Chemistry of Heterocyclic Compounds, Vol.35, No. 5, 1999

HETEROCYCLIZATION OF TROPINONE OXIMES AND 3-METHYL-3-AZABICYCLO[3.3.1]-NONAN-9-ONE WITH ACETYLENE IN A SUPERBASIC MEDIUM

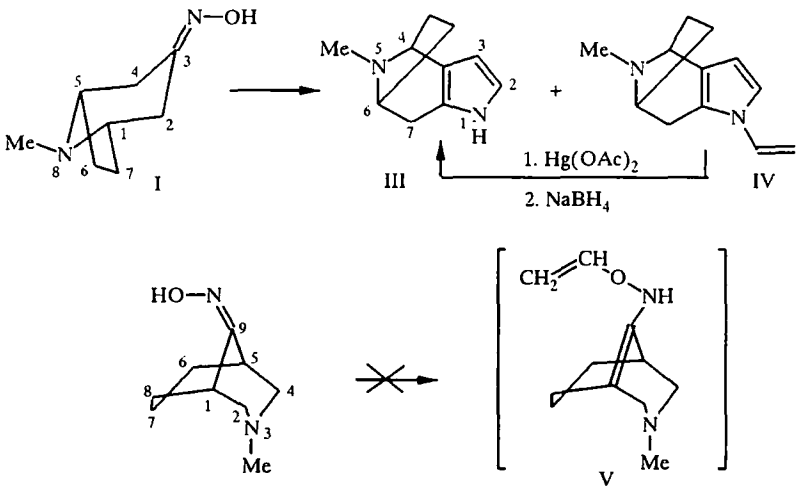
A. V. Varlamov, L. G. Voskresenskii, T. N. Borisova, A. I. Chernyshev, and A. N. Levov

Tropinone oxime reacts with acetylene in superbasic medium to form ordinary products of heterocyclization. The oxime of 3-methyl-3-azabicyclo[3.3.1]nonan-9-one does not undergo heterocyclization due to the impossibility of a [3,3]-sigmatropic rearrangement of its vinyl ether.

The heterocyclization of ketoximes with acetylene in superbasic medium in the presence of metal hydroxides is a preparative method for obtaining substituted and condensed NH- and N-vinylpyrroles [1]. The use of 4-piperidinone oximes in this reaction allows to obtain tetrahydropyrrolo[3,2-*c*]pyridines substituted in the pyridine ring [2] and tetrahydropyrrolo[1,2-*c*]pyrimidines [3].

The most likely mechanism for the heterocyclization of ketoximes with acetylene involves formation of the vinyl ether of the oxime, [3,3]-sigmatropic rearrangement of its enol form to give an aminoaldehyde, and cyclization of the latter to give a pyrrole. The intermediate vinyl ethers and hydroxydihydropyrroles have been isolated as pure compounds and then converted to pyrroles [1].

In order to obtain experimental evidence for the [3,3]-sigmatropic rearrangement of vinyl ether of oxime and determine the range of the Trofimov reaction for cyclic ketones, we studied the heterocyclization of oximes of bicyclic ketones, namely, tropinone (I) and 3-methyl-2-azabicyclo[3.3.1]nonan-9-one (II). The reaction was carried out at 95-100°C in DMSO in the presence of 100 mole % of potassium hydroxide.



Russian International Friendship University, 117923 Moscow, e-mail: avarlamov@sci.pfu.edu.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 683-687, May, 1999. Original article submitted March 17, 1998.

0009-3122/99/3505-0613$22.00©1999 KluwerAcademic/Plenum Publishers

TABLE 1. Chemical Shifts of the Protons (δ, ppm), Multiplicities and Coupling Constants (*J*, Hz) in the ^{1}H NMR Spectra of Compounds I–IV

Compound	1-H	2-H	3-H	4-H	6-H	7-H	8-H	N–CH_3	$H_cC{=}(H_a)H_b$	CH_2–CH_2
I*	3,30 (m)	2*a*-H 2,97 (dd) J_{2a2e} = 14,9 J_{2a1e} = 3,7 2*e*-H 3,28 (d) J_{2a2e} = 14,9	—	4*a*-H 2,21 (dd) J_{4a4e} = 15,6 J_{4a5e} = 3,7 4*e*-H 2,11 (d) J_{4a4e} = 15,6	1,46 (1-H), 1,57 (1-H) 1,99 (2-H) (m)		—	2,35 s	—	1,46 (1H) (m) 1,57 (1H) (m) 1,99 (2H) (m)
II*[2]	1*e*-H 3,43 (m)	2*a*-H 2,29 (m) J_{2a2e} = 11,4 2*e*-H 2,94 (m) J_{2a2e} = 11,4	—	4a-H 2,33 (m) J_{4a4e} = 11,4 4*e*-H 2,11 (d) J_{4a4e} = 11,4	6*a*-H 1,81 (m) $J_{6a6e} = J_{6a7a}$ = 12,8 $J_{6a7e} = J_{6a5e}$ = 6,4 6*e*-H 2,00 (m) J_{6a6e} = 12,8 J_{6e7a} = 12,8	7*a*-H 2,67 (m) $J_{7a7e} = J_{7a6a}$ = J_{7a8a} = 12,8 $J_{7a8e} = J_{7a6e}$ = 6,4 7*e*-H 1,46 (m) J_{7a7e} = 12,8 $J_{7e8a} = J_{7e6a}$ = 6,4	8*a*-H 1,83 (m) $J_{8a8e} = J_{8a7a}$ = 12,8 $J_{8a7e} = J_{8a1}$ = 6,4 8*e*-H 1,96 (m) J_{8a8e} = 12,8 J_{8e7a} = 6,4	2,16 s	—	
III	8,37 (br.)	6,60 (t) $J_{12} = J_{23}$ = 2,7	5,95 (t) $J_{13} = J_{23}$ = 2,7	4,0 (d) $J_{44'}$ = 5,2	3,62 (t) $J_{67A} = J_{67B}$ = 4,7	7A-H 3,07 (dd) J_{7A7B} = 15,8 J_{67A} = 4,7 7B-H 2,29 J_{7A7B} = 15,8 J_{67B} = 4,7 J_{bc} = 9,2	—	2,40 s	—	1,60 (1H) (m) 1,90 (1H) (m) 2,28 (2H) (m)
IV	—	6,81 (d) J_{23} = 2,8	5,98 (d) J_{23} = 2,8	3,81 (d) $J_{44'}$ = 4,9	3,53 (t) $J_{67A} = J_{67B}$ = 4,5	7A-H 3,01 (dd) J_{7A7B} = 15,6 J_{67A} = 4,7 7B-H 2,22 J_{7A7B} = 15,6 J_{67B} = 4,7	—	2,4 s	*a*-H 5,01 (dd) *b*-H 4,58 (dd) *c*-H 6,07 (dd) J_{ab} = 1,2 J_{ac} = 15,9 J_{bc} = 9,2	1,52 (1H) (m) 1,83 (1H) (m) 2,20 (2H) (m)

* 5-H 3,26 ppm (m).

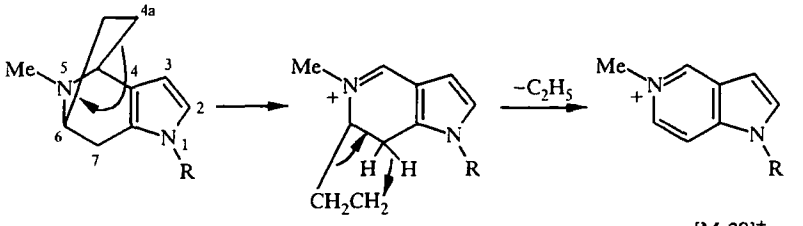
*[2] 5-H 2,42 ppm (m); N–OH 8,75 ppm (br.).

By means of thin-layer chromatography the formation of NH- (III) and N-vinyltetrahydropyrrolo-[3,2-*c*]-pyridines (IV) was established in the heterocyclization of oxime I. In order to facilitate separation of the heterocyclization products, the reaction was carried out until NH-tetrahydropyrrolopyridine III was quantitatively converted to N-vinyl derivative IV, which was obtained in 42% yield.

Product IV were devinylized by an ordinary procedure to yield pyrrolopyridine III [6].

The ^{1}H NMR spectra of pyrrolopyrimidines III and IV (Table 1) show the signals of all the protons with suitable chemical shifts, multiplicities, and coupling constants. Thus, the pyrrole ring protons are recorded as triplets in the case of compound III or doublets in the case of compound IV with coupling constants $J_{12} \sim J_{23} \sim J_{13}$ = 2.7-2.8 Hz characteristic for pyrrole rings. The signal for 4-H in the spectra of compounds III and IV is split into a doublet due to coupling with one of protons of the bridged methylene group, $^3J_{HH} \sim 5$ Hz. The methylene protons 7-H are not magnetically equivalent and the chemical shifts for 7A-H and 7B-H differ by about 0.8 ppm. These protons have a geminal coupling constant $J_{7A7B} \sim 15.6$-15.8 Hz in addition to similar vicinal coupling constants with 6-H. The vinyl group protons in the spectrum of pyrrolopyridine IV give three multiplets with characteristic vicinal ($^3J_{cis}$ = 9.2 Hz, $^3J_{trans}$ = 15.9 Hz) and geminal coupling constants (^2J = 1.2 Hz).

The mass spectra of compounds III and IV have strong molecular ion peaks corresponding to their empirical formulas.



M$^+$
III 162 (39%)
IV 188 (35%)

[M-29]$^+$
III 133 (100%)
IV 159 (100%)

In contrast to tetrahydropyrrolo[3,2-*c*]pyridines, in which the major direction for fragmentation of the molecular ion results from the retro-Diels – Alder reaction [4], fragmentation of compounds III and IV involves initial opening of the bicyclic fragment, hydrogen atom shift, and loss of ethyl radical. The [M - 29] ion peaks have the greatest intensity in the mass spectra. The predominant opening of the $C_{(4)}$–$C_{(4a)}$ bond is a consequence of formation of an intermediate radical–cation with a conjugated double bond system. Doubly-charged ions with *m/z* 66.5 and 79.5 are found in the mass spectra of compounds III and IV, respectively.

Heterocyclization products were not isolated in the case of oxime II and such products were not detected by GC/MS. Only 3-methyl-3-azabicyclo[3.3.1]nonan-9-one formed as a result of retrooxime decomposition was isolated from the reaction mixture (in 25% yield). The lack of heterocyclization in the case of oxime II is likely related to the requirement of formation of enamine form of vinyl ether of the oxime, in which the double bond would be situated at the bridgehead in the small ring (structure V), in order to permit the [3,3]-sigmatropic rearrangement. According to Bredt's rule such a bicyclic compound cannot be formed.

Thus, we have experimentally demonstrated that a [3,3]-sigmatropic rearrangement of the enamine form of vinyl ether of ketoximes is the key step in the heterocyclization of ketone oximes in the Trofimov reaction.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer for KBr pellets. The mass spectra were obtained on a Kratos MS-2 SFR mass spectrometer equipped with direct sample inlet into the ion source at ionizing voltage 70 eV. GC/MS was performed on a HP MS 5988 apparatus using a column (l = 30 m, d = 0.255 mm) packed with RSL-150. The ^{1}H NMR spectra were taken on a Bruker WM-400 spectrometer for 2% solutions of the products in $CDCl_3$ at 20°C. The chemical shifts were measured relative to TMS as the internal standard.

Chemapol silica gel (100×160 μ) was used for column chromatography. Alufol alumina and Silufol silica gel were used for thin-layer chromatography with development by iodine vapor. A sample of tropinone was obtained from Lancaster. 3-Methyl-3-azabicyclo[3.3.1]nonan-9-one was obtained according to House [5]. The ^{1}H NMR spectral data of the products are given in Table 1.

Tropinone Oxime (I). Solution of tropinone (8 g, 0.057 mol), hydroxylamine hydrochloride (8 g, 0.13 mol), and sodium acetate trihydrate (22.3 g, 0.171 mol) in 250 ml of ethanol was refluxed for 4.5 h. The reaction course was monitored by thin-layer chromatography. Ethanol was distilled off and the residue was brought to pH 9-10 by adding 20% aq. KOH and then extracted with chloroform (3×100 ml). The extract was dried over magnesium sulfate. The solvent was distilled off and the residue was recrystallized from a mixture of heptane and ethyl acetate to give 5.2 g (56%) of I as white crystals; mp 125-127°C, R_f 0.5 (Silufol; eluent – 20:1 ethanol–aq. ammonia). Found, %: N 18.66. $C_8H_{14}N_2O$. Calculated, %: N 18.18.

Oxime of 3-Methyl-3-azabicyclo[3.3.1]nonan-3-one (II). Solution of 3-methyl-3-azabicyclo[3.3.1]-nonan-9-one (1.9 g, 0.013 mol), hydroxylamine hydrochloride (1.8 g, 0.026 mol), and sodium acetate trihydrate (5.07 g, 0.039 mol) in 100 ml of ethanol was refluxed for 2 h. The reaction course was monitored by thin-layer chromatography. Ethanol was distilled off. The residue was brought to pH 9-10 by adding 20% aq. KOH and extracted with chloroform (3×50 ml). The combined extracts were dried over magnesium sulfate. Chloroform was distilled off and the residue was crystallized from a mixture of heptane and ethyl acetate to give 1 g (49%) of II as white crystals; mp 104-105°C, R_f 0.5 (Silufol; eluent – 20:1 ethanol–aq. ammonia). Found, %: N 17.86. $C_8H_{16}N_2O$. Calculated, %: N 17.94.

5-Methyl-1-vinyl-4,5,6,7-tetrahydro-4,6-ethanopyrrolo[3,2-*c*]pyridine (IV). Acetylene was bubbled through solution of II (4.2 g, 0.027 mol) and KOH (1.52 g, 0.027 mol) in 50 ml of DMSO at 95°C until the oxime was totally consumed as indicated by thin-layer chromatography on Silufol plates using 20:1 ethanol–aq. ammonia as the eluent. The reaction mixture was poured onto ice and extracted with ether (5×100ml). The ether extract was dried over magnesium sulfate. The residue after distilling off the solvent (3.2 g) was subjected to chromatography on 2.5 × 25 cm column using 1:2 ethyl acetate–hexane as the eluent to give 2.1 g (41%) of IV as yellow oil, which crystallized upon standing, R_f 0.65 (Silufol; eluent – 20:1 ethanol–aq. ammonia). Mass spectrum, *m/z* (I_{rel}, %): 188 (33.8), 187 (2.12), 159 (100), 158 (6.22), 144 (8.4), 132 (17.5), 131 (10.4), 130 (11.4), 117 (16.5), 91 (8.59), 77 (9.71), 42 (14.8). Found, %: C 77.01; H 8.31; N 15.02. $C_{12}H_{16}N_2$. Calculated, %: C 76.59; H 8.51; N 14.89.

5-Methyl-4,5,6,7-tetrahydro-4,6-ethanopyrrolo[3,2-*c*]pyridine (III). Sample of mercuric acetate (0.5 g, 1.6 mmol) was added with stirring to solution of IV (0.15 g, 0.8 mmol) in 30 ml of THF and refluxed for 2 h with monitoring by thin-layer chromatography. Solution of sodium borohydride (0.09 g, 2.4 mmol) in 10 ml of 2 N NaOH was added and the solution was heated at 60-70°C for 2 h. Tetrahydrofuran was distilled off in vacuum and 30 ml of water were added to the residue. The mixture was filtered and the reaction products were extracted with ether (3×100 ml) and dried over magnesium sulfate. Ether was distilled off to yield 0.06 g (49%) of III as light yellow oil, R_f 0.35 (Silufol; eluent – 20:1 ethanol–aq. ammonia). Mass spectrum, *m/z* (I_{rel}, %): 162 (38.9), 161 (4.65), 147 (8.99), 133 (100), 132 (14.8), 120 (11.14), 118 (29.14), 117 (12.48), 105 (17.2), 91 (14.52), 77 (19.4), 63 (12,9), 42 (25.2). Found, %: C 74.23; H 8.57; N 17.34. $C_{10}H_{14}N_2$. Calculated, %: C 74.07; H 8.64; N 17.28.

REFERENCES

1. B. A. Trofimov and A. I. Mikhaleva, *N-Vinylpyrroles* [in Russian], Nauka, Novosibirsk (1984).
2. T. N. Borisova, A. V. Varlamov, N. D. Sergeeva, A. T. Soldatenkov, O. V. Zvolinskii, A. A. Astakhov, and N. S. Prostakov, *Khim. Geterotsikl. Soedin.*, No. 7, 973 (1987).
3. N. S. Prostakov, A. V. Varlamov, T. N. Borisova, and N. D. Sergeeva, *Khim. Geterotsikl. Soedin.*, No. 9, 1286 (1987).
4. E. E. Stashenko, P. I. Zakharov, T. N. Borisova, A. V. Varlamov, B. S. Subbotin, and N. S. Prostakov, *Khim. Geterotsikl. Soedin.*, No. 2, 212 (1988).
5. H. O. House, P. P. Wickham, and H. C. Muller, *J. Am. Chem. Soc.*, **84**, 3139 (1962).
6. C. Gonzalez, R. Greenhouse, R. Tallabs, and J. M. Muchowski, *Canad. J. Chem.*, **61**, 1697 (1983).