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LETTERS

Oxazoline cuprate addition to nitroalkenes: a new route approaching γ-amino acids

Fabio Simonelli,* Giuliano C. Clososki, Alcindo A. dos Santos, Alfredo R. M. de Oliveira, Francisco de A. Marques and Paulo H. G. Zarbin

Universidade Federal do Paraná, Departamento de Química, Laboratório de Ecologia Química e Síntese Orgânica, CP 19081 CEP 81531-990 Curitiba, PR, Brazil

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Abstract—Current studies of oxazoline cyanocuprates addition to conjugated nitroalkenes, and their improved reactivity when compared to lithium oxazoline anions, has shown to be an efficient method for the synthesis of a variety of γ-nitrooxazolines, an interesting intermediate of γ-amino acids. © 2001 Elsevier Science Ltd. All rights reserved.

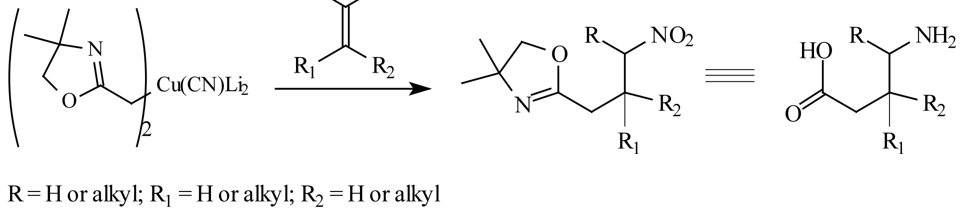
The addition of a carboxymethyl synthon to conjugated nitroalkenes is a useful functionalization and few methodologies have been tested for this purpose.[1] The development and utilization of oxazoline cyanocuprates in reactions with α,β-unsaturated system has been recently carried out in our laboratory. As part of this methodological study, herein, we are presenting the addition of oxazoline cyanocuprates to conjugated nitroalkenes. The addition of 2-methyl-2-oxazolines, a carboxymethyl equivalent, to conjugated nitroalkenes provides a new approach to γ-nitrooxazolines, an interesting intermediate for the preparation of γ-amino acids (Scheme 1).

These nitrooxazolines are versatile intermediates and the selective interconversion of either a nitro or oxazoline group to other functional groups is proving to be a straightforward methodology for the synthesis of lactams and amino acids.

The conjugated nitroalkenes were prepared by a Henry reaction[2] of nitromethane with several carbonyl compounds, followed by dehydration of the resulting 2-nitro alcohol.[3] The conjugated nitrocycloalkenes were obtained by nitromercuration process of the cycloalkenes, followed by base-catalyzed elimination.[4] The reactivity of lithiated 2,4,4-trimethyl-2-oxazoline anion with δ-nitrostyrene was first investigated. However, this reaction provided a poor yield (33%) of the desired product, and some other non-identified by-products (Scheme 2).

On the other hand, when the oxazoline cyanocuprates were prepared from the lithiated 2,4,4-trimethyl-2-oxazoline anion, employing CuCN·2LiCl at −78°C in THF, the reaction with δ-nitrostyrene afforded the 1,4-addition product (**1a**) in 87% yield in a very clean reaction[7] (Scheme 2).

The reaction of this oxazoline cyanocuprates with several other nitroalkenes showed similar results.[8] The yields obtained are summarized in Table 1 and Scheme 3.



R = H or alkyl; R$_1$ = H or alkyl; R$_2$ = H or alkyl

Scheme 1.

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* Corresponding author. Tel.: +55-41-361-3186; fax: +55-41-361-3174; e-mail: simo@quimica.ufpr.br

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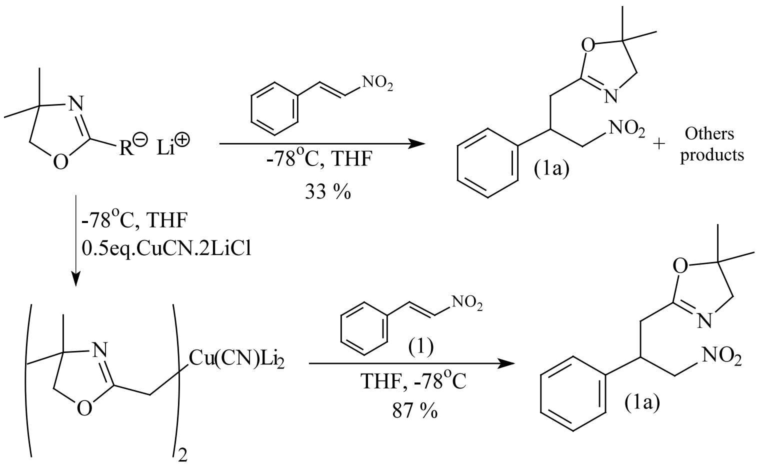
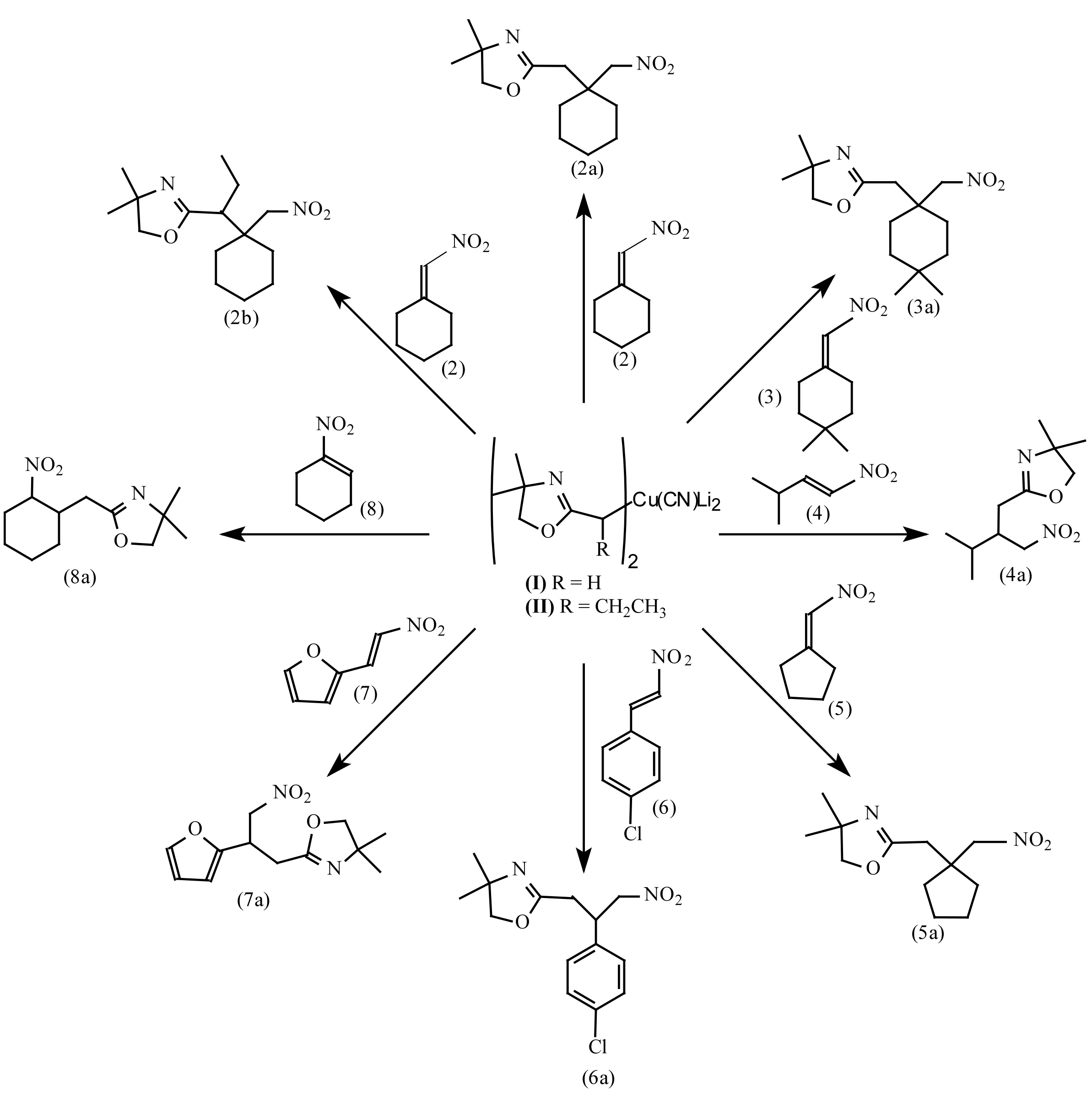


Scheme 2.



Scheme 3.

Table 1. Results of the reaction of oxazoline cuprate with several nitroalkenes

Entry	Cuprate	Nitroalkene	Product	Yield (%)
1	$R_2Cu(CN)Li_2$	**2**	**2a**	96
2	$R'_2Cu(CN)Li_2$	**2**	**2b**	69
3	$R_2Cu(CN)Li_2$	**3**	**3a**	77
4	$R_2Cu(CN)Li_2$	**4**	**4a**	77
5	$R_2Cu(CN)Li_2$	**5**	**5a**	67
6	$R_2Cu(CN)Li_2$	**6**	**6a**	76
7	$R_2Cu(CN)Li_2$	**7**	**7a**	84
8	$R_2Cu(CN)Li_2$	**8**	**8a**	76

R = 2,4,4-trimethyl-2-oxazoline.
R′ = 4,4-dimethyl-2-propyl-2-oxazoline.

We must highlight the preparation of products **2a**, **3a** and **5a**, in which the formation of a quaternary carbon was obtained in good yields. Special attention should be given to the formation of product **2b**, where the cuprate was generated in a secondary carbon resulting in the formation of a tertiary carbon linked to a quaternary one. It should also to be noted that only *anti* adduct[5] **8a** was isolated, when employing the nitroalkene **8**.

This methodology is currently being applied to the synthesis of two γ-amino acids (±)-3-Phenil GABA and (±)-Baclofen, which plays an important role in several nervous system functions.[6] The extension of these results to asymmetric conjugated additions is now being investigated employing chiral oxazolines and/or chiral nitroalkenes.

Acknowledgements

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7. **General procedure**: A flask containing 2,4,4-trimethyl-2-oxazoline (0.48 mL, 4 mmol) and 5 mL of THF under argon, was cooled in a dry ice/acetone bath (−78°C) and *n*-BuLi (2.92 mL, 4.6 mmol) was added dropwise. The resulting solution was cannulated into a solution of CuCN·2LiCl in 5 mL (−78°C) of dry THF. After 15 min, a nitroalkene solution (2 mmol) in 2 mL dry THF was added and stirring was continued for 2 h at −78°C. The reaction mixture was quenched with 2 mL of 10% concentrated NH_4OH in a saturated NH_4Cl solution. The mixture was extracted with ether (3×20 mL) and dried over anhydrous Na_2SO_4. The product was isolated by filtration, followed by solvent removal under vacuum and them purified by flash chromatography.
8. **1a**: IR (neat) 2960, 1660, 1544, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 3H), 1.18 (s, 3H), 2.67 (dd, J = 7.8, 1.4 Hz, 2H), 3.79–3.97 (m, 3H), 4.79 (dd, J = 24.6, 12.7 Hz, 1H), 4.73 (dd, J = 25.8, 12.6 Hz, 1H), 7.20–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.18, 32.13, 41.10, 67.18, 79.11, 79.46, 127.4, 127.93, 129.00, 138.30, 162.46; MS *m*/*z* (%) 263 (6), 216 (100), 217 (16), 144 (10); **2a**: IR (neat) 2927, 1664, 1540, 1375, 1180, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 6H), 1.53 (m, 10H), 2.51 (s, 2H), 2.9 (m, 1H), 3.91 (s, 2H), 4.66 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.12; 25.28; 28.08; 33.18; 33.48; 37.19; 67.02; 78.65; 81.95; 162.76; MS *m*/*z* (%) 255 (75), 254 (1), 224 (15), 178 (11); **2b**: IR (neat) 2932, 1650, 1540, 1450, 1369, 977 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 1.28 (s, 3H), 1.29 (m, 12H), 2.76 (dd, J = 3, 5.8 Hz, 1H), 3.90 (d, J = 12 Hz, 1H), 3.93 (d, J = 12 Hz, 1H), 4.40 (d, 10.8 Hz, 1H), 4.75 (d, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.65, 19.59, 21.24, 25.29, 28.36, 28.56, 30.89, 31.40, 39.28, 44.39, 65.80, 81.16, 165.30; MS *m*/*z* (%) 283 (97), 282 (1), 252 (12), 126 (100); **3a**: IR (neat) 2934, 1664, 1547, 1465, 1362, 1190, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 0.88 (s, 3H), 1.24 (s, 6H), 1.26–1.53 (m, 8H), 2.46 (s, 2H), 3.88 (s, 2H), 4.59 (s, 2H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.29, 28.95, 29.45, 33.99, 36.95, 67.12, 78.68, 81.6, 162.77; MS *m*/*z* (%) 283 (100), 282 (1), 211 (4), 113 (9); **4a**: IR (neat) 2960, 1656, 1540, 1375, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, J = 2.7 Hz, 3H), 0.93 (d, J = 2.7 Hz, 3H), 1.27 (s, 6H), 1.70 (m, 1H), 2.32 (dd, J = 15.3, 7.5 Hz, 1H), 2.39 (dd, J = 15.3, 5.4 Hz, 1H), 2.66 (m, 1H), 3.92 (s, 2H), 4.41 (dd, J = 12.6, 6.3 Hz, 1H), 4.52 (dd, J = 12.6, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.97, 22.62, 24.87, 28.22, 30.09, 32.74, 40.61, 58.21, 67.16, 79.00, 163.4; MS *m*/*z* (%) 243 (100), 242 (2), 196 (4), 140 (7), 113 (9); **5a**: IR (neat) 2962, 1664, 1540, 1375, 1176, 977 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, 6H), 1.65 (m, 8H), 2.54 (s, 2H), 3.86 (s, 2H), 4.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.98, 28.23, 34.76, 35.69, 45.00, 67.10, 78.7, 81.61, 163.05; MS *m*/*z* (%) 241 (100), 194 (10), 164 (6), 113 (38); **6a**: IR (KBr, neat) 2962, 1733, 1664, 1547, 1369, 1245, 819 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 3H), 1.19 (s, 3H), 2.68 (dd, J = 7.5, 4.2 Hz, 2H), 3.84 (s, 1H), 3.85 (s, 1H), 3.81–4.01 (m, 1H), 4.63 (dd, J = 12.9, 8.5 Hz, 1H), 4.77 (dd, J = 12.9, 6.3 Hz, 1H), 7.15–7.22 (m, 2H), 7.27–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.21, 28.27, 31.96, 40.56, 67.34, 79.34, 129.06, 129.35, 130.38, 134.08, 137.06, 162.59; MS *m*/*z* (%) 299 (25), 298 (9), 297 (100), 279 (8), 250 (13); **7a**: IR (neat) 2975, 1664, 1547, 1375,

1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 1.20 (s, 3H), 2.64 (dd, $J=15.00$, 7.8 Hz, 1H), 2.71 (dd, $J=15.00$, 6.90 Hz, 1H), 3.88 (s, 2H), 4.05 (quint, $J=7.05$ Hz, 1H), 4.72 (s, 1H), 4.74 (s, 1H), 6.16 (d, $J=3.3$ Hz, 1H), 6.27 (dd, $J=3.3$, 2.1 Hz, 1H), 7.33 (dd, $J=2.1$, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.05, 28.11, 29.69, 34.82, 67.19, 79.17, 107.23, 110.32, 142.50, 151.48, 162.45; MS m/z (%) 254 (1), 253 (11), 207 (15), 206 (100), 134 (17), 39 (10); **8a**: IR (neat) 2934, 1739, 1656, 1540, 1358, 992 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 6H), 1.7–2.06 (m, 6H), 2.12–2.47 (m, 5H), 3.9 (s, 2H), 4.33 (dt, $J=3.9$, 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.12, 24.35, 28.14, 28.23, 29.66, 31.37, 37.89, 67.02, 78.94, 90.06, 163.1; MS m/z (%) 241 (12), 225 (20), 194 (67), 113 (100), 84 (39).