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RESEARCH ARTICLE

Mild and Efficient Condition for Synthesis of Gabapentin Impurity B and E

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Abstract: Gabapentin (**1**), a widely prescribed anticonvulsant used to treat epilepsy and neuropathic pain. This work describes the synthesis of two potential Gabapentin impurities as per USP and EP. Gabapentin impurity B; 2-(1-cyanocyclohexyl) acetic acid (**2)** was synthesized by oxidative dehydrogenation of Gabapentin API using trichloroisocyanuric acid. Impurity E; 1-(carboxymethyl) cyclohexanecarboxylic acid (**3**) was obtained by acid hydrolysis of **2**. These impurities are characterized by IR, mass spectral data, HPLC RRT and ^{1}H NMR

Keywords: Gabapentin, Anticonvulsant, Impurity, Synthesis, Characterization

Introduction

Gabapentin was invented by Pfizer, launched in 1993 under trade name Neurontin. As a drug, gabapentin was formerly considered structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). However, preliminary studies proposed that gabapentin did not bind to either GABA-A or GABA-B receptors, nor was it transform metabolically into GABA. Gabapentin interacts with a high-affinity binding site in brain membranes, which has recently been identified as an auxiliary subunit of voltage-sensitive Ca^{2+} channels[1]. However, the functional correlate of gabapentin binding is unclear and remains under study. Gabapentin is used as an anticonvulsant and analgesic and also to relieve neuropathic pain and restless leg syndrome[2].

In development stages of bulk pharmaceuticals like synthesis, storage and formulation there are formation of number of impurities due to many reasons like degradation or side reactions. Active pharmaceutical ingredient approved by stringent regulatory authority or the World Health Organization to ensure high quality, safety and efficacy. After formulation of any drug it is important to study the degradation in basic and acidic media in order to know metabolic impurities or degradation impurities[3,4].

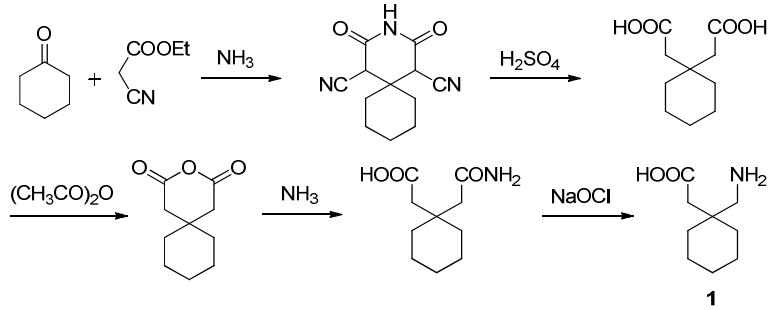
Gabapentin oral liquid solution formulation development project was taken in our Formulation Development department, Gabapentin impurities B and E were required by

analytical development department for study, these were not easily available in market with good purity. Isolation of these impurities by API degradation and separation was not possible. Synthetic methods from readily available raw materials for synthesis of **2** and **3** are not available in literature. Hence, studies were initiated for the synthesis of **2** and **3**.

Experimental

Melting points were determined with a LABINDIA, MR-Vis apparatus. ^{1}H NMR spectra were recorded on a Bruker Advance III 400 MHz with TMS as an internal standard. The IR spectra were recorded in the solid state as KBr dispersion using FT-IR IRAffinity-1, Shimadzu. The mass spectra were recorded on LC-MS API-2000, ABSciex. All solvents and reagents were purchased from Sigma-Aldrich (India) and S. D. Fine Chemicals, Mumbai. The solvents and reagents were used without purification. Reaction yields mention here are not optimized and of isolate products.

Gabapentin (**1**) is chemically known as 1-(aminomethyl)cyclohexaneacetic acid is synthesized in various ways as reported in literature[5], first synthesis was reported by Satzinger *et al.,* back in 1977[5,6]. The most convenient and commonly used synthesis route is reported by Zambon Group[7]. Cyclohexanone reacted with ethyl cyanoacetate in presence of ammonia to give dicyano cyclic imide intermediate which on acid hydrolysis gives cyclohexane diacetic acid. Dehydration of diacid yields cyclic anhydride which on treatment with liquid ammonia gives 1,1-cyclohexanediacetic acid monoamide as a key intermediate. Hoffman degradation of monoamide using sodium hypochlorite give Gabapentin 1 as shown in Scheme 1.



Scheme 1. Gabapentin synthesis

Gabapentin impurity B; 2-(1-cyanocyclohexyl) acetic acid **2** and impurity E; 1-(carboxymethyl) cyclohexanecarboxylic acid **3** as mention in EP and USP monograph as shown in Figure 1. Impurity B and E are structurally close to gabapentin structure. Impurity B contains nitrile group instead of primary amine as in gabapentin similarly carboxylic in impurity E.

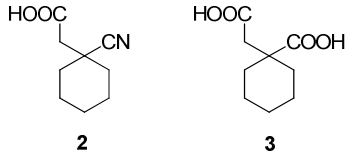
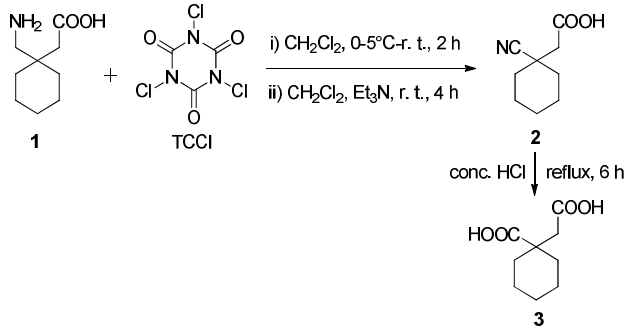


Figure 1. Gabapentin Impurity B and E

2-(1-Cyanocyclohexyl)acetic acid (2)

To a stirred solution of Gabapentin (5.0 g, 0.029 mol) in dichloromethane (200 mL) trichloroisocyanuric acid (6.79 g, 0.029 mol) was added lot wise at 0-5 ºC. The reaction mass

was stirred at room temperature (24-26 ºC) for 2 h. Reaction mass was then filtered through celite bed, filtrate was concentrated under reduced pressure to obtain oily mass (7.0 g). To a stirred solution of above oily mass (7.0 g) in dichloromethane (140.0 mL) triethylamine (12.2 mL, 0.088 mol) was added drop wise and stirred at room temperature for 3 h. Reaction mass was quenched with water (75 mL), organic layer separated and washed with 0.5 N hydrochloric acid (25 mL). Organic layer separated dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain crude product as gummy solid (4.6 g). Crude product was purified by crystallization in dichloromethane / hexane (30 mL, 5:12.5 v/v) to obtain white coloured crystalline solid. Yield (3.2 g, 65%); m.p. 102.0 ºC; HPLC purity 99.43%; IR (cm^{-1}) 2926, 2860, 2233, 1697, 1433, 1294, 1255, 1220, 930, 747, 681; ^{1}H-NMR ($CDCl_3$) δ 7.41 (bs, 1H, COOH), 2.61 (s, 2H, CH_2), 2.08-2.18 (m, 2H, CH_2), 1.62-1.79 (m, 4H, 2×CH_2), 1.32-1.41 (dd, *J* = 4.0, 4.0, 3.2 Hz, 2H, CH_2), 1.14-1.28 (m, 2H) ppm; Mass: *m/z* 168.2 ($M+H^+$), 190.1 ($M+Na^+$).



*1-(Carboxymethyl)cyclohexanecarboxylic acid (**3**)*

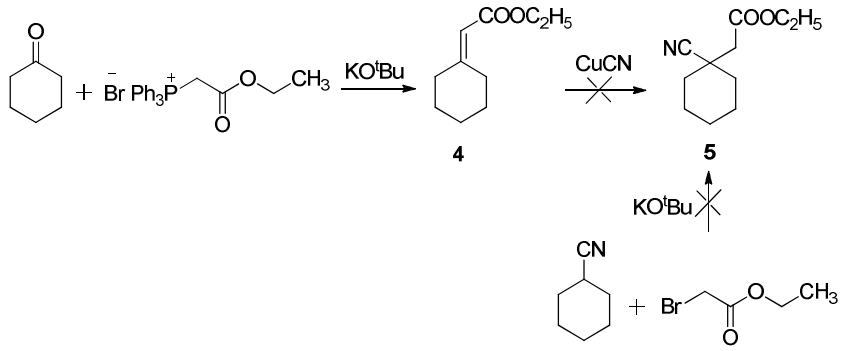
To a stirred solution of **2** (0.60 g, 0.0036 mol) in water (2 mL) conc. hydrochloric acid (6.0 mL) was added slowly at room temperature and heated to reflux for 6 h. Reaction mass was concentrated to get the crude product as (0.5 g). Crude product was purified by crystallization in dichloromethane/hexane (10 mL, 5:12.5 v/v) to obtain as white colored solid product. Yield (0.430 g, 64%) white solid, m.p. 130.1 ºC; HPLC purity 90.26%; IR (cm^{-1}) 3116, 2930, 2857, 1789, 1694, 1445, 1393, 1393, 1202, 920, 665; ^{1}H-NMR ($CDCl_3$) δ 2.68 (s, 2H, CH_2), 1.73-2.85 (dt, *J* = 6.0 & 5.2 Hz, 2H, CH_2), 1.35-1.66 (m, 8H, 4×CH_2) *ppm*; Mass: *m/z* 187.1 $(M+H)^+$, 209.2 $(M+Na)^+$, 185.0 $(M-H)^-$.

Results and Discussion

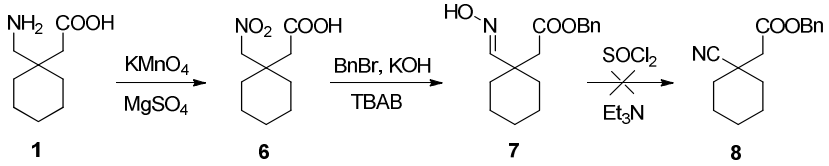
2-(1-Cyanocyclohexyl)acetic acid (**2**) is a key intermediate of Gabapentin which can be synthesized by various ways like enzyme catalyzed hydrolysis of 1-cyanocyclohexane acetonitrile[8] or ester hydrolysis of ethyl 2-(1-cyanocyclohexyl) acetate (**5**).

Ethyl 2-(1-cyanocyclohexyl)acetate (**5**) is a crucial intermediate for synthesis of impurity B and E. Limitation reported methodologies for synthesis of **5** requires toxic reagents like potassium or sodium cyanide. Our objective was to imply mild reagents and conditions for synthesis of these impurities and avoid use of sodium or potassium cyanide. Ethyl 2-cyclohexylideneacetate (**4)** can be easily synthesized by Wittig reaction between cylohexanone and carbethoxymethyl triphenyl-phosphonium bromide under basic media. Initially we treated copper cyanide with **4**, reaction did not work because of poor nucleophilicity of cyanide ion. Another route followed for synthesis of **5**, reacting ethyl bromoacetate with cyanocyclo-hexane in presence of potassium tert-butoxide as shown in Scheme 2.

Another strategy for synthesis of benzyl 2-(1-cyanocyclohexyl)acetate (**8**) was from gabapentin API. Three steps for synthesis involves amino group oxidation to corresponding nitro 2-(1-(nitromethyl)cyclohexyl)acetic acid (**6**) using potassium permanganate followed by carboxylic acid benzyl protection and nitro to oxime to give benzyl 2-(1-((hydroxyimino) methyl)-cyclohexyl) acetate (**7**) in one-pot reaction. Final step was oxime to nitrile conversion using thionyl chloride as per reported procedure[9] did not work well to give benzyl 2-(1-cyanocyclohexyl)acetate (**8**) Scheme 3.



Scheme 2. Synthesis of ethyl 2-(1-cyanocyclohexyl) acetate 5



Scheme 3. Synthesis of benzyl 2-(1-cyanocyclohexyl) acetate 8

While going through literature it was decided to synthesize 2-(1-cyanocyclohexyl) acetic acid (**2**) from Gabapentin (**1**) using dehydrogenative oxidation of amino to corresponding nitrile functional group. This methodology will give the desire molecule **2** in single step starting from readily available Gabapentin (**1**)**.** Some of recently reported methodologies for conversion of amine to nitrile using various reagents such as trichloroisocyanuric acid[10,11], PCBS and TCBDA[12], iodine in aqueous ammonia[13] and Dess-Martin periodinane[14]. It was observed while screening different reaction conditions, Gabapentin either in acidic or basic condition converted easily into corresponding lactam *i.e.* 4,4-pentamethylene-2- pyrrolidinone which is known as impurity A as per EP and USP monograph. Considering pH sensitive amino acid functionality in Gabapentin API, it was necessarily to find neutral reaction condition. We found trichloroisocyanuric acid (TCCI) was good choice of reagent for oxidative dehydrogenation reaction. Accordingly gabapentin API was first treated with TCCI in dichloromethane under neutral condition to give complex, which on treatment with triethyl amine at room temperature gives 2-(1-cyano-cyclohexyl)acetic acid **(2).** Simple solvent purification gives white crystalline solid product in 63% yield with excellent HPLC purity 99.43%. 1-(Carboxymethyl) cyclohexanecarboxylic acid **(3)** could obtain easily from **2** by acid hydrolysis refluxing in hydrochloric acid with good yield and purity as shown in Scheme IV. Both impurities B and E are highly polar as well not visible under UV while performing TLC so it was difficult to develop the column chromatography purification.

Conclusion

Here we have reported method for synthesis of Gabapentin impurity B, 2-(1-cyanocyclohexyl) acetic acid **2** from gabapentin API in single step with very high purity. This synthesis was achieved by using mild reaction conditions and reagents which avoids use of toxic reagents such as potassium or sodium cyanide. Impurity E, 1-(carboxymethyl)cyclohexanecarboxylic acid (**3**) was synthesized from **2** by acid hydrolysis.

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References

1. Goa K L and Sorkin E M, *Drugs*, 1993, **46(3),** 409-427.
2. Taylor C P, Gee N S, Su T Z, Kocsis J D, Welty D F, Brown J P, Dooley D J, Boden P and Singh L, *Epilepsy Res.,* 1998, **29(3),** 233-249; DOI:10.1016/S0920-1211(97)00084-3
3. Pilaniya K, Chandrawanshi H K, Pilaniya U, Manchandani P, Jain P and Singh N, *J Adv Pharm Technol Res*, 2010, **1**, 302; DOI:10.4103/0110-5558.72422
4. Görög S, *Prog Pharmal Biomed Anal*., 2000, **4,** 1-8; DOI:10.1016/S1464-3456(00)--80003-4
5. Johnson D S, Li J J and Yuen P W, *Art Drug Synthesis*, John Wiley & Sons Inc., 2006, 215. DOI:10.1002/9780470134979.ch16
6. Satzinger G, Hartenstein J, Herrmann M and Heldt W, 1976, DE 2460891 A1.
7. Cannata V, Corcella F and Nicoli A, 2002, WO 2002034709 A1.
8. Burns M and Wong J, Patents; 2004, WO2004111256 A1.
9. Czekelius C and Carreira E M, *Angew Chem Int Ed.,* 2005, **44(4)**, 612-615; DOI:10.1002/anie.200461879
10. Chen F E, Kuang Y Y, Dai H F, Lu L and Huo M, *Synthesis*, 2003, **17**, 2629-2631; DOI:10.1055/s-2003-42431
11. Veisi H, *Synthesis*, 2010, **15**, 2631-2635. DOI:10.1055/s-0029-1218827
12. Ghorbani-Vaghei R and Veisi H, *Synthesis*, 2009, **6**, 945-950. DOI:10.1055/s-0028-1087967
13. Iida S and Togo H, *Tetrahedron,* 2007, **63(34)**, 8274-8281; DOI:10.1016/j.tet.2007.05.106
14. Nicolaou K C and Mathison C J N, *Angew Chem Int Ed.*, 2005, **44(37)**, 5992-5997. DOI:10.1002/anie.200501853