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On the C-2 epimerisation of kainoids

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Abstract—The conditions for the epimerisation at carbon C-2 of phenyl kainic acid esters **6** and **7** and *cis*-3-prolinoglutamic esters **10** were systematically addressed. We found that the use of KHMDS in THF gave improved results over the existing procedures. Some mechanistic aspects of this peculiar epimerisation are discussed.

Kainic acid **2** (KA) is a naturally constrained analogue of glutamic acid **1**, the major excitatory amino acid in the mammalian central nervous system (Fig. 1).[1] KA **2** shows high affinity for specific subtypes of glutamate receptors—the KA receptors—and is widely used as a reference tool[2] to mimic the symptoms of neuronal injuries in animal brains such as epilepsy, Alzheimer's disease[3] and Huntington's chorea.[4] KA is the parent member of the large kainoid family[5] including aryl kainoids **3**, acromelic acid (for ex. acromelic acid A **4**) or domoic acid **5**, which are all powerful neuroexcitatory agents.[6]

The pyrrolidine skeleton, in all these molecules (**2**–**5**), embedded three contiguous stereocenters in a typical *trans* (C2–C3), *cis* (C3–C4) arrangement which is a crucial feature for binding to the KA receptor.[7] Recently, a shortage of kainic acid[8] has prompted several groups to search for new efficient synthetic routes towards KA[9] and the corresponding analogues **3**, **4** and **5**.[10] As we are involved in the kainoid area, we proposed a very short synthesis (only six steps) of phenylkainic acid (Ar = Ph in **3**).[11] Our synthetic route afforded compounds **6a** *endo* with a *cis* relationship at carbon C-2 and C-3, and, therefore an additional epimerisation step was required at the carbon C-2 to reach the precursor **8a** (Scheme 1) of the desired bioactive stereomer. This epimerisation step is crucial and has been used in several synthesis of kainoids.[9d,e,g,10b,12] However, in our hands when we tried the reported epimerisation procedures on compound **6a** as well as on **7a** *exo* (to get **9a**, the corresponding *allo* analogue)[10c] no convincing results were obtained.

In this letter, we present a systematic study which led to the proposal of new reaction conditions and relevant mechanistic considerations. It must be emphasised that other teams encountered similar difficulties for the C-2 epimerisation: Rubio,[12a] in a synthesis of KA; Ogasawara, in his synthesis of acromelic acid;[10h] and more recently, Karoyan,[13] faced difficulties for the epimerisation at carbon C-2 of *cis*-3-prolinoglutamic acid diester **10a**. Probably the presence of the acetate appendage at carbon C-3 induces new steric and electronic constraints, which render the C-2 epimerisation much more complex than it is in proline itself (see below). We focussed our study towards the phenyl

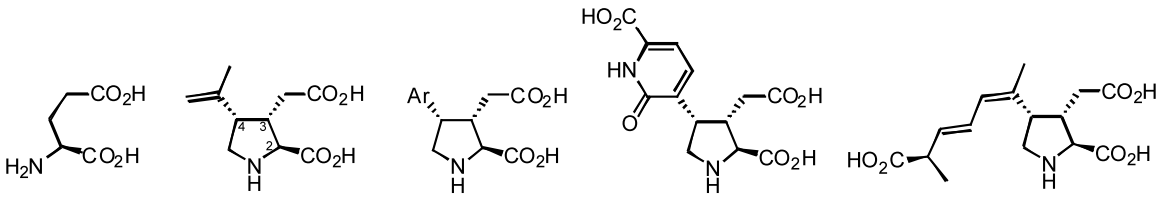

Figure 1. Glutamic acid and kainoid family.

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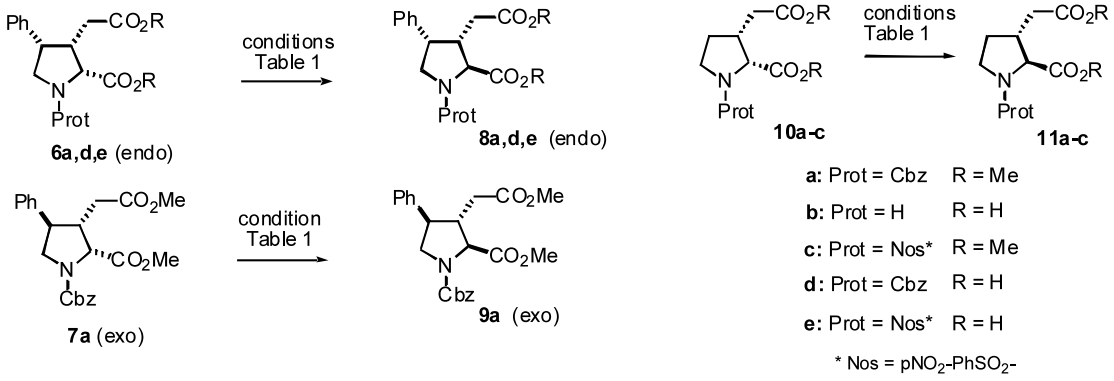
kainoids **6a**,**d**,**e** (*endo*) and **7a** (*exo*) and to the *cis*-3-prolinoglutamic derivatives **10a**–**c** (Scheme 1).[14]

First a series of investigations were performed on *cis*-3-prolinoglutamates **10a**–**c** and then extended to the kainoid precursors **6a**, **6d** and **6e**, and **7a** (see Table 1).[15a] The cognate methods (for **10a** or **10b**, entries 1–6) failed except with LDA (entry 5). In this case epimerisation to the extent of 80% has taken place as revealed by ^{1}H NMR on the crude, but after the isolation step, compound **11a** was obtained in a low yield (<25%). The free acid **10b** (entry 6) was totally inert to strong basic conditions. For **10a**, no improvement was observed with other alkoxides such as *t*BuOK (entry 7). The use of strong bases in polar solvents like DMSO (entries 8–9) afforded partial epimerisation but under rather harsh conditions. Then we found that KH in the presence of crown ethers gave promising results[11] (entries 10–14). However, several limitations were identified, relating firstly to the nature of the protecting group. With the nosyl group **10c** (entries 11) no reaction occurred, whereas with the benzylcarbamate **10a** and **6a** the desired epimerisation took place (entry 10 and 12). Then, the epimerisation failed with the free acid **6d** (entry 13) indicating that the carboxylic esters must be present under these conditions. When the epimerisation proceeded, complete saponification of the two ester appendages at carbons C-2 and C-3 is observed, and an additional treatment with diazomethane is needed for proper characterisations of the adducts. Finally the quality of the 18-crown-6 ether seemed to be critical in our experimental conditions (see entry 12). With pure dry 18-crown-6, (entry 15) no epimerisation was detectable, only *deliquescent* 18-crown-6 ether, recrystallised in acetonitrile, gave satisfactory results. Probably a co-crystallised water molecule plays an important role here. Changing the solvent for methanol did not improve the results (entry 16). Due to those erratic results, and particularly this last point, reproducible and cleaner conditions were highly desirable. Thus we decided to reinvestigate the hexamethyldisilyl azide salts on **10a**, **6a** and **7a**.

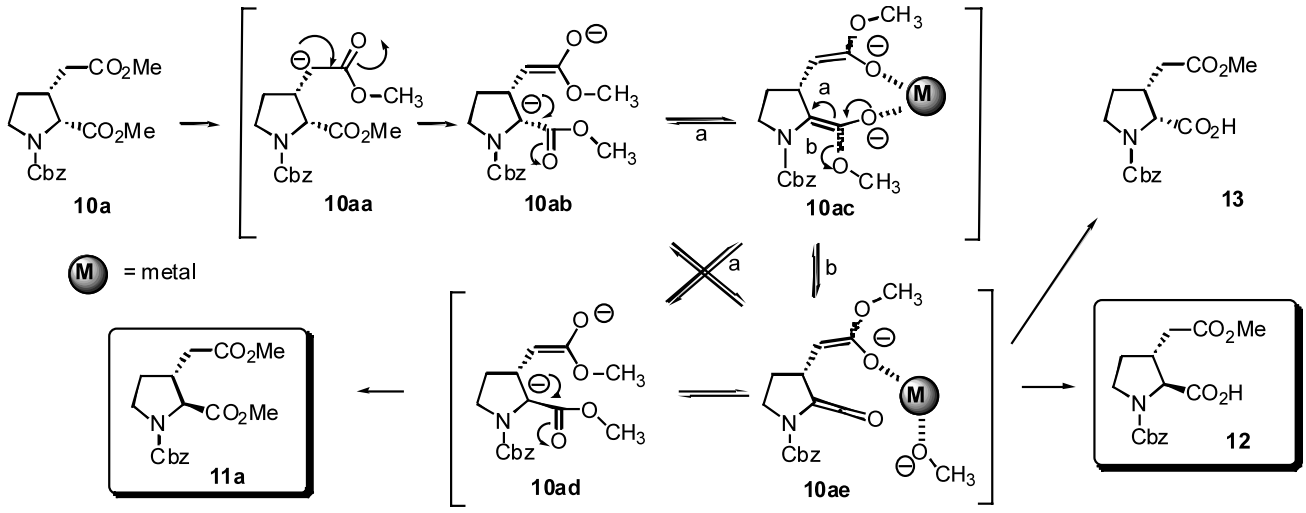


Scheme 1. Epimerisation of kainoids.

Table 1. Epimerisation conditions

Entries	No mol.	Prot	R	Conditions	% *epi.*[15a]	Ref.	Observations
1	**10a**	Cbz	Me	NaH (2.5 equiv.), DBU (5 equiv.), benzene, rt	0	12e,f	
2	**10a**	Cbz	Me	DBU 20°C then 130°C in xylene	0	12d	
3	**10a**	Cbz	Me	LiHMDS (2.5 equiv.), THF, 0°C then MeOH	0	9e,12a	
4	**10a**	Cbz	Me	MeONa, MeOH, reflux	0	12c	
5	**10a**	Cbz	Me	LDA (2.6 equiv.), THF, −55°C, 1 h	(80)	10b,12b	20% purified **11a**
6	**10b**	H	H	KOH 50% (excess) 50°C, 4 h	0	9g	
7	**10a**	Cbz	Me	*t*BuOK (5 equiv.), THF, 70°C 20 h	0		Degradation
8	**10a**	Cbz	Me	MeONa (3 equiv.), MeOH–DMSO, 120°C, 20 h	45		Entry 4+DMSO
9	**10a**	Cbz	Me	BDU (5 equiv.), DMSO, 130°C, 20 h	25		Entry 2+DMSO
10	**10a**	Cbz	Me	KH (3 equiv.), 18–6[a], benzene, 20°C, 16 h	85		Saponification[15b]
11	**10c**	Nos	Me	KH (3 equiv.), 18–6[a], benzene, 20°C, 16 h	0		No reaction
12	**6a**	Cbz	Me	KH (3 equiv.), 18–6[a], benzene, 20°C, 16 h	80	11	Saponification[15b]
13	**6d**	Cbz	H	KH (3 equiv.), 18–6[a], benzene, 20°C, 16 h	0		
14	**6e**	Nos	H	KH (8 equiv.), 18–6[a], benzene, 20°C, 16 h	0		
15	**6a**	Cbz	Me	KH (4 equiv.), 18–6 pur, benzene, 20°C, 16 h	0		No reaction
16	**6a**	Cbz	Me	KH (3 equiv.), 18–6[a], MeOH, 20°C, 16 h	0		No reaction
17	**10a**	Cbz	Me	NaHMDS (2.5 equiv.), THF, 0°C, 2.5 h	70		15% saponif.[15b]
18	**10a**	Cbz	Me	KHMDS (2.5 equiv.), THF, 0°C 6 h	80		Little degradation
19	**7a**	Cbz	Me	KHMDS (3–4 equiv.), THF, 20°C, 16 h	40		>50% saponif.[15b]
20	**6a**	Cbz	Me	KHMDS (5 equiv.), THF, 0–20°C, 16 h	95		> 70% saponif.[15b]

[a] *deliquescent* 18-crown-6 recrystallised in acetonitrile.



Scheme 2. Proposed scenario for epimerisation.

As seen before, LiHMDS failed (entry 3), but gratifyingly NaHMDS in dry THF gave a significative epimerisation ratio of **10a** (70%, entry 17) together with some partial saponification. Even better results were obtained with KHMDS: the epimerisation ratio was now 80% (entry 18). Then these conditions were successfully applied to the epimerisation of the **6a**-(*endo*) or **7a**-(*exo*) phenylkainic esters respectively (entries 19, 20). Again we discovered the following discrepancies: the **7a**-(*exo*) compound is much more resistant to the epimerisation than the corresponding **6a**-(*endo*) one. These results may be ascribed to the steric effect of the phenyl group at C-4, conjugated with the strong 1,2 strength between the Cbz group on the nitrogen and the carboxylate at carbon C-2. During the transformation of **7a**-(*exo*) to **9a**-(*exo*) the phenyl group and the 'epimerised' carboxylate group at C-2 will be located on the same face of the pyrrolidine ring, generating severe steric interactions. Only two repeated reaction cycles gave rise to an epimerisation ratio of 60%. Fortunately, the adducts **9a**-(*exo*) formed and the starting material **7a**-(*exo*) could be separated by flash column chromatography. In contrast for the **6a**-(*endo*) derivative (all *cis* compound), the phenyl group at C-4 has a beneficial effect on the epimerisation, by the virtue of releasing the severe axial constraints present in **6a**. Thus, the reaction proceeds with an efficiency of 95%! (entry 20). These mild conditions proved to be easily reproducible on small or medium scale (1–3 mmol) but some saponification is unavoidable[15b] and an additional treatment with diazomethane is necessary to furnish **8a**-(*endo*) in 60–75% yield.[16]

In order to find a rationale for this peculiar epimerisation process, we propose the following scenario for the epimerisation of **10a**. 2 equiv. of KHMDS are required for performing this reaction, because the methylene protons at the acetate appendage at C-3 are more acidic than the methine proton at C-2.[10b] Thus, the first equivalent deprotonates the acetic side chain and gives **10aa** and the second equivalent of base produces a series of intermediates **10ab**, **10ac** and **10ad** susceptible to undergo the epimerisation. Indeed dianion **10ab** (Scheme 2), in equilibrium with the bis-enolate **10ac** and with the dianion **10ad** is ready to give the desired dimethylester **11a** on quenching. The alternative pathway can be: bis-enolate **10ac**, after losing a methoxylate group, is transformed into ketene **10ae**, as a 'charge decompressed' species and the water quench afforded the desired epimerised mono-acid **12** or the non-epimerised one **13**, resulting from a partial saponification.

It is also worth noticing the influence of the cation associated with the HMDS base with regard to the transient dianion **10ab**–**10ae**. The sizes of the cations are probably providing the following explanation: the lithium cation padlocks the two side chains, whereas sodium or potassium will form a looser chelate with suitable flexibility allowing the epimerisation to proceed (see Scheme 2). The polarity of the solvent is also of importance: THF is better than benzene.

In conclusion we disclosed new conditions for the epimerisation of *cis*-3-prolinoglutamic diesters **10** as well as that of the related phenylkainic compounds **6** and **7**. Our conditions are mild and reproducible. Furthermore our investigations revealed the importance of the protecting group on the pyrrolidinyl nitrogen, a carbamate is essential, and the influence of the aryl side chain at C-4, the *endo* is favored over the *exo* configuration.

Acknowledgements

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References

1. Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365–402.

2. *Kainic Acid as a Tool in Neurobiology*; McGeer, E. G.; Olney, J. W.; McGeer, P. L., Eds.; Raven Press: New York, 1978.
3. Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci.* **1994**, *17*, 31–108.
4. (a) Coyle, J. T.; Schwarcz, R. *Nature* **1976**, *263*, 244–246; (b) McGeer, E. G.; McGeer, P. L. *Nature* **1976**, *263*, 517–519.
5. Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149–4174.
6. (a) Moloney, M. G. *Nat. Prod. Rep.* **1998**, *15*, 205–219; (b) Moloney, M. G. *Nat. Prod. Rep.* **1999**, *16*, 484–498.
7. (a) Tsai, C.; Schneider, J. A.; Lehmann, J. *Neurosci. Lett.* **1988**, *92*, 298–302; (b) Ishida, M.; Shinozaki, H. *Br. J. Pharmacol.* **1991**, *104*, 873–878; (c) Sonnenberg, J. D.; Koch, H. P.; Willis, C. L.; Bradbury, F.; Dauenhauer, D.; Bridges, R. J.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1607–1612.
8. (a) Tremblay, J.-F. *Chem. Eng. News* **2000**, *January 3*, 14–15; (b) Tremblay, J.-F. *Chem. Eng. News* **2000**, *March 6*, 31.
9. For recent routes to kainic acid see: (a) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron* **1999**, *55*, 6153–6166; (b) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139–11143; (c) Clayden, J.; Tchabanenko, K. *Chem. Commun.* **2000**, 317–318; (d) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181–3183; (e) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3194–3204; (f) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199–6207; (g) Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485–487; (h) Hirasawa, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 7587–7590; (i) Ma, D.; Wu, W.; Deng, P. *Tetrahedron Lett.* **2001**, *42*, 6929–6931; (j) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38–39; (k) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727–4733.
10. For recent routes to aryl kainoids or analogues see: (a) Bryans, J. S.; Large, J. M.; Parsons, A. F. *Tetrahedron Lett.* **1999**, *40*, 3487–3490; (b) Maeda, H.; Selvakumar, N.; Kraus, G. A. *Tetrahedron* **1999**, *55*, 943–954; (c) Bryans, J. S.; Large, J. M.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2905–2910; (d) Collado, I.; Ezquerra, J.; Mateo, A. I.; Pedregal, C.; Rubio, A. *J. Org. Chem.* **1999**, *64*, 4304–4314; (e) Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. *Tetrahedron Lett.* **2001**, *42*, 3407–3410; (f) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411–4314; (g) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2588–2596; (h) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 4523–4526; (i) Greenwood, E. S.; Parsons, P. J. *Synlett* **2002**, 167–169.
11. Schneider, M.-R.; Klotz, P.; Ungureanu, I.; Mann, A.; Wermuth, C.-G. *Tetrahedron Lett.* **1999**, *40*, 3873–3876.
12. (a) Rubio, A.; Ezquerra, J.; Escribano, A.; Remuinan, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1998**, *39*, 2171–2174; (b) Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1997**, *62*, 2314–2315; (c) Carpes, M. J. S.; Miranda, P. C. M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1997**, *38*, 1869–1872; (d) Hashimoto, K.; Yamamoto, O.; Horikawa, M.; Ohfune, Y.; Shirahama, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1851–1854; (e) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204–1206; (f) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523–5524.
13. Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 253–255.
14. The preparation of **6**, **7** and **10** will be reported shortly in a full account.
15. (a) The percentage of epimerisation and saponification was determined by ^{1}H NMR experiments. Compounds **10a**–**c**, **6** and **7** are mixtures of two rotamers in a 1/1 ratio. The starting products exhibited signals from 4.45 to 4.80 ppm for the C2 proton (in $CDCl_3$, for the two rotamers present). After the epimerisation took place, signal for C2 proton appeared from 4.00 to 4.20 ppm (see Ref. 10d and ref. in it); (b) Concerning the saponification, the amount was appreciated from the integration of selected signals from ^{1}H NMR spectra.
16. Typical experiment: the starting product **6a**, **7a** or **10a** (0.2 mmol) was dissolved in freshly distilled THF (4 mL) under argon. The mixture was cooled to 0°C and KHMDS solid was added portion wise (4–5 equiv.). The reaction was stirred for 16 h from 0°C to rt and when quenched with dry MeOH (1 mL). The mixture was stirred for two additional hours and a solution of 1N HCl was added to reach pH 1. The products were extracted with AcOEt, washed with water, brine, and dried over $MgSO_4$. The crude (usually 100% yield on weight) was then dissolved in dry CH_2Cl_2 (2 mL) and MeOH (0.5 mL) and placed at 0°C before treatment with an etheral diazomethane solution. After 15 min the reaction was quenched with AcOH and concentrated under vacuum. The crude was purified by silica gel flash column chromatography and affords the pure compound in 60–75% yields. **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (dd, $J=16.0$, 7.5 Hz, 1H), 2.21–2.34 (m, 1H), 3.03–3.08 (m, 1H), 3.60–3.62 (tow s, 5H), 3.69–3.77 (m, 1H), 3.81 (s, 1H), 3.84–3.95 (m, 1H), 4.00–4.07 (m, 1H), 4.15 and 4.20 (tow d, $J=6.4$ Hz, 1H), 5.05–5.30 (m, 2H), 7.03–7.08 (m, 2H), 7.25–7.39 (m, 8H).