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Synthesis and caracterization of isoxazolinic α-quaternary α-amino esters

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Abstract
The synthesis of cyclic α-quaternary α-amino esters (**6-9**) from arylnitrile oxides or pyridylnitrile oxide, generated in situ from aryl oximes (**2-4**) or pyridyl oxime (**5**) and N-Boc dehydroalanine methyl ester (**1**) by 1,3-dipolar cycloaddition is reported. Structures of isoxazolinic α-amino esters (**6-9**) have been established by ^{1}H NMR, ^{13}C NMR and MS spectral data.

Keywords: cycloaddition, nitrile oxide, cyclic amino esters, dehydro-α-amino esters

Introduction
Alpha-amino acids are the fundamental building blocks of peptides and proteins and play essential roles in living organisms. Cyclic α-quaternary α-amino acids are highly sought to be incorporated into the peptide chains in order to make them more rigid and therefore provide information on the most bioactive conformation. Various syntheses of cyclic quaternary amino acids have been described in literature [1]: (i) using cyclic compounds as starting materials [2-4], (ii) construction of the ring by cyclization reactions [5-7] and (iii) cycloaddition and related reactions [8-10].

The isoxazoline ring, in particular, is indeed as an ubiquitous motif resulting from Huisgen [2+3] cycloaddition of alkene with nitrile oxides [11]. This 1,3-dipolar cycloaddition is a powerful technique to functionalize olefins since the isoxazoline ring formed may be regarded as a masked iminoalcohol, hydroxketone or aminoalcohol [12].

In connection with our ongoing program envisaging the syntheses and bio-evaluation of biomolecules [13-14], we report herein the preparation of isoxazolinic α-quaternary α-amino esters by cycloaddition reaction of N-Boc dehydroalanine methyl ester with a series of arylnitrile oxide or pyridylnitrile oxide.

2. Materials and methods
2.1. General comments
^{1}H NMR (300MHz) and ^{13}C NMR (100MHz) spectra were recorded on Bruker spectrometers with chemical shift values (δ) given in part per million (ppm) relative to TMS (0.00 ppm) and using $CDCl_3$ as solvent. Flash chromatography was conducted using flash silica gel 60 (Merck 230-400 mesch). The reaction progress was monitored by TLC using Silica gel 60-F254 plat with visualization under UV light. The high resolution mass spectra (HRMS) were recorded in the ESI mode at the mass Spectrometry Service of the Universidad de Valencia and the data reported in m/e (intensity to 100%). All reagents were purchased from commercial sources and used without further purification. All solvents were dried and distilled prior to their use.

2.2. General procedure for the synthesis of α-isoxazolyl α-amino esters
A two-neck round flask equipped with a dropping funnel was charged with 1.6 mmol of arylaldoxime and 1.7 mmol of dehydroalanine methyl ester dissolved in 10 mL of chloroform. The mixture was maintained at -5 °C with stirring for 10 minutes. Then 8 mL of sodium hypochlorite (NaOCl) was added dropwise. After 2 h of stirring, the organic layer was extracted with diethyl ether and dried over sodium sulfate. The solvent was removed under reduced pressure, yielding a crude product which was purified by column chromatography on silica gel using hexane/ethyl acetate (5:1 v/v) as eluent.

*2.2.1. methyl 5-[(tert-butoxycarbonyl)amino]-3-(4-chlorophenyl) isoxazoline-5-carboxylate (**6**)*
Yellow oil product. Yield: 75%. R*f* = 0.45 (hexane/ethyl acetate: 5:1 v/v). ^{1}H NMR (δ ppm): 1.43 (s, 9H, t-Bu), 3.85-3.89 (m+s, 5H, CH_2+CH_3O), 6.21 (s, 1H, NH), 7.37-7.63 (m, 4H, Ar). ^{13}C NMR (δ ppm): 28.34 ($3CH_3$), 42.43 (CH_2), 53.95 (OCH_3), 81.31 (C-O_{isoxaz}), 92.55 (C-O), 127.36 (C_{Ar}), 128.16 ($2CH_{Ar}$), 129.03 ($2CH_{Ar}$), 136.38 (C_{Ar}), 153.28 (C=O), 155.32 (C=N), 168.06 (C=O). HRMS (ESI): Calcd for $C_{16}H_{20}N_2O_5Cl$(M+H): 355.1055; Found: 355.1060.

*2.2.2. methyl 5-[(tert-butoxycarbonyl)amino]-3-(4-nitrophenyl) isoxazoline-5-carboxylate (**7**)*
White solid product. Mp = 129°C. Yield: 75%. R*f* = 0.40 (hexane/ethyl acetate: 5:1 v/v). ^{1}H NMR(δ ppm): 1.41 (s, 9H, t-Bu), 3.88-3.93 (m+s, 5H, CH_2+CH_3O), 6.30 (s, 1H, NH), 7.85-8.28 (m, 4H, Ar). ^{13}C NMR (δ ppm): 28.17 ($3CH_3$), 41.60 (CH_2), 54.15 (OCH_3), 81.51 (C-O_{isoxaz}), 93.17 (C-O), 124.00 ($2CH_{Ar}$), 127.71 ($2CH_{Ar}$), 135.02 (C_{Ar}), 148.64 (C_{Ar}), 153.17 (C=O), 154.68 (C=N), 167.69 (C=O). HRMS (ESI): Calcd for $NaC_{16}H_{19}N_3O_7$(M+Na): 388.1115; Found: 388.1124.

*2.2.3. methyl 5-[(tert-butoxycarbonyl)amino]-3-(4-methoxyphenyl) isoxazoline-5-carboxylate (**8**)*
Yellow oil product. Yield: 70%. R*f* = 0.40 (hexane/ethyl acetate: 5:1 v/v). ^{1}H NMR (δ ppm): 1.40 (s, 9H, t-Bu), 3.82-3.88 (m+2s, 8H, CH_2+$2CH_3O$), 6.22 (s, 1H, NH), 6.89-7.61 (m, 4H, Ar). ^{13}C NMR (δ ppm): 28.16 (3CH3), 43.30 (CH2), 53.77 (OCH3), 55.36 (OCH3), 81.13(C-O_{isoxaz}), 92.13 (C-O), 114.19 ($2CH_{Ar}$), 121.24 (C_{Ar}), 128.46 ($2CH_{Ar}$), 153.46 (C_{Ar}), 155.83 (C=O), 161.35 (C=N), 168.39 (C=O). HRMS (ESI): Calcd for $NaC_{17}H_{22}N_2O_6$(M+Na): 373.1370; Found: 373.1378.

*2.2.4. methyl 5-[(tert-butoxycarbonyl)amino]-3-pyridin-4-yl isoxazoline-5-carboxylate (**9**)*
White solid product. Mp = 176°C. Yield: 80%. R*f* = 0.43 (hexane/ethyl acetate: 5:1 v/v). ^{1}H NMR (δ ppm): 1.43 (s, 9H, t-Bu), 3.85-3.91 (m+s, 5H, CH_2+CH_3O), 6.39 (s, 1H, NH), 7.54-8.68 (m, 4H, Ar). ^{13}C NMR (δ ppm): 28.15 ($3CH_3$), 41.26 (CH_2), 54.10 (OCH_3), 82.00 (C-O_{isoxaz}), 93.50 (C-O), 120.85 ($2CH_{Ar}$), 136.45 (C_{Ar}), 150.18 (C=N_{Ar}), 153.17 (C=O), 154.61 (C=N), 167.70 (C=O). HRMS (ESI): Calcd for $C_{15}H_{20}N_3O_5$(M+H): 322.1403; Found: 322.0350.

3. Results and discussion

We recently reported a convenient preparative method of a series of glycosyl-isoxazoles and glycosyl-isoxazolines compounds by a simple and efficient 1,3-dipolar cycloaddition of aryl nitrile oxide derivatives with a variety of O-propargyl glycosyles or O-allyl glycosyles [14]. We continued our experiments to apply this method for the preparation of isoxazolinic α-quaternary α-amino esters. The 1,3-dipolar cycloaddition between *p*-chloro/nitro/methoxyphenyl oxides or 4-pyridylnitrile oxide as dipole and N-Boc dehydroalanine methyl ester (**1**) was explored. The dehydroalanine methyl ester (**1**) was obtained by beta-elimination of Boc-Ser(OTs)-OMe according to the method described by Ferreira et al. [15] slightly modified by replacing the DMAP with potassium carbonate in acetonitrile at reflux. The nitrile oxides were prepared *in situ* during the cycloaddition reaction by using conventional method which consists of reacting the sodium hypochlorite (NaOCl) with the corresponding oximes [14]. Reaction between dipoles and dipolarophile was carried out in chloroform at -5°C, leading to a variety of α-isoxazolinic α-amino esters (**6-9** in Scheme 1, Table1). The target products were purified by column chromatography and isolated with good yields (70-80%, see Table 1).

The molecular structures of the new α-isoxazolinic α-amino esters (**6-9**) compounds were established on the basis of the ^{1}H and ^{13}C NMR spectroscopic data and high resolution mass spectrometry. In fact, the ^{1}H NMR spectra of the compounds **6-9** show a multiplet at 3.87 (figure 1a), 3.91, 3.84 and 3.88 ppm respectively, which correspond to the CH_2 of the isoxazolinic ring and the methoxy group. ^{13}C NMR spectra of this compounds exhibit a signal at 155.32 (figure 1b), 154.68, 161.35 and 154.61 ppm respectively, which correspond to the C=N of the isoxazolinic ring. Theoretically, the 1,3-dipolar cycloaddition of nitrile oxide to alkene should form two regioisomers of 3,4-disubstituted and 3,5- disubstituted isoxazolines. However, ^{1}H NMR and ^{13}C NMR spectra indicated that the 1,3-dipolar cycloaddition regiospecifically produced the 3,5-disubstituted isoxazolines. This regioselectivity was in accordance with our previous work [14] and the previously reported results based on the nitrile oxide cycloaddition with terminal alkene [16-18].

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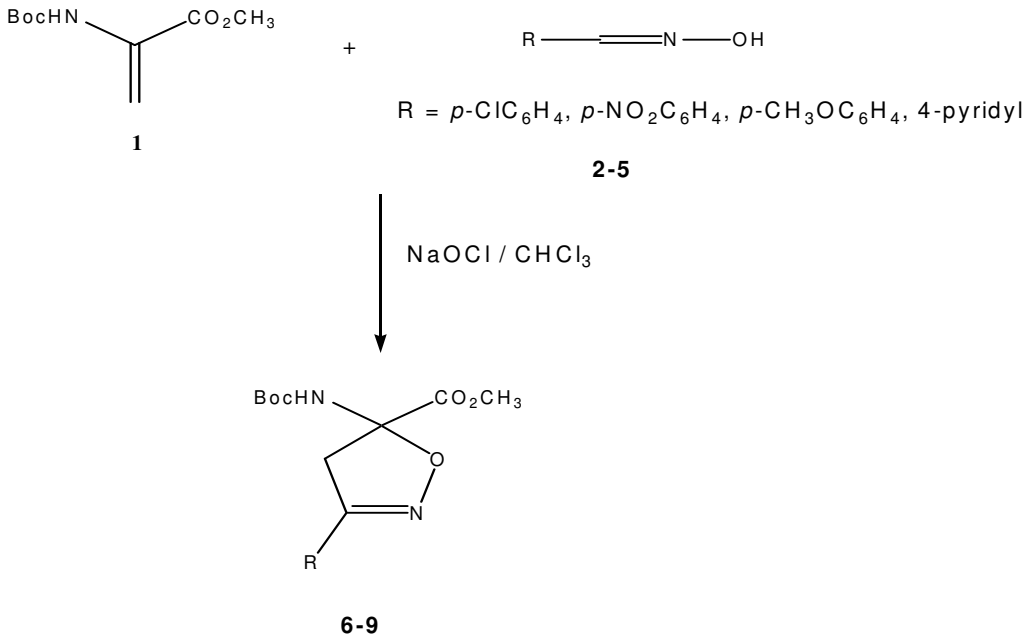

Scheme 1.

Table 1: Synthesis of α-isoxazolinic α-amino esters

Compound	*R*	Yield (%)
6	*p*-ClC_6H_4	75
7	*p*-$NO_2C_6H_4$	75
8	*p*-$CH_3OC_6H_4$	70
9	4-pyridyl	80

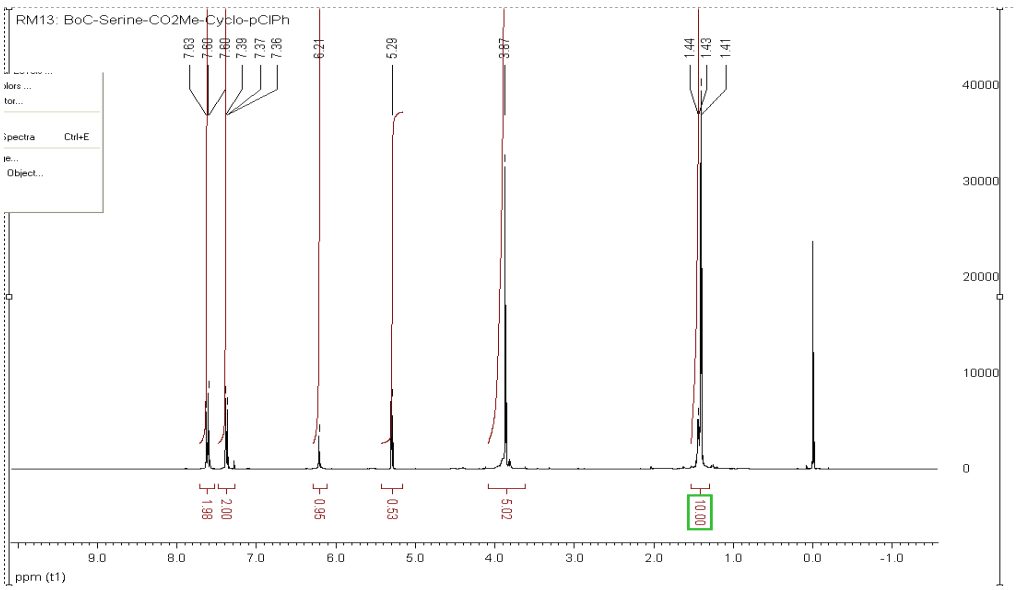

Figure 1a: RMN^{1}H of compound **6**.

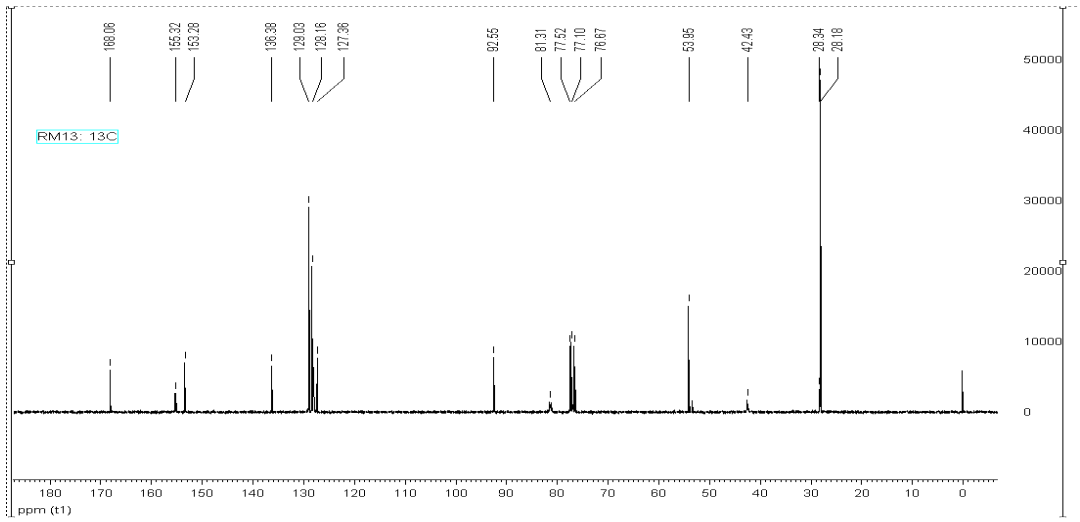

Figure 1b: RMN^{13}C of compound **6**.

Conclusion

The method reported above allows the good yielding preparation of a variety of isoxazolinic α-quaternary α-amino esters by using mild reaction conditions and simple work-up procedures through the 1,3-dipolar cycloaddition of dehydroalanine and a variety of in situ generated aryl nitrile oxides. The molecular structures of the obtained isoxazolinic α-amino esters are supported by NMR spectroscopy and mass spectrometry.

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