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An efficient process of racemization of alpha-ethyl-2-oxo-1-pyrrolidineacetic acid: A levetiracetam intermediate

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ABSTRACT

*(S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid (**3**), an advance intermediate to assemble Levetiracetam, is prepared by resolution of alpha-ethyl-2-oxo-1-pyrrolidineacetic acid (**2**) with (R)-(+)-α-methyl benzyl amine in benzene. Although this process is efficient, there is need to develop an alternative, cost effective and eco friendly process for resolution of compound **2** using ecofriendly solvent in place of Benzene and also there is need to recycle the unwanted (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid and uncrystallized S-acid from the mother liquor which is yet unknown. The purpose of this study is twofold, first being to replace benzene and second the pollution issue to discard generated large amount of undesired isomer during resolution and reduce the cost of **1**. We have developed a novel resolving system in which compound **2** is resolved using eco friendly solvent like toluene pet ether mixture or THF in place of Benzene and racemization process of **4** in which **4** was treated with potassium hydroxide in refluxing methanol and water followed by acidification using hydrochloric acid to give (**2**), the latter intermediate has already been converted into **1**.*

Key words : alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, Benzene, racemization, potassium hydroxide, resolution.

INTRODUCTION

Levetiracetam (Keppra, 1) is marketed for the treatment of Epilepsy. However, epilepsy studies on etiracetam, initiated in 1992, showed the outstanding pharmacokinetic and pharmacological profile for application of the (*S*)-enatiomer, Levetiracetam, which led to the fastest approval of an antiepileptic drug.

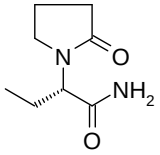

Figure:1 Levetiracetam (1)

It has been reported that Levetiracetam to be 10 times more active against hypoxia and 4 times against ischemia than the corresponding Etiracetam. Epilepsy is a common medical disorder with a prevalence of around 1% of the

general population, requiring prolonged and sometimes lifelong drug therapy[1-6]. Different methods of preparation of Levetiracetam have been described. The original synthesis of (**1**), was evaluated by Henry Morren in 1965 [7], Cavoy and coworkers reported a process for Levetiracetam in which etiracetam isomers were separated by utilizing preparative high performance liquid chromatography[8].

Jean Gobert et al utilized the resolution of (**2**) with (*R*)-(+)-α-methyl benzyl amine in benzene in which *S*-enantiomer of (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid (**3**) preferentially crystallizes out which is then transformed to Levetiracetam (**1**) by reaction with ammonia utilizing the conventional methods [9-11] (Figure-4).

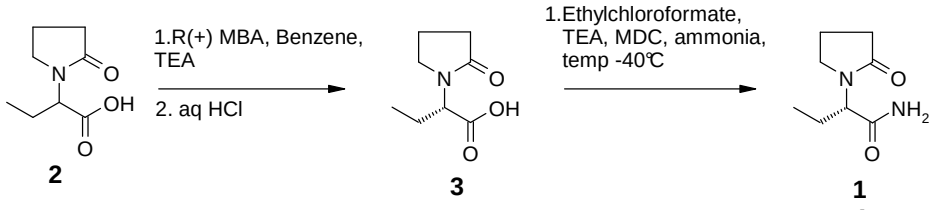

Figure: 4

The above reported method, perhaps the *R* (+) MBA resolution of compound **2** in benzene reported by Jean Gobert was most feasible. However, the disadvantage of to recycle the undesired acid **4** and uncrystallized *S*-acid **3** from the mother liquor during resolution step and could not be racemized.

Very recently Li Yuan and his coworker (Figure-5) reported racemization of undesired acid **4** in which the filtrate after resolution concentrated to half volume and decomposed with 50% NaOH solution, extracted with toluene and aqueous layer was acidified with HCl to afford R-enriched compound **4[**12].The reported process of racemization involved concentration of mother liquor to half and an extraction with 50% NaOH solution followed by acidification of aqueous layer with HCl, filtration and drying afforded R- enriched undesired isomer **4**. It was further treated with acetic anhydride in toluene at reflux temperature to afford racemic compound **2**.

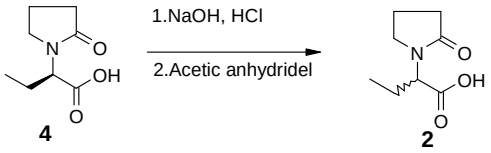

Figure: 5

It is clearly evident that the reported procedure for racemization is far from satisfactory as it involves acetic anhydride is listed US DEA list II precursor and restricted in many other countries. Therefore, we felt a need to an alternative, cost effective and safe method for racemization of compound **4** which can be conveniently employed for commercial applications.

MATERIALS AND METHODS

The ^{1}H NMR spectra were recorded in CDCl3 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 Elemer FT–IR spectrophotometer. The mass spectra were recorded on Applied Biosystems spectrometer. The melting points were determined by using Buchi apparatus .The solvents and reagents were used without purification. SOR was recorded on PerkinElmer Polarimeter 343.

Preparation of (*S*)-α- ethyl-2-oxo-1-pyrrolidine acetamide (1)

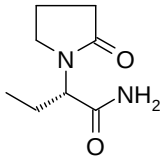

Figure:1

(*S*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid (**3**) (400 g, 2.34 mol) and dichloromethane (2400 mL) were cooled to –30 °C, after which triethylamine (280 g, 2.77 mol) and ethyl chloroformate (350 g, 2.77 mol) was added to the reaction mass simultaneously at –30 °C. Ammonia was bubbled in the reaction mixture for 2.5 h at –30 °C. The solids precipitated were filtered to get 365 gm crude Levetiracetam which was then purified from 8.0 volume of ethyl acetate at reflux temperature followed by cooled to 0-5°C filtered and dried to afford Levetiracetam (**1**) as a white solid (320 g, 80 %). M.P. : 117-119 ^{o}C. [19], Mass (*m/z*) : 171.1 (M^+ + H), 193.1 (M^+ + Na), ^{1}H NMR ($CDCl_3$) : δ 0.88-0.92 (t, 3H, *J* = 4.0 Hz), 1.70 (m, 1H), 1.93-2.00 (m, 3H), 2.35-2.39 (m, 2H), 3.37-3.51 (m, 2H), 4.47-4.50 (t, 1H, *J* = 6.7, 8.9 Hz), 5.90 (brs, 1H), 6.50 (brs, 1H), HPLC purity : 99.98 %, Chiral purity : *S*-enantiomer : 99.91 % and *R*-enantiomer : 0.09 %, SOR $[\alpha]_{25}^{D}$: -91.61 ° (*c* = 1.0, Acetone) [10]. Anal calculated for $C_8H_{14}N_2O_2$: C, 56.40; H, 8.22; N, 16.45. Found C, 56.50 ; H, 8.20; N, 16.35.

Preparation of (*S*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid (3) in mixture of toluene and petroleum ether.

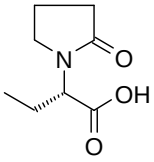

Figure: 2

(*RS*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid (700 g, 4.0 mol) toluene (1000 mL) : petroleum ether (672 mL), *R*-(+)-α-methylbenzylamine (242 g, 2.0 mol) and triethyl amine (207 g, 2.0 mol) were heated at reflux condition for 3h. The solids obtained were cooled to 0-5 ºC, filtered and dried at 60 ºC for 8 h to get 525 gm crude *R*-(+)-MBA salt of (*S*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid which was then crystallized from ethyl acetate (4000 mL) at 70 to 75°C then the reaction mass was cooled to 25-30°C and filtered to yield 433 gm of pure salt. The pure *R*-(+)-MBA salt was dissolved in D.M water (860 mL) and then cooled to 0 to 5°C and adjusted pH 12.6 using 30% sodium hydroxide solution (240 mL) followed by extraction of the aqueous layer with MDC (2100 mL) to remove *R*-(+)-MBA from the reaction mass. The aqueous layer was acidified to pH 1 to 2 using dil hydrochloric acid (48 mL) at 0-5 °C. The solids obtained were filtered and dried at 50 °C to give compound **3** as a white solid (230 g, 33.0 %). Mass (*m/z)* : 171.9 (M^+ + H), 194.0 (M^+ + Na), ^{1}H NMR ($CDCl_3$) : δ 0.94 (t, 3H, *J* = 7.39 Hz), 1.70 (m, 1H), 1.98-2.0 (m, 3H), 2.46 (t, 2H, *J* = 8.1 Hz), 3.36 (m, 1H), 3.60 (m, 1H), 4.64 (m, 1H), 9.82 (brs, 1H), SOR $[\alpha]_{25}^{D}$: -25.82 ° (*c* = 1.0, Acetone) [10], HPLC purity : 99.92 %. .M.P. : 126-128 ^{o}C.

Racemization of (*R*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid (4).[**Undesired isomer**]

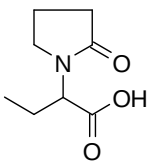

Figure: 3

(*R*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid (**4**) (1.2 kg, 7.01 mol) in methanol (6.0 L) was added to the solution containing potassium hydroxide (0.785 kg, 14 mol) in water (240 mL) and heated under reflux for 20 h. Methanol

was distilled out from the reaction mixture, cooled to ambient temperature and water 600 mL was added to the concentrated mass and acidified to pH~1-2 with dil HCl at 0 to 5 °C. The solids obtained were filtered off, washed with 240 mL cold water and dried at 50-55 °C to give (*RS*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid (**2**) as a white solid (0.864 kg, 72 %). M.P. : 154-156 ^{o}C [19], Mass (*m/z*) : 171.9 (M^+ + H), 194.0 (M^+ + Na), ^{1}H NMR ($CDCl_3$) : δ 0.94-0.96 (t, 3H, *J* = 7.3 Hz), 1.70 (m, 1H), 1.98-2.0 (m, 3 H), 2.46 (t, 2H, *J* = 8.1 Hz), 3.36 (m, 1H), 3.60 (m, 1H), 4.64 (m, 1H), 9.82 (brs, 1 H), HPLC purity : 99.58 %, SOR $[\alpha]_{25}^{D}$: 0.00 °(*c* =1.0, Acetone).

RESULTS AND DISCUSSION

The resolution of alpha-ethyl-2-oxo-1-pyrrolidineacetic acid (**2**) using (*R*)-(+)-α-methyl benzyl amine in benzene as reported in the literature,[9,10] was successfully repeated in our laboratory to give (*S*)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid (**3**) in % theoretical yield with optical rotation -26.0°. The filtrate, after resolution step, was concentrated and subsequently decomposed with an acid to afford **4** with optical rotation +11.88°. The residue obtained after acidification was heated with KOH in refluxing methanol and water for 20 h. Methanol was distilled off completely followed by acidification of the concentrated mass to give (**2**) in 72% yield. The SOR was found 0.00°. (Figure-6)

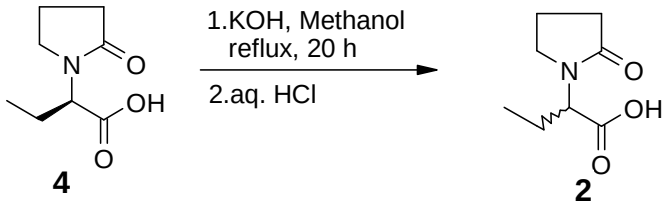

Figure: 6

We envisaged that the possibility of an efficient racemization of (*R*)-enatiomer (**4**) would be by the enolisation of unwanted isomer **4** under basic condition and formation of intermediate **7** followed by enantiorandom reprotonation of the enol compound **7** would produce (*RS*)-α-ethyl-2-oxo-1-pyrrolidineacetic acid (**2**) in good yield (Scheme-4).

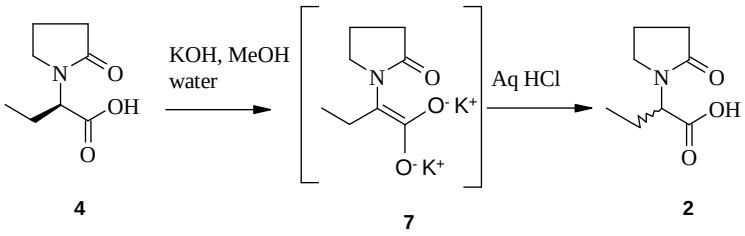

Figure: 7

Table-1: Racemization of compound 4 in different solvents.

Solvent	Temperature °C	SOR $[\alpha]_{25}^{D}$	% Yield
n-Hexane	50-55	3.520	56
$CHCl_3$	60-65	6.277	70
MTBE	60-65	1.961	68
Toluene	100-105	3.201	59
Ethyl acetate	70-75	3.190	55
Methanol and water	**60-65**	**0.000**	**72**

A number of experiments were set up with varying reaction conditions using different solvents like *n*-hexane, ethyl acetate, chloroform, MTBE and toluene were attempted using KOH as the base. However apart from methanol – water mixture all other solvents in KOH were inadequate to racemize the compound **4** back to the desired racemate **2**. In MTBE the racemization of **4** was found to be practical but even after increasing the reaction time the racemization did not reach completion in toluene, ethyl acetate, *n*-hexane, MTBE and chloroform racemization of **4**

was not observed which could supposed to be racemized after increasing the reaction time but practically even after increasing the time racemization of **4** was not possible. Table 1 provides the results.

Reactions were carried out for 20 hrs in 5.0 vol of solvent wrt unwanted isomer once we arrived at a conclusion that methanol and water is the solvent of choice for racemization of **4**, we focused our investigation on finding most suitable base for racemization of **4** which would give best result wrt yield and purity. Reactions were carried out for 20 hrs in 5.0 vol of solvent with respect to unwanted isomer to achieve this a number of experiments were conducted using bases like piperidine, DBU, diisopropylamine, triethylamine, diisopropylethylamine and inorganic bases like KOH, NaOH and NaOMe. Organic bases like piperidine, DBU, diisopropylamine, triethylamine and diisopropylethylamine in methanol were proved to be incapable accomplishing the racemization of **4**. However with NaOH and NaOMe in methanol and water racemization was found to be working but yields were not satisfactory. With KOH in methanol and water mixture racemization was found satisfactory to yield and quality. Results are provided in table-2.

Table-2: Racemization of compound 4 in methanol water using different bases

Base	Temperature °C	SOR $[\alpha]_{25}^{D}$	% Yield
TEA	60-65	3.755	65
DIPA	60-65	3.221	68
Piperidine	60-65	2.981	70
DBU	60-65	1.921	37
DIPEA	60-65	3.801	60
NaOMe	60-65	0.00	40
NaOH	60-65	0.230	45
KOH	60-65	**0.000**	**72**

CONCLUSION

We believe that we have developed a novel method for recycling undesired enatiomer (**4**) in one pot reaction sequence. This protocol has made the process of manufacturing Levetiracetam more efficient. Our newly developed method is highly reproducible and suitable for scale up.

Acknowledgment
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