Synthesis of (-) Baclofen as a Neurotransmitter Inhibitor

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Abstract

Here, we reports enantioselective Michael additions reaction of diethyl malonate with substituted styrene. The yield ranges from 80-65% having enantioselectivity 80-95%. The present strategy useful for the synthesis (-)-Baclofen. Starting from commercially available 4-chlorobenzaldehyde.

Keywords: Michael reaction, Organocatalyst, Nucleophilic addition.

Introduction

The Michael reaction is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbon compound. There have been many reports on enantioselective Michael additions of 2 using chiral catalysts which include Czekelius et.al developed the chiral C₂-symmetric 1, 2-diamine based 1,1'-bi(tetrahydroisoquinoline) Ni (II)-catalyst¹ and (HB)-donor catalysts that bear a 2-aminoquinazolin-4-(1H)-one or a 3-aminobenzothiadiazine-1,1'-dioxide,² thiourea as catalyst³. An azetidinic diamine derived from (-)-ephedrine and derivatized as a thiourea⁴. Chiral trans-cyclohexanediamine-benzimidazole organocatalyst⁵, chiral Ni(II) complex Ni(II)-bis[(R,R)-N,N'-dibenzylycyclohexane-1,2-diamine]Br₂⁶ Bis-(3,5-dimethylphenyl) ((S)-pyrrolidin-2-yl)methanol⁷.

Materials and Methods

(R)-diethyl 2-(1-(4-chlorophenyl)-2-nitroethyl) malonate (3): In two neck round bottom flask was charged with a mixture of Sc(OTf)₃ (133mg, 10 mol%) and (-)–Spartiene (0.062 mL, 10 mol%) in dry THF 5mL was added diethyl malonate (0.523g, 3.26 mmol) followed by addition of Et₃N (0.194 mL, 2.72 mmol). The reaction mixture was stirred for 5 min at rt. Nitrostyrene (0.5 g, 2.72 mmol) in THF was added slowly and reaction stirred (Approx. 4 h) until starting material was totally consumed. Evaporate solvent to dryness, add et al. and Milind D.Nikalje²

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(R)-4-(4-chlorophenyl) pyrrolidin-2-one (5): To the solution of (4) (240 mg, 0.90 mmol) in EtOH (3.6 ml) was added 1N HCl and the aqueous phase was extracted with CHCl₃. The extract was dried over MgSO₄, filtrated and concentrated in vacuo to afford corresponding carboxylic acid (194 mg, 90%). The solution of carboxylic acid (194 mg, 0.81 mmol) in dry THF was added slowly and reaction stirred (Approx. 4 h) until starting material was totally consumed. Evaporate solvent to dryness, add ethyl acetate and transfer to separatory funnel and washed with dil.HCl. Separate the organic layer and dried over sodium sulphate. Filter and concentrate on rotary evaporator to dryness and purified by silica gel column chromatography with hexane/EtOAc (85:15 %) to afford desired product (702 mg, 75 %).

(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 (6).

![Scheme 1](image-url)

**Scheme 1**

Michael Reaction
Results and Discussion

In the sequence of addition of reaction the (-)-spartiene and Sc(OTf)₃ was stirred in dry THF under nitrogen atmosphere which on addition of diethyl malonate followed by addition of Et₃N. The reaction mixture was stirred for 5 min and nitrostyrene in THF was added. The reaction mixture was stirred until starting material was disappeared. This was done after initial designing the reaction of malonate addition on nitrostyrene after optimized reaction and reagent at different condition. It is found that loading of spartiene and (Sc(OTf)₃) 10 mol % in 1:1 is sufficient for the reaction after performing study at 2 equivalent to 5 mol % of spartiene as well Sc(OTf)₃. Coming to the solvent effect used for the reaction we tried number of solvent including CH₂Cl₂, CHCl₃, CCl₄, Toleuene, CH₂Cl₂, Xylene, THF in which THF is found to be suitable solvent for the reaction for getting good yield.

Table-1

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction Time</th>
<th>Yield</th>
<th>Selectivity Ee in %</th>
<th>Sp. Optical Rotation ($c=1,\text{CHCl}_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>Nitrostyrene</td>
<td><img src="image" alt="Nitrostyrene" /></td>
<td>3h</td>
<td>80</td>
<td>70</td>
<td>$[\alpha]^{25}_{D} = -12.8$</td>
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<tr>
<td>2)</td>
<td>4-Chloronitrostyrene</td>
<td><img src="image" alt="4-Chloronitrostyrene" /></td>
<td>4h</td>
<td>75</td>
<td>78</td>
<td>$[\alpha]^{25}_{D} = -7.3$</td>
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<tr>
<td>3)</td>
<td>4-Nitro nitrostyrene</td>
<td><img src="image" alt="4-Nitro nitrostyrene" /></td>
<td>3h</td>
<td>88</td>
<td>72</td>
<td>$[\alpha]^{25}_{D} = -9.10$</td>
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<tr>
<td>4)</td>
<td>2-Nitrobenzaldehyde</td>
<td><img src="image" alt="2-Nitrobenzaldehyde" /></td>
<td>4h</td>
<td>82</td>
<td>75</td>
<td>$[\alpha]^{25}_{D} = -3.6$</td>
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<tr>
<td>5)</td>
<td>3-Nitrobenzaldehyde</td>
<td><img src="image" alt="3-Nitrobenzaldehyde" /></td>
<td>5h</td>
<td>78</td>
<td>70</td>
<td>$[\alpha]^{25}_{D} = -8.87$</td>
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<td>6)</td>
<td>4-Methoxybenzaldehyde</td>
<td><img src="image" alt="4-Methoxybenzaldehyde" /></td>
<td>12h</td>
<td>68</td>
<td>62</td>
<td>$[\alpha]^{25}_{D} = -6.2$</td>
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<td>7)</td>
<td>3-Methoxybenzaldehyde</td>
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<td>8h</td>
<td>70</td>
<td>60</td>
<td>$[\alpha]^{25}_{D} = -6.7$</td>
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<td>8)</td>
<td>2-Chlorobenzaldehyde</td>
<td><img src="image" alt="2-Chlorobenzaldehyde" /></td>
<td>8h</td>
<td>70</td>
<td>78</td>
<td>$[\alpha]^{25}_{D} = -4.8$</td>
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<tr>
<td>9)</td>
<td>Furan-2-carbaldehyde</td>
<td><img src="image" alt="Furan-2-carbaldehyde" /></td>
<td>4h</td>
<td>85</td>
<td>80</td>
<td>$[\alpha]^{25}_{D} = -3.8$</td>
</tr>
<tr>
<td>10)</td>
<td>4-Bromobenzaldehyde</td>
<td><img src="image" alt="4-Bromobenzaldehyde" /></td>
<td>10h</td>
<td>70</td>
<td>66</td>
<td>$[\alpha]^{25}_{D} = -6.7$</td>
</tr>
</tbody>
</table>
In case of introduction of different substitution on aromatic ring, the electron withstanding accelerate the fast rate of reaction while electron donating group decreases the rate of reaction and took longer reaction time with low enantiomeric excess. Notably, high enantioselectivity was also observed in the reaction with substrate incorporating heteroaromatic nitrostyrenes as well good yield.

For instance we found that the all dialkyl malonate was not uniquely effective Michael donor. In case of dimethyl malonate it shows the good yield as well less time to complete the reaction but introduction of chirality is observed very less. While stericly hindered malonate found to enhance the enantioselectivity of product but take more time to complete the reaction.

The spectroscopic data proved the formation of Michael reactions product. In the $^1$H NMR of compound 3 having electron withdrawing group in which -CH$_2$NO$_2$ resonate at the downfield region at $\delta$. 4.87 (m), while CH of diethyl malonate resonate upfield region at 6.38 (d) having coupling constant is $J = 9.3$ Hz. Remaining proton belongs to the aromatic and aliphatic region confirmed the formation of product 3.$^9$ In $^{13}$C-NMR spectroscopy the downfield carbon of CH$_2$NO$_2$ is found at $\delta$. 77.59 which merged in CDCl$_3$ peak. Benzylic carbon showed the upfield region at $\delta$.42.90, while diasteric methylene CH shows at $\delta$. 61.83.

The mass spectra found 310 (M$^+$+1), which confirmed the formation of product 3. We utilized this methodology for the synthesis of (R)-(−)-Baclofen molecule. Strategy for asymmetric synthesis of (R)-(−)-Baclofen is as represented in the Scheme-2. Herein, we made use of asymmetric Michael addition of diethyl malonate to 4-Chlorobenzaldehyde in the presence of Scandium triflate and sparteine as organocatalyst in dry THF.$^{10}$ The reaction was stirred for 4h. The Michael adducts and the entire products were characterized by the spectroscopic method. This methodology is useful for the synthesis of baclofen molecule.$^{11,12}$

In conclusion, we have reported an organocatalytic methodology for the Michael addition of malonate esters to β-aryl nitroolefins and synthesis of Baclofen molecule which furnished the products in good yield and moderate enantioselectivity by using of organocatalyst.

**References**


