Chemistry of Heterocyclic Compounds, Vol. 36, No. 5, 2000

SYNTHESIS OF 13,15-PYRAZOLOPROSTANOIDS

T. V. Chernikhova, E. V. Koroleva, and F. A. Lakhvich

The synthesis of novel prostanoids with a pyrazole fragment in the ω-chain is reported starting from isoxazole derivatives.

Keywords: 13,15-isoxazoloprostanoids, 13,15-pyrazoloprostanoids, enamino ketone, regioselectivity, cycloaddition.

We have previously carried out the synthesis of 13,15-isoxazoloprostanoids **1-3** [1, 2] which have a fully formed prostaglandin (PG) structure (functionalized carbocycle, α- and ω- chains) and can be considered as a group of biologically active analogs of 11-desoxyprostaglandins [3]. These compounds are convenient precursors of prostanoids with an open chain in which the $C_{(13)}$–$C_{(15)}$ fragment of the ω-chain corresponds to one of the possible variants realized by the latent bifunctionality of the isoxazole (isoxazoline) ring. We have reported the fission of the heterocycle of the 13,15-isoxazoloprostanoids **1-3** leading to the corresponding 13-amino-13-en-15-oxoprostanoids **4-6** [2].

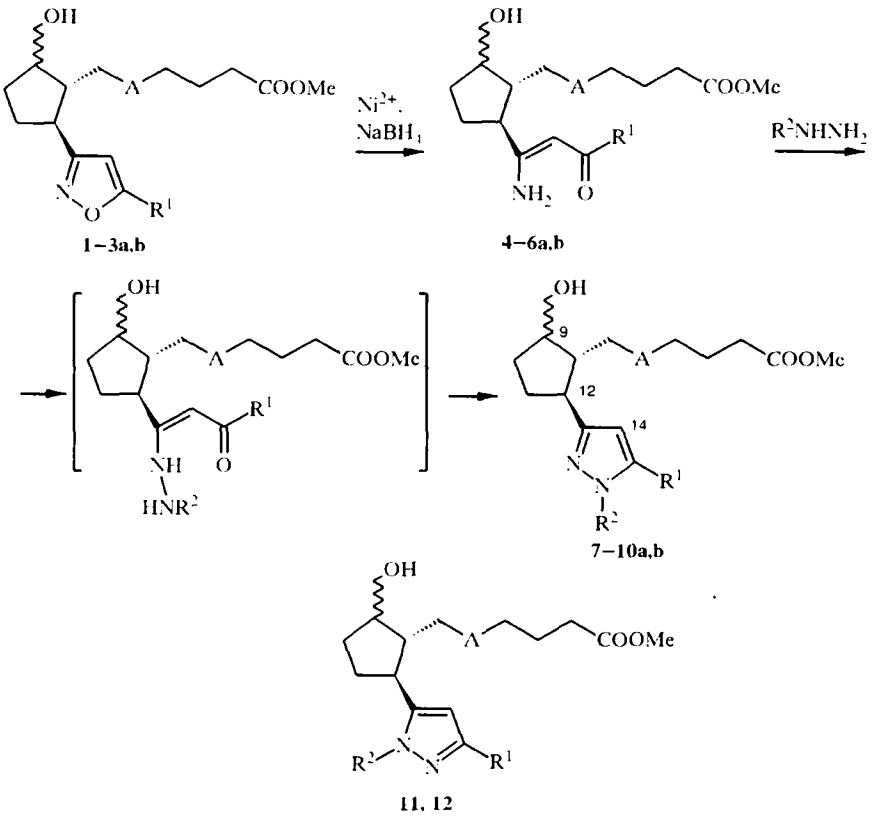
As an extension of our work on the use of this isoxazole strategy for forming the modified ω-chain of the prostanoids [1, 2, 4] we describe in this paper the reactions of the enamino ketones **4-6** with hydrazines as a method for preparing novel modified PG's with a pyrazole fragment in the ω-chain. The starting compounds **1**, **2**, **4**, and **6** in these reactions are a mixture of isomers at the $C_{(9)}$ atom and **3** and **5** are the pure 9α-epimers.

Reaction of phenylhydrazine hydrochloride with compounds **4** and **5** and potassium acetate in aqueous methanol [5] at room temperature for 48 h gives the N-phenyl substituted pyrazoles **7** and **8** respectively and their structures were confirmed by physicochemical methods of analysis (Table 1). Hence, in the IR spectra of the pyrazoles **7** and **8**, in place of the absorption bands for the stretching vibrations of the C=O and C=C bonds (1610, 1530 cm^{-1}) characteristically seen in the spectra of the starting enamino ketones, there is observed a band for the stretching vibration of the C=N group in the pyrazole ring (1550 cm^{-1}) together with the absence of absorptions for the amino group (3200, 3400 cm^{-1}). In their ^1H NMR spectra, the signal for the heteroaromatic proton at $C_{(14)}$ is shifted to lower field (6.02-6.06 ppm) when compared with the signal for the vinyl proton in the starting compounds **4, 5** (5.05-5.08 ppm). A similar shift is experience by the signal for the methine proton at $C_{(12)}$ (from the region 2.3-2.5 to the region 2.8-3.0 ppm), in addition to the appearance of the multiplet signal for the phenyl substituent at 7.4 ppm. The broadened singlet signals of the amino group in the starting enamines are not observed.

Reaction of the enamino ketones **4, 6** with hydrazine hydrate in methanol at room temperature gives the corresponding pyrazoles **9, 10** in 70-80% yield. Their IR spectra (as the spectra of the phenylpyrazoles **7, 8**) show a C=N absorption band at 1560 cm^{-1} and, in contrast to the starting enamino ketones, the absence of absorption bands for the conjugated C=O and C=C bonds as well as the amino group.

The ^1H NMR spectra of compounds **9, 10** (as the spectra of **7, 8**) show a characteristic downfield shift for the signals of the protons at the $C_{(14)}$ atom (in the region of 5.8 and 6.4 ppm respectively) when compared with the signals for the starting enamino ketones **4** and **6** at 5.05 and 5.8 ppm respectively as do the signals of the protons at $C_{(12)}$ (2.3-2.5 to 2.76-3.06 ppm). The spectra of the pyrazoles **9, 10** also show broadened singlet signals for the NH group in the region 3.8-5.2 ppm (**9b** at 7.8 ppm).

Institute of Bioorganic Chemistry, Belarus National Academy of Sciences, Minsk 220141; e-mail: evk@ns.iboch.ac.by. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 629-633, May, 2000. Original article submitted December 15, 1998; revision submitted June 17, 1999.



1–3a,b

4–6a,b

7–10a,b

11, 12

1, 2, 4, 6, 7, 9–11 A = $-CH_2CH_2-$; 3, 5, 8 A = $-(Z)-CH=CH-$;
1, 3, 5, 7–9, 11 $R^1 = C_5H_{11}$-*n*; 2, 6, 10, 12 R^1 = Ph; 7, 8 R^2 = Ph;
9–12 R^2 = H; 1–10 a 9β-H, b 9α-H

The preferred formation of the regioisomers **7-10,** with the substituents R^1 and R^2, bound to the neighbouring C and N atoms, can be explained on the basis of the mechanism of the reaction of hydrazines with enamino ketones [6], according to which the first stage of the synthesis occurs *via* "reenamination" of the starting enamino ketone and formation of a hydrazone with a subsequent cyclization to the pyrazole. This is confirmed by comparison of the ^{1}H NMR spectra of the obtained products with the spectra of the materials related to the structure of the pyrazoles [7]. The chemical shifts of the allyl protons in the pyrazole derivatives are characteristic for the regioisomers and this is due to their different shielding by the C=N and C=C bonds of the heterocycle. From the increased chemical shifts of the 12-H and 16-H protons, the pyrazoles obtained were assigned the regioisomer structures **7-10**. The existence of an overall correlation of the ^{1}H NMR spectra of the pyrazoles **7-10** with those of the corresponding isoxazoles **1-3** should also be noted. Hence, in the spectra of the latter, the 12-H proton is found in the region 2.9-3.1 ppm (2.8-3.1 for the pyrazoles) and the triplet for the methylene protons of the $C_{(16)}H_2$ fragment at 2.7 ppm (2.6 for compounds **7, 9, 10**) and this can serve as indirect confirmation of the structure of the obtained pyrazoles as the regioisomers **7-10**. Moreover, the stereochemistry of the 8-H, 9-H, and 12-H chiral centers in the prostanoid molecule is retained in the reaction process as confirmed by the corresponding ^{1}H NMR spectroscopic parameters [8].

In the synthesis of compounds **9** and **10** there are also formed ~ 5% of regioisomeric pyrazoles **11, 12,** as judged by the ^{1}H NMR spectra of the reaction mixtures. The signals for the 12-H protons in the regioisomeric products **11, 12** are displaced to downfield when compared with the analogous protons of the pyrazoles **9, 10.** Lowering of the regioselectivity of the reaction may be explained by the fact that the hydrazine molecule is less polar and more compact when compared with the phenylhydrazine molecule.

TABLE 1. Physicochemical Characteristics for the 13,15-Pyrazoloprostanoids

Compound	Empirical formula	Found, % / Calculated, %			Mass spectrum, M⁺	IR spectrum, cm⁻¹	^{1}H NMR spectrum, δ, ppm (J, Hz)					
		C	H	N			9-H	12-H	14-H	α-chain *,*²	R^1 *²	R^2
7a	$C_{22}H_{40}N_2O_3$	76.45 / 76.60	9.20 / 9.15	6.52 / 6.36	440	1550, 3400	4.35 t (4.0)	3.00 dt (11.0; 9.0)	6.02 s	2.27 t, CH_2COO; 1.30-2.10 m (21H)	0.86 t, CH_3; 2.60 t, $C_{(16)}H_2$	7.40 m (1H)
7b							4.00 m	2.83 q (7.0)	6.06 s	2.27 t, CH_2COO; 1.30-2.10 m (21H)	0.86 t, CH_3; 2.60 t, $C_{(16)}H_2$	7.40 m (5H)
8a	$C_{22}H_{38}N_2O_3$	74.09 / 73.94	8.79 / 8.73	6.43 / 6.39	438	1550, 3400	4.33 t (4.0)	3.08 dt (11.0; 9.0)	6.03 s	5.42 m, CH=CH; 2.29 t, CH_2COO; 1.30-2.10 m (17H)	0.88 t, CH_3; 2.62 t, $C_{(16)}H_2$	7.40 m (5H)
9a	$C_{21}H_{36}N_2O_3$	68.79 / 69.19	9.78 / 9.96	7.72 / 7.69	364	1560, 3400	4.35 t (4.0)	3.00 dt 11.0; .9.0)	5.82 s	2.25 t, CH_2COO; 1.30-2.10 m (21H)	0.91 t, CH_3; 2.61 t, $C_{(16)}H_2$	5.20 br. s (1H)
9b							4.02 m	2.76 m	5.86s	2.15 t, CH_2COO; 1.30-2.10 m (21H)	0.91 t, CH_3; 2.58 t, $C_{(16)}H_2$	7.80 br. s (1H)
10a	$C_{22}H_{36}N_2O_3$	70.81 / 70.36	8.38 / 8.44	7.65 / 7.82	358	1560, 3400	4.38 t (4.0)	3.06 dt (11.0; 9.0)	6.38 s	2.26 t, CH_2COO; 1.26-2.10 m (15H)	7.40 and 7.75 two m (Ph)	3.83 br. s (1H)
10b							4.08 m	2.86 dd (15.0; 8.0)	6.40 s	2.26 t, CH_2COO; 1.24-2.08 m (15H)	7.38 and 7.74 5H, two m (Ph)	4.50 br. s (1H)

* The spectra of all of the compounds showed a singlet signal for the $COOCH_3$ group at 3.66 ppm.

*² The multiplet signal for the protons of the α-chain obscured the signals for the protons at the $C_{(8)}$, $C_{(9)}$, $C_{(11)}$, (5H), and in the case of compounds **7-9** also those at the $C_{(17)}$-$C_{(19)}$ atoms (6*H*).

EXPERIMENTAL

IR Spectra were recorded as films on a UR-20 spectrophotometer and ^{1}H NMR spectra on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ with TMS internal standard. Mass spectra were obtained on a Varian MAT-311 instrument with an ionization energy of 70 eV. TLC was carried out on Silufol UV-254 (Serva) and Kieselgel 60 F_{254} (Merck) plates in the system chloroform–methanol (85 : 15) and visualized with anisaldehyde. Column chromatography was performed on 40/100 micron silica gel (Czech Republic) and preparative TLC on Kielselgel 60 HF_{254} on glass plates with a hexane–ether gradient elution.

13,15-Isoxazoloprostanoids **1-3** were synthesized [1, 2] by cycloaddition of the corresponding nitrile oxides to phenylacetylene and hept-1-yne and enamino ketones **4-6** [2] were obtained by reductive fission of the isoxazoles **1-3** with sodium borohydride in the presence of nickel sulfate [9]. The basic physicochemical characteristics for the synthesized compounds **7-10**, obtained as oily liquids, are given in Table 1.

Synthesis of Compounds 7, 8. Phenylhydrazine hydrochloride (0.6 mmol) and potassium acetate (0.6 mmol) were added with stirring at room temperature to a solution of enamino ketone **4** or **5** (0.5 mmol) in a mixture of methanol (10 ml) and water (3 ml). After methanol was evaporated in vacuo, the aqueous residue was extracted with ether (3 × 50 ml), and the extract was dried over sodium sulfate. After evaporation of the extract, the residue was chromatographed on a silica gel column (10 g) using an ether–hexane gradient elution.

From compound **4** (0.183 g, 0.5 mmol) there were obtained methyl esters of 9α-hydroxy-13,15-(N-phenyl-3,5-pyrazolyl)prostanoic acid (**7a**, 0.060 g, 33%) and 9β-hydroxy-13,15-(N-phenyl-3,5-pyrazolyl)prostanoic acid (**7b**, 0.022 g, 12%).

Compound **5a** (0.057 g) gave (*Z*)-9β-hydroxy-13,15-(N-phenyl-3,5-pyrazolyl)prost-5-enoic acid methyl ester (**8a**, 0.015 g, 26%).

Synthesis of Compounds 9, 10. Hydrazine hydrate (0.4 mmol) was added with stirring at room temperature to a solution of enamino ketone **4** or **6** (0.3 mmol) in methanol (5 ml) and stirring was continued for 48 h. Methanol was evaporated in vacuo. Preparative chromatography of the residue on Kieselgel 60 F_{254} plates using a mixture of ether and hexane (9 : 1) gave the following: from 0.058 g of compound **4** 0.026 g (45%) of 9α-hydroxy-13,15-(1H-3,5-pyrazolyl)prostanoic acid methyl ester (**9a**) and 0.015 g (25%) of 9β-hydroxy-13,15-(1H-3,5-pyrazolyl)prostanoic acid methyl ester (**9b**); from 0.100 g of enamino ketone **6** 0.061 g (61%) of 9α-hydroxy-13,15-(1H-3,5-pyrazolyl)-15-phenyl-16,17,18,19,20-pentanorprostanoic acid methyl ester (**10a**) and 0.019 g (20%) of 9β-hydroxy-13,15-(1H-3,5-pyrazolyl)-15-phenyl-16,17,18,19,20-pentanorprostanoic acid methyl ester (**10b**).

REFERENCES

1. F. A. Lakhvich, T. V. Yankova, E. V. Koroleva, L. G. Lis, and A. A. Akhrem, *Zh. Org. Khim.*, **24**, 1665 (1988).
2. F. A. Lakhvich, E. V. Koroleva, and T. V. Chernikhova, *Khim. Geterotsikl. Soedin.*, No. 3, 389 (1992).
3. B. B. Kuz'mitskii, M. B. Golubeva, I. G. Dal'kov, N. A. Mizulo, V. N. Romanova, G. A. Shafranskaya, A. N. Golikov, E. V. Koroleva, T. V. Yankova, and F. A. Lakhvich, *Izv. Akad. Nauk, Beloruss. SSR., Ser. Khim.*, No. 6, 72 (1987).
4. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, I. P. Antonevich, A. A. Pap, and L. G. Lis. *Zh. Org. Khim.*, No. 10, 2242 (1981).
5. A. Alberola, C. Andres, G. A. Ortega, and R. Pedrosa, *J. Heterocycl. Chem.*, **21**, 1575 (1984).
6. U. Hanefeld, C. W. Rees, A. J. P. White, and D. J. Williams, *J. Chem. Soc., Perkin Trans. 1*, No. 13, 1545 (1996).
7. A. Alberola, L. F. Antolin, P. Caudrado, A. M. Gonzales, M. A. Laguna, and F. J. Pulido, *Synthesis*, No. 3, 203 (1988).
8. A. A. Akhrem and E. V. Koroleva, *Izv. Akad. Nauk, Beloruss. SSR., Ser. Khim.*, No. 6, 103 (1978).
9. E. V. Koroleva, F. A. Lakhvich, and T. V. Yankova, *Khim. Geterotsikl. Soedin.*, No, 11, 1576 (1987).