamine

Typical procedures for 5-chloro-2-formylpyrrole preparation include chlorination of pyrrole and further VHR without purification of 2-chloropyrrole. The reaction yielded a complex mixture of products, from which (*Z*)-1-(3,5-dichloro-2-pyrrolidin)-N,N-dimethylmethanamine was isolated by flash-chromatografy with a moderate yield (Scheme 1).

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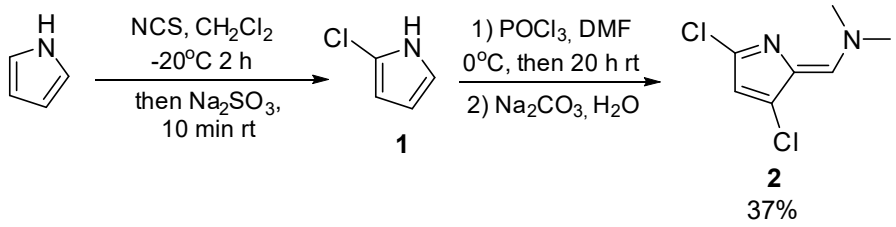

Scheme 1. The reaction of 2-chloropyrrole with the Vilsmeier-Haack reagent.

The obtained product was characterized using ^{1}H and ^{13}C NMR spectroscopy, HRMS and X-ray crystallography. In ^{1}H NMR spectrum singlet signals of methyl groups were observed at 3.31 and 3.66 ppm, singlet signals were also observed at 6.16 (=CHNMe$_2$) and 7.17 ppm (CH of pyrrole fragment). In ^{13}C NMR, all signals of alkene fragments are observed at 113–145 ppm for heterocyclic and vinylidene carbons, and methyl groups gave signals at 40.5 and 47.5 ppm.

2.2. XRD studies

Single crystal X-ray studies were performed. Obtained substance in crystal has monoclinic $P2_1/n$ space group with two molecules in the asymmetric unit M1 and M2. The fragment of the structure with corresponding labeling scheme is shown in Figure 1a. The conformation of molecules is planar with intramolecular C-H···N interactions (C7-H···N2 ($d_{H\cdots N2}$ = 2.20 Å) and C13-H···N4 ($d_{H\cdots N4}$ = 2.22 Å)).

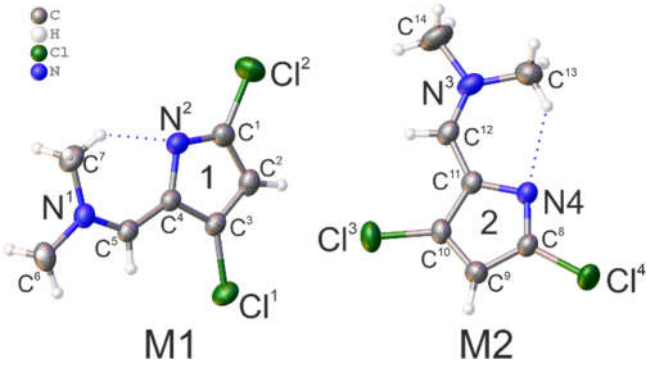

Figure 1. Molecular structure, atom and cycle numbering of R-HRH with anisotropic displacement ellipsoids drawn at 50% probability level.

M1 molecules form dimer connected by C$_6$-H···Cl$_1$ and C$_7$-H···π^1 interactions (π^1 is N2-C1-C2-C3-C4 ring), dimers are packing into chain along *a*-axis (Fig. 2a and b). M2 molecules also form dimers and chains along *a*-axis, but intermolecular interactions are absent. Chains M1 and M2 are connected to each other by C2-H···Cl3 interactions (Fig. 2c).

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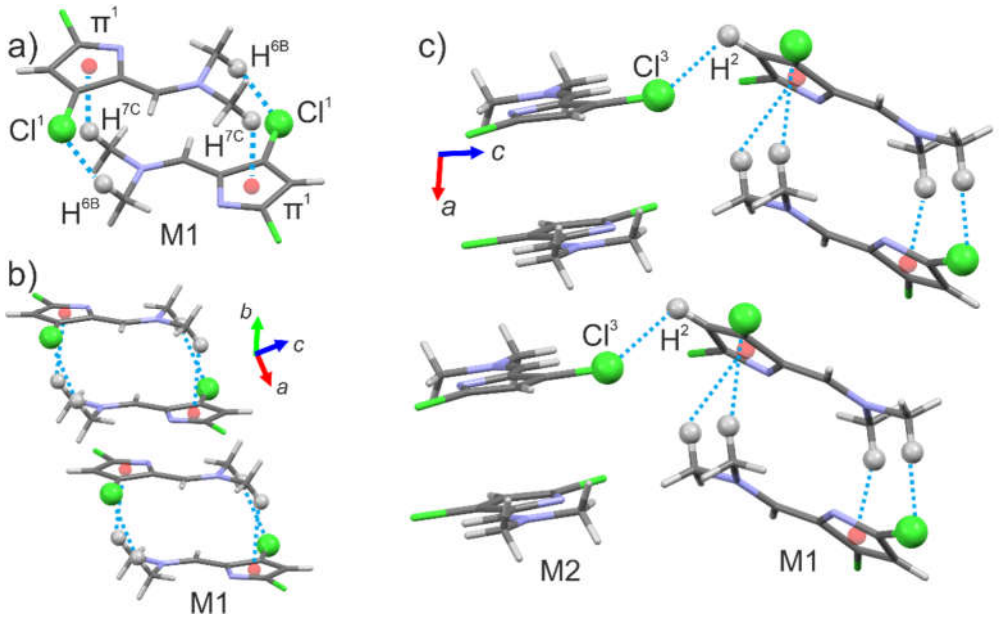

Figure 2. Fragments of R-HRH crystal structure forming a) dimer between M1 molecules connected by C_6-H···Cl_1 and C_7-H···π^1 interactions; b) chain of M1 molecules along *a*-axis; c) M1 and M2 chains along *a*-axis.

3. Materials and Methods

All chemicals were purchased from commercial sources and used without additional purification unless otherwise noted. The progress of reactions was monitored by thin-layer chromatography (TLC) on Sorbfil Silica 60 F254 on aluminum sheets with UV visualization. Column chromatography was performed by using 100–200 mesh silica gel. NMR spectra were recorded on Bruker Avance-400 (400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C) spectrometer; chemical shifts of ^{1}H and ^{13}C{^{1}H} are provided in ppm, with solvent signals serving as the internal standard (^{1}H = 7.24 ppm and ^{13}C = 77.16 ppm for $CDCl_3$). The masses of molecular ions were determined by high-resolution mass spectrometry (HRMS) by means of a DFS Thermo Scientific instrument (EI, 70 eV). X-ray diffraction data for compound was collected at 296 K using a Bruker KAPPA APEX II diffractometer with graphite monochromated MoK_α radiation. Absorption corrections were applied using SADABS [9]. The structure was solved by SHELXT [10]. Refinement was carried out by the full-matrix least-squares technique with SHELXL [10] using OLEX2 [11] software. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were calculated at idealized positions according to the riding model.

Synthesis of 2-chloro-1H-pyrrole (1).

5.17 ml (75 mmol) of pyrrole was added to 200 ml of dry CH_2Cl_2. The solution was cooled to -20°C. Then, to the cooled mixture a 10.46 g (78 mmol) of NCS was added. The obtained mixture was stirred for 10 min and was kept at the temperature -20°C for 2 hour. A 9.87 g (78 mmol) of Na_2SO_3 was added, the resulting mixture was stirred for 10 min. After that, 150 ml water and 100 ml CH_2Cl_2 were added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with water (3 × 100 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure at room temperature. The product was used without purification.

^{1}H NMR (δ, 300.13 MHz, $CDCl_3$): 6.11 (m, 1H, NH-CH=C<u>H</u>), 6.21 (t, 1H, J = 3.4 Hz, NH-CCl=C<u>H</u>), 6.66 (m, 1H, NH-C<u>H</u>=CH), 8.08 (s, 1H, NH).

Synthesis of (*Z*)-1-(3,5-dichloro-2H-pyrrol-2-ylidene)-*N*,*N*-dimethylmethanamine (2).

To an ice-cooled solution of 4.86 mL (52 mmol) $POCl_3$ a 4.03 mL (52 mmol) DMF was added dropwise an Ar atmosphere. After the addition, 70 ml of dry CH_2Cl_2 was added, and then a solution of 4.8 g (47 mmol) 2-chloro-1H-pyrrole in 50 ml dry CH_2Cl_2 was added dropwise while cooling to 0°C in an Ar atmosphere. The resulting mixture was stirred for 20 hours rt. After that, solution of 25 g

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Na_2CO_3 in 100 ml water was added, and the mixture was stirred for 50 min. Then, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was washed with water (3 × 100 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluent: EtOAc : Hex = 1 : 1. Light yellow solid. Yield = 2.27 g (37%).

^{1}H NMR (δ, 300.13 MHz, $CDCl_3$): 3.36 (s, 3H, Me_1), 3.72 (s, 3H, Me_2), 6.21 (s, 1H, Cy C-H), 7.22 (s, 1H, -C=C<u>H</u>-NMe_2).

^{13}C NMR (δ, 100.6 MHz, $CDCl_3$): 40.5, 47.5, 113.1, 126.3, 131.8, 144.2, 144.4.

HRMS (EI, *m*/*z*): calculated for $C_7H_8{}^{35}Cl_2N_2$ - 190.0059, found - 190.0063

X-ray Structure Determination: crystal data for $C_7H_8Cl_2N_2$, M = 191.05 g mol^{-1}, colourless elongated prism, crystal dimensions 1.00 × 0.62 × 0.18 mm, monoclinic, space group $P2_1/n$, a = 7.3574(3), b = 15.7753(6), c = 15.4311(6) Å, β = 100.599(2)°, V = 1760.46(12) Å^3, Z/Z′ = 8/2, D_{calc} = 1.442 g cm^{-3}, R1 = 0.037, wR2 = 0.109, R_{int} = 0.036, S = 1.05. Data have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2360994.

4. Conclusions

In summary, (*Z*)-1-(3,5-dichloro-2-pyrrolidin)-*N*,*N*-dimethylmethanamine was obtained as side product of 2-chloropyrrole formylation with Vilsmeier reagent.

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Data Availability Statement: The X-Ray data are available in a publicly accessible repository.

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

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