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1,3-Cycloaddition of nitrile oxides in ionic liquids. An easier route to 3-carboxy isoxazolines, potential constrained glutamic acid analogues

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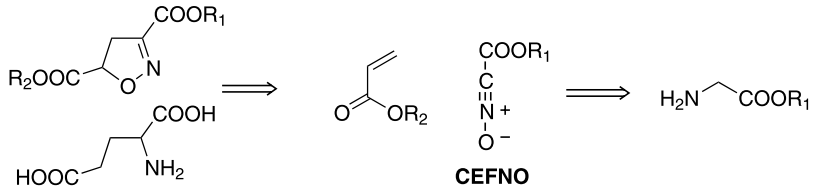
Abstract—Several improvements in the cycloaddition of carboethoxyformonitrile oxide (CEFNO) with different alkenes are observed in the ionic liquids [bmim][BF_4] and [bmim][PF_6]. The possibility of obtaining good yields of the corresponding isoxazolines opens the way towards parallel collections of glutamic acid (Glu) analogues.

Glutamic acid is a central excitatory neurotransmitter acting through two heterogeneous families of membrane associated receptors. Their activation produces a large spectrum of physiological functions in the healthy and in the diseased central nervous system (CNS).[1] These receptors, including all the recently discovered subtypes, are potential therapeutic targets. Consequently the design and the synthesis of new ligands are of great interest in the CNS drug discovery process.[2]

Isoxazoles and isoxazolines have found several important applications as lead structures for new Glu ligand design.[3] Following our interest in developing new strategies for the generation of molecular diversity,[4]we became interested in the preparation of small libraries of 3-carboxy 1,2-isoxazolines, one of the most simple structures resembling Glu in a constrained form (Scheme 1).

Cycloaddition of carboethoxyformonitrile oxide (CEFNO) with acrylates is the most straightforward approach to dicarboxy-isoxazolines that provides an acceptable level of molecular diversity. Consequently, we decided to investigate this reaction in order to let it amenable for the preparation of arrays of molecules in a parallel way. Most of the reported procedures[3b,5] generated CEFNO in situ by base treatment of the ethyl chlorooximidoacetate derived from glycine[6] as originally described by Kozikowski.[7]

Following that report, ethyl glycine was transformed in good yields into compound **2** and this product, after purification by crystallization, was dissolved in diethyl ether together with ethyl acrylate and to this mixture a base (Et_3N) was slowly added to generate CEFNO for the immediate cycloaddition. In our hands, this route produced the required product **3** in low yields (20–30%) together with larger amounts of furoxane **4**. As reported in the original paper and further confirmed by the experience of other authors, the addition of the base with a syringe pump and the use of large amounts of the dipolarophile increased the yields of **3** to 45%.



Scheme 1.

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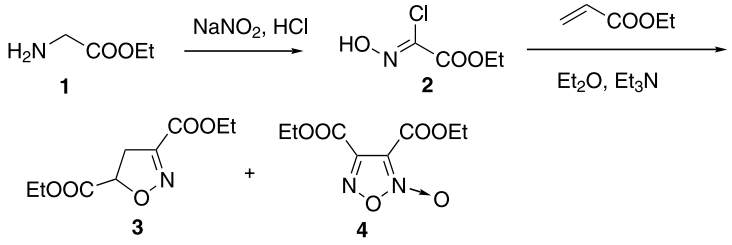
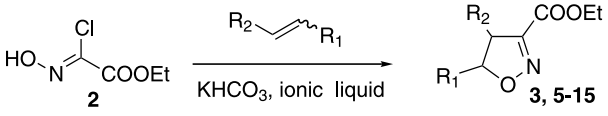
When the same protocol was applied to other dipolarophiles (as diethyl malonate or acrylonitrile) we always obtained low yields of the corresponding isoxazolines contaminated by furoxane **4** (Scheme 2).

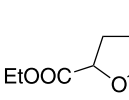
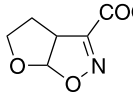
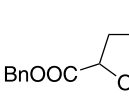
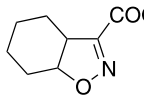
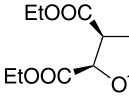
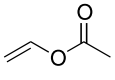
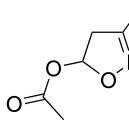
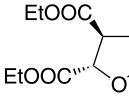
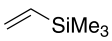
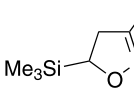
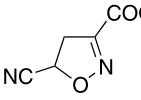
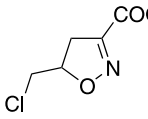
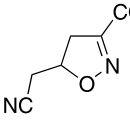
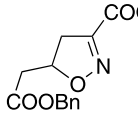
As these conditions are unsuitable for the development of a parallel synthesis, we started to investigate different conditions. Furoxane **4** was formed by dimerization of unstable CEFNO that did not conclude the cycloaddition with the acrylate and this is the reason why a slow addition with a syringe pump is required in order to get good yields of the cycloadduct. In order to verify if a more polar environment could stabilize CEFNO, we tried the reaction in an ionic liquid[8] ([bmim][BF_4]) and we were pleased to observe that isoxazoline **3** was formed rapidly and in high yield. Moreover, the amount of furoxane formed was largely reduced. To explore the potential and the limits of this new procedure of cycloaddition, we repeated the protocol using different alkenes obtaining always isoxazolines **5**–**15** in good yields without the need of chromatographic separation.

In a typical procedure 0.65 mmol of alkene were mixed with $KHCO_3$ (0.65 mmol) in [bmim][BF_4] (0.2 g), solid CEFNO (0.65 mmol) was added and the mixture stirred at room temperature for 5–12 h. When the starting materials were disappeared, the mixture was treated



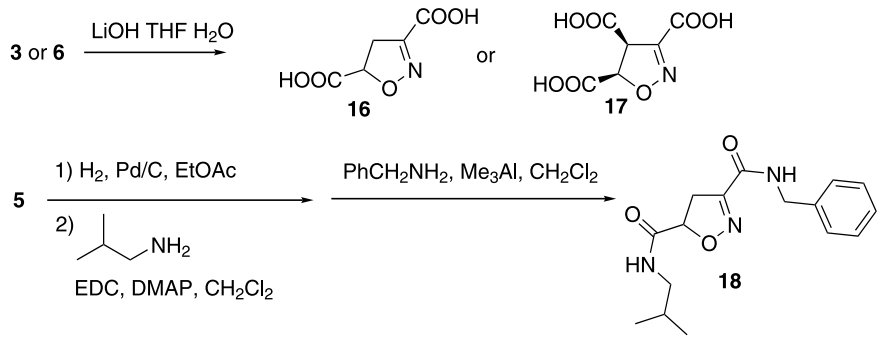
Scheme 2.



Dipolarophile	Ionic liquid[a]	Product[b]	Dipolarophile	Ionic liquid[a]	Product[b]
	A	 **3** (58%)		A	 **10** (78%)
	B	 **5** (92%)		A	 **11** (55%)
	A	 **6** (68%)		B	 **12** (91%)
	A	 **7** (79%)		B	 **13** (78%)
	A	 **8** (95%)		A	 **14** (55%)
	A	 **9** (56%)		A	 **15** (56%)

a) **A** : [bmim][BF_4]. **B** : [bmim][PF_6] . b) Yields of isolated crude products (single products at ^{1}H NMR analisys). Yields in brackets

Scheme 3.



Scheme 4.

with an organic solvent immiscible with the ionic liquid (diethyl ether, THF or EtOAc) that selectively extracted the isoxazolines. The organic solvent was evaporated and the products isolated in the yields reported in Scheme 3 and with purities ranging from 80 to 95% (^{1}H NMR analysis, 200 MHz). Analytical samples were further purified by column chromatography.

In any case investigated, we observed exclusively the formation of the 5-substituted isoxazolines as suggested by the low field values of the CH signal located around δ 4.0–5.0.[9]

As reported in Scheme 3, the reaction gave good yields (as expected) with electron-rich alkenes and even conjugated dipolarophiles were successfully transformed into the corresponding isoxazolines, expanding the potentials of this reaction.[10] To our knowledge, this is the first example of the improvement in the cycloaddition of nitrile oxides using ionic liquids.[11] The only limitation concerns the reaction with benzyl crotonate that gave product **15**. Probably the presence of the ionic liquid in basic medium induced the thermodynamically unfavorable migration of the double bond to the terminal position, generating a more reactive alkene that immediately gave rise to the cycloaddition.

Compounds **3** and **6** were transformed into the corresponding acids **16** and **17** whereas, from compound **5**, an array of derivatives may be prepared. Compound **18** in Scheme 4 was synthesized, as an example for the preparation of arrays of isoxazoline carboxamides, by deprotection of the carboxyl group in position 5, (H_2 Pd/C in $CHCl_3$, 96% yield) coupling with an amine EDC, DMAP, CH_2Cl_2, 89% yield) followed by amidation of the ethyl ester in position 3 carried out in the presence of Me_3Al.

In conclusion, we have demonstrated that 1,3-cycloaddition of relatively unstable nitrile oxides can be conveniently carried out in ionic liquids opening new possibilities towards the synthesis of new potential conformationally constrained glutamic acid analogues or arrays of other polyfunctionalized isoxazolines.

Acknowledgements

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9. Characterization of selected products: **3**: oil; R_f 0.38 (*n*-hex/ethyl acetate: 4/1); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 5.14 (dd, $J=9.6$ and 8.1 Hz, 1H, H-5), 4.37–4.18 (m, 4H, 2×OCH_2CH$_3$), 3.46 (d $J=8.1$ Hz, 2H, H-4), 1.40–1.22 (m, 6H, 2×OCH$_2$$CH_3$); MS: $C_9H_{13}NO_5$, 216 $[M+1]^+$.
5: oil; R_f 0.33 (*n*-hex/ethyl acetate: 4/1); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 7.34 (s, 5H, Ph) 5.24–5.14 (m, 6H, CH_2Ph, H-5), 4.32 (q, $J=7.2$ Hz, 2H, OCH_2CH$_3$), 3.46 (d, $J=8.7$ Hz, 2H, H-4), 1.33 (t, $J=7.2$ Hz, 3H, OCH$_2$$CH_3$); MS: $C_{14}H_{15}NO_5$, 278 $[M+1]^+$.
8: oil; R_f 0.46 (*n*-hex/ethyl acetate: 4/1); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 5.36 (dd, $J=9.8$ and 8.2 Hz, 1H, H-5), 4.37 (q, $J=7.2$ Hz, 2H, OCH_2CH$_3$), 3.59 (d, $J=8.2$ Hz, 2H, H-4), 1.36 (t, $J=7.2$ Hz, 3H, OCH$_2$$CH_3$); ^{13}C NMR (200 MHz, $CDCl_3$, 25°C): δ 158.89 (COOEt), 151.10 (C=N), 68.00 (C-5), 62.86 (OCH_2CH$_3$), 39.94 (C-4), 13.99 (OCH$_2$$CH_3$); MS: $C_7H_8N_2O_3$, 169 $[M+1]^+$.
9: oil; R_f 0.17 (*n*-hex/ethyl acetate: 7/3); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 5.11–4.96 (m, 1H, H-5), 4.36 (q, $J=7.2$ Hz, 2H, OCH_2CH$_3$), 3.52–3.37 (four lines, A part of an ABX system, 1H, CH_2CN) 3.17–3.05 (four lines, B part of an ABX system, 1H, CH_2CN), 2.74 (d, $J=5.8$ Hz, 2H, H-4), 1.35 (t, $J=7.2$ Hz, 3H, OCH$_2$$CH_3$); MS: $C_8H_{10}N_2O_3$, 183 $[M+1]^+$.
12: oil; R_f 0.40 (*n*-hex/ethyl acetate: 4/1); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 6.68 (d, $J=7.3$ Hz, 1H, H-5), 4.25 (q, $J=7.0$ Hz, 2H, OCH_2CH$_3$), 3.43–3.30 (four lines, A part of an ABX system, 1H, H-4) 3.15–3.05 (four lines, B part of an ABX system, 1H, H-4), 1.96 (s, 3H, OCH$_3$), 1.26 (t, $J=7.0$ Hz, 3H, OCH$_2$$CH_3$); MS: $C_8H_{11}NO_5$, 202 $[M+1]^+$.
15: oil; R_f 0.60 (*n*-hex/ethyl acetate: 4/1); the NMR data for **15** were collected at 200 MHz in $CDCl_3$ at 25°C. In order to define the structure of **15**, the following experiments were performed: ^{1}H, ^{13}C, DEPT, COSY. ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 7 33 (s, 5H, Ph), 5.25–5.17 (m, 6H, CH_2Ph, H-5), 4.32 (q, $J=7.3$ Hz, 2H, OCH_2CH$_3$), 3.44–3.30 (four lines, A part of an ABX system, 1H, CH_2O) 3.04–2.94 (four lines, B part of an ABX system, 1H, CH_2O), 2.91–2.82 (four lines, A part of an ABX system, 1H, H-3) 2.72–2.60 (four lines, B part of an ABX system, 1H, H-3), 1.34 (t, $J=7.3$ Hz, 3H, OCH$_2$$CH_3$); ^{13}C NMR: δ 169.19 (COOBn), 160.33 (COOEt), 151.42 (C=N), 135.28 (*ipso*), 128.51, 128.31, 128.17 (Ph), 79.25 (C-5), 66.68 (CH_2Ph), 61.97 (OCH_2CH$_3$), 39.37 (C-4), 38.65 (CH_2COOBn), 13.96 (OCH$_2$$CH_3$); MS: $C_{15}H_{17}NO_5$, 292 $[M+1]^+$.
18: oil; R_f 0.17 (*n*-hex/ethyl acetate: 1/1); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ 7.29 (s, 5H, Ph) 6.91 (bb, 1H, NH), 6.58 (bb, 1H, NH), 5.08 (t, $J=8.5$ Hz, 1H, H-5), 4.49 (d, $J=6.0$ Hz, 2H, CH_2CH(CH$_3$)$_2$), 3.58 (s, 2H, CH_2Ph), 3.20–3.02 (m, 2H, H-4), 1.83–1.69 (m, 1H, CH$_2$$CH$(CH$_3$)$_2$), 0.90 (s, 3H, CH$_2$CH($CH_3$)$_2$), 0.86 (s, 3H, CH$_2$CH($CH_3$)$_2$); MS: $C_{16}H_{21}N_3O_3$, 304 $[M+1]^+$.
10. In some cases the formation of furoxane **4** could not be prevented, thus yields were lower. Nevertheless, as furoxane remained preferentially in the ionic liquid, the products could be isolated pure without chromatography.
11. The rate acceleration of the cycloaddition of imidates derived from diethylmalonate and electron rich aromatic aldehydes in ionic liquid has been reported: Dubreuil, J. F.; Buzureau, J. P. *Tetrahedron Lett*. **2000**, *41*, 7351.