Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 4703–4705

Aza analogs of kainoids by dipolar cycloaddition ☆

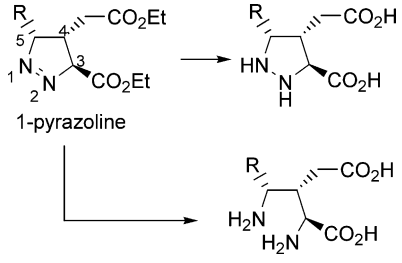
Mingping Di and Kathleen S. Rein*

Department of Chemistry and Biochemistry, Florida International University, Miami, FL 33199, USA

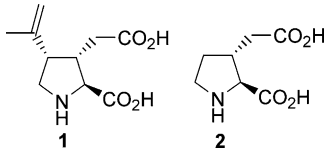
Received 14 March 2004; revised 15 April 2004; accepted 16 April 2004

Abstract—The 1,3-dipolar cycloadditions of diazoalkanes with *trans*-diethyl glutaconate yield 1-pyrazolines, which isomerize to 2-pyrazolines or are oxidized to pyrazoles. The 2-pyrazolines may serve as precursors to novel glutamate analogs or aza analogs of kainoids. The regioselectivity of the 1,3-dipolar cycloadditions of diazoalkanes and *trans*-diethyl glutaconate and isomerization of the 1-pyrazolines to 2-pyrazolines are evaluated.

Recently there has been a great deal of interest in the synthesis of novel amino acids for the preparation of peptide mimics.[1] Carreira and co-workers reported the diastereoselective synthesis of aza proline and aspartic acid analogs via dipolar cycloaddition of trimethylsilyldiazomethane and chiral acrylamides.[2–4] The use of *trans*-diethyl glutaconate as the dipolarophile provides the 1-pyrazoline products, which may serve as precursors either to novel γ-amino glutamate analogs or to aza analogs of kainoids (Scheme 1). The kainoids are a class of pyrrolidine dicarboxylates that exhibit both excitatory and excitotoxic activities.[5] These effects are a result of the ability of the kainoids to act as glutamate receptor agonists and to activate ionotropic glutamate receptors.



Scheme 1.



1 **2**

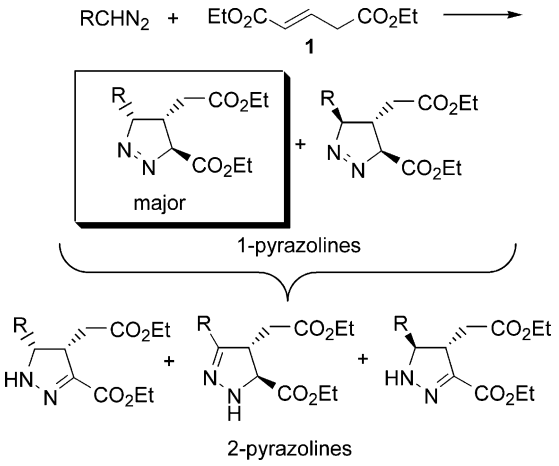
Figure 1. Structures of kainic acid and CPAA.

The parent of this group of compounds is α-kainic acid (**1**, Fig. 1). Many synthetic and naturally occurring kainoids that either vary in the configuration of one or more of the three contiguous stereocenters or in the nature of the substituent at the 4-position of the pyrrolidine ring, have been studied. The activity of the kainoids is effectively lost if the absolute configuration of any one of the three stereocenters is inverted.[6] Further, the activity of the unsubstituted kainoid, 2-carboxy-3-pyrrolidine-3-acetic acid (CPAA) (**2**, Fig. 1) is significantly less than that of kainic acid.[7]

Kainic acid is isolated from the seaweed *Diginea simplex*[8] and has been used in Asian countries as a treatment for intestinal worms in children. In addition it is used extensively by neuropharmacologists for the study of glutamate receptors. Several years ago, the world's sole supplier of kainic acid discontinued this product. Numerous syntheses of kainoids have been published,[9] however none have proven to be practical. In an effort to identify a less costly alternative to kainic acid we are investigating the dipolar cycloaddition of diazoalkanes with *trans*-diethyl glutaconate to produce aza analogs of kainoids. Herein we report our preliminary studies of

Keywords: Dipolar cycloaddition; Kainoids; Pyrazole; Pyrazolines.
☆ Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2004.04.097
* Corresponding author. Tel.: +1-3053-486682; fax: +1-3053-483772; e-mail: reink@fiu.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.097



Scheme 2.

the dipolar cycloaddition between diazoalkanes and *trans*-diethyl glutaconate.

1,3-Dipolar cycloadditions of diazoalkanes and alkenes yield 1-pyrazolines (Scheme 2). When the dipolarophile is an α,β-unsaturated ester, diazoalkane HOMO-dipolarophile LUMO interactions dictate that the regioselectivity is such that the terminal nitrogen of the diazoalkane attacks the α-carbon of the ester (Scheme 2).[10] However, anomalous additions have also been observed.[11,12] Addition to the dipolarophile is stereospecific and *syn*, thus the relative configuration of the dipolarophile is conserved in the cycloadduct. The substituents at the 4- and 5-positions of the pyrazoline ring may be either *cis* or *trans*, depending on the nature of the substituents. The *cis*-relative configuration will be favored if π-interactions are present in the transition state.[13] Thus the 1,3-dipolar cycloaddition of *trans*-diethyl glutaconate with diazoalkanes should provide the appropriate 3,4-*trans*-, 4,5-*cis*-relative configurations in the cycloadducts. However, 1-pyrazolines tend to be unstable and can either become oxidized to the pyrazoles or, if it results in conjugation, will isomerize to the 2-pyrazolines with the direction of double bond isomerization dependent on the substituents. Thus, at least one of the newly formed stereocenters is lost.

The results of the 1,3-dipolar cycloaddition between *trans*-diethyl glutaconate and diazoalkanes are summarized in Table 1 and Figure 2. The 1-pyrazolines either isomerized to the 2-pyrazolines or became oxidized to the pyrazoles. Because of the tendency of the 2-pyrazolines to become oxidized (phenyl substituted pyrazolines in particular), they were converted to the Cbz derivatives, which tends to inhibit oxidation, for full charac-

Table 1. 1,3-Dipolar cycloaddition of diazoalkanes and *trans*-diethyl glutaconate

R	# equiv $RCHN_2$	Conditions	Yield (%)[a]	Product ratio a:b[c]
H	2.2	Et_2O, 23 °C, 15 h	90	0:100
Ph	0.9	THF, −78 to 23 °C, 15 h	73	80:20
CO_2Et	1.2	C_6H_6, reflux, 72 h	39	13.5:0:1 (**5a**:**5b**:**7**)
CO_2Et	1.2	$PhCH_3$, reflux, 72 h	37	4:0:1 (**5a**:**5b**:**7**)
CO_2Et	2	C_6H_6, reflux, 72 h	64	3:0:1 (**5a**:**5b**:**7**)
CO_2Et	2	$PhCH_3$, reflux, 72 h	89	3:0:1 (**5a**:**5b**:**7**)
TMS	6	$PhCH_3$/hexane, 23 °C, 3 d	58 (96[b])	1.7:1[d]

[a] Purified.
[b] Based on recovered diethyl glutaconate.
[c] Determined by NMR.
[d] Regioisomers were not specifically assigned.

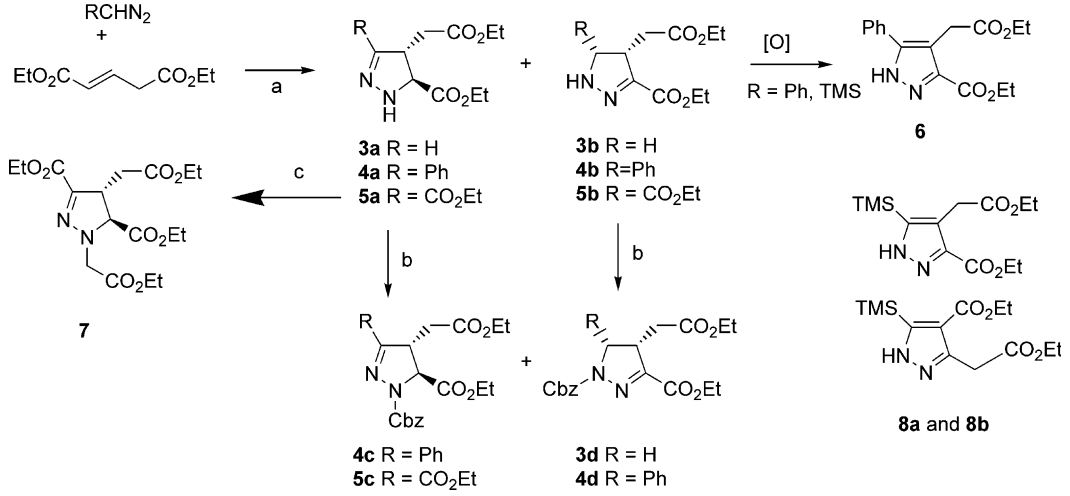


Figure 2. (a) See Table 1 for conditions; (b) Cbz-chloride, CH_2Cl_2, $NaHCO_3$ (aq); (c) N_2CHCO_2Et/Δ.

terization. The cycloaddition of diazomethane and *trans*-diethyl glutaconate yielded, as expected, a single 2-pyrazoline product (**3b**) in 90% yield. The cycloaddition of phenyldiazomethane[14] and *trans*-diethyl glutaconate yielded two 2-pyrazoline adducts (**4a** and **4b**) in a ratio of 4:1 and an overall yield of 73%. On standing, this mixture readily oxidizes to a single pyrazole (**6**) confirming the expected regioselectivity. The regioisomers (**4a** and **4b** and their Cbz derivatives) are readily distinguished on the basis of ^{13}C and ^{1}H NMR. The relative configuration of the 3,4-substituents of **4a** is expected to be *trans* and is confirmed by the similarity of the ^{1}H NMR to similarly substituted 2-pyrazolines[15] and [4,5]-dehydropyrrolidines.[16] The relative configuration of the 4,5-substituents of **4b** is assigned as *cis* on the basis of the vicinal coupling constant (12 Hz)[15] and the large upfield shift of one of the diastereotopic α-methylene protons (δ 2.12 ppm and δ 2.09 ppm for **4b** and **4d**, respectively, compared to a range from δ 2.51 to δ 2.95 for **3d**, **4a**, **4c**, **5a**, and **5c**). This large upfield shift is consistent with 3,4-*cis*-substituted kainoids with an aromatic ring at the 4-position[15,16] and is also consistent with a recent empirical analysis of NMR data of various natural and synthetic kainoids.[17] We did not observe the *trans*-isomer of **4b**, suggesting that the relative stereoselectivity of the cycloaddition is *cis*. Ethyldiazoacetate was unreactive at room temperature due to the electron withdrawing effect of the carbonyl. Thus the cycloaddition was carried out in refluxing benzene or toluene providing the *trans*-isomer **5a**, along with a by-product **7**, which arose from carbene insertion into the N–H bond of the 2-pyrazoline, **5a**. Assignment of relative configuration of **5a** was based on coupling constants of the ring protons.[15] Assignment of relative configurations of **7** was confirmed by conversion of **5a** to **7** by treatment with ethyldiazoacetate. The use of 2 equiv of ethyldiazoacetate in refluxing toluene or benzene improved the overall yield, but also increased the proportion of the by-product. Failure to identify the *cis*-product, **5b** suggests either that the preferred stereoselectivity of the cycloaddition is *trans* or that the double bond isomerization is regioselective toward the *cis*-substituted carbonyl group, by virtue of the relief of torsional strain in a *cis–trans*-substituted 1-pyrazoline intermediate.

In contrast to a recent report that the cycloaddition of trimethylsilyldiazomethane and chiral acrylamides produced 2-pyrazolines via proteodesilylation[3], the reaction between *trans*-diethyl glutaconate and trimethylsilyldiazomethane, in our hands, failed to provide 2-pyrazolines. Instead, a mixture of pyrazoles (**8a** and **8b**) in a ratio of 1.7:1 was obtained. Apparently, the regioselectivity of the cycloaddition is partially reversed as the size of R increases and steric effects overcome electronic effects.

The dipolar cycloadditon of diazoalkanes and *trans*-diethyl glutaconate provides the appropriate pyrazoline ring, which may be converted into aza analogs of kainoids. Unfortunately one of the newly formed stereocenters is lost. Efforts are underway to develop chiral auxiliaries to control the absolute stereochemistry of the cycloaddition and for the reduction of the pyrazoline ring to the pyrazolidine.

Supplementary material

General synthetic procedures and spectroscopic data for all new compounds are included in the supplementary material. The supplementary data is available online with the paper in ScienceDirect.

Acknowledgements

This work was supported by NIH ES07938 and ES05705. This is contribution number P200404 from the Center of Excellence in Biomedical and Marine Biotechnology. M.D. is grateful for a Presidential Enhanced Assistantship from the University Graduate School at FIU.

References and notes

1. *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; Elsevier Science, Ltd: New York, NY, 1999.
2. Guerra, F. M.; Mish, M. R.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4265–4267.
3. Mish, M. R.; Guerra, F. M.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 8379–8380.
4. Sasaki, H.; Carreira, E. M. *Synthesis* **2000**, *1*, 135–138.
5. Ben-Ari, Y.; Cossart, R. *Trends Neurosci.* **2000**, *23*, 580–587.
6. Johansen, T. N.; Greenwood, J. R.; Frydenvang, K.; Madsen, U.; Krogsgaard-Larsen, P. *Chirality* **2003**, *15*, 167–179.
7. Tsai, C.; Schneider, J. A.; Lehmann, J. *Neurosci. Lett.* **1988**, *92*, 298–302.
8. Ueno, Y.; Nawa, H.; Ueyanagi, J.; Morimoto, H.; Nakamori, R.; Matsuoka, T. *J. Pharm. Soc. Jpn.* **1955**, *75*, 807–811.
9. Wood, M. E.; Fryer, A. M. *Adv. Nitrog. Heterog.* **1998**, *3*, 159–218.
10. Houk, K. N. *J. Am. Chem. Soc.* **1972**, *94*, 8953–8955.
11. Eberhard, P.; Huisgen, R. *Tetrahedron Lett.* **1971**, *45*, 4337–4342.
12. Houk, K. N.; Domelsmith, L. N.; Strozier, R. W.; Patterson, R. T. *J. Am. Chem. Soc.* **1978**, *100*, 6531–6533.
13. Huisgen, R.; Eberhard, P. *Tetrahedron Lett.* **1971**, *45*, 4343–4346.
14. Creary, X. *Org. Syn.* **1993**, *Col. Vol. 7*, 438–441.
15. Baldwin, J. E.; Fryer, A. M.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5255–5272.
16. Maeda, H.; Selvakumar, N.; Kraus, G. A. *Tetrahedron* **1999**, *55*, 943–954.
17. Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2597–2601.