Synthesis of 1*H*- and 1-vinyl-2-pyridylpyrroles by the Trofimov reaction

Olga V. Petrova, Albina I. Mikhaleva,* Lyubov N. Sobenina, Elena Yu. Schmidt and Emilia I. Kositsyna

Irkutsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 35 6046; e-mail: admin@irioch.irk.ru

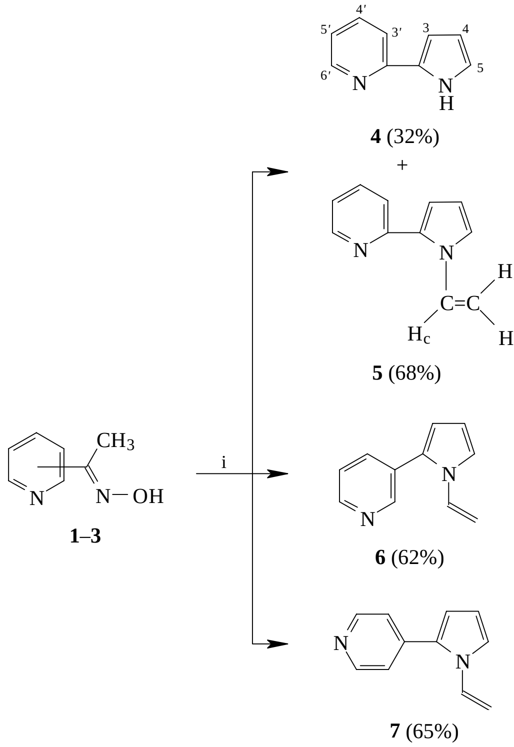
A one-pot synthesis of 2-(2-pyridyl)-1*H*-pyrrole and 1-vinyl-2-(2-pyridyl)-, 1-vinyl-2-(3-pyridyl)- and 1-vinyl-2-(4-pyridyl)-pyrroles from oximes of 2-acetyl-, 3-acetyl- and 4-acetylpyridine and acetylene under pressure (16–25 atm) in a KOH/DMSO system has been carried out (105–120 °C, 3 h) to reveal for the first time the applicability of the Trofimov reaction for the preparation of alkaloids of the nicotine series.

Among numerous synthetic routes to substituted pyrroles the preparation of pyrroles with pyridine substituents occurs infrequently and is not efficient. Thus, 1-methyl-2-(3-pyridyl)-pyrrole (nicotyrine) was prepared either by irradiation of a benzene nicotine solution containing benzophenone[1] or by desulfuration of bis[1-methyl-2-(3-pyridyl)pyrrol-3-yl]disulfide in the presence of the Raney nickel in THF.[2] Compounds of this type are of interest as analogues of the natural alkaloid, nicotine.

The goal of the present work was to investigate whether a one-pot transformation of oximes of 2-acetylpyridine **1**, 3-acetylpyridine **2** and 4-acetylpyridine **3** to 1*H*- **4** and 1-vinyl-2-pyridylpyrroles **5**–**7** could be carried out by the Trofimov reaction.[3–6]

A study of oxime acetylpyridine pyrrolization (with oxime **1** as an example) under atmospheric acetylene pressure (115–120 °C, 6 h) has shown the pyrrole **4** to be the only reaction product (6%, GLC). Regeneration of 2-acetylpyridine (50%) becomes the prevailing reaction seemingly due to the nucleophilic addition of hydroxy anion to the oxime C=N bond.

Under comparable conditions (100–120 °C, 6–8 h, atmospheric acetylene pressure) it is possible to obtain from alkylfuryl-(thienyl)ketoximes and acetylene a mixture of heteroarylpyrroles and their *N*-vinyl derivatives in total yield 50–60%, ketones being formed in negligible amounts.[7,8] Dialkyl- and alkylheteroarylketoximes undergo pyrrolization with the same ease.[3] Thus, the decrease in reactivity in going to 2-acetylpyridine oxime is evident.



Reagents and conditions: i, HC≡CH, KOH/DMSO.

Heating (105–110 °C, 3 h) of the oxime **1** with acetylene under pressure (initial pressure 16 atm) in the presence of an equimolar quantity of KOH gives a mixture of pyrroles **4** and **5** (yield 32 and 36%, respectively) which can be separated by preparative TLC.[†]

Increasing of the temperature up to 120 °C (under the same reaction conditions) leads selectively to *N*-vinyl derivative **5** (yield 68%).

The *N*-vinylpyrroles **6** (yield 62%) and **7** (yield 65%) were

---

[†] *General experimental details.* NMR spectra ^{13}C (125.7 MHz) and ^{1}H (500 MHz) were recorded on a Varian VXR-500 spectrometer. ^{13}C NMR spectra of oximes ([^{2}H$_6$]DMSO) δ: **1** 154.45, 154.32 (C=N, C-2), 148.24 (C-6), 135.73 (C-4), 122.88, 119.38 (C-3, C-5), 9.77 (CH_3); **2** 151.21 (C=N), 149.18, 146.64 (C-2, C-6), 132.85 (C-4), 132.71 (C-3), 123.24 (C-5), 11.15 (CH_3); **3** 151.47 (C=N), 149.64 (C-2, C-6), 144.14 (C-4), 119.83 (C-3, C-5), 10.66 (CH_3). ^{13}C–^{13}C SSCC measurements were performed by ^{13}C satellite analysis employing the INADEQUATE technique.

A typical experimental procedure for the synthesis of 2-(2-pyridyl)-1*H*-pyrrole **4** and 1-vinyl-2-pyridylpyrroles **5**–**7** is as follows:
(*a*) The corresponding oxime (**1**–**3**) and an equimolar quantity of KOH in 20–25 ml of DMSO were heated (120 °C) with acetylene (initial pressure 16 atm at room temperature and 25 atm at the reaction temperature) in a rotating autoclave (0.25 l) for 3 h. Dilution with water (1 : 3), extraction with diethyl ether and vacuum distillation gave *N*-vinylpyrroles **5**–**7**.
(*b*) At 105–110 °C and under otherwise equal conditions from the oxime **1** the pyrroles **4** (yield 32%) and **5** (yield 36%) were prepared as a mixture and isolated by preparative TLC [Al_2O_3, petroleum ether (bp 70–100 °C) : ether = 3 : 1].

For **4**: yield 32%, mp 88–89 °C (from petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.82 (br. s, H-1), 8.45 (d, H-6′), 7.62 (td, H-4′), 7.54 (m, H-3′), 7.04 (t, H-5′), 6.88 (t, H-5), 6.70 (t, H-3), 6.28 (t, H-4). IR (ν/cm^{-1}, KBr): 600, 620, 650, 700, 730, 740, 770, 870, 920, 990, 1030, 1095, 1110, 1140, 1150, 1280, 1310, 1440, 1470, 1550, 1595, 3460 (NH in CCl_4). Calc. for $C_9H_8N_2$ (%): C 74.97, H 5.59, N 19.43. Found (%): C 74.83, H 5.72, N 19.21. MS, *m/z*: 144 (M$^+$).

For **5**: yield 68%, bp 121–122 °C (3 mmHg), d_4^{20} 1.2190, n_D^{20} 1.6458. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.61 (d, H-6′), 7.86 (dd, H-c), 7.75 (td, H-4′), 7.54 (d, H-3′), 7.22 (m, H-5), 7.08 (m, H-5′), 6.58 (dd, H-3), 6.28 (t, H-4), 5.19 (d, H-a, J_{trans} 15.8 Hz), 4.75 (d, H-b, J_{cis} 8.8 Hz). IR (ν/cm^{-1}): 610, 660, 720, 780, 870, 970, 1000, 1040, 1080, 1110, 1150, 1195, 1250, 1270, 1295, 1330, 1405, 1450, 1480, 1595, 1640, 3000, 3040, 3100. Calc. for $C_{11}H_{10}N_2$ (%): C 77.62, H 5.92, N 16.46. Found (%): C 77.08, H 6.75, N 16.41.

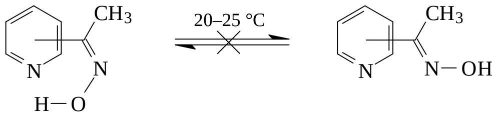
For **6**: yield 62%, bp 148–150 °C (4 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.65 (dd, H-2′), 8.54 (dd, H-6′), 7.67 (dt, H-4′), 7.32 (dd, H-5′), 7.83 (dd, H-c), 7.15 (t, H-5), 6.32 (m, H-3, H-4), 5.20 (dd, H-a), 4.75 (dd, H-b). IR (ν/cm^{-1}): 595, 605, 650, 705, 795, 805, 875, 950, 980, 1025, 1060, 1080, 1110, 1120, 1190, 1245, 1295, 1305, 1320, 1350, 1400, 1430, 1450, 1470, 1490, 1570, 1595, 1640, 3020, 3100. Calc. for $C_{11}H_{10}N_2$ (%): C 77.62, H 5.92, N 16.46. Found (%): C 76.90, H 6.32, N 15.73.

For **7**: yield 65%, bp 112–115 °C (1 mmHg), mp 30–31 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.58 (d, H-2′, H-6′), 7.23 (d, H-3′, H-5′), 7.11 (dd, H-5), 6.88 (dd, H-c), 6.40 (dd, H-3), 6.29 (t, H-4), 5.22 (dd, H-a), 4.79 (dd, H-b). IR (ν/cm^{-1}): 495, 580, 595, 630, 670, 720, 805, 815, 870, 950, 990, 1030, 1050, 1080, 1180, 1205, 1245, 1295, 1305, 1315, 1350, 1400, 1420, 1460, 1495, 1540, 1600, 1640, 3020, 3100. Calc. for $C_{11}H_{10}N_2$ (%): C 77.62, H 5.92, N 16.46. Found (%): C 77.18, H 6.37, N 15.97.

prepared selectively from oximes of 3-acetylpyridine **2** and 4-acetylpyridine **3**, respectively, at 120 °C (3 h, initial acetylene pressure 16 atm).

In analysing the reasons for this fact it should be noted that the starting oximes **1**–**3** are pure *E*-isomers (IR, NMR). Thus, in the IR spectrum ($CHCl_3$) for oxime **1** at a concentration completely excluding intramolecular hydrogen bonds ($C < 0.0001\ \mathrm{mol\ dm^{-3}}$) there is only one absorption band at $3576\ \mathrm{cm^{-1}}$ corresponding to the free OH group stretching vibration. The absorption bands of the free OH group are at 3577 and $3574\ \mathrm{cm^{-1}}$ for oximes **2** and **3**, respectively. Contrary to the expectations, there are no absorption bands characterizing the anticipated intramolecular hydrogen bond between the OH group proton and the pyridine ring nitrogen atom and this excludes the presence of acetylpyridineoxime *Z*-isomers.

The oxime **1**–**3** configurations were confirmed by an approach based on the stereospecificity of ^{13}C–^{13}C direct spin–spin coupling constants (SSCC) between ^{13}C carbon nuclei of the oxime and methyl group carbons.[9] This constant for the oximes **1**–**3** is 43.5, 42.3 and 42.9 Hz, respectively, and coincides with that in the corresponding ketones (43.9, 42.9, 43.9 Hz), which indicates a *syn*-orientation of the lone-pair nitrogen atom with respect to the pyridine ring, *i.e.* supports an *E*-configuration of the oximes **1**–**3**.



Z *E*

The *Z*-configuration of the ketoximes is known to be most reactive in the Trofimov reaction.[3] When the E $\rightleftarrows$ Z transition is hindered under the reaction conditions an unreacted *E*-isomer is isolated from the reaction mixture.[10] The reduced tendency of the oximes **1**–**3** to pyrrolization with acetylene is quite understandable taking into account that at room temperature they exist only in the *E*-configuration. It is likely that on increasing the temperature and under the action of a catalyst (KOH), configurational transformations of the oximes **1**–**3** do occur, leading to the pyrroles **4**–**7**, but less readily, since the $E \longrightarrow Z$ isomerization of the starting ketoxime presents a rate-determining stage in the overall process.

The present work was fulfilled with the financial support of the Russian Foundation for Basic Research (grant no. 96-03-33263a).

References

1 J. Cossy and J. P. Pete, *Tetrahedron Lett.*, 1978, 4941.
2 R. M. Acheson, M. J. Ferris, S. R. Critchley and D. J. Watrin, *J. Chem. Soc., Perkin Trans. 2*, 1980, 326.
3 B. A. Trofimov and A. I. Mikhaleva, *N-Vinilpirroly* (*N-Vinylpyrroles*), Nauka, Novosibirsk, 1984 (in Russian).
4 B. A. Trofimov, *Adv. Heterocycl. Chem.*, 1990, **51**, 177.
5 B. A. Trofimov, *Pyrroles. Part Two: The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles*, ed. A. Jones, Wiley, New York, 1992, pp. 131–298.
6 B. A. Trofimov and A. I. Mikhaleva, *Heterocycles*, 1994, **37**, 1193.
7 B. A. Trofimov, A. I. Mikhaleva, R. N. Polovnikova, S. E. Korostova, R. N. Nesterenko, N. I. Golovanova and V. K. Voronov, *Khim. Geterotsikl. Soedin.*, 1981, 1058 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1981, 783].
8 S. E. Korostova, A. I. Mikhaleva, R. N. Nesterenko, N. V. Maznaya, V. K. Voronov and N. M. Borodina, *Zh. Org. Khim.*, 1985, **21**, 406 [*J. Org. Chem. USSR* (*Engl. Transl.*), 1985, **21**, 367].
9 L. V. Krivdin, G. A. Kalabin, R. N. Nesterenko and B. A. Trofimov, *Tetrahedron Lett.*, 1984, **25,** 4817.
10 B. A. Trofimov, A. I. Mikhaleva, A. N. Vasil'ev, V. A. Lopyrev, I. A. Titova, V. M. Bzhezovsky and M. V. Sigalov, *Khim. Geterotsikl. Soedin.*, 1981, 1422 (in Russian).

Received: Moscow, 14th December 1996
Cambridge, 19th February 1997; Com. 6/08404D