

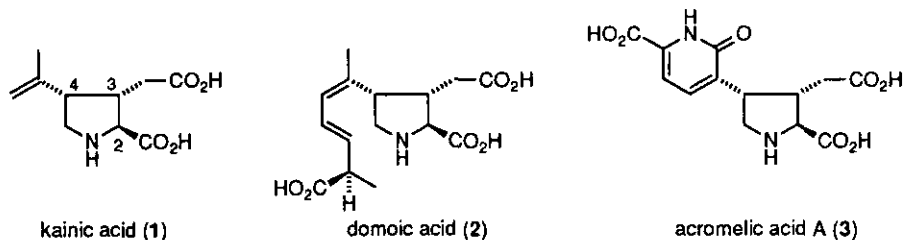
CONSTRUCTION OF 3,4-DISUBSTITUTED TETRAHYDRO-FURAN RING BY RADICAL CYCLIZATION. A MODEL STUDY FOR KAINOID SYNTHESIS†

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Abstract - Radical cyclization for construction of the 3,4-disubstituted tetrahydrofuran ring was attempted. The radical was produced through a charge-transfer complex under irradiation conditions.

Kainoids, such as kainic (1), domoic (2), and acromelic acids (A; 3), are a group of unusual amino acids.¹ They contain the L-glutamic acid moiety in their structure that causes strong neuroexcitatory activity in mammalian central nervous systems through an interaction with the excitatory amino acid receptor (glutamate receptor).² We developed several synthetic methods for these amino acids and their analogs and estimated their biological activities.³ They showed extraordinary potent depolarizing activity which depends on the nature of the C4-substituents. Also, their activity strength seemed to parallel the HOMO energy of their C4-substituents.⁴ Our kainoids have been strongly requested as reagents to study neuropharmacology and physiology and we have been seeking simpler synthetic methods for these compounds. We would now like to describe a successful model reaction which is directly applicable to the construction of the proline ring, which is common structure of the kainoids, having various aromatic side groups with a high HOMO energy attached to the C4 position.



The reaction is a radical ring closure of 4-arylethoxy-2-butenolate derivatives into 4-aryl-3-carboxymethyltetrahydrofurans. For the radical production, Wagner's reaction was applied. He and his coworkers reported that 2,2,2-trifluoroacetophenone and toluene produce the exciplex by electron transfer under irradiation which affords a benzyl radical and ketyl-type radical after proton transfer from toluene to

† Dedicated to Dr. Bernhard Witkop in celebration of his 80th birthday.

the ketone (Figure 1).⁵ The selection of an appropriate pair of electron donors (with higher HOMO energy level) and acceptors (with lower LUMO energy level) would easily produce these type of radicals under irradiation.

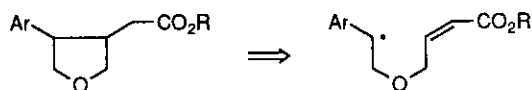
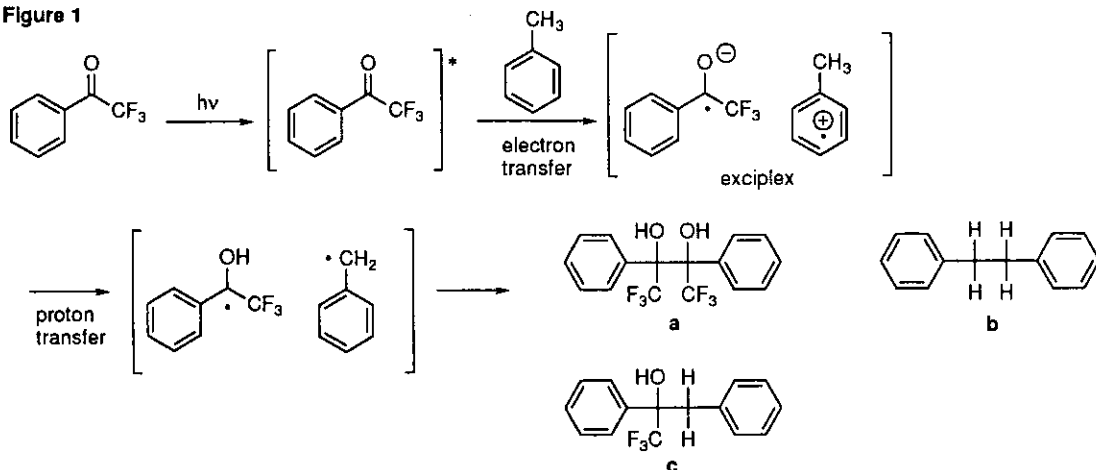


Figure 1



The radical cyclization was performed using three unsaturated esters and a nitrile which were prepared as follows (Figure 2). Starting from 2-methoxyphenylacetic acid (**4**), reduction with LiAlH_4 followed by allylation of the resulting alcohol gave an allyl ether, which was exposed to ozonolysis to afford the aldehyde (**5**). The aldehyde (**5**) was converted to the α,β -unsaturated ester (**6**) and the nitrile (**7**) by the Horner-Emmons reactions. The aldehyde (**5**) was also converted to the esters (**9**) and (**11**) by the Knoevenagel condensation. These prepared unsaturated compounds were then subjected to the radical cyclization. In a quartz test tube, the substrate and 2,2,2-trifluoroacetophenone were dissolved in acetonitrile, which was irradiated with a high pressure mercury lamp at 20 ~ 25°C.

Figure 2

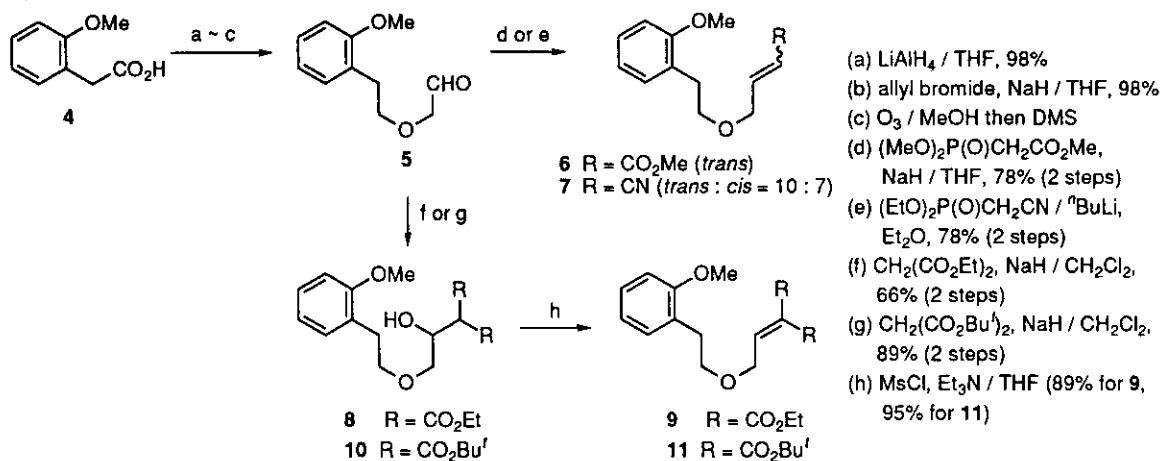
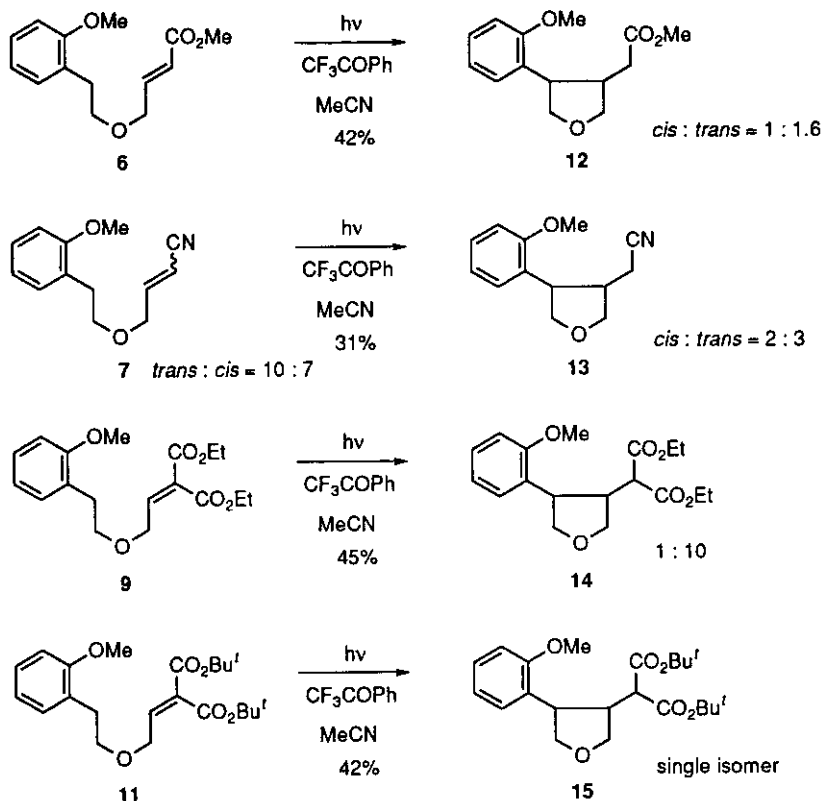


Figure 3



The ester (**6**) gave the cyclization product (**12**) in 42% yield as a mixture of *cis* and *trans* isomers in a ratio of 1:1.6. The *trans* isomer was purified and the stereochemistry was determined. The nitrile (**7**) (a mixture of *cis* and *trans* isomers in 7:10 ratio) also gave tetrahydrofuran (**13**) in 31% yield as a mixture of stereoisomers (*cis* : *trans* = 2:3). Cyclization of the malonic ester types (**9**) and (**11**) also proceeded to give cyclized products (**14**) and (**15**) in 45 and 42% yields, respectively. The former gave a mixture of stereoisomers in a 1:10 ratio, while the latter gave a single isomer. Based on a comparison of the ^1H NMR data with those of **12**, the major isomer should be the *trans* isomer. Both isomers of the cyclized products were not interconvertible upon exposure to the same photoreaction conditions. These types of radical cyclizations usually proceed with *cis* isomer selectively,⁶ but in these cases, steric hindrance between the C3 and C4-substituted groups could be the major factor controlling the stereoselectivity. It might also be caused by the stability of the benzyl radical. The product yield did not depend on the quantity of the 2,2,2-trifluoroacetophenone used and the coupling products corresponding to **b** and **c** were not observed. At this time, acetonitrile was the solvent that produced the best yield. These reactions preferably proceeded with the *trans* isomer, but the stereoselectivity would be improved by modification of the acceptor site and the yields would be improved by acceleration of the proton transfer step. Further studies along this line are now underway.

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