# A NEW APPROACH TO THE SYNTHESIS OF 16-HETERO-PROSTANOIDS VIA ISOXAZOLE INTERMEDIATES

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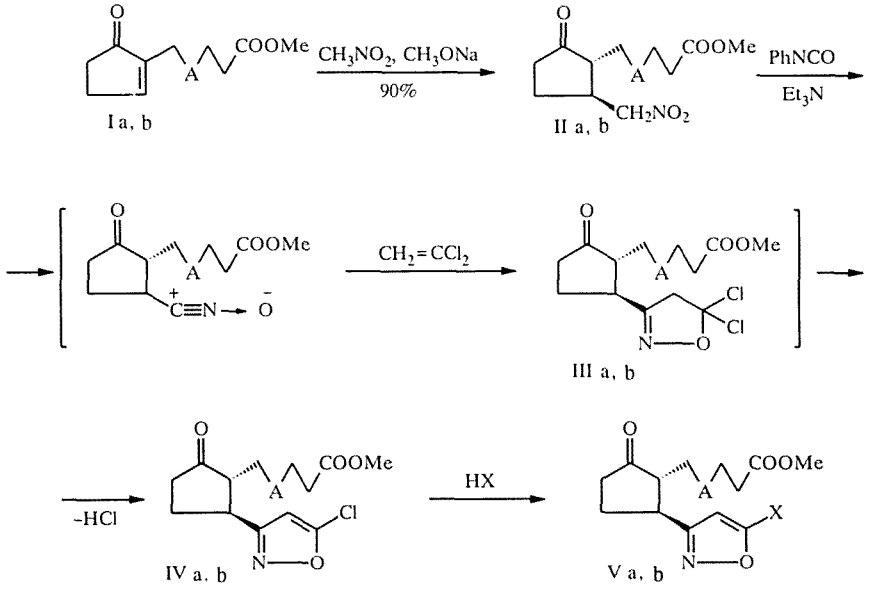
The universality of the nitrile oxide method for the synthesis of isoxazole derivatives and the wide range of transformations of the latter, with or without the participation of the heterocycle, explains their widespread use in the synthesis of many natural products as a synthon with latent bifunctionality [1, 2]. As part of our study of "nitrile oxide (isoxazole) technology" for the formation of natural or modified ω-chain prostanoids [3, 4], we describe in this note a three step method for the formation of molecules of the 13,15-isoxazoloprostanoids of the 11-desoxy-$E_1$ with 16-heteroatom substituents using the widely used prostanoid synthons I.

For example, the products of conjugate addition of nitromethane to 2-methoxycarbonylalkyl(alkenyl)cyclopent-2-en-1-ones Ia and b —the nitromethylene derivatives IIa and b — are sources of nitrile oxides, generated under standard conditions [3], which react *in situ* with 1,1-dichloroethylene. The 5,5-dichloroisoxazoles products formed by regioselective 1,3-cycloaddition rearrange spontaneously under the reaction conditions to the 2-methoxycarbonylalkyl(alkenyl)-3-(-5-chloroisoxazolyl)cyclopentan-1-ones IVa and b. The latter contain a chlorine atom at position 5 of the heterocycle which is capable of nucleophilic replacement by alcohol, amine or thiol groups (see scheme).




I—V a A = $(CH_2)_3$; b A = $(CH_2)_2CH=CH$; V X = OR, SR, $NR^1R^2$

Methanolysis of the chloroisoxazoles Va and b occurs almost quantitatively on boiling in methanol containing potassium carbonate. Amines and thiols react with the chloroisoxazoles as their lithium derivatives formed at 0 to −15°C. For example, lithium thiophenolate, obtained by treatment of thiophenol with 1.4 M butyllithium solution, reacted with the chloroisoxazole IVa in tetrahydrofuran at 0-20°C to give the methyl ester (Va, X = SPh).

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A solution of a nitromethyl derivative IIa or b (1.5 mmol) in 1,1-dichloroethylene (10 ml) was added dropwise with stirring to a solution of phenyl isocyanate (3 mmol) and triethylamine (3 mmol) in 1,1-dichloroethylene (6 ml) under argon at 30-35°C without overheating the reaction mixture and evaporating the solvent. Stirring was continued until the nitromethylcyclopentanone II starting material had disappeared (TLC monitoring), the reaction mixture was filtered, the filtrate was absorbed on aluminum oxide and the dichloroethylene removed by elution with hexane. The product was extracted with ether and purified further by column chromatography on silica gel if necessary; yield 55-60%.

**2α-(6-Methoxycarbonylhexyl)-3β-[3-(5-chloroisoxazolyl)]cyclopentan-1-one (Ia).** IR Spectrum (film): 1735, 1600, 745 $cm^{-1}$. $^1H$ NMR Spectrum (in $CDCl_3$): 1.3-1.9 (12H, m), 2.29 (2H, t, $CH_2COOMe$), 2.0-2.3 (3H, m), 3.21 (1H, dt, HCC=N), 3.68 (3H, s, OMe), 6.12 ppm (1H, s, HC=CCl). $M^+$ 327.

**2α-(6-Methoxycarbonylhept-4-enyl)-3β-[3-(5-chloroisoxazolyl)]cyclopentan-1-one (Ib).** IR Spectrum (film): 1740, 1615, 740 $cm^{-1}$. $^1H$ NMR Spectrum (in $CDCl_3$): 1.2-2.1 (12H, m), 2.33-2.42 (5H, m), 3.18 (1H, dt, HCC=N), 3.68 (3H, s, OMe), 5.32 (2H, m, HC=CH), 6.10 ppm (1H, s, HC=CCl). $M^+$ 339.

**2α-(6-Methoxycarbonylhept-4-enyl)-3β-[3-(5-methoxyisoxazolyl)]cyclopentan-1-one (Vb).** IR Spectrum (film): 1740, 1615 $cm^{-1}$. $^1H$ NMR Spectrum (in $CDCl_3$): 1.2-2.1 (12H, m), 2.33-2.50 (5H, m), 3.23 (1H, dt, HCC=N), 3.66, 3.68 (3H, s, s, OMe), 5.32 (2H, m, HC=CH), 6.00 ppm (1H, s, HC=CCl). $M^+$ 335.

**2α-(6-Methoxycarbonylhexyl)-3β-[3-(5-phenylthioisoxazolyl)]cyclopentan-1-one (Va).** IR Spectrum (film): 1740, 1605 $cm^{-1}$. $^1H$ NMR Spectrum (in $CDCl_3$): 1.2-2.6 (17H, m), 2.95 (1H, m, HCC=N), 3.83 (3H, s, Ome), 5.6 (1H s. $H_{isoxazolyl}$), 7.3 ppm (5H, m, Ph) $M^+$ 389.

Information on the reaction of the chloroisoxazoles with nucleophiles will be presented in a separate paper.

## REFERENCES


1. P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, and D. Simoni, Synthesis, No. 10, 857 (1987).
2. F. A. Lakhvich, E. V. Koroleva, and A. A. Akhrem, Khim. Geterotsikl. Soedin., No.4, 435 (1989).
3. A. A. Akhrem, F. A. Lakhvich, V. A. Kripach, I. P. Antonevich, A. A. Pap and L. G. Lis, Zh. Org. Khim., **17**, 2242 (1981).
4. F. A. Lakhvich, T. V. Yankova, E. V. Koroleva, L. G. Lis, and A. A. Akhrem, Zh. Org. Khim., **24**, 1665 (1988).