International Journal of Chemical and Physical Sciences, ISSN:2319-6602
IJCPS Vol. 4 Special Issue – NCSC Jan-2015
www.ijcps.org

Synthesis of γ-Amino Butyric Acid as a Neurotransmitter Inhibitor using Asymmetric Michael addition of Diethyl Malonate to Nitrostyrene

M. N. LOKHANDE [1], M. D. NIKALJE [2]

[1] Organic chemistry synthesis laboratory, MNG Science College Babhulgaon-445101, INDIA
[2] Department of Chemistry, University of Pune-411007, INDIA
Corresponding author: lokhande.mahendra@yahoo.com

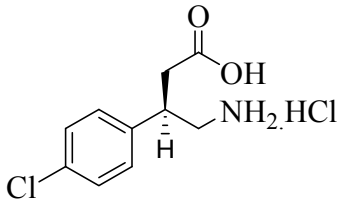
Abstract

A simple synthetic strategy was developed towards the synthesis of (*R*)-Baclofen. The synthetic strategy involved four steps having overall yield 48 % and 96% ee.

Key words: Michael addition, Decarboxylation, hydrolysis.

Introduction:

The Michael reaction is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound.[1] It belongs to the larger class of conjugate additions. This is one of the most useful methods for formation of C-C bonds.[2] Many asymmetric variants exist for the asymmetric Michael addition to nitroalkenes has been developed as a powerful tool in organic synthesis because Michael adducts, optically active nitroalkanes, are versatile building blocks for agricultural and pharmaceutical compounds.[3-8] γ-Amino butyric acid (GABA) plays an important role as an inhibitory neurotransmitter in the central nervous system (CNS) of mammalians and the deficiency of GABA is associated with diseases that exhibit neuromuscular dysfunctions such as epilepsy, Huntington's and Parkinson's diseases, etc. Baclofen is a lipophilic analogue of GABA, and it is widely used as an antispastic agent.[9-12] Although there have been many reports for enantioselective Michael additions with chiral catalysts, including metal-based catalysts and multimetallic catalysts as well as organic catalysts, practical Michael additions of 1,3-dicarbonyl compounds to nitroalkenes remain largely unexplored except for reactions with chiral Mg catalysts and optically active thiourea as efficient catalysts.[13]

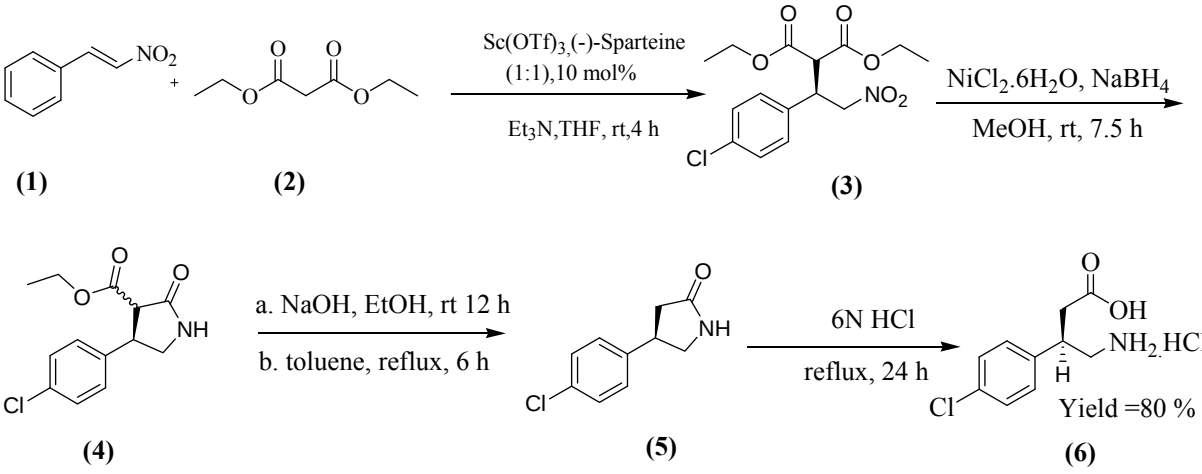


(*R*)-Baclofen

Although Baclofen is commercialized in its racemic form, it has been reported that its biological activity resides exclusively in the (*R*)-enantiomer.[15] We next applied enantioselective Michael addition reaction for the synthesis of (*R*)-(-)-Baclofen.[16-18]

Result and Discussion:

Strategy for asymmetric synthesis of (*R*)-(-)-Baclofen is as represented in the following **Scheme 1**. Herein, we made use of asymmetric Michael addition of diethyl malonate to 4-Chlorobenzaldehyde in the presence of Scandium triflate and spartiene as organocatalyst in dry THF. The reaction was stirred for 7h for formation of product **(3)**. The Michael adduct **(3)** was characterized by the spectroscopic method by ^{1}H NMR it shows the benzylic proton of CH resonate at δ 4.21-4.26 as multiplate and merged in quartet of CH_2 of diethyl malonate and other peak belong to doublet of -CH_2 NO_2 which resonate at δ 3.77 and remaining signals belong to aromatic proton. Its ^{13}C NMR spectrum showed carbon signal at δ 77.00, 54.24, and 41.89 corresponding to benzylic CH and homobenzylic CH_2 of nitrostyrene, another homobenzylic CH of malonate. Its molecular mass was confirmed by LC MASS at 366.1687 (M^++Na).



SCHEME 1

The Michael adducts containing nitro group **(3)** is reduced with sodium borohydride with catalytic $NiCl_2$ in MeOH at room temperature. It result in the formation of intermediate amine which subsequently cyclise to generate lactonamide **(4)**. It confirmed by appearance of δ 3.36-3.47, 3.51-3.57 for 2H of -CH_2NO_2 and Benzylic CH resonate multiplate at δ 4.10-4.14 the remaining proton belong to the aromatic group. The absence of one of the ethyl ester clearly indicates the formation of lactonamide **(4)**. Its ^{13}C NMR spectrum also indicated the overall downfield shift of the carbon signals. To the solution of compound **(4)** in EtOH was added 1N NaOH at room temperature and the product was extracted with $CHCl_3$. The formed intermediate was refluxed with toluene until disappearance of starting material, approximately 6h required to complete the decarboxylation. The formed compound **(5)** was characterized by the ^{1}H NMR in which the homobenzylic proton resonate at δ 3.28-3.36 as quintet, while in the CH_2CO

the two proton gives signal at different position as doublet of doublet at δ 3.58-3.69 and 3.73-3.77 respectively. The aromatic proton resonates at δ 7.09-77.15 and 7.21-7.25 as doublet confirming the formation of compound and in its ^{13}C NMR the benzylic CH gives peak at δ 37.85. The compound **(5)** was finally hydrolyzed with 6N HCl affording enantiomerically pure (*R*)-(-)-Baclofen **(6)** as its hydrochloric Salt.[19]

Conclusion

In conclusion, we have prepared novel organocatalysts as (-)-spartiene and $Sc(OTf)_3$ complex. The catalyst found useful for the Michael addition reaction. Using this we succeed in the total synthesis of (*R*)-(-)-Baclofen with a simple and mild procedure.

Acknowledgements

Authors are thankful to Department of Chemistry, University of Pune) for financial support and infrastructural facility and Mahendra Lokhande is thankful to Principal, MNG science college, Bhabhulgaon.

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[19] Experimental Section: (R)-4-amino-3-(4-chlorophenyl)butanoic acid hydrochloride (6) :The solution of (5) (107 mg, 0.55 mmol) in 6N HCl (2.7 mL) was refluxed at 100 °C. After 24 h, the reaction mixture was concentrated in vacuo to afford (R)-(–)-Baclofen (129 mg, 94%) as colorless solid. M.P. : 188-189°C [α]D25 = –3.68o (c 0.65, H2O), lit.–3.7o (c 0.65, H2O, 99 % ee) 1H-NMR (300MHz, D2O) : δ. 2.73-2.82 (dd, 1H, J = 9.5, 16.5 Hz), 2.85-2.91 (dd, 1H, J = 5.5, 16.2 Hz), 2.92-2.94 (m, 1H), 3.24-3.48 (m, 1H), 7.36-7.49 (m, 4H). 13C-NMR (75 MHz, D2O) : δ 175.44, 138.28, 136.95, 133.32, 129.37, 128.26, 127.82, 43.77, 39.90, 38.18.