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EFFICIENT SYNTHESIS OF MILNACIPRAN HYDROCHLORIDE WITH ATOM ECONOMY APPROACH

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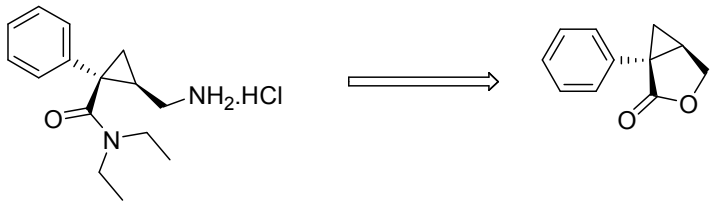
1. Abstract
The short and efficient synthesis of milnacipran has been achieved from the commercial available cis(±)1-Phenyl-3oxabicyclo[3.1.0]hexane-2-one using the atom economy concept and the target compound was achieved with reduction of azide in presence of Raney nickel, toluene and methanol recovery and reuse also established



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2. Keywords: Milnacipran, Atom economy, Raney nickel.

3. Introduction
Chemical industry is focusing from many years on some classic synthetic processes of important starting chemicals or crucial chemicals produced in high volume as intermediates in synthetic industrial reactions. The intention is to reduce the synthetic stages, to lower the energy use, to increase efficiency with higher yields and to minimize waste. Every Green Chemistry textbook describe the big successes of the last decades in the field of new synthetic routes for industrial chemicals. The first is the synthesis of **Ibuprofen**, the second is the synthesis of **Adipic acid** [I].

Milnacipran (**1**) was first approved for the treatment of major depressive episodes in France in December 1996. It is currently marketed (as Ixel) for this indication in over 45 countries worldwide including several European countries as Austria, Bulgaria, Finland, France, Portugal, and Russia. It is also available in Japan (as Toledomin) and Mexico (as Dalcipran). Cypress Bioscience bought the exclusive rights for approval and marketing of the drug for any purpose in the United States and Canada in 2003 from the manufacturer Laboratoires Pierre Fabre.

In January 2009 the U.S. Food and Drug Administration (FDA) approved Milnacipran (under the brand name Savella) only for the treatment of fibromyalgia, making it the third medication approved for this purpose in the United States. In July and November 2009, the European Medicines Agency refused marketing authorization for a milnacipran product (under the brand name Impulsor) for the treatment of fibromyalgia [II].

Milnacipran was developed by Laboratoires Pierre Fabre (USA) sold under the commercial name of savella. The synthesis of milnacipran was performed in 4 steps with the production of secondary by products and waste. The main problem is this synthesis had poor atom economy [III]. The concept of Atom Economy was developed by Barry Trost of Stanford University [IV, V] (US), for which he received the Presidential Green Chemistry Challenge Award in 1998. It is a method of expressing how efficiently a particular reaction makes use of the reactant atoms. The calculation of atom economy

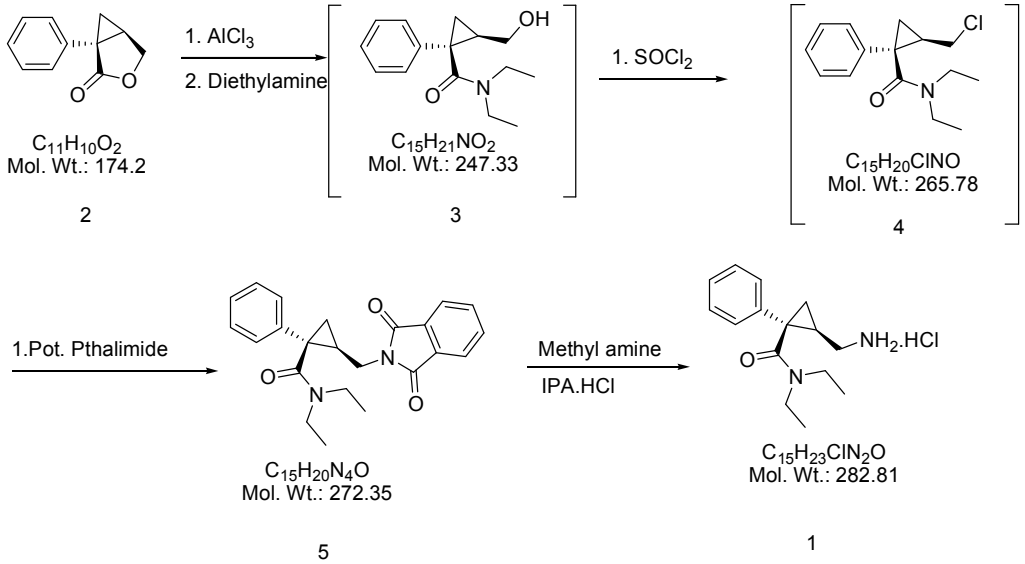
$$\textbf{Atom economy} = \frac{\textbf{Mass of atoms in desired product}}{\textbf{Mass of atoms in reactans}} \textbf{ X 100\%}$$

This approach does not take yield into account, and does not allow for the fact that many real-world processes use deliberate excess of reactants. It does, however, help in comparing different pathways to a desired product. Our new approach make more convenient and environment friendly synthesis of Milnacipran Hydrochloride.

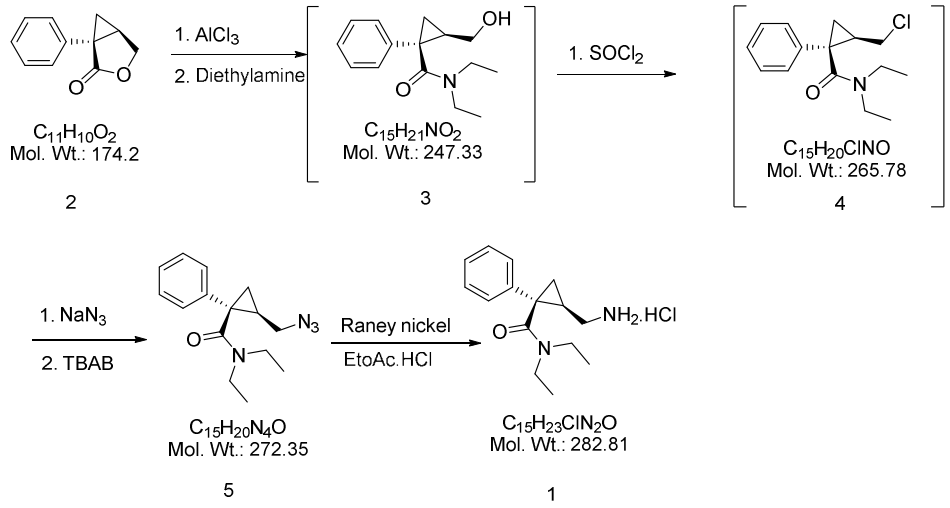
4. Results and discussion:

The initial synthesis, observed under the "Green" principles, had many disadvantages. The starting chemical could not be incorporated into the product example to introduce amine group (5) in the product potassium phthalimide used, during de-protection phthalzine is the main by product along with product, impurities also formed due to improper de-protection of phthalic anhydride producing lots of by-products and waste [VI]. The 4 steps of the synthetic route was consuming chemicals and energy while lowering the yield of the final product (Scheme-1).

Scheme-1.



Scheme 2: New Route



Synthesis of Milnacipran with azide route proceeds through Apple reaction condition ($NaN_3/CBr_4/PPh_3$) gave azide derivative (**6**) but it is not environment friendly approach most of the atoms are not incorporating in the desired product [VII], Only azide group incorporated in the molecule rest of the chemicals eliminates from the process, it produces lots of waste in to the environment. Synthesis of milnacipran by Gabriel synthesis i.e. aminolysis of (1S*,2R*)-2-((1,3-dioxoisoindolin-2-yl)methyl)-N,N-diethyl-1-phenylcyclopropane-carboxamide by using 40% aq. mono methylamine four potential impurities were reported [6] (Figure 1) Based on the spectral data, these impurities were characterized as N1-(((1R*,2S*)-2-(diethylcarbamoyl)-2-phenylcyclopropyl) methyl)-N2-methyl phthalamide (**7**), 2-(((1R*, 2S*)-2-(diethylcarbamoyl)-2-phenylcyclopropyl)methylcarbamoyl) benzoic acid (**8**), N1,N2-bis(((1R*,2S*)-2-(diethylcarbamoyl)-2-phenylcyclopropyl)methyl) phthalimide (**9**) and ((1R*,2S*)-2-(diethylcarbamoyl)-2-phenyl cyclopropyl)methyl-2carbamoyl banzoate (**10**).

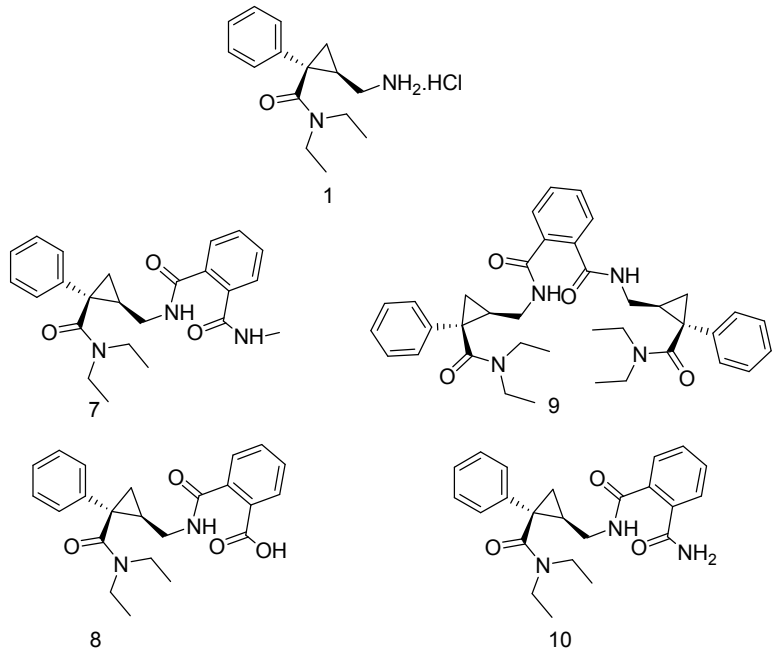


Figure 1: Structure of (±)-milnacipran and its impurities

Azide derivative preparation method with phase transfer catalyst and sodium azide reported by microlabs, but final reduction was carried out under Staudinger reaction conditions it involves the usage of triphenylphosphine (PPh_3), this moiety not incorporated in the final molecule, more over it generates triphenylphosphine oxide as a process waste [VIII] .New scheme also involves 4 steps, first 2 steps are similar to old scheme in toluene, recovery percentage of toluene would be better than dichloromethane. Experiments are performed with recovered toluene, results were as good as fresh solvent. Removal of residual quantity of Toluene is always easier than dichloromethane. Next step is the simple azide reaction with corresponding chloro compound, followed by catalytic hydrogenation with cheaply available Raney nickel. In both the synthetic routs the starting material is cis(±)1-Phenyl-3oxabicyclo[3.1.0]hexane-2-one, the innovation in the new method was conversion of Azide to Amine with Raney nickel. We have studied the reaction conditions at different time, temperatures, catalyst loading levels and optimized reaction conditions. A catalyst of Nickel (Raney nickel) was used thus decreasing reaction time and increasing product yield.

5. Azide to Amine screening

a) Reaction time screening

Azide to Amine conversion time represented in table 1, 1 hour and 2 hours reaction gone for the completion, product conversion percentage is ~60-75% only, after 3 hours product percentage increased significantly same profile observed even after 5 hours. Based on this data 3- 5 hours is the optimum reaction time for Azide to Amine conversion.

Table-1

Entry	Catalyst	Solvent	Time (hours)	Temp °C	Conversion%
1	Raney Ni	Methanol	1.0	50-55	~50
2	Raney Ni	Methanol	2.0	50-55	~70
3	Raney Ni	Methanol	3.0	50-55	> 95
4	Raney Ni	Methanol	4.0	50-55	> 95

b) Reaction temperature screening

Reaction temperature range studied from the range 25-55 °C, reaction not completed at 25, 30 and 45 °C temperature, conversion is less than 80 % even after 5 hours, whereas at 50-55 °C conversion is more than 95%. This data suggest us that the optimum reaction temperature for azide to amine conversion is 50-55 °C.

Table-2

Entry	Catalyst	Solvent	Temp °C	Time (hours)	Conversion%
1	Raney Ni	Methanol	25-30	4	~40
2	Raney Ni	Methanol	30-35	4	~70
3	Raney Ni	Methanol	40-45	4	~ 80
4	Raney Ni	Methanol	50-55	4	> 95

c) Catalyst loading

Table-3

Entry	Catalyst loading %(w/w)	Solvent	Temp °C	Time (hours)	Conversion%
1	10	Methanol	50-55	4	~30
2	20	Methanol	50-55	4	~50
3	30	Methanol	50-55	4	~70
4	40	Methanol	50-55	4	~ 85
5	50	Methanol	50-55	4	> 95

Since Pd/C catalyst is expensive, we have chosen Raney Ni as a catalyst. Raney Ni loading studied from 10 to 50% , product percentage was less than 85 % with 10 to 40 %(w/w) of catalyst, optimum conversion observed with 50% of catalyst loading.

In the old and new synthetic routes initial three steps involves almost same atom economy, whereas at a last step atom economy is 30% more with new scheme when compared with old scheme (Table-4).

Table 4: Atom economy calculation table of old method vs new method

Step name	**Old method economy**	**New scheme atom economy**
Stage1	69%	69%
Stage2	72%	72%
Stage3	83%	82%
Stage4	61%	91%

In new a scheme 4th step by product is nitrogen, after completion of reaction catalyst filtration, followed by methanol recovery and reuse would be helpful for the environment.

6. Conclusion:

The our new synthetic route of milnacipran is a classic example of how Green Chemistry ideas can influence to the better the industrial synthetic methods, not only from the point of economic efficiency, but also from the point of more effective science and technology methods.

7. Experimental Section:

1. Synthesis of cis (±)-1-phenyl-1-diethylaminocarbonyl-2-hydroxymethylcyclopropane (3) Aluminum chloride (23 g), was suspended in (100 ml) toluene and then added diethylamine (25 g) under stirring at room temperature, slowly cool to 0-5°C, stir for 10 minutes raise the RM temperature to 10-15 °C, cis(±)1-Phenyl-3oxabicyclo[3.1.0]hexane-2-

one (20 g) was dissolved in toluene (60 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 mixture was turned in to reddish brown murky and quenched with ice-cooled water (140ml). The organic layer was collected and washed with water and hydrochloric acid. Organic layer was directly taken as such for the next step. (**3** Yield = 0.99, atom economy = 0.99, Stoichimetric factor = 1.585 and Reaction mass efficiency = 0.618).

2. Synthesis of cis (±)-1-phenyl-1-diethylaminocarbonyl-2-chloromethyl cyclopropane (4)

Thionyl chloride (18.4 g) was slowly added to the above toluene layer (**3**, 28.39 g) over the period of 1 hour at 10-15 °C. The reaction mass was stirred for 1 hour at reflux 10-15 °C. After completion of the reaction, the reaction was turned in to yellow color solution and quench with TEA, This was dried and taken for the next stage without any further purification. (**4**, Yield = 0.99, atom economy= 0.725, Stoichiometric factor =1.1126 and Reaction mass efficiency = 0.645).

3. Synthesis of cis (±)-1-phenyl-1-diethylaminocarbonyl-2-azidomethyl cyclopropane (5)

Sodium azide (7.4g) and tetrabutylammonium bromide (catalytic amount) added the above toluene layer (**4**, 30.507 g) at below room temperature. The reaction mass was refluxed for 5-7 hours. After completion of the reaction diluted the reaction mass with DM water, separate the organic layer, dried the organic layer, followed by distillation to minimum volume of the reaction mass, add methanol distill the trace amount of toluene from reaction mixture completely, take the organic layer and proceed for the next step. (**5**, Yield = 0.894, atom economy= 0.823, stoichimetric factor =0.9982 and reaction mass efficiency = 0.737). ^{1}H NMR: ($CDCl_3$, 400MHz) δ: 0.54 (t, 3H, *J*=7.2Hz), 1.09 (t, 3H, *J*=7.2Hz), 1.20 (dd, 1H, *J*=4.8Hz), 1.55 (t, 1H, *J*=6.0Hz), 1.94- 2.02 (m, 1H), 3.05-3.60 (m, 2H), 3.38 (d, 2H, J=7.2 Hz), 3.45-3.60 (m, 2H), 7.20-7.37 (m, 5H); m/z: 273.42 (M+1).

4. Synthesis of 2-(aminomethyl)–N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochlorid(1) The Crude compound (**5,** 27.969 g.**)** obtained was dissolved in methanol (100ml) and was taken to RBF at room temperature. Raney nickel 15g was added to the RBF and the mixture was refluxed for 3-4 hours at 50-60°C. Progress of reaction is monitored by TLC in 10% Ethyl actate in n-hexane mobile phase and Palladium carbon was filtered using celite bed and the filtrate was evaporated, 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, Yield = 1, atom economy = 0.897, stoichimetric factor =0.9882 and reaction and mass efficiency = 0.937). Mp 178-180 °C. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ: 0.90 (t, 3H, *J*=7.2Hz), 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); ^{13} C NMR: ($CDCl_3$, 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).

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