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A cost effective one-pot racemization process of 3-(Carbamoylmethyl)-5-methylhexanoic acid: A Pregabalin Intermediate

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ABSTRACT

This paper describes a simple, cost-effective and one pot process for racemization of undesired (S)-3-(carbamoylmethyl)-5-methylhexanoic acid, which produced during the resolution step. The unwanted S-enantiomer was converted into the symmetrical glutarimide derivative in the presence of a catalytic amount of DMAP or pyridine in refluxing toluene followed by hydrolysis with an alkali.

Key words: 3-(Carbamoylmethyl)-5-methylhexanoic acid; 4-dimethylaminopyridine; 3-isobutylglutarimide; Pregabalin; racemisation.

INTRODUCTION

Pregabalin **1** ((*S*)-(+)-3-aminomethyl-5-methylhexanoic acid) is a novel and potent anticonvulsant agent for the treatment of epilepsy and pain [1]. It has also been found to be more active than Gabapentin in preclinical models of epilepsy [2]. It has more potent and robust activity in various models of epilepsy, neuropathic pain and anxiety [3] **(Figure 1)**.

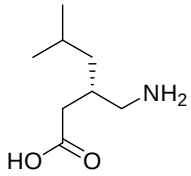

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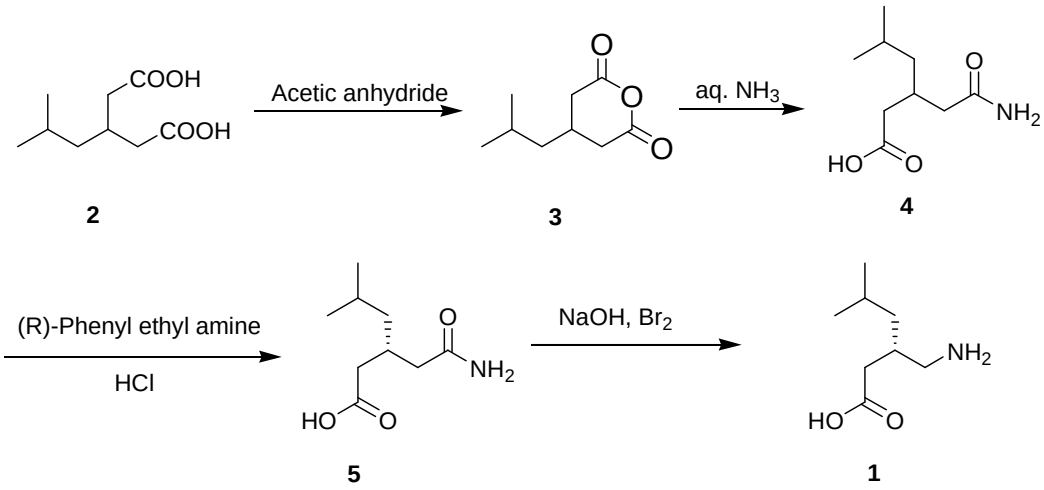
Figure 1: Chemical Structure of Pregabalin 1

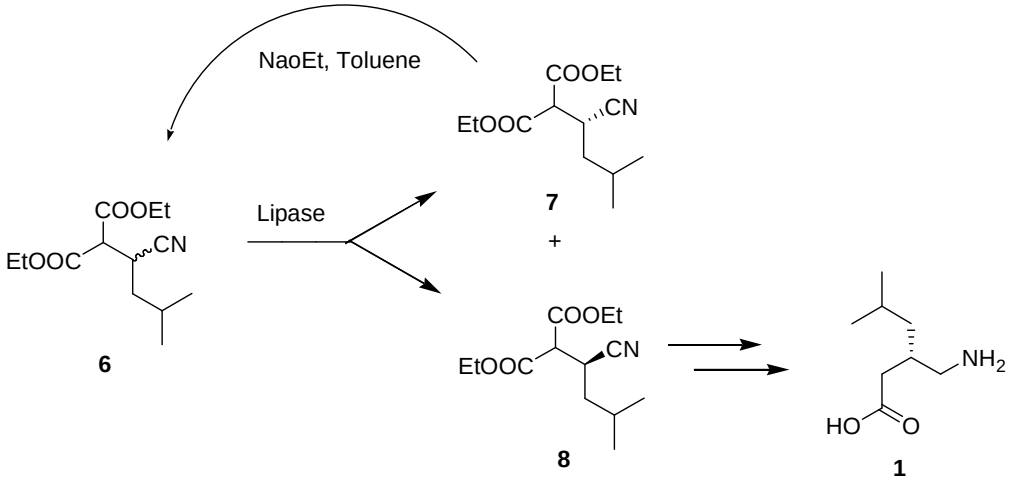
Pregabalin **1** synthesis was first reported by Hoekstra et al. [4, 5] and later reviewed by Ordonez and Cativiela [6]. Most preferred Pregabalin **1** manufacturing process comprises conversion of 3-isobutyl glutaric acid **2** into 3-isobutylglutaric anhydride **3** followed by aminolysis produces racemic 3-(carbamoylmethyl)-5- methylhexanoic acid **4**. Resolution of the intermediary amide **4** with (*R*)-(+)-1-phenylethylamine in chloroform and ethanol mixture into *R*-enantiomer of 3-

(carbamoylmethyl)-5- methylhexanoic acid **5**, which is then transformed into pregabalin **1** via Haffmann reaction **(Scheme 1)**.



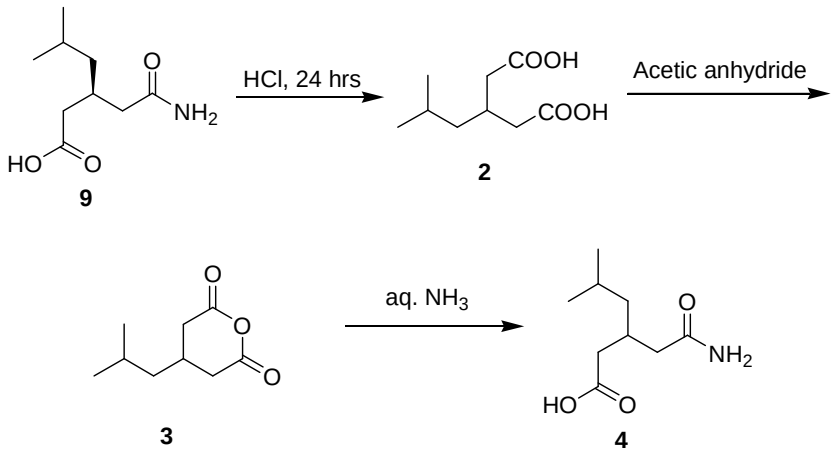
Scheme 1: General Synthetic approach of Pregabalin 1

A chemoenzymatic process was reported [7] in the literature for the resolution of racemic-2-carboxyethyl- 3-cyano-5-methylhexanoic acid ethyl ester **6** with lipase enzyme to give (*S*)- 2-carboxyethyl-3-cyano-5- methylhexanoic acid **8**. Subsequently **8** was subjected to decarboxylation followed by reduction to provide **1**. In this route, the unwanted enantiomer (*R*)-2-carboxyethyl-3-cyano-5- methylhexanoic acid **7** was racemized to **6** with NaOMe/toluene **(Scheme 2)**.



Scheme 2: Lipase enzyme synthetic approach of Pregabalin 1

Racemization of **9** was reported in the literature [4, 5] which 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 *tert*-butyl ether and concentrated. The resulting 3-isobutylglutaric acid **2** was converted into **4** by treating with aceticahydride followed by aqueous ammonia solution **(Scheme 3)**.



Scheme 3: General racemization process of compound 9

Pregabalin was synthesized according to the scheme I successfully in lab. After the resolution of **4**, the filtrate contains unwanted S-enantiomer **9**, unreacted *R* (+)-phenyl ethyl amine. Unwanted enantiomer **9** was obtained by the extraction of filtrate into diluted sodium hydroxide solution followed by the acidification with hydrochloric acid. Isolated **9** was analysed for both isomer contents by chiral HPLC. It contained typically around 80-90% of the undesired *S*-enantiomer **9** along with 10-20% of the *R*-enantiomer **5**.

The reported racemization process (Scheme III) is not satisfactory and not eco-friendly in commercial scale as it requires a number of steps, hazardous reagents, and long reaction times. Therefore, we want to develop an alternative, cost-effective, and safe method of racemization of **9**.

MATERIALS AND METHODS

Temperatures are reported as reacton mass temperatures. Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 as solvent, and tetramethylsilane (TMS) as internal standard. Data are reported as follows: chemical shift, multiplicity (s: singlet, brs: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet), coupling constants (J in Hz) and integration. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up. All the solvents and reagents used were of commercial grade.

Racemisation of (*S*)-3-(Carbamoylmethyl)-5-methylhexanoic Acid, 4. To a stirring solution 200 mL toluene and 3-(carbamoylmethyl)-5-methylhexanoic acid (**9**) (containing ~15% of *R*-enantiomer) (40.0 g, 213 mmol), 4-dimethylaminopyridine (0.68 g, 0.02 mole) is added at 25^{o}C and heated under reflux for 2 hours and collected water by azotropically. After completion of 3-isobutylglutarimide **10** formation, it is cooled to 60^{o}C and added 100 mL 10% sodium hydroxide solution. After 1 hour at 60^{o}C, the reaction mixture is cooled to ambient temperature and the layers are separated. Cooled the aqueous layer to 0-5^{o}C and adjusted the mass pH to less than 1.0 with conc HCl. Filtered the separated solid and washed with cold water and dried at 65-70^{o}C under reduced pressure to give racemic 3-(carbamoylmethyl)-5- methyl hexanoic acid **4** as an off white crystalline solid (,85%). Mp 106.5-108.2^{o}C. Purity 99.86% (by HPLC). Assay 99.23% (by HPLC). IR(KBr): 3364, 3221, 2963, 1702, 1668, 699. ^{1}H NMR (400 MHz, DMSO-*d6*): δ0.82 (s,

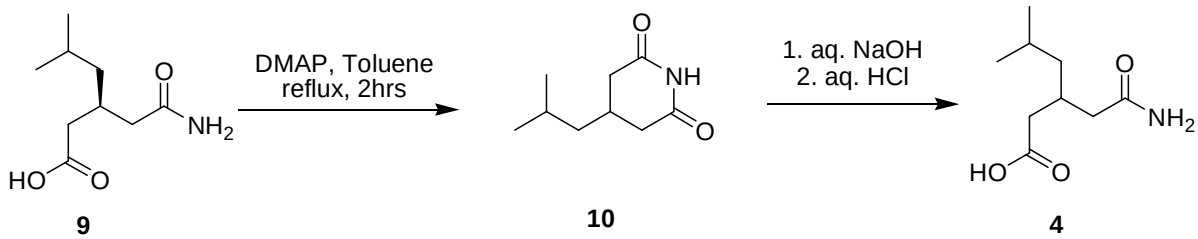
6H, -CH_3), 1.10 (m, 2H, -CH_2-), 1.55-1.65 (m, 1H, -CH-), 1.96-2.07 (m, 2H, -CH_2-), 2.10-2.24 (m, 3H, -CH_2-, -CH-), 6.74 (s. 1H, -NH), 7.27 (s, 1H, -NH), 12.01 (s, 1H, -COOH) ppm. MS (70 eV, EI): *m/z* (%) 188.3 (M+1). $C_9H_{17}NO_3$ (187.24): C - 57.73, H - 9.15, N - 7.48, O - 25.64%. Found: C - 57.72, H - 9.17, N - 7.49, O - 25.66%.

Spectral data of 3-isobutylglutarimide 10: IR (KBr, cm^{-1}) 3355, 2954, 2923, 1733, 1685. ^{1}HNMR (400 MHz, DMSO-d6) δ0.9 (s, 6H, -CH_3), 1.24 (m, 2H, -CH_2-), 1.68 (m, 1H, -CH-), 2.2 (m, 2H, -CH_2-), 2.4 (m, 1H, -CH-), 2.7 (m, 2H, -CH_2-), 10.6 (s. 1H, -NH). MS (70eV, EI): *m/z* (%) 167.93 (M-H). $C_9H_{15}NO_2$ (169.22): C - 63.88, H - 8.93, N - 8.28, O - 18.91%. Found: C - 63.86, H - 8.94, N - 8.2, O - 18.94%.

RESULTS AND DISCUSSION

The object of our work was to convert *S*-enantiomer **9** of 3-(carbamoylmethyl)-5-methylhexanoic acid **2** into racemic **4** via a cyclic imide **10** and then hydrolyze *in situ* with sodium hydroxide.

Typically, after resolution step, the chloroform filtrate contained approximately 10-20% of the *R*-enantiomer and 80-90% of *S*-enantiomer **9** of 3-(carbamoylmethyl)-5-methylhexanoic acid **4**. The mother liquor was extracted with 10% sodium hydroxide solution and then acidification with concentrated hydrochloric acid followed by filtration and drying resulted unwanted enantiomer **9**. This unwanted enantiomer was refluxed with catalytic amount of 4-Dimethylaminopyridine (DMAP) in toluene for 2 hours [8, 9] and collected water azotropically. At this stage sodium hydroxide solution was added, and the reaction mixture was heated at 60 °C for 1 h and followed by acidification of the reaction to give racemic 3-(carbamoylmethyl)-5-methylhexanoic acid, **4**, in 85% yield **(Scheme 4)**.



Scheme 4: Proposed racemization process of compound 9

In order to optimize the process, DMAP and pyridine were used and these bases gave good results. A number of solvents were used for racemization process to optimize the reaction time and percentage of racemization.

The reaction of **9** with DMAP in refluxing toluene was completed after 2 hours of refluxing and the intermediate 3-isobutylglutarimide **10** isolated and confirmed by the 1H NMR and mas spectral data. 10% sodium hydroxide solation was added to the intermediate **10** and maintained at 60^{o}C for 1 hour followed by the acidification gave **4** as an off white solid and confirmed by 1H NMR and mass spectral data.

The cyclisation step occurred smoothly at the refluxing temperatures of all the solvents used. As indicated in the table (**Table 1**), the cyclization of **9** was completed within 2 hours in toluene and other low boiling solvents have taken more time. In addition, toluene removes water in the form of azeotrope more effectively, thereby reducing the cyclisation time.

Table 1: Racemization of compound 9 with various bases and solvents

Entry No.	Base	Solvent	Reaction time (hrs)	Chiral purity by HPLC (area %)
1	DMAP	Toluene	2	*R*-isomer: 50.01; *S*-isomer: 49.99
2	DMAP	n-Hexane	6	*R*-isomer: 50.09; *S*-isomer: 49.91
3	DMAP	Chloroform	5.5	*R*-isomer: 49.98; *S*-isomer: 50.02
4	DMAP	Dichloromethane	10	*R*-isomer: 50.04; *S*-isomer: 49.96
5	DMAP	Cyclohexane	8	*R*-isomer: 50.10; *S*-isomer: 49.90
6	Pyridine	Toluene	3	*R*-isomer: 50.03; *S*-isomer: 49.97
7	Pyridine	n-Hexane	6.5	*R*-isomer: 49.92; *S*-isomer: 50.08
8	Pyridine	Chloroform	7	*R*-isomer: 49.95; *S*-isomer: 50.05
9	Pyridine	Dichloromethane	12	*R*-isomer: 50.03; *S*-isomer: 49.97
10	Pyridine	Cyclohexane	10	*R*-isomer: 50.05; *S*-isomer: 49.95

A superior method of racemization of (*S*)-3-(carbamoylmethyl)-5-methylhexanoic acid **9** in a one-pot reaction sequence was developed, which has made the process of manufacturing Pregabalin [10-12] more efficient.

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