Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1927–1929

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

The Synthesis of 4-Arylsulfanyl-Substituted Kainoid Analogues from *trans*-4-Hydroxy-L-proline

Jack E. Baldwin,* Gareth J. Pritchard† and Douglas S. Williamson

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK

Received 14 April 2000; revised 16 June 2000; accepted 19 June 2000

Abstract—The potent neuroexcitatory activity of kainoid amino acids in the mammalian CNS places new analogues in high demand as tools for neuropharmacological research. A range of 4-arylsulfanyl-substituted kainoids has been synthesised in a parallel fashion via mesylate displacement by a number of aromatic and heteroaromatic thiolates upon (2*S*,3*S*,4*R*)-1-benzoyl-3-*tert*-butoxycarbonylmethyl-4-methanesulfonyloxy pyrrolidine-2-carboxylic acid methyl ester **8**, which is obtainable in eight steps from *trans*-4-hydroxy-L-proline **5**.

The kainoids are a class of non-proteinogenic amino acids, which have been isolated from a number of marine and fungal sources.[1] Both their intriguing general structure **1**, and broad spectrum of biological activity provide the impetus for their study. As well as insecticidal and anthelmintic properties,[2] they have been shown to display powerful neuroexcitatory activity in the mammalian central nervous system, by acting at the kainate sub-class of ionotropic glutamate receptors.[3] Structure–activity studies[4] performed on the parent compound, kainic acid **2**[5] and also acromelic acid A **3**[6] have established the main criteria for bioactivity; the most potent analogue disclosed thus far being compound **4**.[7] Since this observation was made, several other syntheses of phenylkainoids have been published.[8] Recent efforts within this laboratory have focussed on developing methodology for the synthesis of further analogues of the phenylkainoids, in a manner that may be applicable to parallel synthesis.[9] In this letter, we report the synthesis of a novel class of 4-arylsulfanyl substituted kainoids based on the cheap and readily available *trans*-4-hydroxy-L-proline **5**, a by-product of collagen hydrolysis.

Previous work has shown that the ketone **6** is obtainable in multigram quantities from *trans*-4-hydroxy-L-proline **5** in a six step sequence (Scheme 1).[10] Treatment of the ketone **6** with sodium borohydride in methanol afforded the alcohol **7** as a single diastereomer,‡ indicating that hydride attack had occurred from the face of the carbonyl group unhindered by the 2-C ester substituent. The resulting alcohol **7** was reacted with methanesulfonyl chloride and triethylamine in dichloromethane, which afforded the mesylate **8**§ (mp 132–133 °C, $[\alpha]_D$ −82 (*c* 0.25, CH_2Cl_2)) in 91% yield over two steps.

It was envisaged that the mesylate **8** could undergo S_N2 displacement by appropriate nucleophiles, thus setting up the desired kainoid stereochemistry around the pyrrolidine ring. We noted, however, the findings of the Shirahama group,[11] who described an example in which a tosylate attached to a kainoid core was displaced by lithium phenyl cuprate with retention of configuration. Additionally, Young et al.[12] had unsuccessfully attempted displacement of a mesylate by Grignard reagents and organocuprates on a similar pyrrolidine system; the present authors observed similar unreactivity when the mesylate **8** was reacted with a range of carbon nucleophiles.

*Corresponding author. Tel.: +44-1865-275671; fax: +44-1865-275632; e-mail: jack.baldwin@chem.ox.ac.uk

†Present address: Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK.

‡The stereochemistry, was confirmed by deprotection of compound **7** (6M $HCl_{(aq)}$, Δ then Dowex® 50WX8-100 ion exchange resin) and NOED experiments on the resulting product.

§The various thiolate salts required were prepared from their corresponding thiols,[13] general procedure: to a stirred solution of sodium methoxide (1 mol equiv) in methanol was added the thiol (1 mol equiv). After 3 h, the mixture was evaporated, the residue washed with diethyl ether to remove excess thiol traces, and then dried in vacuo to give the thiolate in essentially quantitative yield.

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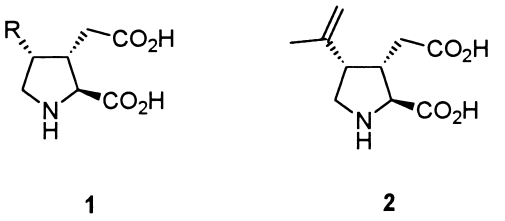
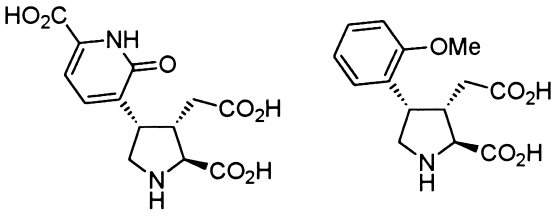
PII: S0960-894X(00)00352-8

We wish to report, however, that the mesylate group of compound **8** could be displaced by sulfur anions, affording a range of 4-arylsulfanyl-substituted kainoid analogues in protected form. For example, treatment of the mesylate **8** with the sodium salt of 2-mercapto-1-methylimidazole in dimethyl sulfoxide at 90 °C afforded compound **9a** in 55% yield (Scheme 2). The process was shown to be applicable to a wider range of aromatic and heteroaromatic thiols, as shown in Table 1.

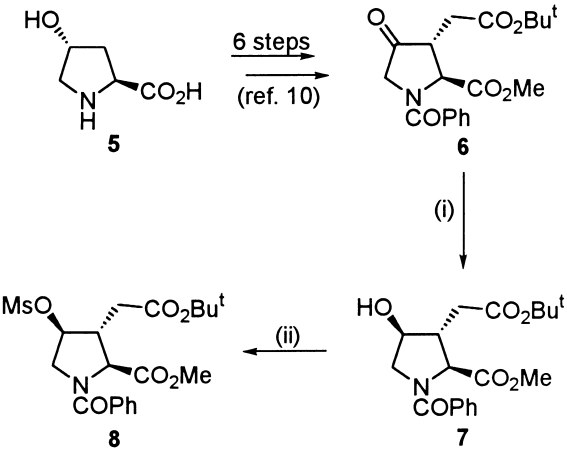


1 **2**

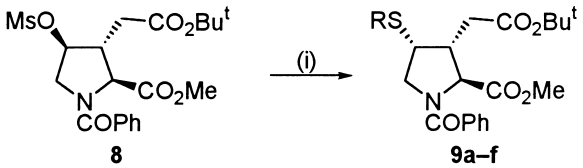


3 **4**

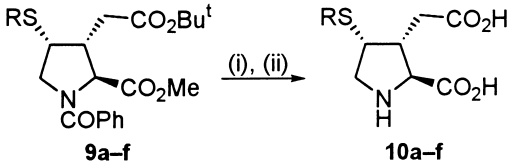
Compounds **9a**–**f** were treated with 6 M aqueous hydrochloric acid at reflux, and then subjected to ion-exchange chromatography (Dowex® 50WX8-100) (Scheme 3). As indicated in Table 2, deprotected amino acids **10a**–**c** were obtained in good to excellent yields. In



Scheme 1. (i) $NaBH_4$, MeOH; (ii) MsCl, Et_3N, CH_2Cl_2, 91% (over two steps).



Scheme 2. (i) RS^-Na^+ (5 mol equiv), Me_2SO, 90 °C.



9a–f **10a–f**

Scheme 3. (i) 6 M $HCl_{(aq)}$ Δ; (ii) Dowex® 50WX8-100 ion-exchange resin.

Table 1. Reaction of the mesylate **8** with thiolates

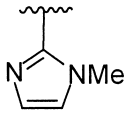
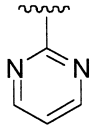
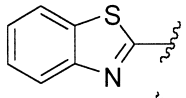
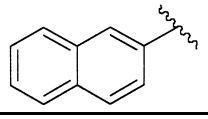
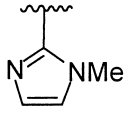
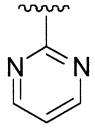
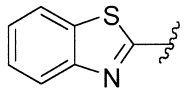
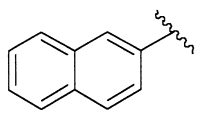
Entry	R	Product	Yield (%)
1		**9a**	55
2	Ph	**9b**	53
3	*o*-MeOPh	**9c**	53
4		**9d**	47
5		**9e**	53
6		**9f**	25

Table 2. Deprotection of compounds **9a**–**f**

Entry	R	Product	Yield (%)
1		**10a**	77
2	Ph	**10b**	71
3	*o*-MeOPh	**10c**	97
4[a]		**10d**	—
5[a]		**10e**	—
6[b]		**10f**	—

[a]Partial decomposition of the product occurred.
[b]Product insoluble.

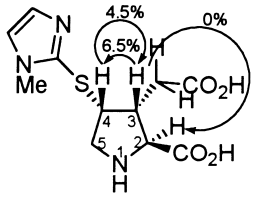


Figure 1. NOED spectroscopic data for compound **10a**.

cases **10d** and **e**, where the pyrimidine and benzothiazole functionality were susceptible to hydrolysis, isolation of the desired material was not possible. Compound **10f** proved to be highly insoluble, making handling and characterisation impractical.

The stereochemistry of compound **10a** was confirmed by NOED spectroscopic experiments, the key data from which is presented in Figure 1. Irradiation of the signal pertaining to 4-H enhanced the 3-H signal by 4.5% and, conversely, irradiation of the 3-H signal enhanced the 4-H signal by 6.5%. There was no enhancement of the 3-H proton upon irradiation of the 2-H signal, neither was there a through-ring interaction between 2- and 4-H. Additionally, the signals in the ^{1}H NMR spectrum of the methylene group adjacent to the carboxyl group of compounds **10a**–**c** had a characteristic splitting pattern, which has been observed in analogous compounds.[9]

In summary, a novel class of 4-arylsulfanyl-substituted kainoid amino acids have been synthesised from commercially available *trans*-4-hydroxy-L-proline **5**. Despite some limitations, this route should allow the preparation of more 4-C heteroaromatic kainoid analogues by parallel nucleophilic substitutions on the mesylate **8**. The prepared compounds are currently undergoing biological evaluation for their use as neuropharmacological tools for the study of kainate receptors in the CNS.

Acknowledgements

We thank F. Hoffmann-La Roche for financial support and Dr Andrew M. Fryer for helpful discussions.

References and Notes

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