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Rearrangement of 5′,6′,7′,8′-tetrahydro-1′*H*-spiro(cyclohexane-1,2′-quinazolin)-4′(3′*H*)-one during the Vilsmeier reaction

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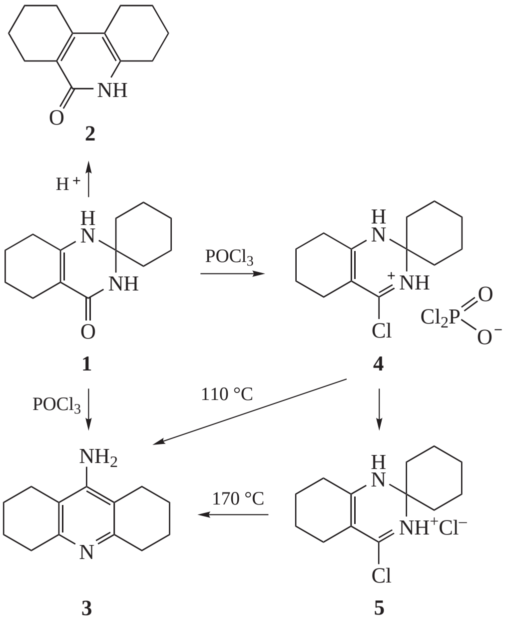
Treatment of 5′,6′,7′,8′-tetrahydro-1′*H*-spiro(cyclohexane-1,2′-quinazolin)-4′(3′*H*)-one with $POCl_3$ and DMF gives a mixture of 1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile and 4,5-diformyl-2,3,6,7,8,10-hexahydroacridine-8a(1*H*)-carbonitrile, both products resulting from cascade transformations of the primary Vilsmeier intermediates.

5′,6′,7′,8′-Tetrahydro-1′*H*-spiro(cyclohexane-1,2′-quinazolin)-4′(3′*H*)-one **1** available from cyclohexanone and urea[1,2] is known to undergo interesting acid-catalyzed rearrangements.[2,3] On treatment with strong acids such as TsOH or polyphosphoric acid at 220 or 135 °C, respectively, octahydrophenanthridone **2** is formed[3] (Scheme 1). On refluxing compound **1** in toluene with 8 to 10-fold excess of $POCl_3$ for 10–24 h, 10-aminooctahydroacridine **3** is produced.[4] When the reaction time is shortened to 1 h, imidoyl chloride salt **4** can be isolated. This salt can be transformed into the related hydrochloride **5** when carefully treated with methanol or water. Both salts are readily converted into aminoacridine derivative **3** on heating to 110 or 170 °C, respectively[4] (Scheme 1).



Scheme 1

Herein, we studied the Vilsmeier formylation of spiro compound **1** anticipating to obtain the typical monoformyl derivative. Instead, two other unexpected products **6** and **7** were isolated (Scheme 2).

The structure of the products obtained was established from IR, ^{1}H and ^{13}C NMR and mass spectra.[5,†,‡] Additionally, X-ray analysis was carried out for diformyl derivative **7**, which ultimately confirmed its structure (Figure 1, for detailed description, see Online Supplementary Materials).[§]

To study the mechanism of the formation of derivatives **6** and **7**, imidoyl chloride **5** was similarly treated with DMF and $POCl_3$. Considering that imidoyl chloride **5** is thermally stable and cannot rearrange under these conditions, the next step in the process should be an electrophilic attack of the Vilsmeier reagent on molecule **5**. This attack may be directed to carbon atoms A or B (see Scheme 2). In fact, when imidoyl chloride **5** was a starting material, the yield of final products was higher,

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[†] Compound **6** was obtained earlier from octahydroacridine, Pr^i_2NLi and Pr^i_2NCN.[5]

[‡] *1,2,3,4,5,6,7,8-Octahydroacridine-4-carbonitrile* **6** *and 4,5-diformyl-2,3,6,7,8,10-hexahydroacridine-8a(1*H*)-carbonitrile* **7**.

Procedure A. 11 ml of $POCl_3$ was gradually added to 12 ml of DMF with stirring and ice-cooling, and the mixture was allowed to stay at room temperature for 0.5 h. Then, 8.8 g (0.04 mol) of compound **1** suspended in 10 ml of DMF was added to this mixture with stirring and ice-cooling. The reaction mixture was allowed to stay at room temperature for 4–5 days, then poured onto ice, and neutralized with K_2CO_3 solution. The solid precipitate was filtered off and treated with ethanol; the insoluble part was 1.1 g (10%) of compound **7**, mp 255–257 °C. It was purified by crystallization from DMF. IR (KBr, ν/cm^{-1}): 3462, 3047, 2958, 2841, 2226, 1667, 1635, 1548, 1435, 1127, 846. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 13.03 (s, 1H), 9.44, 9.56 (2s, 2 H), 6.15 (s, 1H), 1.63–2.90 (m, 12 H). ^{13}C NMR (100 MHz, DMSO-d_6): 18.2, 21.5, 22.0, 24.1, 29.4, 31.9, 35.8, 110.1, 110.7, 118.8, 124.4, 132.0, 138.3, 140.2, 192.1, 194.1. ESI-MS, *m/z*: 268 (M^+).

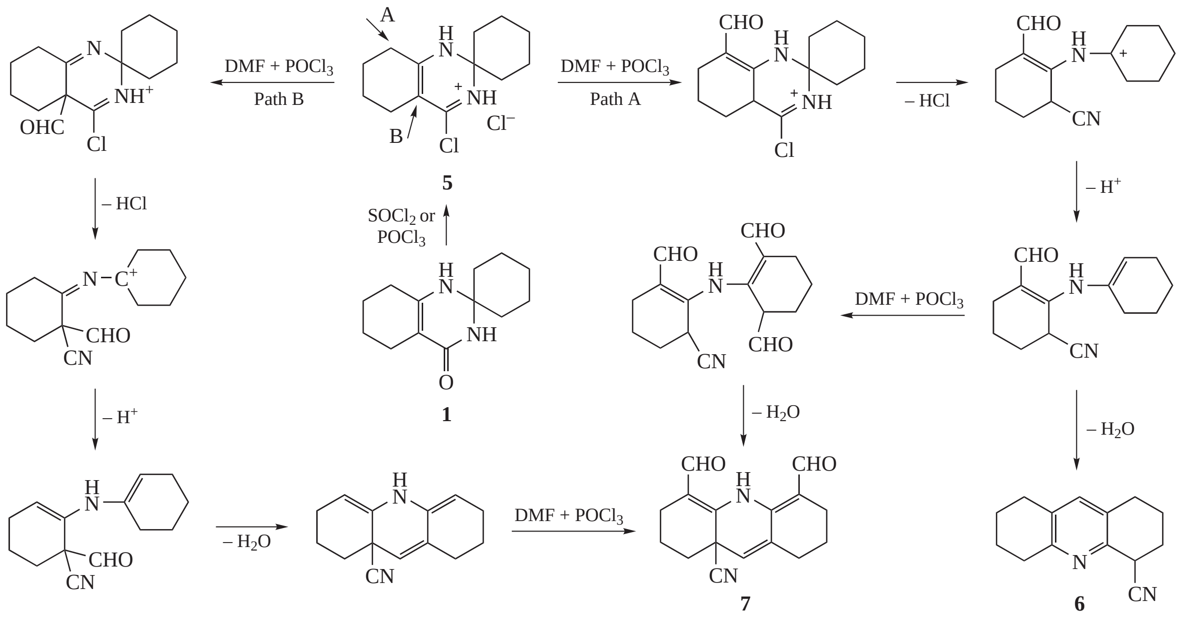
The ethanol solution was diluted with water, the precipitate formed was filtered off and dried. The yield of **6** was 3.5 g (42%), mp 92 °C (lit.,[5] 88–90 °C). IR (KBr, ν/cm^{-1}): 2937, 2855, 2237, 1600, 1561, 1452, 710. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.30 (s, 1H), 4.27 (distorted dd, 1H, J_{cis} 5.92 Hz, J_{trans} 6.22 Hz), 1.60–2.80 (m, 14H). ESI-MS, *m/z* (%): 212 (M^+).

*Procedure B. Step 1. 4'-Chloro-5',6',7',8'-tetrahydro-1'*H*-spiro(cyclohexane-1,2'-quinazoline) hydrochloride* **5**. Thionyl chloride (1.9 ml) was added to a suspension of spiroquinazoline **1** (6 g, 0.027 mol) in 30 ml of toluene with stirring and ice-bath-cooling. The mixture was stirred for 1 h and allowed to stay at room temperature for 15 h. The precipitate was filtered off and washed with diethyl ether, the yield of salt **5** was 7.3 g (98%), mp 160 °C (lit.,[4] 157–160 °C).

Step 2. 0.36 ml (0.004 mol) of $POCl_3$ was added to 0.93 ml of DMF with stirring and ice-cooling and allowed to stay at room temperature for 0.5 h. This mixture was then added with stirring and ice-cooling to a solution of hydrochloride **5** (1 g, 0.004 mol) in 2 ml of DMF and left overnight. The products were isolated as in the procedure A. Yield of **6** was 0.41 g (53%), mp 90–91 °C; yield of **7** was 0.1 g (10%), mp 255–257 °C.

Similarly, when 1 g (0.004 mol) of hydrochloride **5**, 1.1 ml (0.012 mol) of $POCl_3$ and 5 ml of DMF were used, yield of **6** was 0.1 g (12%), mp 90 °C and yield of **7** was 0.4 g (40%), mp 255–257 °C.

For spectral characteristics of compounds **6** and **7**, see also Online Supplementary Materials.



Scheme 2

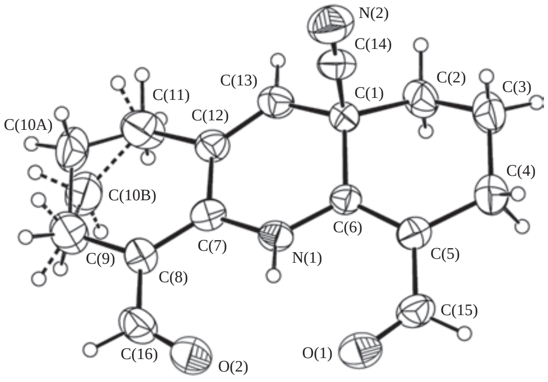


Figure 1 Molecular structure of compound **7**. Displacement ellipsoids of non-hydrogen atoms shown at 30% probability level.

which confirms our supposition of the initial formation of salt **5** during the course of the process.

Formylation at atom A leads to cyclization with the formation of aromatic pyridine ring and the termination of the process, whereas formylation at atom B prevents aromatization, so the second formylation becomes possible. An alternative way of compound **7** formation by formylation at atom A seems less rational.

Compound **1** is known to add electrophiles at the same positions in chlorination and the Mannich aminomethylation,[2,6] which indirectly confirms the suggested reaction route. The mechanism of formation of a hydrogenated pyridine cycle is to some extent analogous to that of the Povarov reaction.[7]

In compound **7**, both formyl groups do not possess typical aldehyde properties due to the conjugation with NH groups. Moreover, NH group of this compound is acidic enough and gives salts on treatment with alkalis. Such chemical properties of compound **7** comply with its IR and NMR spectral data.

To conclude, we believe that analogous rearrangements accompanying the formylation may also occur in other similar systems lacking spiro fragments. At present, such investigations are in progress where influence of the steric and electronic factors on the rearrangement direction are studied. Using this rearrangement, we aim to access new syntheses of pyridine, quinoline and acridine derivatives.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.03.017.

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[§] *Crystal data*. X-ray diffraction study of the single crystal of compound **7** ($C_{16}H_{16}N_2O_2$, $M = 268.31$, monoclinic, space group $P\bar{1}$) was performed on an Xcalibur 3 diffractometer (graphite monochromated MoKα radiation, $\lambda = 0.71073$ Å). At 298 K: $a = 8.288(6)$, $b = 8.352(5)$ and $c = 10.055(4)$ Å, $\beta = 105.07(5)°$, $V = 671.8(7)$ Å^3, $Z = 2$, $d_{calc} = 1.326$ g cm^{-3}, μ(MoKα) = = 0.09 mm^{-1}. 5070 reflections were measured up to $\theta_{max} = 50.0°$, 2361 unique ($R_{int} = 0.072$) which were used in all calculations. Structure was solved by direct methods and refined by full-matrix least squares using SHELX-97[8] software. H-atoms positions were located from difference electron density maps and refined in riding model approximation with $U_{iso} = 1.2U_{eq}$ of the carrier atom. During refinement C_{sp^3}–C_{sp^3} bond length in disordered fragment were restrained to 1.520(5) Å. Refinement was converged at $wR_2 = 0.267$ (all data), $R_1 = 0.089$ [952 reflections with $I > 2\sigma(I)$], GOF = 1.01.

CCDC 821558 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.