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A Facile Route to Polysubstituted *N*-Benzyl Pyroglutamates

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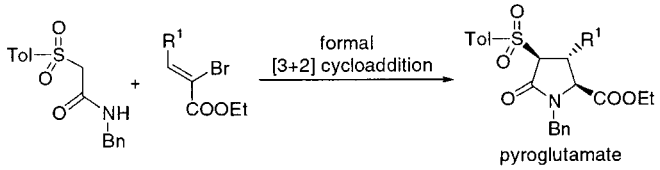
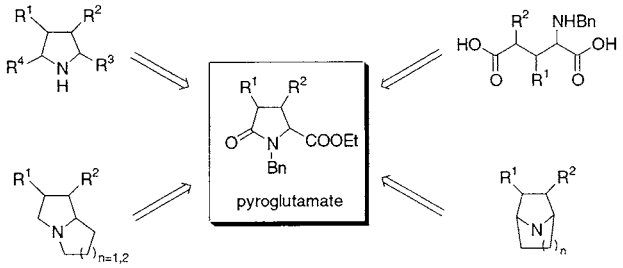
ABSTRACT



Base-induced coupling/cyclization reactions of α-sulfonylacetamide with various ethyl (*Z*)-2-bromo-2-propenoates have been carried out. The polysubstituted pyroglutamate carbon skeleton, with three contiguous asymmetric centers, was built up in one step. A ring-closure mechanism is proposed for the reactions.

Pyroglutamic acid derivatives are prevalent scaffolds that serve as crucial building blocks for numerous syntheses of natural products and nitrogen heterocycles and have been previously reviewed.[1] The possibility of modification and functionalization of the carboxylic group and the lactam ring allows the preparation of many types of natural products as well as biologically active molecules. These interesting compounds contain the following basic carbon skeletons: (i) pyrrolidines[2] and kainoid acid derivatives,[3] (ii) pyrrolizidines, indolizidines,[4] and other fused azabicyclic compounds,[5] (iii) *N*-bridged bicyclic compounds,[6] and (iv) differently substituted α- or γ-amino acid derivatives[7] (Scheme 1). As a result, pyroglutamic acid derivatives have become target molecules for many synthetic efforts. It is necessary to develop new short routes to this class of compounds.

Scheme 1. Applications of Pyroglutamate



Previously, we reported an efficient synthesis of 3- or 4-substituted 5-sulfonyl glutarimides **8** via a stepwise [3 + 3] strategy with α-sulfonylacetamide **1** and α,β-unsaturated esters **3**.[8] We have successfully accomplished some applications for the syntheses of natural products[9] and potential drugs[8a,10] via this facile [3 + 3] annulation. In the

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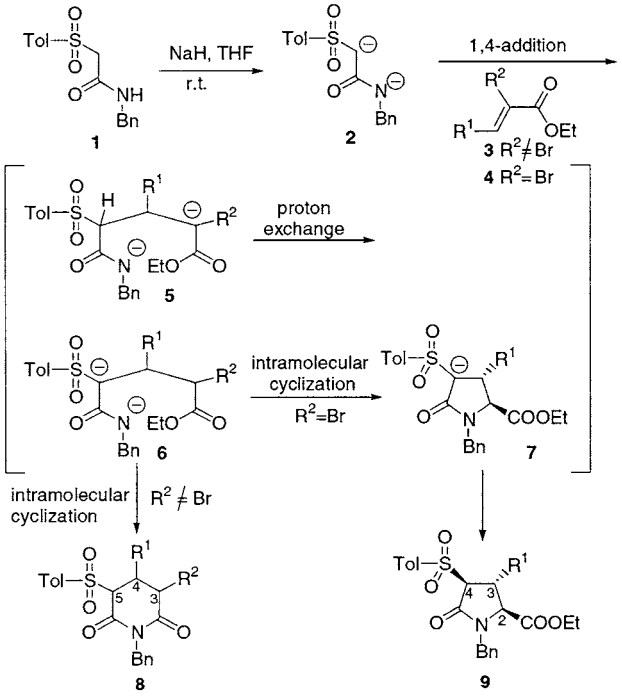
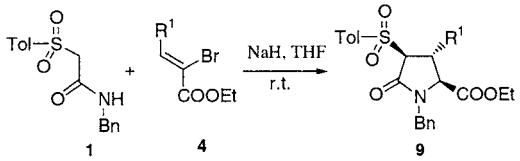
continuation of our previous investigation on the chemistry of α-sulfonylacetamide **1**, we developed an efficient synthesis of polysubstituted *N*-benzyl ethyl pyroglutamates **9**, potential precursors of the corresponding pyroglutamic acids, by formal [3 + 2] cycloaddition reaction[11] (Scheme 2).

Scheme 2



As outlined in Scheme 2, after the reaction of **1** with sodium hydride (3 equiv), the resulting dianion **2** reacted with α,β-unsaturated esters (**3**, R²1Br) to afford the corresponding 3-substituted toluenesulfonyl glutarimides **8**.[8a]

Table 1. Cycloaddition Reactions of Acetamide **1** with Various Ethyl (*Z*)-2-bromo-2-propenoates **4** Provide Pyroglutamates **9**



no.	4	R^1	9	yield[a] (%)
1	**4a**	$CH(OCH_3)_2$	**9a**[b]	63
2	**4b**	CH_3	**9b**[b]	68
3	**4c**	$CH_2CH_2CH_3$	**9c**[b]	64
4	**4d**	C_6H_5	**9d**[b]	50
5	**4e**	$CH_2OCH_2C_6H_5$	**9e**[b]	51
6	**4f**	$CH_2CH_2CH_2OCH_2C_6H_5$	**9f**	55
7	**4g**	3,4-$(OCH_3)_2C_6H_3$	**9g**	50
8	**4h**	4-$NO_2C_6H_4$	**9h**	24

[a] All product yields were based on α-toluenesulfonyl acetamide **1**. [b] The stereochemistries of **9a**−**e** were confirmed by X-ray analysis.

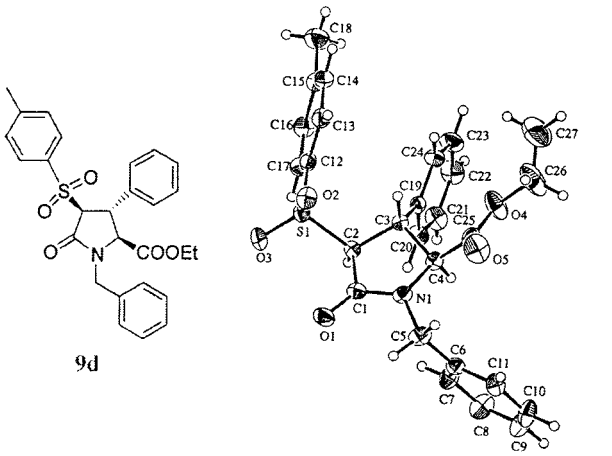
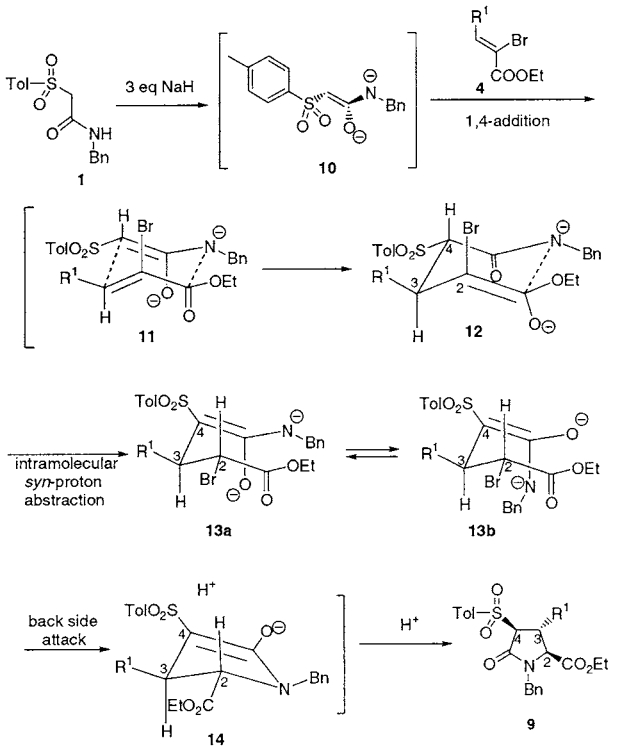


Figure 1. X-ray crystallography of pyroglutamate **9d**.

However, when dianion **2** reacted with ethyl (*Z*)-2-bromo-2-propenoates (**4**, R² = Br),[12] the cyclized pyroglutamates **9** were obtained as a single diastereomer in which the substituents at C_2 and C_3 and C_3 and C_4 are trans to each other. Some representative results are shown in Table 1. The stereochemistries of **9a**−**e** were established by X-ray analysis (Figure 1).[13] The stereochemistries of **9f**−**h** were determined by comparing their ^{1}H NMR spectra with those of **9a**−**e**.

To account for the outstanding stereoselectivity of these [3 + 2] cycloaddition results, we propose a reaction mechanism as shown in Scheme 3. Treatment of **1** with

Scheme 3



sodium hydride gave *Z*-form enolate **10** with two bulky groups trans to each other. 1,4-Addition reaction of **10** to **4** via more stable chair form transition states **11** then formed enolate **12**, which rapidly carried out an intramolecular syn-proton abstraction to furnish **13a** or **13b** with *R*-configuration at C_2.[14] Intramolecular cyclization of **13** provided **14**. To avoid severely eclipsed interaction, protonation of **14** in the work up process yielded **9** stereoselectively.

In conclusion, we have explored a formal [3 + 2] strategy that is synthetically useful for constructing polysubstituted pyroglutamates with three contiguous chiral centers in one step. This reaction has high diastereoselectivity and will be useful to organic chemists. We are currently studying the scope of this process as well as additional applications of the methodology to the synthesis of pyrrolizidines and indolizidines.

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Supporting Information Available: Additional spectroscopic data for all new compounds (^{1}H NMR in $CDCl_3$) and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Compounds **9a**−**e** were recrystallized from ethyl acetate, and the X-ray crystallographic analysis succeeded in confirming the stereochemistry. CCDC 203823−203827 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

(14) Intermolecular proton abstraction will give products with both *R*- and *S*-configurations at C_2, which cannot explain the diastereoselectivity of this reaction.