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preparation of 2-(2'-carboxy-3'-ethylcyclopropyl)glycine

Kamil Godula

William Donaldson
Marquette University, william.donaldson@marquette.edu

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Synthesis of Cyclopropanes Via Organoiron Methodology: Preparation of 2-(2’-carboxy-3’-ethylcyclopropyl)glycine

Kamil Godula
Department of Chemistry, Marquette University, Milwaukee, WI
William A. Donaldson
Department of Chemistry, Marquette University, Milwaukee, WI

Abstract
A route to 1,2,3-trisubstituted cyclopropanes has been developed. The relative stereochemistry at the three cyclopropane centers is established by nucleophilic attack on the pentadienyl ligand on the face opposite to iron and subsequent oxidatively induced reductive elimination with retention of configuration. This methodology was applied to the synthesis of 2-(2’-carboxy-3’-ethylcyclopropyl)glycines. The diastereomeric glycine dimethyl esters are separable as their diphenylmethylene imines.

The conformationally restricted glutamate analogs (2S,1’S,2’S,3’R)- and (2R,1’S,2’S,3’R)-ECCG’s 5a and 5b were prepared in five steps (17 and 15% yield, respectively) from (pentadienyl)Fe(CO)₃⁺ (1R)-6.
l-Glutamic acid is the major excitatory neurotransmitter for a wide variety of receptors in mammalian systems. The selective activation of different glutamate receptors may depend on recognition of a particular conformation of this flexible molecule. For this reason, the synthesis and evaluation of conformationally restricted 2-(2′-carboxycyclopropyl)glycines has led to the discovery of ligands with mGluR specificity. In particular the extended conformation, as exemplified by compounds 1–4, is believed to be a requirement for binding to the mGluR1 and mGluR2 receptors, while the presence and electronic nature of the 3′-substituent may distinguish between agonist and antagonist activity. As part of our overall program on the development of a novel iron-mediated formation of substituted cyclopropanes, we herein report on the preparation of 2-(2′-carboxy-3′-ethylcyclopropyl)glycines, (2S,1′S,2′S,3′R)-5a and (2R,1′S,2′S,3′R)-5b.

We have previously reported that the nucleophilic attack of malonate anions to (1-methoxy-carbonylpentadienyl)Fe(CO)3+ (rac-6) proceeds predominantly at an internal carbon, on the face of the pentadienyl ligand opposite to iron, to afford (pentenediyl)iron complexes (rac-7) (Scheme 1). Furthermore, oxidatively induced-reductive elimination of rac-7 gives the vinylcyclopropanecarboxylate rac-8. It was envisioned that this sequence of reactions might be applicable to the synthesis of 2-(3′-substituted-2′-carboxycyclopropyl)glycines.

Scheme 1.

Reaction of rac-6 with the anion derived from methyl nitroacetate gave the (pentenediyl)iron complex rac-9a/b as a mixture of diastereomers (Scheme 2). Treatment of rac-9a/b with CAN gave rac-10a/b. The relative stereochemistry about the cyclopropane ring in 10a/b was assigned as indicated on the basis of the magnitude of the vicinal couplings ($J_{1′-2′}=J_{2′-3′}=5.3$ Hz). Reduction of 10a/b, followed by reaction with benzophenone imine gave a mixture of rac-11a and rac-11b, which were separable by column chromatography. The structure of rac-11a was confirmed by single-crystal X-ray analysis. Beginning with (1R)-6, this sequence of reactions gave (-)-11a and (+)-11b. The 2S configuration (-)-11a was assigned by comparison of the sign of its specific rotation with that of a series of 13 N-diphenylmethylene imines of l-amino esters. Both (-)-11a and (+)-11b were assessed to be >80% ee by 1H NMR spectroscopy in the presence of Eu(hfc)$_3$ (CDCl$_3$). Separate hydrolysis of (-)-11a or of (+)-11b gave the cyclopropylglycine hydrochloride salts 5a or 5b in excellent yield.

Scheme 2.
In summary, a route to 2-(2′-carboxy-3′-ethylcyclopropyl)glycines has been developed. Attempts to prepare other conformationally restricted glutamate analogs from 10a/b will be reported in due course.

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References

7. The X-ray structure of rac-11a was determined by Professor Douglas Stephan. Details of this will be reported separately.