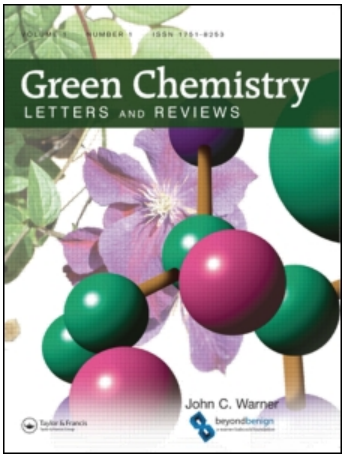

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[a] Innovation Plaza, IPDO, R&D, Dr. Reddy's Laboratories Ltd., Qutubullapur, R.R. Dist, Andhra Pradesh, India [b] Center for Environmental Science, Institute of Science and Technology, J.N.T. University, Hyderabad, Andhra Pradesh, India

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RESEARCH LETTER

An alternate synthesis of levetiracetam

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[a]*Innovation Plaza, IPDO, R&D, Dr. Reddy's Laboratories Ltd., Survey Nos. 42, 45,46 & 54, Bachupally, Qutubullapur, R.R. Dist. 500073, Andhra Pradesh, India;* [b]*Center for Environmental Science, Institute of Science and Technology, J.N.T. University, Kukatpally, Hyderabad 500 072, Andhra Pradesh, India*

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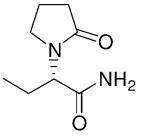
Development of a new strategy for the synthesis of levetiracetam **1** is described. This strategy involves solvent-free condensation, metal-catalyzed oxidation, and amidation. Solvent-free condensation and metal-catalyzed oxidation make this synthesis a more eco-friendly alternative for the synthesis of levetiracetam.



Levetiracetam 1

Keywords: solvent-free condensation; metal-catalyzed oxidation; amidation; levetiracetam

Levetiracetam **1** has been used for the management of various epileptic disorders for more than two decades. Since its launch in 2000, levetiracetam has emerged as one of the most prescribed anti-epileptic medicines. Epilepsy is a widely known medical disorder with an occurrence of around 1% of the general population, which requires extended or sometimes lifelong treatment (*1*). In this context, the effectiveness and affordability of the medicine become stringent. Moreover, there are many synthetic approaches presented in the literature (*2–6*), but most of them suffer from either high cost or environmental burden.

There are many ways to synthesize levetiracetam **1**. One of them involves a protection–deprotection approach (*7–10*). In this case, the synthesis starts with benzoyl protection followed by oxidation of (*S*)-aminobutyric acid to afford the corresponding *N*-benzoyl protected (*S*)-aminobutyric acid. After *N*-benzoyl deprotection and subsequent amidation, (*S*)-aminobutyramide can be obtained. The chemoselective butyrolactam ring formation, using 4-chlorobutyryl chloride and amide, was then performed to obtain levetiracetam **1**. In this step, two moles of corrosive hydrochloric acid are generated, which is not environmentally benign.

Bio-catalysis has gained momentum as a means for making industrial processes for active pharmaceutizal ingredients (APIs) more cost effective and eco-friendly (*11*). Recently, a bio-catalytic process was developed that involves an enzymatic resolution of a *rac*-2-pyrrolidinonyl nitrile catalyzed by nitrile hydratases to obtain **1**. The nitrile intermediate was prepared by an alkylation of 2-pyrrolidinone with *rac*-2-chloro-butylnitrile. A bio-engineered enzyme, nitrile hydratase mutant, was used to effect the resolution which offered excellent productivity (100 g/L-d), good resolution yield (43%), and high stereoselectivity (94% ee). The atom efficiency of this process was found to be excellent due to the fact that the undesired (*R*)-enantiomer could be recycled (*11*). The drawbacks of this process are that most of the synthetic steps were carried out in aqueous media, as well as the isolation of intermediates or end products, which requires extraction using excessive amounts of solvent or distillation of water requiring high energy consumption.

In order to develop a non-infringing route we have developed a scalable process that involves

*Corresponding author. Email: rakeshwarb@drreddys.com

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solvent-free condensation, metal-catalyzed oxidation, and amidation. Herein, we describe the cost effective, atom economical synthesis of levetiracetam **1**.

As outlined in the novel approach (Figure 1), the synthesis of **1** starts with the solvent-free condensation of γ-butyrolactone **2** and (*S*)-aminobutanol **3** under heating or microwave irradiation conditions to afford intermediate **4**. These two units (**2** and **3**) were bridged through an amide linkage which may be sensitive to racemization at higher temperature or under microwave along with heating conditions. The RuO_2/NaOCl-catalyzed oxidation of alcohol **4** was performed to obtain the penultimate acid intermediate **5**. Amidaion of **5** was achieved through mixed anhydride which was formed *in situ*. Treatment of the mixed anhydride with various ammonium salts afforded levetiracetam **1**.

The condensation of γ-butyrolactone with amines is presented in the literature (*12–16*). Referring to the nature of the reaction, which requires higher temperature, we attempted the condensation employing solvents such as toluene which can remove water azeotropically. However, the best results were obtained under solvent-free conditions as summarized in Table 1. The maximum yield (93%) was obtained at 225°C in 10 h (Table 1, entry 1). There were some experiments conducted thermally in the presence of catalytic amounts of 4 Å MS, phosphoric, *p*-toluene sulfonic, methane sulfonic, boric acids, all of which offered no advantage over yield and purity.

We also attempted the condensation under microwave irradiation conditions which provided exciting results (Table 1). The condensation performed thermally required longer reaction times (several hours). However, in the case of thermal reaction, an accelerated reaction rate was observed and the transformation was very clean and high yielding. In contrast, the best yield was obtained at 200°C in 1 h under 100 W microwave irradiation (81.7%) (Table 1, entry 22). Noticeably, the condensation between lactone **2** and amionoalcohol **3** passes through intermediate **6** in the synthesis of **4**.

Moreover, there was no need to isolate the intermediate **4** as it was found to be more than 82–93% pure. Interestingly, we did not observe any racemization during condensation of **2** and **3** to obtain **4** as downstream chemistry afforded enantiomerically pure acid derivative **5** and thereafter title compound **1**.

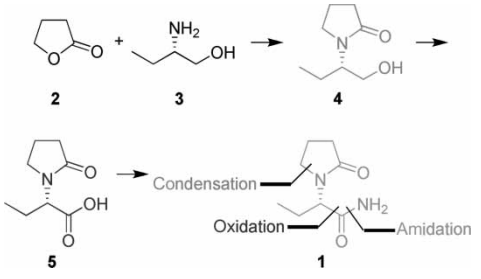


Figure 1. Novel approach to the synthesis of levetiracetam **1**.

The oxidation of an alcohol to an acid is well known reaction (*17–19*) that can be applied to our system. In the next step, oxidation of the alcohol was performed by employing a catalytic amount of RuO_2 in the presence of sodium hypochlorite (NaOCl). This method was moderately effective, but more environmentally benign in comparison to the method where $KMnO_4$ has been used. In the $KMnO_4$ mediated oxidation (*20*), the isolation of the product is very difficult due to the acid **5** being trapped in MnO_2 sludge. Advantageously, in the catalytic method, the isolation of the hygroscopic acid product **5** was possible with reasonably better yield (64.8%) and purity (91.9%) as shown in Table 2.

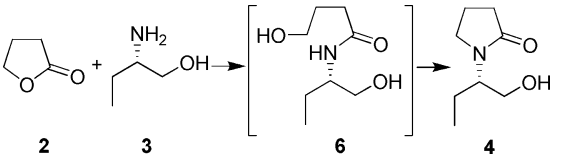
In the final step, an amidation was performed first by preparing the mixed anhydride with ethyl chloroformate and a subsequent nucleophilc substitution with ammonia to afford desired product **1** in good yields. We employed a number of ammonia sources including ammonia gas, ammonium acetate, and ammonium chloride. In most of the cases, the yield and purity varied by not more than 2–3% as summarized in Table 3. The reaction which employes ammonia gas afforded the product in the best yield and purity at the expense of affording ethyl formic acid and essentially producing no by-product from the ammonia source.

After optimizing all these three steps, we prelude a comparatively greener and novel synthesis which is depicted in Scheme 1. The novel synthesis of **1** commences with the solvent-free condensation of (*S*)-aminobutanol **3** and γ-butyrolactone **2** affording the condensed alcohol **4** in quantitative yield. Ruthenium oxide (RuO_2)-catalyzed [in combination with sodium hypochlorite (NaOCl)] oxidation of resulting alcohol **4** afforded advanced acid intermediate **5**.

Ammonia gas treatment of the mixed anhydride of acid **5** yielded the title compound **1** in comparable yields with the first generation synthesis as shown in Scheme 1.

In conclusion, we have demonstrated the second generation synthesis of levetiracetam **1**, presented in Scheme 1 that features the solvent-free condensation. No protection and deprotection steps are involved and the generation of salt waste is completely avoided. Moreover, the metal-catalyzed oxidation of alcohol **4** to advanced intermediate **5** makes the synthesis attractive and eco-friendly.

Table 1. Synthesis of alcohol **4** under thermal or MW conditions.



2 **3** **6** **4**

Entry	Reaction conditions (temp. in °C/time in min.)	Percentage of **6**	Percentage of **4**
1	**225/600**	**1.79**	**93.0**
2	224/480	3.73	91.0
3	220/240[a]	2.37	71.1
4	215/480	5.58	92.5
5	180/1440[b]	13.6	82.6
6	180/780[c]	8.09	90.1
7	170/2160[d]	6.72	86.9
8	160/480[e]	9.07	76.4
9	105/240[f]	2.02	73.7
10	120/15[g]	92.66	5.2
11	120/20[g]	93.59	5.2
12	130/10[g]	89.8	9.1
13	130/15[g]	89.4	9.5
14	140/10[g]	87.7	11.1
15	140/05[g]	90.7	8.05
16	150/30[g]	31.44	64.4
17	150/60[g]	30.09	67.6
18	170/5[g]	41.64.	57.3
19	170/30[g]	24.2	73.5
20	170/60[g]	32.56	66.6
21	200/30[g]	14.70	76.4
22	**200/60[g]**	**8.81**	**81.7**
23	110/8[h]	Trace	Trace

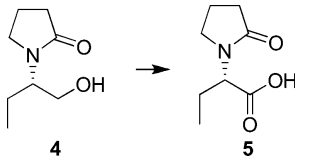
[a]4 Å MS.
[b]10 mol% MsOH.
[c]10 mol% PTSA.
[d]10 mol% H_3PO_4.
[e]5 mol% H_3PO_4.
[f]10 mol% $B(OH)_3$.
[g]MW irradiation.
[h]Toluene.
Note: bold - best results.

Experimental

^1H and ^{13}C NMR spectra were recorded on 400 and 200 MHz (Varian Gemini NMR spectrometer), respectively. The chemical shifts are reported in δ ppm relative to TMS. The FT IR spectra were recorded using a Perkin-Elmer 16650 FT IR spectrometer. Mass spectra (70 eV) were recorded on HP-5989A LC-MS spectrometer. The melting points were determined by using the capillary method and a melting point apparatus, and are uncorrected. The solvents and reagents were used without further purification. Optical rotations were measured with at 25°C. Microwave reactor specifically designed for holding reactions at a set temperature (Discover, CEM Corporation) was used.

All reactions were performed in flame-dried glassware under nitrogen. THF and Et_2O were dried and distilled from Na/benzophenone. Hexane and ethyl acetate were freshly distilled from CaH_2. Thin layer chromatography (TLC) analyses were performed on a silica gel 60 F254 precoated-plates (250 μm layers). All retention factors (R_f) are on silica gel TLC plates unless otherwise noted. TLC visualizations were performed with 5% phosphomolybdic acid (0.2 M in 2.5% conc. H_2SO_4/EtOH (v/v)), I_2 vapor, or UV light. Commercial reagents were used without further purification unless specifically noted. Column chromatography was performed using 100–700 times excess 32–64 μm grade silica gel. Products separated by chromatography are specified in elution order. In

Table 2. Synthesis of acid **5** using RuO_2 catalyst.



4 **5**

Reaction conditions (temp. in °C/time in h)	Catalyst RuO_2 (mol%)	NaOCl (eq.)	pH	Yield (%)	Purity (%)	Base
0–5/2	0.62	5.0	13–13.5	64.8	91.9	NaOH
0–5/2	0.62	5.0	12–12.5	50	90.9	NaOH
0–5/2	0.62	5.0	9.5–10.5	45	90.7	K_2CO_3
0–5/2	0.62	5.0	9–10	53	88.4	$NaHCO_3$
0–5/2	0.62	5.0	9–10	50	63.7	$NaHCO_3$
0–5/2	0.62	5.0	9–10	50	64.7	$NaHCO_3$
0–5/2	0.62	5.0	9–10	74	32	$NaHCO_3$

some cases the yields of products containing residual amounts of solvent were corrected for the solvent peak integration in ^1H NMR spectra and specified individually in the data sections. The purity of reaction products was estimated to be $\geq$90–95% by TLC and NMR analyses unless specified otherwise.

Synthesis of (S)-α-ethyl-2-oxo pyrrolidine ethanol 4

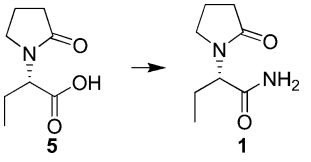
Method A

A mixture of γ-butyrolactone **2** (100 g, 1.16 mol) and D (+)-2-amino butanol **3** (103 g, 1.16 mol) was heated at 225°C in an autoclave under N_2 atmosphere. The reaction was started at room temperature and 10 kg/cm^2 pressure was applied and temperature was increased to 225°C over a period of 1 h. After stirring the reaction mixture for 10 h at 225°C and 25 kg/cm^2 pressure, the progress of reaction was monitored by TLC and high-performance liquid chromatography (HPLC) analysis. The HPLC purity of the crude reaction mass containing **4** was found to be 92%.

Method B

A mixture of γ-butyrolactone **2** (0.50 g, 5.8 mmol) and D (+)-2-amino butanol **3** (0.51 g, 5.8 mmol) was

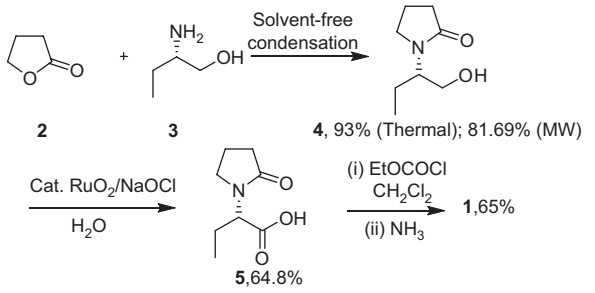
Table 3. Amidation to access **1** using different ammonia source.



5 **1**

Reaction conditions (temp. in °C/time in h)	Ethyl chloro-formate (eq.)	Triethylamine (eq.)	Ammonia source (eq.)	Yield (%)	Purity (%)
0–5/5	3.2	2.4	2.2 NH_4OAc	56	99.6
0–5/5	3.0	2.0	2.2 NH_4OAc	40	98.9
0–5/5	3.0	3.0	2.0 NH_4OAc	60.4	98.4
−40/5	1.2	1.2	2.0 NH_4OAc	60.6	98.3
0–5/5	3.0	2.0	2.0 NH_4OAc	60	83.8
0–5/5	3.0	3.0	2.0 NH_4Cl	70	98.3
0–5/5	3.0	3.0	2.0 NH_4Cl	53.3	99.1
40/5	–	–	20 NH_4OAc[a]	70	10
40/5	–	–	10 NH_4OAc[b]	60	13.8
−40/5	1.12	1.2	NH_3 gas[c]	65	99.5

[a]10 mol% $B(OH)_3$.
[b]10 mol% $PhB(OH)_2$.
[c]Quantity was not measured (bubbled till solid formation).



Scheme 1. Green approaches for the synthesis of levetiracetam **1**.

heated at 200°C (temperature was recorded digitally) in a microwave reactor specifically designed for holding reactions at a set temperature (Discover, CEM Corporation) for 1 h. Progress of the reaction was monitored by TLC and HPLC analysis. The reaction mass obtained was substantially pure (HPLC: 82%) and forwarded directly to next step. A small portion (0.10 g) of the crude reaction mass was purified by column chromatography to afford pure **4** as a brown liquid: $[\alpha]_D^{25}$ −24.4; ($c = 0.97$, $CHCl_3$); R_f: 0.45 [3:7 (EtOAc: Hexane)]; IR (CHCl3) ν_{max} 3411, 2966, 1651, and 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, $J = 6$ Hz), 1.40–1.65 (m, 2H), 1.95–2.15 (m, 3H), 2.38–2.45 (m, 2H), 3.25–3.68 (m, 4H), 3.85–3.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 18.2, 21.1, 31.5, 43.5, 55.7, 62.6, 176.6.

Synthesis of (S)-2-(2-oxopyrrolidin-1-yl) butyric acid 5

RuO_2 (5.2 mg, 0.62 mol%) was added to a mixture of **4** (1.0 g, 6.3 mmol) and 3% aq. solution of $NaHCO_3$ (20 mL) at 25°C. The resulting heterogeneous mixture was stirred for 5 min. Reaction mixture was cooled to 0°C and 4.5% aq. solution of NaOCl (31 mmol, 53 mL) was added from an addition funnel over a period of 1 h. The pH of the resulting mixture was maintained at 13 by the addition of 50% aq. solution of NaOH (50 mL). The progress of the reaction was monitored by TLC. After 3 h, 0.1 g of solid $NaHSO_3$ was added to the reaction mixture and stirred for 15 min. The reaction mass was extracted with dichloromethane (3 × 25 ml). The combined organic layers were washed with 50% aq. solution of NaOH, dried over Na_2SO_4 and evaporated to obtain **5** in 64% yields (0.7 g) as a solid. $[\alpha]_D^{25}$ −23.6; ($c = 0.97$, CHCl3); R_f: 0.34 [1:9 (MeOH: $CHCl_3$)]; IR ($CHCl_3$) ν_{max} 3411, 2966, 1651, and 1464 cm^{-1}. The other analytical and spectroscopic data of **5** coincide with those reported in literature (*1*).

Synthesis of levetiracetam 1

Triethyl amine (19.6 mL, 0.14 mol) was added to a solution of **5** (20.0 g, 0.12 mol) in dichloromethane (130 ml) over a period of 15 min at −40 to −30°C. Ethyl chloroformate (12.4 ml, 0.13 mol) was added slowly (10 min) to the reaction mixture under stirring for an additional 30 min. Thereafter, ammonia gas was bubbled through the reaction mass at −40 to −30°C. After stirring for four–five h, the reaction mixture was warmed up to 25–30°C, the precipitated salt was filtered and washed with dichloromethane (3 × 60 ml) and filtrate was concentrated under vacuum at below 40°C to afford crude **1** as white solid. The toluene was added to the crude material, stirred for 1 h, filtered and dried the semi purified product **1**. Thereafter, the compound **1** was dissolved again in hot ethyl acetate (106 ml) at 60°C, subsequently cooled to 25–30°C and filtered. The desired compound **1** was re-crystallized in hot ethyl acetate (2 × 106 ml) at 60°C, subsequently cooled to 25–30°C, filtered and dried at 35–40°C to obtain product in 65% yield (13 g) and 99.9% purity (by chiral HPLC) as a white solid: mp 116°C (lit[3c] 117°C); R_f: 0.34 [3:7 (EtOAc: Hexane)]; IR (KBr) ν_{max} 3362, 3200, 2991, 2911, 1676, 1491, 1457, and 1383 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 0.91 (t, 3H, $J = 7.5$ Hz), 1.60–1.75 (m, 1H), 1.90–2.09 (m, 3H), 2.38–2.47 (m, 2H), 3.34–3.55 (m, 2H), 4.44 (dd, 1H, $J = 6.7$, 8.6 Hz) 5.74 (br, 1H s), 6.45 (br, 1H, s).

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