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SYNTHESIS OF EPOXYCARBONYL PYRROLINE DERIVATIVES BY CYCLOADDITION OF BENZONITRILIO *p*-NITROPHENYL-METHANIDE TO α,β-UNSATURATED EPOXY KETONES

A. M. Zvonok, V. Librando, E. B. Okaev, and S. G. Mikhalyonok

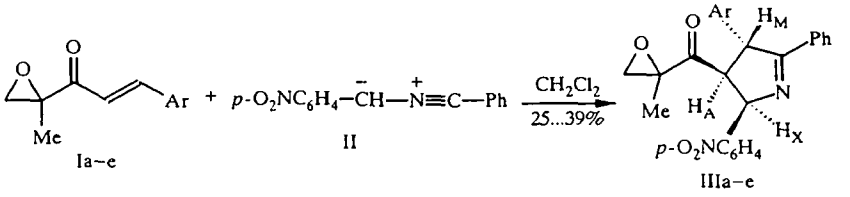
The cycloaddition reaction of benzonitrilio p*-nitrophenylmethanide to α,β-unsaturated epoxy ketones gives a mixture of stereoisomeric epoxycarbonyl pyrrolines. Only one of the isomers was isolated as pure compound. The structure, stereo- and regiochemistry of the isolated products was established by NMR and NOE measurements as well as by mass spectral data.*

1,3-Dipolar cycloaddition reactions are among the most widely used methods of heterocyclic ring construction. The main advantage of the cycloaddition strategy is its versatility, which allows one to obtain various highly functionalized heterocyclic systems stereoselectively and under mild conditions.

In our earlier works [1, 2] we have found that several partially hydrogenized nitrogen heterocycles containing the oxirane ring are able in some cases to undergo intramolecular oxidative-reductive rearrangement. This rearrangement results in the reduction of the oxirane ring and aromatization of the heterocycle. The mechanism of these transformations was postulated to be similar to the first step of other anionotropic reactions of epoxides [3]. However, at present little is known about the generality and synthetic utility of these rearrangements. According to the proposed mechanism, epoxycarbonyl derivatives of pyrroline, pyrazoline, isoxazoline, etc. can be potential substrates for such reactions. So, the synthesis of the title compounds was performed for further studies of their intramolecular transformations.

RESULTS AND DISCUSSION

The reaction of unsaturated epoxy ketones Ia-e [4] with benzonitrilio *p*-nitrophenylmethanide II (generated by the known method of Huisgen [5] from the corresponding imidoyl chloride) yielded the pyrrolines IIIa-e as the only isolable products.



a Ar = Ph, b Ar = *p*-MeC_6H_4, c Ar = *p*-$MeOC_6H_4$, d Ar = *p*-$EtOC_6H_4$, e Ar = *p*-ClC_6H_4

It has been found that the yield of pyrrolines IIIa-e depends greatly upon the reaction temperature. The optimal conditions seem to be −8 to −10°C. At the higher temperature the share of side processes rises greatly, and at the lower one the reaction rate decreases substantially without a considerable increase in yield. When an equimolar ratio of reagents was used, the unreacted epoxy enones Ia-e were present in the reaction mixture after completion (see Table 1). An additional amount of

Department of Organic Chemistry, Belarus State University of Technology, Minsk 220630, Belarus. Dipartimento di Scienze Chimiche, Universita, 95125, Catania, Italy. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 630-633, May, 1998. Original article submitted September 10, 1997.

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TABLE 1. Yield Dependence upon Conditions and m.p. of Pyrrolines IIIa-e

Compound	m.p., °C	Yields of IIIa—e, % depending on temperature and ratio I/II, mol/mol		
		15...20 °C, I : II = 1/1	-8...-10 °C, I : II = 1/1	-8...-10 °C, I : II = 1/2
IIIa	217...218	19	30	39
IIIb	175...177	—	18	25
IIIc	190...191	15	—	27
IIId	207...208	15	23	29
IIIe	192...193	12	—	25

nitrile ylide may be consumed in the competing reaction, cycloaddition at the carbonyl group, which was observed to be even the dominant process in the cycloaddition of the same nitrile ylide to dibenzalacetone [6] and 3,4-diphenylcyclopentadienones [7]. When twice the amount of the nitrile ylide was used, the yield of pyrrolines IIIa-e increased slightly. No signals of pyrrolines IIIa-e were found in the ^{1}H NMR spectra of the reaction mixtures after isolation of compounds IIIa-e, providing evidence that these products were not partially lost during isolation.

Upon TLC examination of the reaction mixture, several by-products (with one prevailing) were found in every case. Although some of their spectral characteristics allow one to suggest the structure of isomeric pyrrolines for them, there are not enough data to judge with confidence about their regio- and stereochemistry. Isolation of by-products appeared to be hardly possible, due to their instability. Additional efforts in this direction are being performed at present.

The structure of compounds IIIa-e has been confirmed by NMR and IR data. Thus, their IR spectra contained the characteristic bands of C=O (1700-1705 cm^{-1}) and C=N (1615-1620 cm^{-1}) double bonds. In the NMR spectra of compounds IIIa-e, the pyrroline ring protons appear at 3.61-3.71 (H_A), 5.12-5.21 (H_M), and 5.99-6.04 (H_X) ppm, with the coupling constants J = 5.7-6.5 Hz, J = 1.9-2.0 Hz, and J = 9.1-9.4 Hz. Based on the chemical shifts, we identified H_A as H at α-carbonyl C atom, and H_M and H_X as protons at benzyl carbons connected with Ar and *p*-$NO_2C_6H_4$, respectively. The coupling constants provide evidence of the *cis*-configuration for H_A and H_X, and the *trans*-configuration for H_A and H_M; the latter is in agreement with the conservation of double bond stereochemistry after cycloaddition [5]. The additional confirmation of the ascribed stereo- and regiochemistry was obtained from NOE data. The irradiation of H_A gave rise to a positive Overhauser effect at H_X, and vice versa. At the same time, the H_M irradiation produced no enhancement of H_A and H_X signals. Moreover, when epoxy enone Ia deuterated at the α-position of the double bond was used in this reaction, the H_A signal and coupling constants of H_A were absent in the ^{1}H NMR spectrum. So, we can ascribe the above stereochemistry for compounds IIIa-e.

It should be noted, however, that the relative configuration of the oxirane ring chiral center cannot be determined from these data.

The mass spectra of pyrrolines IIIa-e showed the major fragmentation peaks corresponding to the elimination of the benzonitrile and the acylium cation, and the retro-cycloaddition process. The most intensive peak was ascribed to the product of consequent loss of benzonitrile and the epoxycarbonyl group.

Investigation of side products in this cycloaddition reaction, as well as studies of the reactivity of the synthesized cycloadducts towards intramolecular rearrangements, is the subject of further research.

EXPERIMENTAL

Melting points were uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Specord IR-75 spectrophotometer, ^{1}H NMR on a modified Tesla BS-567 A spectrometer, and chemical shifts are reported in ppm from internal $(CH_3)_4Si$ and referred to $CDCl_3$ solutions. The ^{13}C spectrum for compound IIIa was obtained on a Varian Gemini 300 NMR spectrometer. Mass spectra were recorded on a VG-70SQ mass spectrometer. Reaction mixtures were analyzed by TLC on silica gel GF 254 (Merck).

Cycloaddition of Benzonitrilio *p*-Nitrophenylmethanide to Compounds Ia-e. General Procedure. To a magnetically stirred solution of the corresponding epoxy enone (5-mmol) and N-(*p*-nitrobenzyl)benzimidoyl chloride (for amount, see Table 1) in 12 ml of dry methylene chloride, a solution of triethylamine (equimolar to N-(*p*-nitrobenzyl)benzimidoyl chloride) in 25 ml of dry methylene chloride was added dropwise during 4 h at the appropriate temperature (see Table 1). The reaction mix-

ture was additionally stirred at the same temperature for 0.5 h, and then successively washed with 10% acetic acid, 10% $NaHCO_3$, and water (3 times). The organic layer was separated, dried with sodium sulfate, and evaporated *in vacuo* at 20-25°C. Compounds IIIa-e were obtained by recrystallization of the residue from methanol or ethanol, and their yields and melting points are given in Table 1.

4-(2,3-Epoxy-2-methylpropionyl)-5-(*p*-nitrophenyl)-2,3-diphenyl-1-pyrroline (IIIa): ^1H NMR ($CDCl_3$): 0.78 (3H, s, CH_3), 2.56 (1H, d, J = 4.4 Hz, CH−O), 2.71 (1H, d, J = 4.4 Hz, CH−O), 3.71 (1H, dd, H_A, J = 6.1, 9.4 Hz), 5.21 (1H, dd, J = 6.1, 1.9 Hz, H_M), 6.04 (1H, dd, J = 9.4, 1.9 Hz, H_X), 7.30 (total 10H, m, Ar), 7.80 (2H, m, Ph), 8.18 ppm (2H, d, J = 8.6 Hz, *p*-$O_2NC_6H_4$). NMR ^{13}C ($CDCl_3$): 15.60, 51.19, 56.64, 56.72, 58.86, 59.65, 76.49, 123.41, 127.35, 127.43, 128.41, 128.87, 129.35, 129.51, 130.94, 132.47, 140.55, 145.92, 175.13, 207.24 ppm. Mass spectrum: *m/z* (%) 426 (2.1), 341 (17.7), 340 (6.8), 323 (9.4), 239 (20.8), 238 (100), 222 (8.3), 193 (8.2), 192 (36.0), 191 (19.8), 189 (5.0), 178 (5.6), 165 (16.9), 131 (6.2), 115 (9.6), 103 (6.5), 91 (7.0), 89 (13.8), 77 (6.8). Found, %: C 73.15; H 5.14; N 6.43. $C_{26}H_{22}N_2O_4$. Calculated, %: C 73.23; H 5.20; N 6.57.

4-(2,3-Epoxy-2-methylpropionyl)-3-(*p*-methylphenyl)-5-(*p*-nitrophenyl)-2-phenyl-1-pyrroline (IIIb): ^1H NMR ($CDCl_3$): 0.78 (3H, s, CH_3), 2.26 (3H, s, CH_3−Ar), 2.58 (1H, d, J = 4.4 Hz, CH−O), 2.69 (1H, d, J = 4.4 Hz, CH−O), 3.67 (1H, dd, J = 5.9, 9.2 Hz, H_A), 5.14 (1H, dd, J = 5.9, 2.0 Hz, H_M), 5.99 (1H, dd, J = 9.2, 2.0 Hz, H_X), 7.00, 7.30 (total 9H, m, Ar), 7.78 (2H, m, Ph), 8.17 ppm (2H, d, J = 8.6 Hz, *p*-$O_2NC_6H_4$). Mass spectrum: *m/z* (%) 440 (2.3), 355 (12.6), 337 (17.3), 253 (21.7), 252 (100), 239 (9.8), 238 (54.0), 236 (5.0), 207 (5.0), 206 (15.8), 205 (9.2), 193 (5.0), 192 (22.5), 191 (17.5), 190 (5.0), 189 (5.2), 165 (17.7), 145 (5.3), 129 (5.2), 115 (8.1), 105 (7.3), 89 (15.0). Found, %: C 73.49; H 5.40; N 6.24. $C_{27}H_{24}N_2O_4$. Calculated, %: C 73.62; H 5.49; N 6.36.

4-(2,3-Epoxy-2-methylpropionyl)-3-(*p*-methoxyphenyl)-5-(*p*-nitrophenyl)-2-phenyl-1-pyrroline (IIIc): ^1H NMR ($CDCl_3$): 0.78 (3H, s, CH_3), 2.58 (1H, d, J = 4.6 Hz, CH−O), 2.69 (1H, d, J = 4.6 Hz, CH−O), 3.65 (1H, dd, J = 5.9, 9.2 Hz, H_A), 3.74 (3H, s, OCH_3), 5.13 (1H, dd, J = 5.9, 2.0 Hz, H_M), 5.99 (1H, dd, J = 9.2, 2.0 Hz, H_X), 6.77 (2H, d, J = 8.7 Hz, *p*-$CH_3OC_6H_4$), 7.00 (2H, d, J = 8.7 Hz, *p*-$CH_3OC_6H_4$), 7.35 (5H, m, Ar), 7.75 (2H, m, Ph), 8.16 ppm (2H, d, J = 8.6 Hz, *p*-$O_2NC_6H_4$). Mass spectrum: *m/z* (%) 456 (3.3), 371 (9.0), 353 (7.1), 306 (9.4), 269 (19.4), 268 (100), 239 (7.7), 238 (42.6), 222 (8.1), 221 (5.0), 192 (14.0), 191 (8.5), 178 (5.3), 165 (11.3), 161 (5.1), 136 (13.7), 121 (5.6), 89 (9.4). Found, %: C 70.95; H 5.26; N 6.04. $C_{27}H_{24}N_2O_5$. Calculated, %: C 71.04; H 5.30; N 6.14.

4-(2,3-Epoxy-2-methylpropionyl)-3-(*p*-ethoxyphenyl)-5-(*p*-nitrophenyl)-2-phenyl-1-pyrroline (IIId): ^1H NMR ($CDCl_3$): 0.79 (3H, s, CH_3), 1.36 (3H, t, J = 6.9 Hz, CH_3 from OC_2H_5), 2.57 (1H, d, J = 4.4 Hz, CH−O), 2.68 (1H, d, J = 4.4 Hz, CH−O), 3.65 (1H, dd, J = 5.7, 9.1 Hz, H_A), 3.95 (2H, q, J = 6.9 Hz, CH_2 from OC_2H_5), 5.12 (1H, dd, J = 5.7, 2.0 Hz, H_M), 5.99 (1H, dd, J = 9.4, 1.9 Hz, H_X), 6.75 (2H, d, J = 8.8 Hz, *p*-$C_2H_5OC_6H_4$), 6.97 (2H, d, J = 8.8 Hz, *p*-$C_2H_5OC_6H_4$), 7.32 (5H, m, Ar), 7.77 (2H, m, Ph), 8.16 ppm (2H, d, J = 9.1 Hz, *p*-$O_2NC_6H_4$). Mass spectrum: *m/z* (%) 470 (4.4), 385 (10.2), 367 (5.0), 320 (13.3), 283 (21.3), 282 (100), 239 (9.0), 238 (49.5), 208 (9.5), 207 (8.5), 192 (14.8), 191 (7.7), 175 (9.2), 165 (12.5), 150 (18.8), 107 (5.0), 105 (10.2), 91 (5.6), 89 (10.2), 77 (7.1). Found, %: C 71.39; H 5.43; N 5.74. $C_{28}H_{26}N_{25}$. Calculated, %: C 71.48; H 5.57; N 5.95.

3-(*p*-Chlorophenyl)-4-(2,3-epoxy-2-methylpropionyl)-5-(*p*-nitrophenyl)-2-phenyl-1-pyrroline (IIIe): ^1H NMR ($CDCl_3$): 0.77 (3H, s, CH_3); 2.55 (1H, d, J = 4.3 Hz, CH−O), 2.70 (1H, d, J = 4.3 Hz, CH−O), 3.61 (1H, dd, J = 6.5, 9.2 Hz, H_A), 5.18 (1H, dd, J = 6.5, 2.0 Hz, H_M), 6.00 (1H, dd, J = 9.2, 2.0 Hz, H_X), 7.01 (2H, d, J = 8.7 Hz, *p*-ClC_6H_4), 7.30 (7H, m, Ar), 7.73 (2H, m, Ph), 8.15 ppm (2H, d, J = 8.6 Hz, p-O_2NC_{6H4}). Mass spectrum: *m/z* (%) 462 (0.8), 460 (2.5), 377 (7.5), 376 (7.9), 375 (22.3), 359 (7.9), 358 (5.0), 357 (21.0), 275 (7.0), 274 (38.3), 273 (19.8), 272 (100), 256 (11.5), 239 (15.6), 238 (85), 228 (6.9), 227 (6.9), 226 (19), 225 (6.5), 221 (6.0), 193 (6.7), 192 (37.9), 191 (32.7), 190 (8.5), 189 (12.7), 178 (5.8), 166 (5.5), 165 (29.2), 164 (5.0), 160 (5.8), 149 (5.0), 125 (7.9), 115 (7.5), 102 (5.0), 89 (24.9), 77 (7.0). Found, %: C 67.59; H 4.47; N 5.93; Cl 7.58. $C_{26}H_{21}ClN_2O_4$. Calculated, %: C 67.75; H 4.59; N 6.08; Cl 7.69.

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