

Research Article

An Efficient Synthesis of Milnacipran Hydrochloride via Reductive Amination of Aldehyde

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An efficient synthesis of milnacipran hydrochloride has been accomplished. The important application of this paper is the reductive amination of aldehyde to primary amine with water soluble reagents. This method provides a high yield of primary amine as the major product, reduces the number of steps, and discourages by-products.

1. Introduction

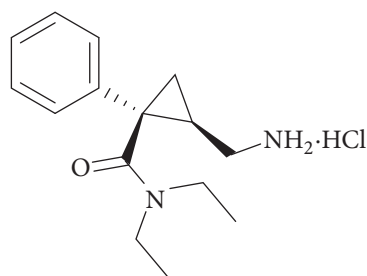
Milnacipran hydrochloride is an antidepressant inhibiting the recapture of serotonin-noradrenaline recommended in the treatment of depression. US Food and Drug Administration (FDA) approved milnacipran under the brand name of Savella® for the treatment of fibromyalgia [1, 2]. Several research groups [3–6] show high interest to devise an efficient synthesis of milnacipran with high enantiomeric purity. Because it is hydrophilic molecule with low lipophilicity makes this molecule differ from other drugs. Due to features, milnacipran exhibits almost ideal pharmacokinetics in humans (see Scheme 1).

Interesting structural features combined with the important biological activity of milnacipran have attracted us to attempt its synthesis through the oxidation and reductive amination method.

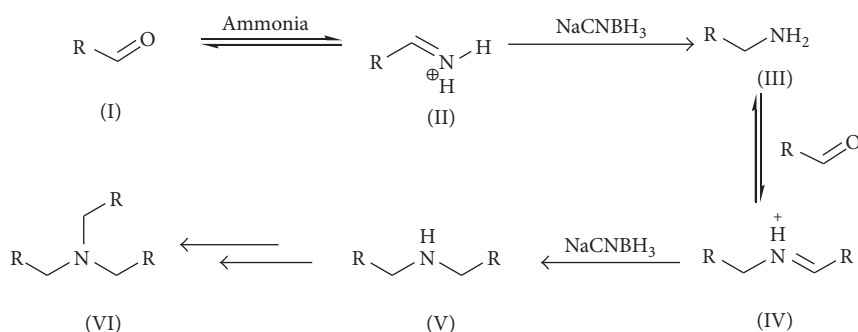
The primary amines are important building blocks in pharmaceutical and agrochemical industries and also useful applications in organic chemistry. The primary amine of milnacipran acts as chromophore and based on hydrophilic makes this molecule differ from other drugs. The synthesis of primary amine is very challenging reaction to avoid the overalkylation when employed metal reductive amination.

Generally protecting groups have been employed when preparing primary amines via metal hydride reductive amination to control the overalkylation [3–9]. Protecting groups have an important role in organic synthesis [10–13]. On the other hand, the incorporation of protecting group into synthetic route increases the total number of steps, decreases yield, and decreases atom economy [14]. Protecting groups also add functional groups and structural complexity to a molecule, which can have detrimental effects on orthogonality and reactivity. In metal hydride reductive aminations, the use of protecting groups is crucial to prevent overalkylation [15, 16] (Scheme 2). In this reaction aldehyde (I) reacts with ammonia to form an imine (II) that is subsequently reduced with sodium cyanoborohydride (NaCNBH_3) [17] to give the desired amine product (III). Without a protecting group, multiple alkylation events typically occur, resulting in the formation of the undesired secondary (V) or tertiary (VI) amine products. To avoid protecting groups as well as overalkylation, we attempted using excess of ammonia or adjusting pH through reductive amination.

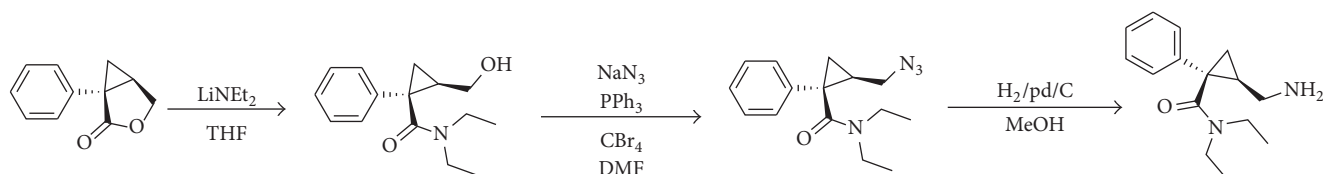
Several strategies have already been developed for the synthesis of milnacipran in their racemic and pure form [3–6, 18, 19]. However, all these routes were involving the



SCHEME 1



SCHEME 2: Reductive amination of aldehydes.



SCHEME 3

synthesis of the primary amine group through protection and deprotection. The protection and deprotection of potassium phthalimide significantly reduce the atom economy, yield, and increase the impurities as well as number of steps [20, 21]. Some synthetic protocols required special handling and more precautions, such as lithium amide and hydrogenation. Shuto et al. reported the synthesis of milnacipran with expensive and more cautious reagents such as sodium azide and Appel reaction conditions followed by hydrogenation (Scheme 3) [22, 23]. By the comparison our synthetic route is more reliable, more atom economy, and cost effective route with less by-products.

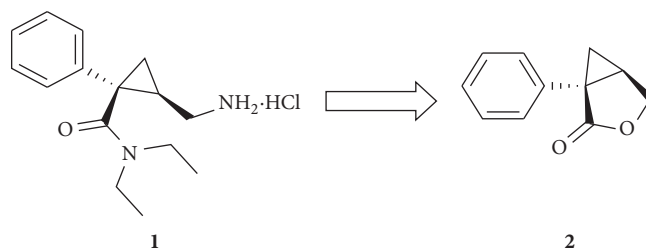
To overcome all these issues, we report a practical synthesis of milnacipran hydrochloride using a combination of oxidation and reductive amination.

2. Results and Discussion

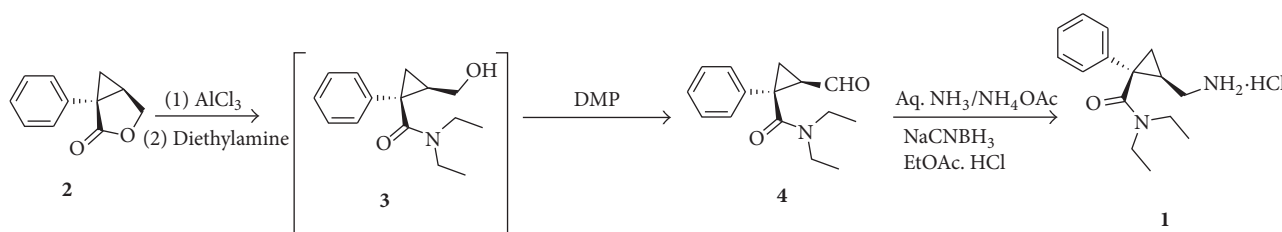
Our synthetic strategy is outlined in Scheme 4. The target primary amine compound **1** could be prepared from commercially available compound [24] (1*S**, 5*R**)-1-phenyl-3-oxabicyclo[3.1.0]hexane-2-one (**2**).

3. Synthesis of Milnacipran Hydrochloride

The synthesis of milnacipran hydrochloride synthesis starts with commercially available compound [25] **2**. The treatment of compound **2** with aluminum chloride and diethylamine at room temperature afforded a ring opening alcohol **3** (Scheme 5). The alcohol compound **3** after workup directly proceeded to oxidation with Dess-Martin periodinane [DMP; 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1-*H*)-one]; this reagent has several advantages over chromium and DMSO-based oxidation reagents that include milder conditions such as lower temperature, neutral pH, shorter reaction times, higher yields, simplified workups, high chemoselectivity, tolerance of sensitive functional groups, and a longer shelf life time. Oxidation with Swern reagent is tedious and hazardous; the by-products are dimethyl sulfide (Me₂S), carbon monoxide (CO), and carbon dioxide (CO₂). Two of the by-products, dimethyl sulfide and carbon monoxide, are very toxic volatile compounds; due to low boiling point dimethyl sulfide easily evaporates into atmosphere; this contributes to the already abundant pollution in the atmosphere. To overcome these challenges, Swern oxidation was replaced with the DMP reagent. From scale up point of view, DMP oxidation is much easier



SCHEME 4: Retrosynthesis of milnacipran.



SCHEME 5

TABLE 1: Solvent volume optimization.

Entry	Reagent	DCM (mL)	Yield (%)
1	DMP	5	40
2	DMP	10	60
3	DMP	15	70
4	DMP	20	95

TABLE 2: Reagent mole equivalent optimization table.

Entry	DMP ^b	Solvent	Yield%
1	0.8	DCM	50
2	0.9	DCM	70
3	1.0	DCM	83
4	1.1	MDC	95

b: Dess-Martin periodinane reagent.

than Swern oxidation. Several parameters were selected to optimize the oxidation reaction, including solvent volumes and mole equivalents of reagent.

Oxidation of compounds **3** to **4** solvent volumes mentioned at Table 1, entries 1, 2, and 3 indicates that less volume of dichloromethane (DCM) is not favoured for this reaction. As per entry 4 higher volumes (20 volumes) are optimum for the DMP oxidation.

DMP reagent optimization mentioned in Table 2, entries 1 and 2, shows poor yields due to incomplete reaction, whereas entry 3 is the optimum amount of reagent to get best results. Entry 4 also indicates that 1.1 eq of DMP reagent is the suitable quantity to complete the reaction. Compound **3** was confirmed by ¹H-NMR, significant peak observed at 9.05 δ ppm for aldehyde.

Reductive amination step depends on the various factors like number of moles of reagent, pH, reaction time, and temperature. Reductive amination was tried at different pH

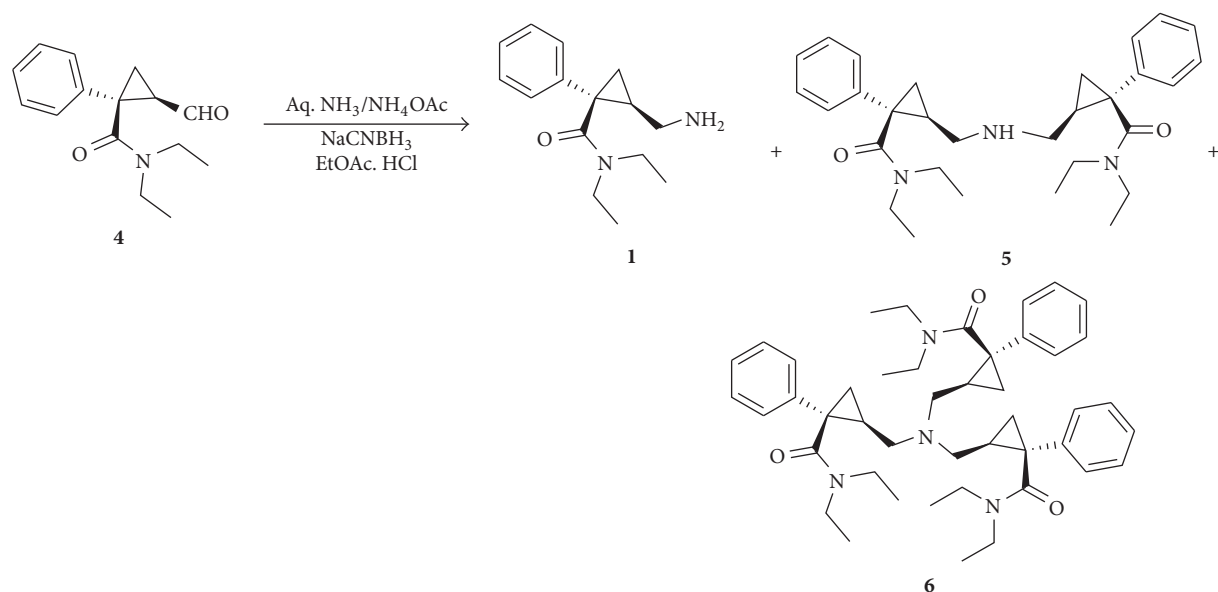
conditions as indicated in Table 3 and reaction optimization studied by adding additives like acetic acid and aq. ammonia solution. As mentioned in the table entry 1 was performed by adding acetic acid to the reaction, multiple number of spots was observed in the TLC, based on the theory, the probable side products were mentioned in the Scheme 6, and next entries 2 and 3 indicate incremental usage of ammonia gradually shifting towards chemoselectivity of reductive amination. Entry 4 clearly represents the higher volumes of ammonia or maintaining pH 12 is the key factor to increase the chemoselective reductive amination of aldehyde **4**.

Second factor is the reaction temperature. Reaction was not proceeded at RT (entry 1, Table 4) to give desired primary amine **1**. TLC showed reaction stopped at imine step only. Entry numbers 2 and 3 indicate that gradual increase in temperature enhances the conversion of compound **1**. 70–75°C range is the optimum temperature for reductive amination of aldehyde **3**.

Metal hydride plays the main role in the reduction during reductive amination; to understand the impact of mole equivalent of NaCNBH₃ some optimization results were mentioned in Table 5. Entry number 1 indicates that 0.5 eq of reagent is not good enough to complete reaction; same way entry numbers 2 and 3 also indicate that this reaction requires more eq of reagent (NaCNBH₃). Entry 4 clearly indicates that reductive amination of aldehyde and ammonia requires 3 eq of reagent to get maximum conversion of compound **1**.

Reaction time is also the important factor to achieve desired product with highest yield; entry number 1 indicates 1 hr is not enough to complete this reaction; as per Table 6 (entries 2 and 3) 2–4 hrs is also not sufficient for reductive amination reaction. Reaction time 6 hrs (entry 4, Table 6) is optimum reaction time to get maximum yield of compound **1**.

Finally the optimized conditions for the synthesis of compound **1** from aldehyde **3** were 40 eq of aq. ammonia, 3 eq of sodium cyanoborohydride, 20 volumes of ethanol, and



SCHEME 6: Overreductive amination.

TABLE 3: pH of the reaction mixture.

Entry	Additive	pH	Ratio ^a (1:5)	Yield %
1	AcOH	7	1:1	40
2	Aq. NH ₃ (5 eq)	8	4:1	50
3	Aq. NH ₃ (10 eq)	10	10:1	65
4	Aq. NH ₃ (40 eq)	12	20:1	75

a: ratios calculated based on TLC profile.

TABLE 4: Reductive amination reaction temperature.

Entry	Ethanol mL	Temp °C	Yield%
1	20	RT	No rxn
2	20	40	25
3	20	55	57
4	20	75	75

TABLE 5: NaCNBH₃ mole eq optimization.

Entry	NaCNBH ₃ eq	Temp °C	Yield%
1	0.5	75	28
2	1	75	45
3	2	75	55
4	3	75	75

TABLE 6: Reaction time optimization.

Entry	Reagent	Temp °C	Rxn time (h)	Yield%
1	NaCNBH ₃	75	1	28
2	NaCNBH ₃	75	2	45
3	NaCNBH ₃	75	4	55
4	NaCNBH ₃	75	6	75

6-7 hrs reaction time with saturated solution of ammonium acetate. Based on optimized conditions, we attempted gram

scale synthesis of milnacipran hydrochloride (1). Characterization of 2-(aminomethyl)-N,N-diethyl-1-phenyl cyclopropane carboxamide hydrochloride (1) was done by proton ¹H NMR, ¹³C NMR, and mass; significant broad amine peak is observed at 8.82 δ ppm and disappearance of peak at ~ 9.05 ppm, which is related to corresponding aldehyde peak. *m/z* peak is observed at 247.2 which is M+1 of milnacipran hydrochloride 1.

4. Conclusion

We have demonstrated the synthesis of milnacipran hydrochloride with an efficient approach. We employed different conditions to obtain adequate experimental conditions such as pH, temperature, and sodium cyanoborohydride reagent. In addition, the employment of reductive amination of aldehyde with sodium cyanoborohydride selectively produces primary amine with high yielding. Finally, we have developed a mild method for the conversion of the aldehyde into primary amine using reductive amination method.

5. Experimental Section

5.1. Synthesis of (1S,2R)-1-Phenyl-2-(hydroxymethyl)-N,N-diethyl Cyclopropane Carboxamide (3). Aluminum chloride (22 g) was suspended in (150 mL) CH₂Cl₂ and diethylamine

(25 g) was then added under stirring at room temperature, slowly cooled to 0–5°C, and stirred for 10 minutes, and the RM temperature was raised to 10–15°C; 20 gm of cis(±)1-phenyl-3-oxabicyclo[3.1.0]hexane-2-one was dissolved in CH₂Cl₂ (50 mL) and added to the reaction mass for 1 hour at 10–15°C. The temperature of the reaction mass was raised at room temperature and stirred for 1 hour. After completion of the reaction, the reaction mass was quenched in ice-cooled water (140 mL). The organic layer was collected and washed with water and hydrochloric acid. Aqueous layer was back extracted with CH₂Cl₂ (2 × 100 mL); combined organic layer was directly taken as such for the next step.

5.2. Synthesis of (1S,2R)-1-Phenyl-2-formyl-N,N-diethyl Cyclopropane Carboxamide (4). To a solution of **3** (1 eq) in CH₂Cl₂ (400 mL) was added Dess-Martin periodinane (1.1 eq) at RT and the resulting solution was stirred for 2 hours at RT. The reaction mixture was quenched with a saturated solution of Na₂SO₃ and NaHCO₃; the reaction mixture was passed through a pad of celite. The combined organic phase was dried over anhydrous Na₂SO₄, concentrated, and purified by column chromatography (silica gel: AcOEt/hexane, 1:2) to give **4** as a white solid (95%). ¹H-NMR: (400 MHz, CDCl₃) δ: 0.69 (3H, t, J = 7.0 Hz), 1.11 (3H, t, J) 7.0 Hz), 1.71 (1H, dd, J) 5.5, 8.5 Hz), 2.28 (1H, dd, J = 5.5, 6.0 Hz), 2.50 (1H, ddd, J = 6.0, 6.0, 8.5 Hz), 3.18 (1H, dq, J = 14.0, 7.0 Hz), 3.26 (1H, dq, J = 14.0, 7.0 Hz), 3.42 (1H, dq, J = 14.0, 7.0 Hz), 3.46 (1H, dq, J) 14.0, 7.0 Hz), 7.23–7.38 (5H, m), 9.05 (1H, d, J = 6.0 Hz). LC-MS 246.26 (M+1) peak found with purity 98%.

5.3. Synthesis of 2-(Aminomethyl)-N,N-diethyl-1-phenyl Cyclopropane Carboxamide Hydrochloride (1). To a solution of **4** (1.0 eq) in a saturated solution of NH₄OAc in ethanol (20 mL) were added NaCNBH₃ (3 eq) and 30% aqueous ammonia (8 mL). The mixture was stirred at reflux for 6 hrs, cooled to RT, and concentrated under reduced pressure to get crude product. Ethyl acetate hydrochloride was added to the crude product; corresponding hydrochloride salt was isolated and filtered under vacuum to get **1** as a crystal (23 g, 70%). Mp 178–180°C. ¹H NMR: (CDCl₃, 400 MHz) δ: 0.90 (t, 3H, J = 7.2 Hz), 1.11 (t, 3H, J = 7.2 Hz), 1.76–1.83 (m, 2H), 2.45 (m, 1H), 3.35–3.40 (m, 4H), 3.73–3.76 (m, 1H), 7.10–7.29 (m, Ar, 5H), 8.82 (br, s, 2H); ¹³C NMR: (CDCl₃, 100 MHz) δ: 11.9 (1C, CH₃), 12.6 (1C, CH₃), 17.8 (1C, CH₂), 24.9 (1C, CH), 39.2 (1C, N-CH₂), 41.66 (1C, N-CH₂), 42.4 (1C, N-CH₂), 125.4 (Ar, 2C), 126.7 (Ar, 1C), 128.5 (Ar, 2C), 138.1 (Ar, 1C), 170.1 (1C, amide); m/z: 247.2 (M+1).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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