# Regioselective *ortho*-formylation of hydroxy-substituted spironaphthooxazine

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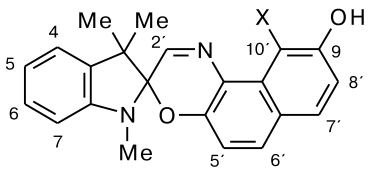
Formylation of photochromic 9´-hydroxy-1,3,3-trimethyl-1,3-dihydrospiro[2*H*-indole-2,3´-3´*H*-naphtho[2,1-*b*][1,4]oxazine] with the paraformaldehyde—$MgCl_2$—$Et_3N$ system or by the Reimer—Tiemann reaction proceeds at the *ortho*-position to the hydroxy group to form 10´-formyl derivative.

**Key words:** formylation, the Reimer—Tiemann reaction, paraformaldehyde, spiro[indole-2,3´-naphtho[2,1-*b*][1,4]oxazines].

*o*-Hydroxybenzaldehydes are known as valuable intermediates in organic chemistry.[1] Photochromic spironaphthooxazines containing this structural fragment could have been used for further modifications in the synthesis of new photochromic bi- and polyfunctional compounds, promising objects for the development of molecular switches and logical devices.[2—4]

Formylation of aromatic compounds is an important reaction in organic chemistry.[5] At the same time, its application often requires the use of dangerous reagents[6] or is characterized by low yields of the target products.[5] In the present work, we successfully used two methods for the formylation of photochromic 9´-hydroxy-1,3,3-trimethyl-1,3-dihydrospiro[2*H*-indole-2,3´-3´*H*-naphtho[2,1-*b*]-[1,4]oxazine] (**1**).




**1, 2**

X = H (**1**), CHO (**2**)

We assumed that the hydroxy group present in the molecule of compound **1** would facilitate the formylation and make it more regioselective. We first used already known method for the formylation of phenols with paraformaldehyde in the presence of anhydrous magnesium dichloride and triethylamine.[7] According to the literature data, this method is simple to perform, provides good yields with low content of side products. We obtained by this method the only product **2** in 23% yield, whose structure was established by $^1$H NMR spectroscopy (Table 1) and elemental analysis.

Then, we carried out formylation of the starting compound **1** by a modified Reimer—Tiemann method[8] using a phase-transfer catalyst to obtain the same product **2** in 20% yield.

Both reactions are accompanied by the formation of side products and incomplete conversion of the starting compound **1**, that makes isolation of the target product **2** difficult. According to the TLC data, conversion of **1** is higher than 50%, however, chromatographic isolation of product **2** on silica gel gives only low preparative yield for it, apparently, due to decomposition of **2** on the adsorbent. Though both formylation methods used in this work allow one to reach virtually the same yields of the target product, formylation with paraformaldehyde in the presence of the anhydrous magnesium dichloride—triethylamine system seems more preferable, since it is simpler to carry out, leads to the formation of lesser amount of side products and, therefore, makes it possible to isolate and reuse the starting compound.

Comparison of the $^1$H NMR spectra of compounds **1** and **2** in $CDCl_3$ unambiguously indicates that the formyl group in compound **2** is at position 10´ (see Table 1). The spectrum of product **2** has no doublet for H(10´), the doublet of doublets for H(8´) is transformed to a doublet with the *ortho*-constant 8.9 Hz, the signal for H(7´) is displaced downfield by 0.17 ppm, since the H(7´) atom is in the *para*-position with respect to the electron-withdrawing formyl group. The signal at δ 11.37 was assigned to the aldehyde proton. Assignment of the most downfield signal at δ 13.8 to the hydroxyl proton was confirmed by the experiment with addition of $D_2O$ to a solution of compound **2** in $CDCl_3$, which resulted in almost complete

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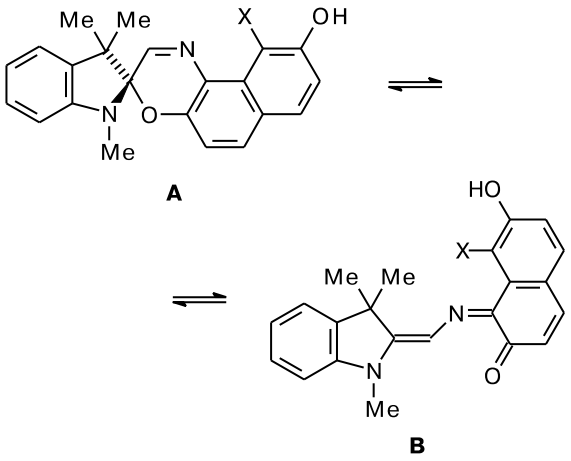
**Table 1.** $^1$H NMR spectra of photochromic spiro compounds at 25 °C in $CDCl_3$

| Compound | δ (*J*/Hz) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $CMe_2$ | NMe | H(4) | H(5) | H(6) | H(7) | H(2′) | H(5′) | H(6′) | H(7′) | H(8′) | H(10′) | OH | CHO |
| **1** | 1.35 (s), 1.36 (s) | 2.76 (d) | 7.09 (d, *J* = 7.2) | 6.90 (t, *J* = 7.3) | 7.22 (dd, *J* = 7.8, *J* = 7.3) | 6.58 (d, *J* = 7.8) | 7.71 (s) | 6.84 (d, *J* = 8.8) | 7.58 (d, *J* = 8.8) | 7.65 (dd, *J* = 8.8) | 7.02 (d, *J* = 8.8, *J* = 2.5) | 7.87 (d, *J* = 2.5) | 6.00 (br.s) | — |
| **2** | 1.35 (s), 1.57 (s) | 2.80 (s) | 7.09 (d, *J* = 7.2) | 6.92 (t, *J* = 7.3) | 7.24 (dd, *J* = 7.8, *J* = 7.3) | 6.60 (d, *J* = 7.8) | 7.70 (s) | 6.91 (d, *J* = 8.8) | 7.59 (d, *J* = 8.8) | 7.82 (d, *J* = 8.9) | 7.01 (d, *J* = 8.9) | — | 13.80 (s) | 11.37 (s) |

disappearance of this signal due to the exchange process. Such a strong downfield shift of the signal for the OH group in the spectrum of compound **2** as compared to **1** is due to a hydrogen bond with the neighboring formyl group in compound **2**.

From the conditions for the formylation reaction of compound **1** with paraformaldehyde, $MgCl_2$, and triethylamine, it follows that both the closed spirocyclic form **A** and opened merocyanine form **B** present in the solution in thermal equilibrium can react under weakly basic conditions (Scheme 1).

**Scheme 1**




In the molecule of 2-naphthol, which is a good model of the right parts of both forms **A** and **B** of compound **1** because of the remote position of the phenol hydroxy group from the spiro cycle to be opened, formylation by different methods occurs exclusively at position 1, that is due to its highest nucleophilicity.[9] Apparently, possible steric hindrance, which can be created in the molecule of **1** by the annulated 1,4-oxazine ring, plays no decisive role in the formation of the intermediate products resulting in formylation at position 10′.

The Reimer—Tiemann reaction proceeds under strongly basic conditions, *i.e.* the corresponding phenoxide anion of the closed form **A** or merocyanine form **B** reacts with the intermediate dichlorocarbene and again, like with 2-naphthol, the product of 10′-formylation is formed.

Compound **2** possesses photochromic properties. The electronic absorption spectra of compound **2** in toluene (Fig. 1), ethanol, and acetonitrile under exposure to the UV irradiation exhibit a new strong structured absorption band in the visible region of the spectrum with the maximum about 620 nm, that is due to the transition of the molecule from the starting spirane form **A** to the photoinduced form **B** with the dissociated C—O spiro bond. For the colored form of compound **2**, no noticeable shift of the long-wave maximum is observed in the absorption spectra with the increase in polarity of the solvent ($\lambda_{max}$ = 609 nm in toluene, 613 nm in ethanol, and 612 nm in acetonitrile), that apparently indicates the presence of a labile equilibrium between the bipolar and quinonoid structures of the opened form **B**. For the solutions of compound **2** in toluene and acetonitrile, the high rate of thermal relaxation of the photoinduced merocyanine form to the starting spi-

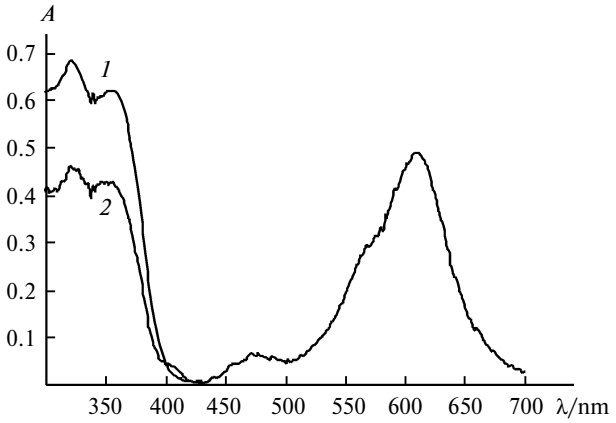



**Fig. 1.** Electronic absorption spectra of compound **2** in toluene before (*1*) and after exposure to the light with λ = 365 nm at 10 °C (*2*); $C = 1 \cdot 10^4$ mol $L^{-1}$.

rane one is observed. The highest stability of the colored form at room temperature is observed in the case of the solution of **2** in ethanol, which likely results from the stabilization of the opened form due to the specific interaction (by the formation of hydrogen bonds) with the solvent molecules.

## Experimental

NMR spectra were recorded on a Bruker WM-400 spectrometer at 25 °C in $CDCl_3$, absorption spectra were recorded on a Multi-Spec-1501 spectrophotometer. Acetonitrile, toluene, and ethanol of spectrophotometric grade were used as solvents. Samples cooled to 10 °C were exposed to the light of the DRSh-1000 lamp through the interference optical filter ($\lambda$ = 365 nm).

Plates with silica gel (Merck) and the benzene—acetone (9 : 1) solvent system were used for TLC, silica gel 35—70 μm (Aldrich) was used for column chromatography. Anhydrous $MgCl_2$ (Sigma) was used in the reactions; anhydrous MeCN and anhydrous $Et_3N$ were obtained by distillation over $CaH_2$, paraformaldehyde was dessicated over $P_2O_5$.

9′-Hydroxy-1,3,3-trimethyl-1,3-dihydrospiro[2*H*-indole-2,3′-3′*H*-naphtho[2,1-*b*][1,4]oxazine] (**1**) was synthesized according to the method described earlier.[10]

**10′-Formyl-9′-hydroxy-1,3,3-trimethyl-1,3-dihydrospiro-[2*H*-indole-2,3′-3′*H*-naphtho[2,1-*b*]oxazine] (2).** ***A.*** A mixture of hydroxyspirooxazine **1** (0.344 g, 1 mmol), anhydrous $MgCl_2$ (0.1425 g, 1.5 mmol), and anhydrous $Et_3N$ (0.38 g, 3.75 mmol) in anhydrous MeCN (20 mL) was stirred for 15 min in a flask purged with argon and equipped with a magnetic stirrer and a reflux condenser. Then, anhydrous paraformaldehyde (0.2 g, 6.75 mmol) was added to the thus formed blue solution, which was refluxed for 5 h at 75 °C. The solution was cooled to ~20 °C and poured into water (20 mL), followed by addition of HCl (2 *M*) to pH = 4—5 and extraction with diethyl ether. The extract was washed with brine (50 mL) and water until neutrality. The ethereal layer was dried with $MgSO_4$. The solvent was evaporated on a rotary evaporator and the residue was subjected to column chromatography on silica gel with benzene as an eluent. Photochromic fraction with $R_f$ = 0.82 (benzene—acetone (9 : 1)) was isolated, which was compound **2** (0.03 g, 23%), light beige powder, m.p. 169—173 °C. Found (%): C, 73.80; H, 5.67; N, 7.55. $C_{23}H_{20}N_2O_3$. Calculated (%): C, 74.18; H, 5.41; N, 7.52.

***B.*** A mixture of hydroxyspirooxazine **1** (0.344 g, 1 mmol), NaOH (0.32 g, 8 mmol) in water (1 mL), cetyltrimethylammonium bromide (0.004 g), and 1,4-dioxane (1 mL) with 4% of isobutanol was stirred for 0.5 h in a flask equipped with a magnetic stirrer and an efficient reflux condenser at 65—70 °C, then chloroform (0.16 mL, 2 mmol) was added keeping the temperature ~70 °C, heating and stirring were continued for another 2 h. The reaction mixture was cooled to ~20 °C, HCl (2 *M)* was added carefully to pH = 5—6, and the mixture was extracted with chloroform (4×10 mL). The combined extract was washed with water and dried with sodium sulfate. The solvent was evaporated on a rotary evaporator and the residue was subjected to column chromatography on silica gel with benzene as an eluent. Photochromic fraction with $R_f$ = 0.82 (benzene—acetone (9 : 1)) was isolated (0.06 g, 19.9%), m.p. 159—163 °C, light beige powder, which was identical to product **2** synthesized by method ***A*** in its m.p., TLC data, and $^1$H NMR spectrum.

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