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SHORT COMMUNICATION

# A convenient approach for vinylation reaction in the synthesis of 5-vinyl-2-pyrrolidinone, a key intermediate of vigabatrin

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## Abstract

A convenient, safe and cost-effective method for carrying out the key vinylation of 5-ethoxy-2-pyrrolidinone (**8**) in the preparation of 5-vinyl-2-pyrrolidinone (**2**) in the presence of potassium carbonate is described. This present procedure is developed by replacing inherently hazardous ethyl magnesium bromide with inexpensive and eco-friendly potassium carbonate. The reaction was performed on a multi-gram scale, with vinyl magnesium bromide as the vinylation reagent, in an 81% yield to give the 5-vinyl-2-pyrrolidinone with excellent purity and without the need for chromatography.

**Keywords** Vigabatrin · Anti epileptic drug · Potassium carbonate · 5-Vinyl-2-pyrrolidinone · Key intermediate

## Abbreviations

| | |
|---|---|
| THF | Tetrahydrofuran |
| $ZnCl_2$ | Zinc chloride |
| $CuBr_2$ | Copper (II) bromide |
| CuI | Copper (I) Iodide |
| $BF_3OEt_2$ | Boron trifluoride diethyl etherate |

## Introduction

Vigabatrin [γ-vinyl GABA or 4-amino-5-hexenoic acid] (**1**), marketed as the racemate under the brand name Sabril, a synthetic analogue of GABA (γ-aminobutyric acid), is a highly selective enzyme-activated inhibitor of GABA-T in mammalian brain. Inhibition of GABA-T by γ-vinyl GABA, which replaces GABA as a substrate for GABA-T, increases the level of GABA in the central nervous system (CNS). Vigabatrin is, therefore, useful for the treatment of disorders associated with depletion of GABA levels in the central nervous system (CNS) such as tardive dyskinesia, schizophrenia and epilepsy (Fig. 1) (Grant and Heel 1991). Vigabatrin is also used to treat seizures in succinic semialdehyde dehydrogenase deficiency (SSADHD), which is an inborn GABA metabolism defect that causes intellectual disability, speech disturbance, hypotonia, seizures and ataxia through the accumulation of γ-hydroxybutyric acid (GHB). Vigabatrin helps lower GHB levels through GABA transaminase inhibition. However, this is in the brain only; it has no effect on peripheral GABA transaminase, so the GHB keeps building up and eventually reaches the brain (Phillip et al. 2004).

It is extremely challenging for the organic chemist is to produce a quality, safe, reproducible synthetic schemes within the developmental space. Several synthetic methods were well documented in the literature for the synthesis of vigabatrin (**1**). One literature report (Maurice and Gerard 1980) describes the preparation of vigabatrin by the condensation of two commercially accessible raw materials diethylmalonate (**3**) and 1,4-dichloro-2-butene (**4**) to afford 1,1-bis-ethoxycarbonyl-1,2-vinylcyclopropane (**5**) (Scheme 1). Compound **5** is treated with ammonia gas in formamide at 120 °C to afford 3-carboxamido-5-vinyl-2-pyrrolidinone (**6**). Hydrolysis of compound **6** in the presence of sodium ethoxide in ethanol and subsequent de-carboxylation with acetic acid generated 5-vinyl-2-pyrrolidinone (**2**). Hydrolysis of compound **2** in the presence of aqueous HCl and consequent purification through column chromatography afforded vigabatrin (**1**).

The major disadvantages of this synthetic route including more number of synthetic steps, poor yields, expensive raw

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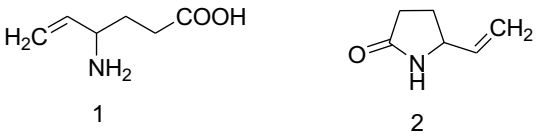
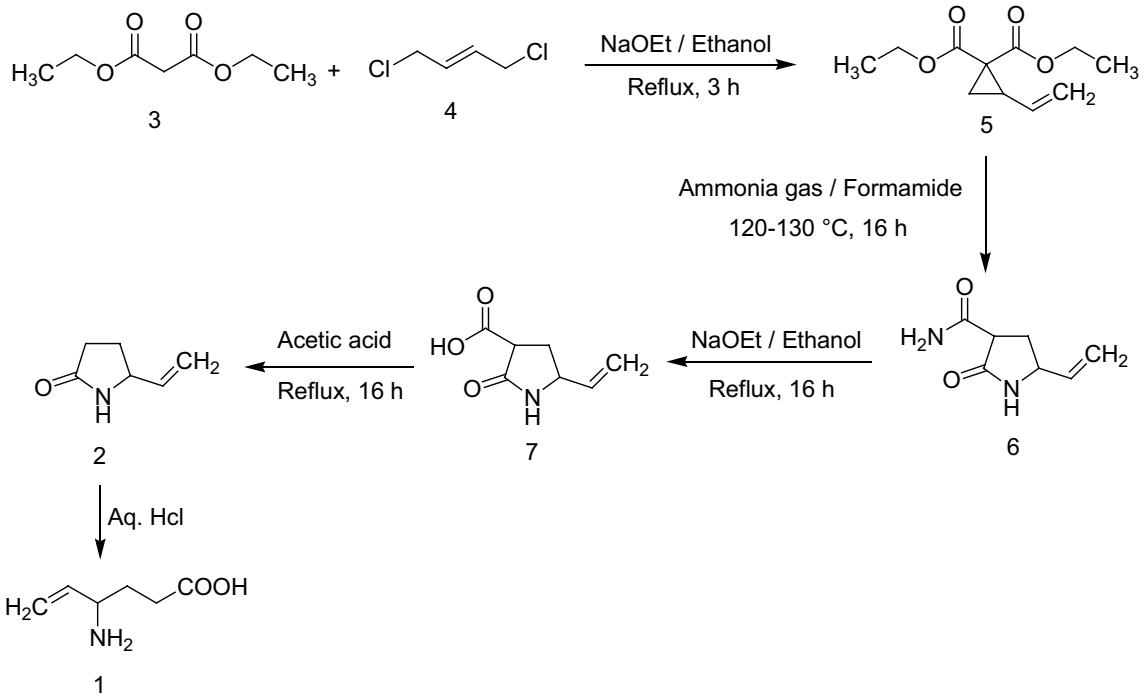


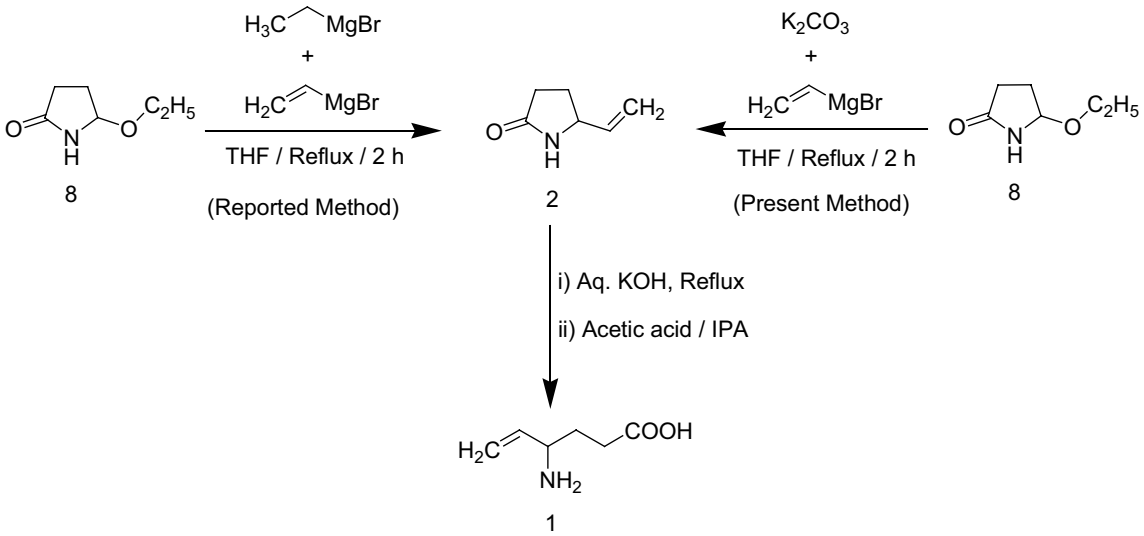

**Fig. 1** Chemical structures of vigabatrin (**1**) and 5-vinyl-2-pyrrolidinone (**2**)

materials, reagents and the time cycle is for the synthesis is more. Furthermore, column chromatography is essential to isolate the pure compound. Hence, this process is not preferable for the large scale synthesis.

Another concise approach for the synthesis of 5-vinyl-2-pyrrolidinone (**2**) is reported (Marie-Christine et al. 2011) (Scheme 2) by vinylation of 5-ethoxy-2-pyrrolidinone (**8**)




**Scheme 1** Reported preparation of 5- vinyl-2-pyrrolidinone as per literature (Maurice and Gerard 1980)




**Scheme 2** Reported synthesis (Marie-Christine et al. 2011) and present synthesis of 5-vinyl-2-pyrrolidinone (**2**)

with vinyl magnesium bromide in the presence of ethyl magnesium bromide. Hydrolysis of 5-vinyl-2-pyrrolidinone (**2**) is in the presence of KOH resulted vigabatrin. Though, this process is facile enough, the disadvantage is the unnecessary usage of ethyl magnesium bromide as a base. The commercial availability of ethyl magnesium bromide is only 26%w/v in THF. Thus, it reduces the occupancy of the batch size in the large scale production. In addition, the excess usage of THF also makes this process non eco-friendly.

Despite, several synthetic protocols have been reported for the synthesis of 5-vinyl-2-pyrrolidinone (Marie-Christine et al. 2011; Hao-Jie et al. 2017; Weiss et al. 2011; Silverman et al. 1996; Wei and Knaus 1993, 1994; Coulton et al. 1990; Rolf et al. 1995) and vigabatrin (Maurice and Gerard 1980; Marie-Christine et al. 2011); we herein reported a new process that obviates previous disadvantages and limitations. In our approach, a simple and eco-friendly and reproducible manufacturing process for the preparation of 5-vinyl-2-pyrrolidinone (**2**) is described.

## Results and discussion

The proposed synthesis was also commenced with 5-ethoxy-2-pyrrolidinone (**8**) from commercially accessible succinimide (Marie-Christine et al. 2011). As per literature (Marie-Christine et al. 2011), 1 mol equivalent of base reagent and another 1.5 mol equivalent of vinylmagnesium bromide were required for the manufacturing of **2** from **8** in this nucleophilic substitution (vinylation) reaction. Our aim was to substitute ethyl magnesium bromide (used as a base) with any other inexpensive and eco-friendly reagents/catalysts.

Consequently, we screened several inorganic base reagents including potassium carbonate ($K_2CO_3$), potassium-*t*-butoxide (KO-*t*-Bu), sodium methoxide (NaOMe), and Magnesium hydroxide [$Mg(OH)_2$]. Surprisingly, product conversion was identical, while $K_2CO_3$ was employed as base for vinylation reaction. Conversely, we observed no product formation, while KO-*t*-Bu was tested as a base. Furthermore, the product formation was less, while NaOMe and $Mg(OH)_2$ were employed as a base reagent. The results are presented in Table 1.

In addition, we examined a few Lewis acids including $ZnCl_2$, $CuBr_2$, CuI and $BF_3.OEt_2$ to replace ethyl magnesium bromide in vinylation reaction. However, all the Lewis acids showed hardly any impact on the vinylation reaction. The screening studies are presented in Table 1. From the above extensive study, we perceived that, $K_3CO_3$ has a significant role on vinylation reaction as a base.

After achieving the product formation of **2** with $K_2CO_3$, we shifted our focus to understand the role of $K_2CO_3$ and optimize its mole ratio for vinylation reaction. During the optimization of **2**, vinyl magnesium bromide was kept constant and the mole ratios of potassium carbonate were altered. Consequently, our initial experiment was commenced in a mixture of 1 mol equivalent of $K_2CO_3$ and 1.5 mol equivalent of vinyl magnesium bromide and achieved 82% of product formation. Subsequently, we reduced the mole ratio of $K_2CO_3$ to 0.5 equivalents and achieved 81% of product formation. After achieving the similar results, we then performed the reaction with 0.25 equivalents of $K_2CO_3$. Surprisingly, same yield (81%) and quality was observed, while 0.25 equivalents of $K_2CO_3$. To understand the impact of $K_2CO_3$, we attempted to prepare **2** using 1.5 as well as 2.0 mol equivalents of vinyl magnesium bromide (without using $K_2CO_3$). Nevertheless, the yields were correspondingly decreased to 71% and 75%, respectively. Considering these results, we anticipated that, potassium carbonate was acted as a catalyst as well as a base. The optimization studies of $K_2CO_3$ are presented in Table 2.

Subsequently, hydrolysis of 5-vinyl-2-pyrrolidinone (**2**) in the presence of potassium hydroxide resulted desired vigabatrin (**1**).

**Table 1** Reagent screening studies of 5-vinyl-2-pyrrolidinone

| Entry | Reagent 1 | Moles of reagent 1 | Vinyl magnesium bromide moles | Yield % |
|---|---|---|---|---|
| 1 | $K_2CO_3$ | 1.0 | 1.5 | 82 |
| 2 | KO-*t*-Bu | 1.0 | 1.5 | No reaction |
| 3 | NaOMe | 1.0 | 1.5 | 60 |
| 4 | $Mg(OH)_2$ | 1.0 | 1.5 | 67 |
| 5 | $ZnCl_2$ | 1.0 | 1.5 | No reaction |
| 6 | $CuBr_2$ | 0.1 | 2.5 | 80 |
| 7 | CuI | 0.1 | 1.5 | 60 |
| 8 | $BF_3OEt_2$ | 1.0 | 1.5 | No reaction |

**Table 2** Mole equivalents and reagent screening studies of potassium carbonate

| Entry | $K_2CO_3$ moles | Vinyl magnesium bromide moles | Yield % |
|---|---|---|---|
| 1 | 1.0 | 1.5 | 82 |
| 2 | 0.5 | 1.5 | 81 |
| 3 | 0.25 | 1.5 | 81 |
| 4 | – | 1.5 | 71 |
| 5 | – | 2.0 | 75 |

## Conclusion

A simple, safe and convenient approach towards the synthesis of 5-vinyl-2-pyrrolidinone, a key intermediate of vigabatrin was described. This procedure may offer an attractive

method to prepare 5-alkyl or vinyl-2-pyrrolidinone derivatives. In addition, introduction of $K_2CO_3$ in the synthesis of 5-vinyl-2-pyrrolidinone makes the whole process simple, eco-friendly and cost effective.

## General information

Unless otherwise stated, all melting points were uncorrected and were determined on a Reichert Thermopan apparatus. The purity/impurity ratios of compounds **1** and **2** were determined by Waters Alliance 2695 separations module system and 2487 dual $\lambda$ absorbance detector. HPLC measurements were run on Sperisorb C6, 250 mm × 4.6 mm, 5 µm (Make: Waters) and Partsil 10 SCX, 250 mm, 4.6 mm, 10 µm (Make: Hi Chrom) connected in series at 25 °C with flow rate of 1.0 ml/min and the run time of 60 min. $^1$H and $^{13}$C NMR spectra were recorded by a Bruker Avance 300 MHz and Varian 500 MHz spectrometer using TMS as internal standard in $D_2O$ and DMSO-$d_6$. The $^1$H chemical shift values were reported in the δ scale relative to TMS (δ 0.00) and the $^{13}$C chemical shift values were given relative to DMSO-$d_6$ and $D_2O$ as internal standards. The IR spectra were recorded as KBr pellets using Perkin Elmer Spectrum One Fourier Transform (FT) IR spectrophotometer. High-resolution mass spectral (HRMS) analyses were performed using the electro spray ionization (ESI) method on Xevo G2 QTOF mass spectrometer. All raw materials were purchased from commercial sources and used without purification.

## Experimental

### Synthesis of 5-vinyl-2-pyrrolidinone (2)

To a stirred -15 to -10 °C solution of 5-ethoxy-2-pyrrolidinone (**8**) (25 g, 0.19 mol) in tetrahydrofuran (150 mL), potassium carbonate (6.7 g, 0.04 mol) was added under nitrogen atmosphere. To this suspension, vinyl magnesium bromide (1 M, 297 mL, 0.28 mol) was added portion wise over 1 h. The heterogeneous reaction mixture was warmed and stirred under a gentle reflux for 2 h. After cooling the reaction mixture to 0 °C, a mixture of $H_2O$ (250 mL) and acetic acid (50 mL) was added cautiously by maintaining the temperature between 0–20 °C. The insolubles were removed through hyflo bed filtration. The volatiles in the filtrate were concentrated and the residue was extracted with DCM (250 mL). The organic layer was separated and evaporated under reduced pressure to afford (*RS*)-5-vinyl-2-pyrrolidinone (17.5 g, 81%) as dark brown colour syrup. Purity by HPLC: 97.97%; $^1$H NMR (300 MHz, $D_2O$): 1.60–1.70 (m, 1H), 2.08–2.24 (m, 3H), 4.00–4.06 (m, 1H), 5.02–5.18 (m, 1H), 5.75–5.86 (m, 1H), 7.83 (s, 1H); $^{13}$C NMR (300 MHz, $D_2O$): 8.96, 25.79, 28.43, 30.19, 56.62, 181.15; GCMS (m/z): 111;

### Synthesis of vigabatrin (1)

To a stirred solution of potassium hydroxide (12.6 g, 0.22 mol) in $H_2O$ (23 mL), 5-vinyl-2-pyrrolidinone (25 g, 0.22 mol) was added. The reaction mass was warmed and stirred for 2 h under reflux. The reaction mixture was diluted with isopropanol (200 mL) after cooling to 25–30 °C. To this solution, acetic acid (13.5 g, 0.22 mol) was added portion wise over 30 min. The slurry was stirred for 2 h at 20–30 °C and subsequently for 2 h at 0–5 °C. The precipitated product was collected by filtration and dried to afford **1** (13 g, 74%) as an off-white solid. Purity by HPLC: 99.67%; $^1$H NMR (300 MHz, $D_2O$): 0.97–1.02 (t, 3H), 1.63–1.77 (m, 2H), 1.85–1.97 (m, 2H), 2.31–2.36 (m, 2H), 3.20–3.25 (t, 1H); $^{13}$C NMR (300 MHz, $D_2O$): 31.58, 36.08, 56.64, 123.76, 135.6, 184.02; HRMS (ESI) calculated for $C_6H_{13}NO_2$ $(M+H)^+$ 130.0868, found: 130.0888;

**Supplementary information** Supplementary information file containing $^1$H, $^{13}$C NMR, HRMS and HPLC chromatogram of compound **1**; $^1$H NMR, GCMS and HPLC chromatogram of compound **2** is available at the journal website at http://link.springer.com/journal/10593.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

## References

Coulton S, Francois I, Southgate R (1990) Synthesis of γ-lactam analogues of 1-acetoxy carbapenem derivatives. Tetrahedron Lett 31:6923–6926. https://doi.org/10.1016/S0040-4039(00)97208-3

Grant SM, Heel RC (1991) A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. Drugs 41:889–926. https://doi.org/10.2165/00003495-199141060-00007

Hao-Jie R, Yong-Feng C, Fan-Fan L, Jin Q (2017) Synthesis of γ-lactams by mild, *O*-benzoquinone-induced oxidation of pyrrolidines containing oxidation-sensitive functional groups. J Org Chem 82(1):532–540. https://doi.org/10.1021/acs.joc.6b02562

Marie-Christine D, Bienayme H, Popowycz F, Lemair M (2011) Process for the preparation of 4-amino-5-hexenoic acid from succinimide by reduction, vinylation and hydrolysis. EP Patent: 2,537,827 A1

Maurice GW, Gerard JL (1980) US Patent: 4,235,778

Phillip LP, Robbins E, Philip KC, Gasior M, Gibson KM (2004) Succinic semialdehyde dehydrogenase deficiency. Gene reviews. University of Washington, Seattle. Retrieved 6 Sept 2010

Rolf F, Werner H, Eenst H, Hardo S (1995) Process for the preparation of gammavinylpyrrolidones from primary amines and gammavinylbutyrolactones. EP Patent: 6,320, 23 A1

Silverman RB, Bichler KA, Leon AJ (1996) Mechanisms of inactivation of γ-aminobutyric acid aminotransferase by 4-amino-5-fluoro-5-hexenoic acid. J Am Chem Soc 118(6):1241–1252. https://doi.org/10.1021/ja9527885

Wei Z-Y, Knaus EE (1993) A practical procedure for the synthesis of 5-substituted γ-lactams. Org Prep Proced Int 25:255–258. https://doi.org/10.1080/00304949309457960

Wei Z-Y, Knaus EE (1994) A mechanism-based cleavage of lactam-carbamates. Tetrahedron Lett 35:847–848. https://doi.org/10.1016/S0040-4039(00)75979-X

Weiss ME, Kreis LM, Lauber A, Carreira EM (2011) Cobalt-catalyzed coupling of alkyl iodides with alkenes: deprotonation of hydridocobalt enables turnover. Angew Chem 50:11125–11128. https://doi.org/10.1002/anie.201105235