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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

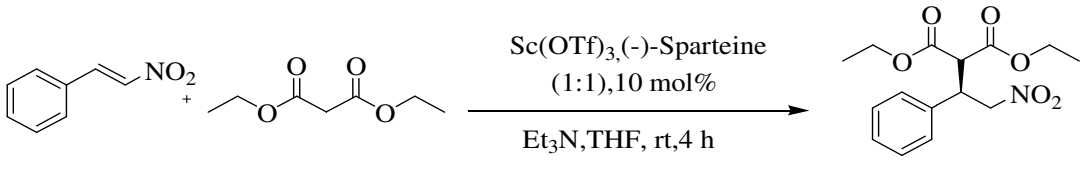
The Michael reaction is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound. There have been many reports on enantioselective Michael additions of **2** using chiral catalysts which include Czekelius *et.al* developed the chiral C_2-symmetric 1, 2-diamine based 1,1'-bi(tetrahydroisoquinoline) Ni (II)-catalyst[1] and (HB)-donor catalysts that bear a 2-aminoquinazolin-4-(1H)-one or a 3-aminobenzothiadiazine-1,1- dioxide,[2] thiourea as catalyst[3], An azetidinic diamine derived from (-)-ephedrine and derivatized as a thiourea[4], Chiral trans-cyclohexanediamine-benzimidazole organocatalyst[5], chiral Ni(II) complex Ni(II)-bis[(R,R)-N,N'-dibenzylcyclohexane-1,2-diamine]Br_2,[6] Bis-(3,5-dimethylphenyl) ((S)-pyrrolidin-2-yl)methanol[7].

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 Et_3N (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 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-(4-chlorophenyl) pyrrolidin-2-one (5): To the solution of **(4)** (240 mg, 0.90 mmol) in EtOH (3.6 ml) was added 1N NaOH (1.1 mL) at rt. After 30 min, the reaction mixture was concentrated in vacuo. To the residue was added H_2O and 5N HCl and the aqueous phase was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, filtrated and concentrated in vacuo to afford corresponding carboxylic acid (194 mg, 90%). The solution of carboxylic acid (194 mg, 0.81 mmol) in toluene (11 mL) was refluxed at 140°C. After 6 h, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (MeOH/$CHCl_3$ = 10/90) to afford desired product **(5)** (148 mg, 93%) as colorless needle.

(*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)**.



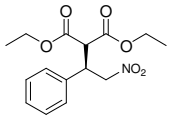
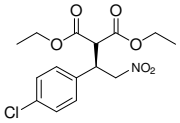
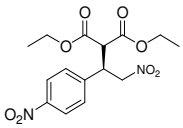
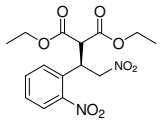
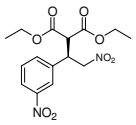
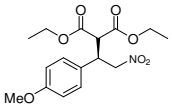
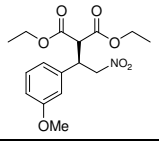
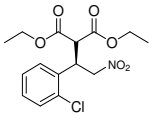
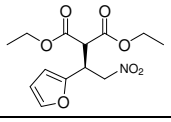
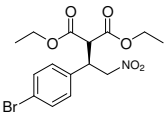
(1) **(2)** Yield =80 % **(3)**

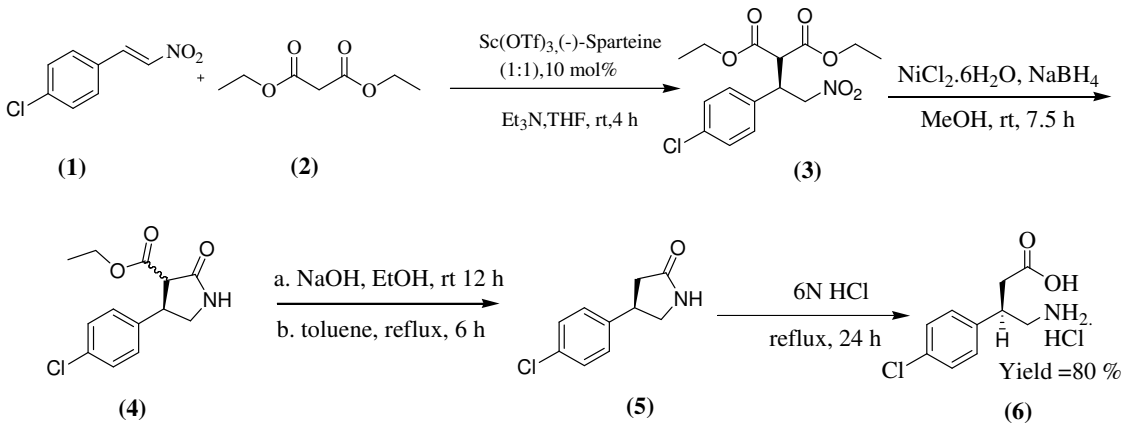
Scheme-1
Michael Reaction

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 Et_3N. 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 CH_2Cl_2, $CHCl_3$, CCl_4, Toleuene, CH_2Cl_2, Xylene, THF in which THF is found to be suitable solvent for the reaction for getting good yield[8].

Table-1
Effect of various substituted Nitrostyrene

Sr No	Substrate	Product	Reaction Time	Yield	Selectivity Ee in %	Sp. Optical Rotation (*c*=1,$CHCl_3$)
1)	Nitrostyrene		3h	80	70	$[\alpha]^{25}_D$ = -12.8
2)	4-Chloronitrostyrene		4h	75	78	$[\alpha]^{25}_D$ = - 7.3
3)	4-Nitro nitrostyrene		3h	88	72	$[\alpha]^{25}_D$ =- 9.10
4)	2-Nitrobenzaldehyde		4h	82	75	$[\alpha]^{25}_D$ = - 3.6
5)	3-Nitrobenzaldehyde		5h	78	70	$[\alpha]^{25}_D$ = -8.87
6)	4-Methoxybenzaldehyde		12h	68	62	$[\alpha]^{25}_D$ = - 6.2
7)	3-Methoxybenzaldehyde		8h	70	60	$[\alpha]^{25}_D$ = - 6.7
8)	2-Chlorobenzaldehyde		8h	70	78	$[\alpha]^{25}_D$ = - 4.8
9)	Furan-2-carbaldehyde		4h	85	80	$[\alpha]^{25}_D$ = - 3.8
10)	4-Bromobenzaldehyde		10h	70	66	$[\alpha]^{25}_D$ = - 6.7



Scheme-2
Strategy for asymmetric synthesis of (*R*)-(-)-Baclofen

In case of introduction of different substitution on aromatic ring, the electron withdrawing 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 sterically 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_2NO_2 resonate at the downfield region at δ. 4.87 (m), while CH of diethyl malonate resonate upfield region at δ.3.81 (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_2NO_2 is found at δ. 77.59 which merged in $CDCl_3$ peak. Benzylic carbon showed the upfield region at δ.42.90, while diasteric methylene CH shows at δ. 61.83.

The mass spectra found 310 (M^++1), which confirmed the formation of product **3**. We utilized this methodology for the synthesis of (-)-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 spartiene 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].

Conclusion

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.

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