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# Unexpected aspect of the Fischer indolization of propiophenone (5-chloro-2-methoxyphenyl)hydrazone

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**The Fischer indolization of propiophenone (5-chloro-2-methoxyphenyl)hydrazone gives 4-chloro-7-methoxy-3-methyl-2-phenyl-1*H*-indole and unexpected 6-chloro-3-methoxy-3-methyl-2-phenyl-3*H*-indole.**

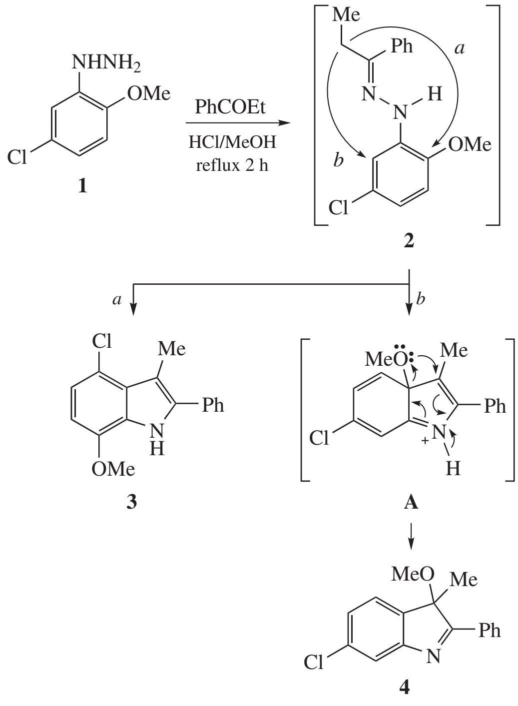
The Fischer rearrangement has been known since late 19th century; however, publications that uncover new aspects of its mechanism continue appearing in the literature.[1] Most reports are concerned with the abnormal course of this reaction and are summarized in ref. 2.

According to data reported so far,[2,3] arylhydrazones bearing alkoxy or alkylthio groups at the *ortho* position give several other products apart from the expected 7-alkoxy- or 7-alkylthioindoles. These reactions are characterized as *ortho*-C-6 abnormal Fischer indolizations.

During systematic studies undertaken by our research group on the synthesis of 2-arylhydroxyindoles with fungicidal properties,[4] we decided to accomplish the Fischer indole synthesis starting from (5-chloro-2-methoxyphenyl)hydrazine **1** and appropriate ketones. To this, (5-chloro-2-methoxyphenyl)hydrazine **1** was condensed with propiophenone by heating in HCl/MeOH (generated by dissolution of acetyl chloride in MeOH) and the crude intermediate hydrazone **2** was subjected to the Fischer cyclization by heating in the same medium (Scheme 1). Two products were isolated from this reaction, 7-methoxyindole **3** (formed through pathway *a*, yield 26%) and indoline **4** (formed through pathway *b*, yield 11%).

Indoline **4** is probably produced due to the migration of the methoxy group from position 3a to position 3 of the intermediate **A** and subsequent aromatization of the benzene moiety.

The structures of compounds **3** and **4** were established using NMR spectroscopy, mass spectrometry, elemental analysis[†] and X-ray analysis (for **4**, Figure 1).[‡] All signals in the $^1$H and $^{13}$C NMR spectra of compounds **3** and **4** were assigned on the basis of the



**Scheme 1**

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[†] NMR spectra were measured on a Bruker AM-300 spectrometer in DMSO-$d_6$ solutions at 300 and 75 MHz for $^1$H and $^{13}$C, respectively.

For **3**: yield 26%, mp 96–97 °C. $^1$H NMR, $\delta$: 2.54 (s, 3H), 3.91 (s, 3H), 6.62 (d, 2H, *J* 8.3 Hz), 6.91 (d, 2H, *J* 8.2 Hz), 7.36–7.40 (m, 1H), 7.46–7.51 (m, 2H), 7.55–7.60 (m, 2H), 11.45 (s, 1H). $^{13}$C NMR, $\delta$: 102.50, 107.23, 110.46, 116.87, 119.46, 125.82, 127.36, 127.46, 128.27, 128.94, 132.08, 135.93, 145.21. Found (%): C, 70.59; H, 5.02; N, 5.08. Calc. for $C_{16}H_{14}ClNO$ (%): C, 70.72; H, 5.19; N, 5.15. HRMS, *m/z*: 272.0843 (calc. for $[M+H]^+$: 272.0837).

For **4**: yield 11%, mp 112–113 °C. $^1$H NMR, $\delta$: 1.58 (s, 3H), 2.82 (s, 3H), 7.39 (d, 1H, *J* 7.6 Hz), 7.49 (d, 1H, *J* 7.8 Hz), 7.58–7.60 (m, 3H), 7.68 (s, 1H), 8.25 (d, 2H, *J* 7.1 Hz). $^{13}$C NMR, $\delta$: 24.36, 52.55, 89.24, 121.03, 123.67, 126.20, 127.71, 128.96, 131.06, 131.95, 133.99, 137.72, 153.87, 179.86. Found (%): C, 70.43, H, 5.06, N, 5.10. Calc. for $C_{16}H_{14}ClNO$ (%): C, 70.72; H, 5.19; N, 5.15. HRMS, *m/z*: 272.0839 (calc. for $[M+H]^+$: 272.0837).

[‡] *Crystallographic data.* Crystals of **4** ($C_{16}H_{14}ClNO$, $M$ = 271.73) are orthorhombic, space group $P2_12_12_1$, at 120 K: $a$ = 6.5442(8), $b$ = 9.7896(11) and $c$ = 21.292(2) Å, $V$ = 1364.1(3) Å$^3$, $Z$ = 4 ($Z'$ = 1), $d_{\mathrm{calc}}$ = 1.323 g cm$^{-3}$, $\mu$(MoK$\alpha$) = 2.71 cm$^{-1}$, $F$(000) = 568. Intensities of 11787 reflections were measured with a Bruker SMART 1000 CCD diffractometer [$\lambda$(MoK$\alpha$) = 0.71072 Å, $\omega$-scans, $2\theta < 56°$] and 3575 independent reflections [$R_{\mathrm{int}}$ = 0.0439] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against $F^2$ in the anisotropic–isotropic approximation. The H(C) atom positions were calculated and refined in the isotropic approximation in riding model with the $U_{\mathrm{iso}}$(H) parameters equal to 1.2$U_{\mathrm{eq}}$(C$_i$), for methyl groups equal to 1.5$U_{\mathrm{eq}}$(C$_{ii}$), where $U$(C$_i$) and $U$(C$_{ii}$) are the equivalent thermal parameters of the carbon atoms to which corresponding H atoms are bonded. The refinement converged to $wR_2$ = 0.1073 and GOF = 1.005 for all independent reflections [$R_1$ = 0.0445 was calculated against $F$ for 2819 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[5]

CCDC 851897 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, 2011.

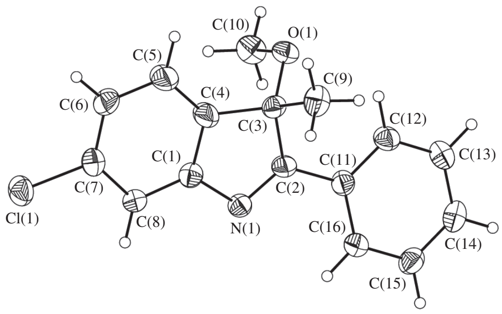

**Figure 1** General view of the molecule of **4** in representation of atoms *via* thermal ellipsoids at 50% probability level.

2D NOESY, HSQC and HMBC spectra. The most marked difference in the $^1$H NMR spectra of products **3** and **4** is the position of signals of the methyl and methoxy groups at C-3 and C-7 carbon atoms (in **3**). Where both groups are located at C-3 in **4**, their chemical shifts are 1.58 and 2.82 ppm, whereas in **3** they are 2.54 and 3.91 ppm, respectively. In addition, cross-peaks were detected between protons of the methoxy group and H-6 (6.62 ppm) in the NOESY spectrum of **3**, meanwhile in **4** correlations of the methoxy group protons with H-4 (7.49 ppm) and with the 2-phenyl group *ortho* protons (8.25 ppm) were observed, which confirms their spatial proximity. In the $^{13}$C NMR spectra of compounds **3** and **4**, essential differences were found as well, particularly in the chemical shifts of C-2 (135.93 ppm for **3** and 179.86 ppm for **4**) and C-3 (110.46 and 89.24 ppm, respectively). The signals from quaternary carbon atoms were assigned on the basis of the correlations with protons *via* two or three bonds in the HMBC spectrum.

Although indolines of type **4** are known,[6] they have been prepared by another route. Their Fischer rearrangement-based synthesis has been presented in this paper for the first time.

In conclusion, we have found out a new product, 6-chloro-3-methoxy-3-methyl-2-phenyl-3*H*-indole, obtained by the abnormal Fischer indolization of propiophenone (5-chloro-2-methoxyphenyl)hydrazone.

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