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An Efficient Process of Racemization of 3-(Carbamoylmethyl)-5-methylhexanoic acid: A Pregabalin Intermediate

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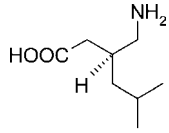
Abstract:

A simple and cost-effective process for racemization of undesired (*S*)-3-(carbamoylmethyl)-5-methylhexanoic acid (9), produced during the resolution step, is described. The literature procedure is fraught with many difficulties including number of steps and hazardous reagents. We have developed a one pot process for the above-mentioned racemization of *S*-enantiomer. The basic objective is to convert *S*-enantiomer into the symmetrical glutarimide derivative followed by hydrolysis with an alkali. The transformation of 9 into glutarimide derivative (10) has been achieved with piperidine in refluxing toluene.

Introduction

(*S*)-3-Aminomethyl-5-methylhexanoic acid (pregabalin, **1**)

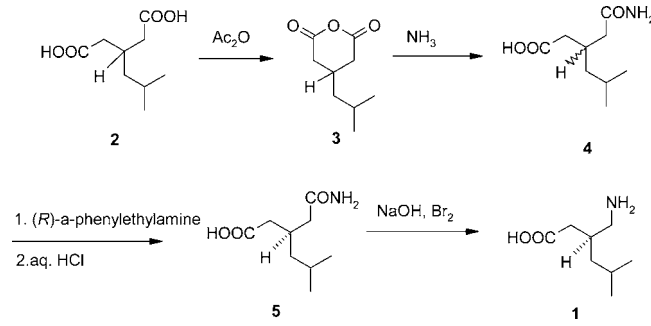


Pregabalin **(1)**

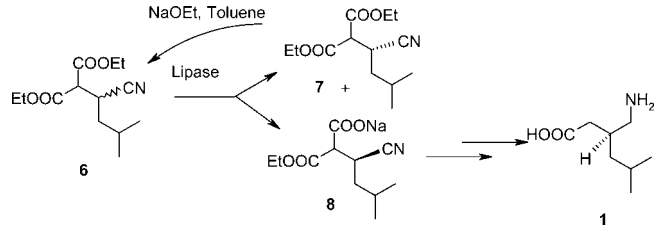
was designed as a more potent substitute of gabapentin, an anticonvulsant drug used for naturopathic pain treatment.[1] The first synthesis of pregabalin (**1**) was evaluated by Hoekstra et al.[2,3] and later reviewed by Ordonez and Cativiela.[4] One of the preferred processes of pregabalin manufacturing (Scheme 1) comprises aminolysis of 3-isobutylglutaric anhydride (**3**) obtained from 3-isobutylglutaric acid (**2**) followed by resolution of the intermediary amide **4** with (*R*)-(+)-1-phenylethylamine in chloroform. The *R*-enantiomer of 3-(carbamoylmethyl)-5-methylhexanoic acid (**5**) preferentially crystallizes out which is then transformed into pregabalin (**1**).

Very recently Martinez and co-workers reported[5] a chemoenzymatic process for pregabalin (**1**) in which commercially available lipase was employed to resolve racemic-2-carboxyethyl-3-cyano-5-methylhexanoic acid ethyl ester (**6**) to give (*S*)-2-carboxyethyl-3-cyano-5-methylhexanoic acid (**8**). Subsequently **8** was subjected to decarboxylation and reduction to provide **1**. This new route (Scheme 2) undoubtedly improved the efficiency and ensured smooth racemization of unwanted (*R*)-enantiomer **7**.

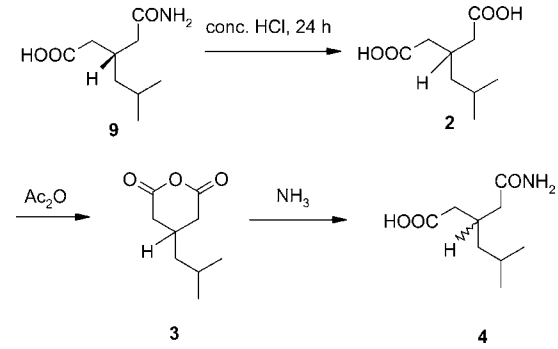
Scheme 1



Scheme 2



Scheme 3



In our laboratory Scheme 1 of pregabalin **1** was successfully accomplished. The filtrate, after the resolution step, was subsequently decomposed with an acid and analysed for percentages of both enantiomers. It contained typically around 85% of the undesired *S*-enantiomer **9** along with 15% of the *R*-enantiomer **5**. In order to make this process economically viable, the racemization of **9** from the mother liquor was a necessity. The reported procedure (Scheme 3) of racemization of **9** involved an extraction of the chloroform filtrate with aqueous sodium hydroxide solution followed by acidification of aqueous layer with concentrated hydrochloric acid. The acidic solution was heated under reflux for 24 h, extracted with methyl

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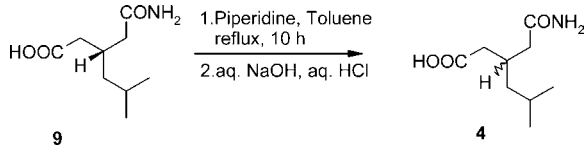
Scheme 4



9 4

Table 1. **Racemization of 9 with various bases in refluxing toluene**

sr. no.	base	chiral purity by HPLC
1	piperidine	*R*-isomer: 50.01, *S*-isomer: 49.99
2	DBU	*R*-isomer: 50.01, *S*-isomer: 49.98
3	diisopropylamine	*R*-isomer: 50.86, *S*-isomer: 49.14
4	diisopropylethylamine	*R*-isomer: 47.21, *S*-isomer: 52.78
5	triethylamine	*R*-isomer: 37.57, *S*-isomer: 62.42

tert-butyl ether and concentrated. The resulting symmetrical 3-isobutylglutaric acid (**2**) was transformed into racemic **4** by the documented procedure.[2,3]

It is clearly evident that the reported racemization process (Scheme 3) is far from satisfactory as it requires a number of steps, hazardous reagents, and long reaction times. Therefore, we felt a need to develop an alternative, cost-effective, and safe method of racemization of **9**. In our opinion the most appropriate and straightforward method would be to design a protocol in which the racemization of a 5:1 mixture into a 1:1-mixture of 3-(carbamoylmethyl)-5-methylhexanoic acid (**4**) should occur in one pot.

Results and Discussion

The basic premise of our objective was to convert (*S*)-enantiomer **9** of 3-(carbamoylmethyl)-5-methylhexanoic acid into the symmetrical cyclic imide **10** and then hydrolyze *in situ* with an alkali to produce racemic **4** in one pot.

Typically, the mother liquor, after separation of the *R*-enantiomer **5** as a salt, contained approximately 15−20% of the *R*-enantiomer and 80−85% of the *S*-enantiomer **9** of 3-(carbamoylmethyl)-5-methylhexanoic acid. The mother liquor was concentrated, the salt was decomposed, and then the residue was heated with piperidine in refluxing toluene for 10 h (Scheme 4). At this stage sodium hydroxide solution was added, and the reaction mixture was heated at 60 °C for 1 h. This was followed by acidification of the reaction to give racemic 3-(carbamoylmethyl)-5-methylhexanoic acid, **4**, in 78% yield. In order to optimize the process, a number of bases were used, and Table 1 shows the results. With the exception of triethylamine, almost all the bases gave good results.

Before we arrived at toluene as a preferred solvent for racemisation, a number of solvents were studied as shown in Table 2.

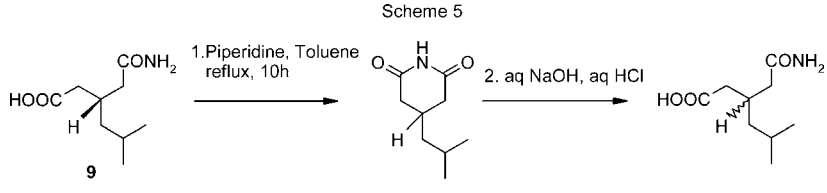
In order to confirm that the reaction goes through 3-isobutylglutarimide **10**, the reaction of **9** with piperidine in refluxing toluene was terminated after 10 h of refluxing.[6,7] The product isolated was confirmed as **10** by the ^{1}H NMR and mass spectroscopic data. The reaction mechanism for this transformation is difficult to envisage at this juncture. However, we are planning future studies to address this issue. The isolated glutarimide **10** was transformed into racemic **4** by treating with aqueous NaOH solution.

The cyclisation step occurred smoothly at the refluxing temperature of toluene. As indicated in Table 2, the other low-boiling solvents were inadequate to carry out the cyclisation step. In addition, toluene removes water in the form of azeotrope, thereby effecting the cyclisation step. The fact that a number of bases had been successfully employed for the

Table 2. **Racemization of 9 with different bases and solvents**

sr. no.	base	solvent	chiral purity by HPLC
1	piperidine	*n*-hexane	*R*-isomer: 27.24, *S*-isomer: 72.75
2	piperidine	ethyl acetate	*R*-isomer: 11.13, *S*-isomer: 88.86
3	piperidine	chloroform	*R*-isomer: 18.93, *S*-isomer: 81.06
4	piperidine	MTBE	*R*-isomer: 15.46, *S*-isomer: 84.53
5	DBU	*n*-hexane	*R*-isomer: 34.01, *S*-isomer: 65.98
6	DBU	ethyl acetate	*R*-isomer: 15.90, *S*-isomer: 84.09
7	DBU	chloroform	*R*-isomer: 18.05, *S*-isomer: 81.94
8	DBU	MTBE	*R*-isomer: 35.08, *S*-isomer: 64.91
9	diisopropylamine	*n*-hexane	*R*-isomer: 15.27, *S*-isomer: 84.72
10	diisopropylamine	ethyl acetate	*R*-isomer: 17.84, *S*-isomer: 82.15
11	diisopropylamine	chloroform	*R*-isomer: 20.37, *S*-isomer: 79.62
12	diisopropylamine	MTBE	*R*-isomer: 15.03, *S*-isomer: 84.96
13	diisopropylethylamine	*n*-hexane	*R*-isomer: 15.58, *S*-isomer: 84.41
14	diisopropylethylamine	ethyl acetate	*R*-isomer: 16.87, *S*-isomer: 83.12
15	diisopropylethylamine	chloroform	*R*-isomer: 17.74, *S*-isomer: 82.25
16	diisopropylethylamine	MTBE	*R*-isomer: 33.25, *S*-isomer: 66.74
17	triethylamine	toluene	*R*-isomer: 37.57, *S*-isomer: 62.42

Scheme 5



9 10 4

racemization process in refluxing toluene (Table 1), the physical properties of bases had an insignificant role to play.

Conclusion

We believe that we have developed a superior method of racemization of (*S*)-3-(carbamoylmethyl)-5-methylhexanoic acid in a one-pot reaction sequence (Scheme 5). This protocol has made the process of manufacturing pregabalin[8−10] more efficient.

Experimental Section

The ^{1}H NMR spectra were recorded in DMSO-d_6 on Varian 400 MHz; the chemical shifts were reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state KBr dispersion using Perkins-Elmer FT-IR spectrophotometer. The mass spectra were recorded on an Applied Biosystems spectrometer. The melting points were determined by using Buchi apparatus. The solvents and reagents were used without purification. The chiral HPLC was recorded on chiral AD-H (250 mm × 4.6 mm) at 210 nm and eluted with *n*-hexane/ethanol/TFA (950:50:1).

Racemisation of (*S*)-3-(Carbamoylmethyl)-5-methylhexanoic Acid (9). A mixture of piperidine (0.68 g, 8 mmol), (*S*)-3-(carbamoylmethyl)-5-methylhexanoic acid (**9**) (containing ∼15% of *R*-enantiomer) (40.0 g, 213 mmol), and toluene (200 mL) was heated under reflux for 10 h. It was cooled to 60 °C and 10% sodium hydroxide solution (200 mL) was added. After 1 h at 60 °C, the reaction mixture was cooled to ambient temperature and the layers were separated. The aqueous layer was cooled to 0−5 °C and acidified with conc HCl (∼64 mL). The solid obtained was filtered and washed with cold water and dried at 50−55 °C to give crude 3-(carbamoylmethyl)-5-methyl hexanoic acid (**4**). Recrystallization from ethyl acetate gave the racemic product **4** (31 g, 78%), as a white solid, mp: 108−110 °C, Lit.[3] mp 106−108 °C, IR (KBr): 3356, 3211, 2963, 2511, 1700, 1668, 1587, 1461 cm^{-1}, MS (*m/z*): 126, 142, 168, 186, ^{1}H NMR (DMSO-d_6): δ 0.85(d, 6H) 1.10−1.20 (m, 2 H), 1.50−1.70 (m, 1 H), 2.0−2.2 (m, 5 H), 6.75 (s, 1 H), 7.25 (s, 1 H), 12.0 (s, 1 H).

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Acknowledgment

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Supporting Information Available

Additional characterization data of compounds **4**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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