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A facile synthesis of 3-aryl pyroglutamic acid. Facile synthesis of baclofen and chlorpheg☆

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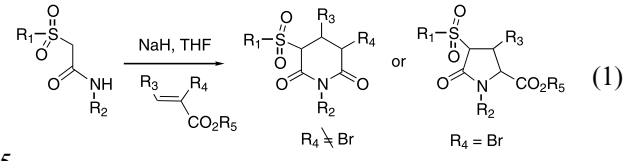
Abstract—A facile synthesis of 3-aryl pyroglutamic acids via stepwise [3+2] annulation and desulfonated hydrolysis is reported. Base-induced coupling/cyclization reactions of α-sulfonylacetamide with various β-functional groups of (*Z*)-2-bromoacrylates yielded three contiguous chiral centers on the polysubstituted pyroglutamates system with *trans–trans* orientation in a one-pot synthesis. This facile strategy was used to synthesize amino acid derivatives baclofen and chlorpheg. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Recently, we reported a facile [3+3] annulation reaction between different α-sulfonylacetamide derivatives and a series of the α- or β-, aryl- and alkyl-substituted acyclic α,β-unsaturated alkyl esters that lead to corresponding glutarimides (piperidine-2,6-diones) in good yields.[1] We have already presented some successful methodologies[1a–d,f,j] for the syntheses of natural products[1b,c,f,k] and potential drugs[1a,d,g–i,k,l] via this facile [3+3] annulation. When the α,β-unsaturated esters containing a α-bromo group, the stepwise [3+2] annulation[2] with α-sulfonylacetamide was applied to produce the pyroglutamic skeleton as shown in Eq. (1). This is quite a different strategy compared to the previous method. Here, we apply the facile [3+2] route to five-carbon atom amino acids via the pyroglutamic skeleton.



55 (1)

Pyroglutamic acids can serve as key building blocks for the synthesis of a variety of five-carbon atom amino acids.[3–5] We are interested in generalization of this facile [3+2] route for five-carbon atom amino acids to afford the corresponding 3-aryl substituted derivatives,[6] which are extraordinary useful compounds in the de novo design of peptides with rationally modified three-dimensional structures and biological functions.[7]

It is important to select an appropriate pyroglutamic skeleton for the synthesis of five-carbon atom amino acids, such as α- or γ-amino acid derivatives.[8] Racemic baclofen[9] (Lioresal®; Baclon®) [4-amino-3-(4-chlorophenyl)butanoic acid] and chlorpheg[10] [3-(4-chlorophenyl)glutamic acid] are model compounds for β-aryl substituted amino acids; Baclofen is a lipophilic analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and chlorpheg is a selective L-homocysteic acid (HCA) uptake inhibitor. During the last decade, a number of specific agonists or antagonists for the $GABA_B$ receptor site have been developed.[9] However, baclofen is the only selective and therapeutically useful $GABA_B$ agonist.[9] Baclofen is used in the treatment of spasticity caused by disease of the spinal cord, particularly traumatic lesions. Chlorpheg, a glutamic acid analogue, have been shown to selectively enhance the excitatory, depolarizing actions of L-HCA (in comparison with L-Glu) on amphibian and mammalian central nervous system neurons.[10]

We report here a five-step and four-step routes for preparing racemic baclofen[11] and chlorpheg,[12] respectively, starting from the reaction product of the facile [3+2] annulation reaction.

Keywords: glutarimides; stepwise [3+2] annulation; baclofen; chlorpheg; pyroglutamic acid.

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2. Results and discussion

2.1. Preparation of α-sulfonylacetamides 2 and α-bromoesters 3

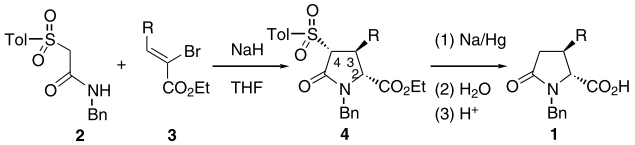
Benzylamine was treated with chloroacetyl chloride and triethylamine to produce α-chloro acetamide, which was then treated with *p*-toluenesulfinic acid sodium salt to give α-sulfonylacetamide **2** in 85% yield from the two-steps reaction. Treatment of four aryl aldehydes (a, C_6H_5; b, 4-FC_6H_4; c, 4-ClC_6H_4; d, 3-OC_5H_9-4-OCH_3-C_6H_3) with $Ph_3P{=}C(Br)CO_2Et$ gave α-bromoesters **3a**∼**d** in 75∼86% yield. Acetamide **2** and esters **3** were the reasonable starting materials for the synthesis of pyroglutamate skeleton via the stepwise [3+2] reaction.

2.2. Synthesis of 3-aryl pyroglutamate skeleton

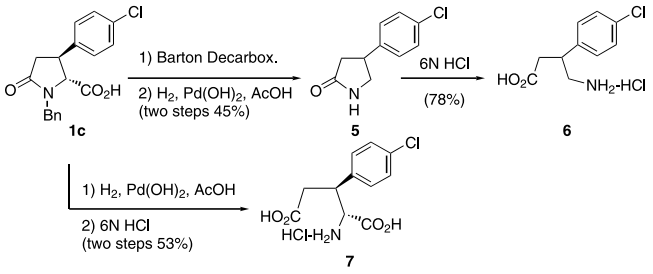
The one-pot synthesis began with the reaction of α-sulfonylacetamide **2** with (*Z*)-β-substituted α-bromoesters **3** (NaH/THF)[1] and proceeded through the stereo- and regioselective annulation with appropriate carbonyl substrate in a [3+2] mode, resulting in the overall formation of single pyroglutamate isomers **4** with three contiguous chiral centers in 41∼61% yields (see Scheme 1). The reaction mechanism for the outstanding stereoselectivity of the annulation reaction has been proposed as follows. Presumably, (*Z*)-form esters **3** reacted with dianion of **2**, after 1,4-addition, ring closure by substitution of bromide could then follow, providing cyclized products **4** with substituents at C_2 and C_3 also C_3 and C_4 in *trans* configuration to each other. The structure of **4a** (R = C_6H_5) was determined by single-crystal X-ray analysis. The one-pot desulfonation and hydrolysis[13] of **4** was accomplished by treatment of **4** with 6% sodium amalgam (Na/Hg) and sodium phosphate, after addition of water to the resulting mixture and then acidification, yielded acids **1** in 60∼79% yields.

2.3. Synthesis of baclofen (6) and chlorpheg (7)

Due to its biological and pharmacological importance, there have been several reports on the total synthesis of baclofen[11] and chlorpheg.[12] As shown in Scheme 2, we report a new approach for the total synthesis of baclofen (**6**) and chlorpheg (**7**) from acid **1c**. Barton and co-workers have described a decarboxylation procedure of *N*-protected α-amino acids and peptides wherein the stereochemistry of the reaction molecule is preserved



Scheme 1. Synthesis of 3-aryl pyroglutamic esters **4** and acids **1**.



Scheme 2. Synthesis of baclofen (**6**) and chlorpheg (**7**) hydrogen chloride.

completely.[14] The decarboxylation procedure was successfully applied to acid **1c**, subsequent debenzylation produced pyrrolidin-2-one **5**. Finally, hydrolysis of compound **5** by treatment with 6N hydrochloric acid yielded baclofen hydrochloride (**6**). In the synthesis of chlorpheg, acid **1c** progressed through debenzylation and hydrolysis to produce chlorpheg hydrochloride (**7**).

3. Conclusion

In conclusion, we explored a one-pot cycloaddition strategy that is synthetically useful for constructing ethyl pyroglutamates and utilized the method to achieve the synthesis of baclofen and chlorpheg. We are currently studying the scope of this process as well as additional application of the methodology to the synthesis of pyrrolizidines and indolizidines.

4. Supplementary material

Experimental procedures and photocopies of ^1H NMR ($CDCl_3$ or D_2O) spectral data for **1a**∼**c**, **4a**∼**d** and **5**∼**7** were supported.

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