EFFICIENT SYNTHESIS OF BAYLIS-HILLMAN ADDUCTS AND DERIVATIVES

C.Kokila
Department of Chemistry,
Prince Shri Venkateswara Padmavathy Engineering College,
Ponmar
Chennai-600127
e.mail: kokila0216@gmail.com

M.Arun Kumar
Department of Chemistry,
Loyala Institute Of Technology,
Palanchur,
Chennai-600123
e.mail: arunkumarchem18@gmail.com

Abstract

An improvement in the rates **of** Baylis-Hillman adducts which are allylic alcohol derivatives, can be formed most often by the reaction of activated olefins and carbonyl compounds. The reactions proceeded expediently at 0°C under catalysis by 1,4-diazabicyclo[2,2,2]octane (DABCO)to afford the desired adducts.

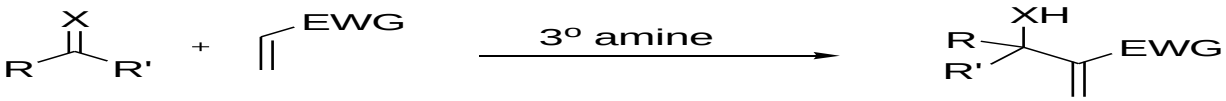
The optimized conditions are indicative of the presence of the more ordered transition states involved in these reactions, Supporting the previously suggested mechanism for similar reactions.

Keywords: Activated Olefins , Carbonyl Compounds,DABCO

Introduction

The Baylis-Hillman reaction is one of the most powerful carbon-carbon bond forming methods in organic synthesis. The Baylis-Hillman adducts which are allylic alcohol derivatives, can be formed most often by the reaction of activated olefins and carbonyl compounds. The Baylis-Hillman adducts have been widely used as intermediates for the synthesis of some useful compounds which have both synthetic and biological applications.

This is basically a three component reaction, involving activated alkene, carbon electrophile and tertiary amine as a catalyst leading to the formation of carbon-carbon bond between the position of the activated alkene and carbon electrophile thus providing densely functionalized molecule.



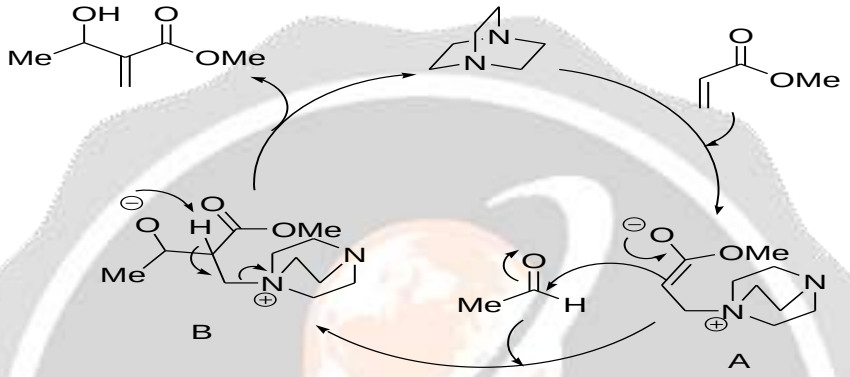
X = O, NR_2; EWG = electron withdrawing group

Mechanism of Baylis-Hillman Reaction:

Mechanism of this reaction is believed to proceed through the Michael-initiated addition-elimination sequence. The most generally accepted mechanism of the amine-catalyzed reaction is illustrated in Scheme 1, taking the reaction between methyl acrylate (as an activated olefin) and benzaldehyde (as an electrophile) under the catalytic influence of DABCO as a model case.

The first step in this catalytic cycle involves the Michael-type nucleophilic addition of the tertiary amine to the activated alkene (Methyl acrylate) to produce a zwitterionic enolate **A**, which makes a nucleophilic attack on the aldehyde in an aldol fashion to generate zwitterionic enolate **B**. Subsequent proton migration and release of the catalyst provide the desired multifunctional molecules as shown in scheme1.

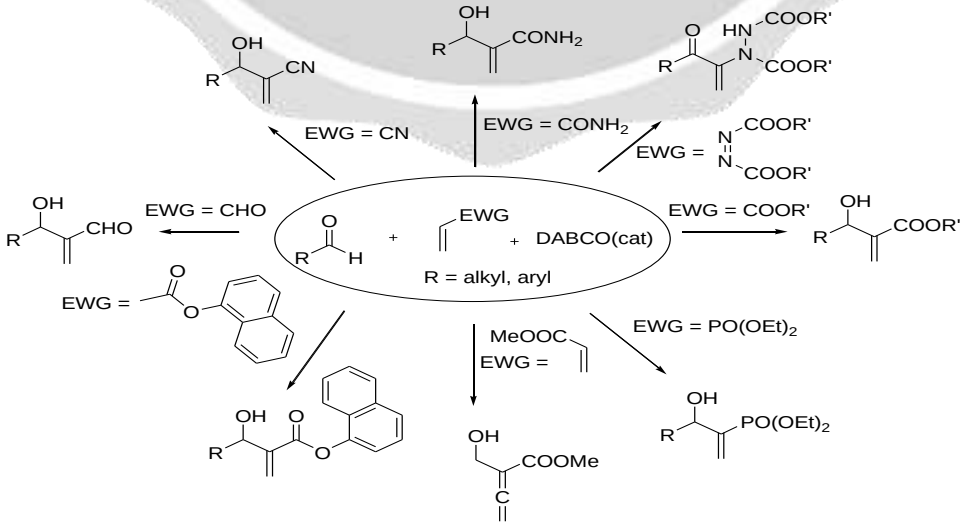
Scheme 1



Essential Components

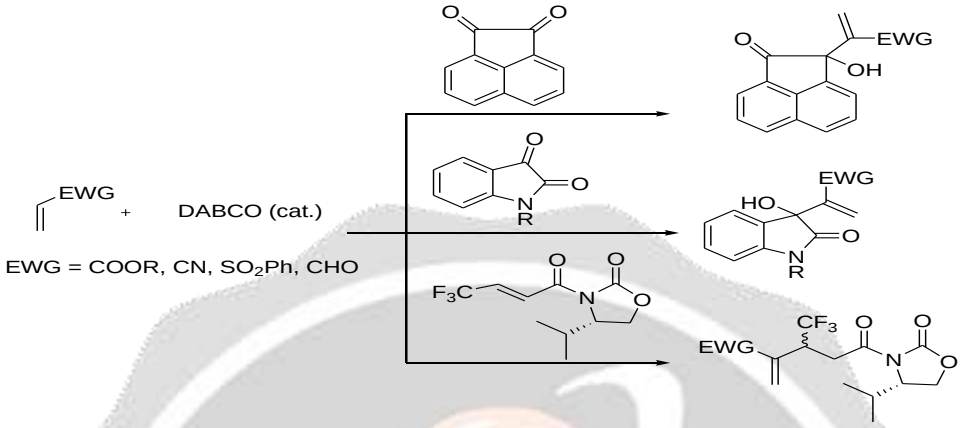
During the past 15 years, the Baylis-Hillman reaction has seen exponential growth in terms of all the three essential components. Thus a variety of activated alkenes such as acrylic ester, acrylonitrile, vinyl ketone, phenyl vinyl sulfone, phenyl vinyl sulfonate, vinyl phosphonate, allenic ester and acrolein have been employed as shown in Scheme 2.

Scheme 2



In the electrophile component, variety of aldehydes such as aliphatic, aromatic, heteroaromatic, α, β-unsaturated aldehydes, *para* formaldehyde (formalin) and functionalized aldehydes, ketones, ketoesters, aldimines, non-enolizable ketones have been employed in the Baylis-Hillman reaction (Scheme 3).

Scheme 3



A variety of tertiary amines such as diazabicyclo-(2,2,2)-octane (DABCO) (**1)**, diazabicycloundecane (DBU) (**2)**, indolizine (**3)**, quinuclidine (**4)**, 3-hydroxyquinuclidine (**5)**, 3-quinuclidinone (**6)** 4-*N*,*N*-dimethylamino pyridine (4-DMAP) (**7),** Imidazole (**8)**, proline (**9)**, and triethylamine (**10)** have been employed as catalysts in the Baylis-Hillman reaction (figure1). However, DABCO remains to be the catalyst of choice for organic chemists.

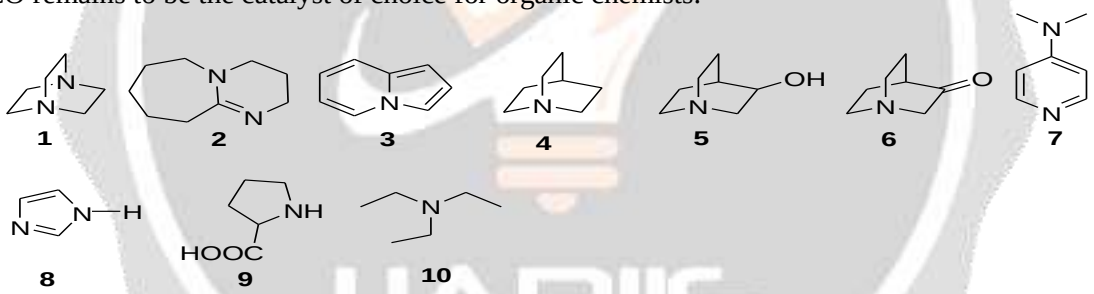


Figure 1

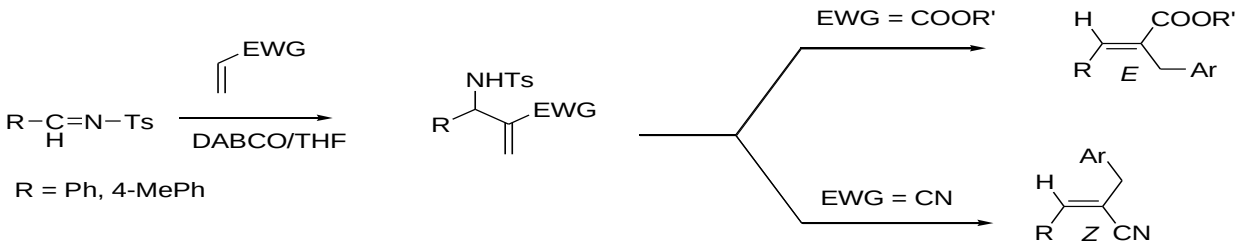
Applications of Baylis-Hillman Reactions

Several efforts have already been meticulously and articulately made in the direction leading to the development of facile and simple methodologies for a variety of organic transformations involving high levels of stereoselectivities.

Friedel-Crafts Reaction

The utility of acetates of the Baylis-Hillman adducts as novel stereodefined electrophiles in the Friedel-crafts reaction has been well demonstrated [8].(Scheme 4)

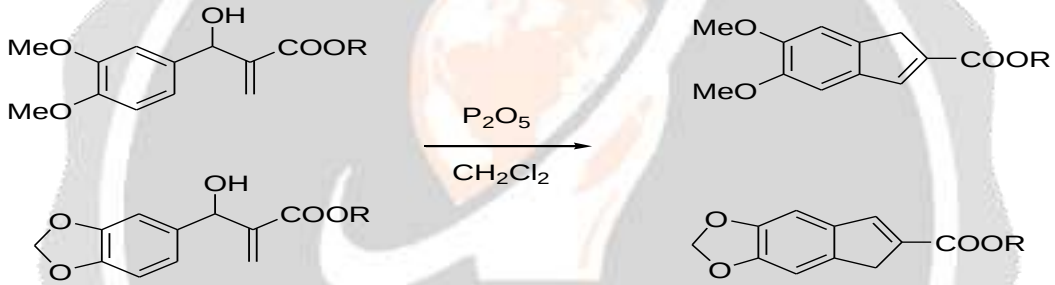
Scheme 4



Intramolecular Friedel-Crafts Reaction

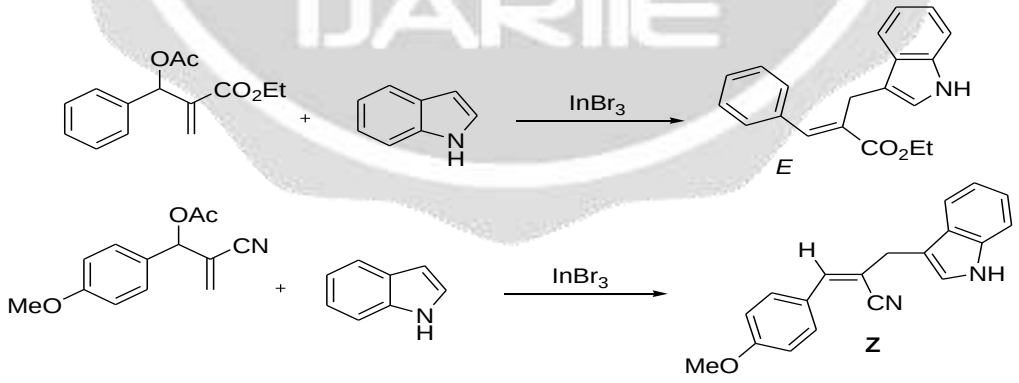
The intramolecular Friedel-Crafts reaction of the Baylis-Hillman adducts using P_2O_5 leading to the formation of functionalized indene derivatives have been reported recently[9]. However, the reaction was limited to the Baylis-Hillman adducts derived from benzaldehyde with electron donating substitutent (Scheme 5).

Scheme 5

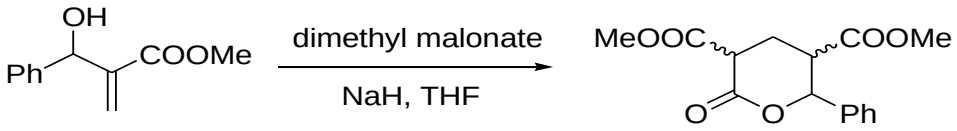


J.S.Yadav *et al* [10]successfully developed a first example of the C-alkylation of indoles with Baylis-Hillman acetates and using $InBr_3$ as a catalyst (Scheme 6).

Scheme 6

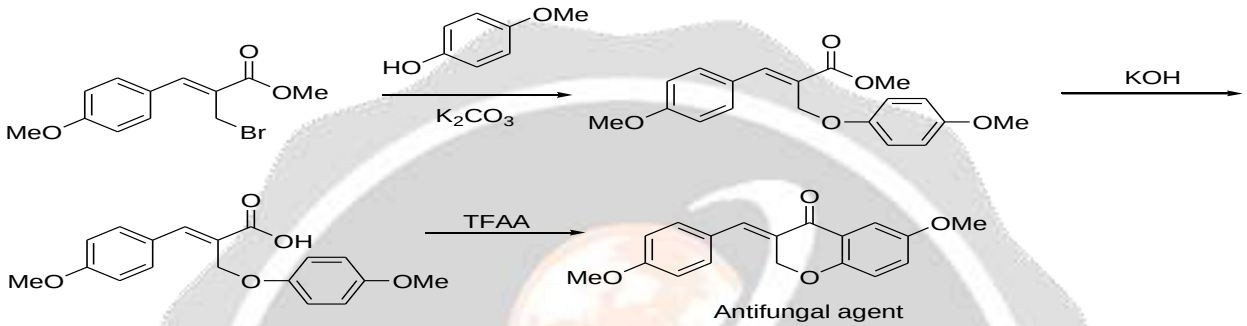


Foucaud *et al* [11] reported the synthesis of *γ*-butyro lactones in the reaction of the Baylis-Hillman adduct with stabilized carbanion derived from dimethyl malonate in THF using NaH.



Some of the cyclic compounds prepared from Baylis-Hillman adducts are used as drugs. For example, recently Basavaiah *et al*[14] have reported the synthesis of (*E*)-3-(4-methoxybenzylidene)-6-methoxychroman-4-one, an antifungal agent in very good yield according to scheme 7.

Scheme 7



Similarly Basavaiah *et al* [15] also developed a novel protocol for the synthesis of (*E*) -2-arylideneindan-1-ones *via* Friedel-Crafts alkylation and Friedel-Crafts acylation reaction led to cylisation product (Scheme 8).

Scheme 8

EXPERIMENTAL WORK

PREPARATION OF METHYL-2-(HYDROXY (PHENYL) METHYL) ACRYLATE

REACTION:

CHEMICALS REQUIRED:

- BENZALDEHYDE.
- METHYLACRYLATE.
- DABCO

PROCEDURE:

A mixture of benzaldehyde (1g), methylacrylate (0.96g) and DABCO (0.21g) was kept at room temperature for few days. The reaction mixture was diluted with ethylacetate (100ml) and added 100mlof 2N HCl solution. The organic layer extracted was then washed with water (100ml) aqueous saturated brine solution (75ml) and then dried over anhydrous Na_2SO_4. The solvent was then evaporated. The crude product thus obtained was purified by column chromatography (silica gel in 2% of ethyl acetate in hexane) to provide the desired methyl-2-(hydroxy(phenyl)methyl)acrylate.

RESULT:

Yield = 80%

IR = 3475, 1703, 1623, 1439, 1149

^{1}H NMR (300 MHz): δ 3.65 (s, 3H), 5.50 (s, 1H), 5.83 (s, 1H), 6.29 (s, 1H), 7.24-7.35 (m, 5H).

PREPARATION OF METHYL-2-(HYDROXY-(*o*-TOLYL) METHYLACRYLATE

REACTION:

CHEMICALS REQUIRED:

- 2-METHYLBENZALDEHYDE.

- METHYLACRYLATE
- DABCO.

PROCEDURE:

A mixture of 2-methylbenzaldehye (1g), methylacrylate (0.84 g) and DABCO (o.18g) was kept at room temperature for few days. The reaction mixture was then diluted with ethylacetate (100ml) and added 100ml of 2N HCl solution, washed with water (100ml) and aqueous saturated brine solution (75ml). The organic layer extracted was then dried over anhydrous Na_2SO_4. The crude product thus obtained was purified by column chromatography (silica gel in 2% of ethyl acetate in hexane) to provide the desired, methyl-2-(hydroxy-(*o*-tolyl)methylacrylate.

RESULT:

Yield = 68%

PREPARATION OF METHYL-2-(HYDROXY-(p-TOLYL) METHYL) ACRYLATE

REACTION:

CHEMICALS REQUIRED:

- 4-METHYLBENZALDEHYDE.
- METHYLACRYLATE.
- DABCO.

PROCEDURE:

A mixture of 4- methylbenzaldehyde (1g), methylacrlate (0.84g) and DABCO (0.18g) was kept at room temperature for few days. The reaction mixture was then dilutee with ethylacetate (100ml) and added 100ml of 2N HCl solution, washed with water (100ml) and aqueous saturated brine solution (75ml). The organic layer extracted was them dried over anhydrous Na_2SO_4. The solvent was then evaporated. The crude product thus obtained was purified by column chromatography (silica gel in 2% of ethyl acetate in hexane) to provide the desired alcohol, methyl-2-(hydroxyl-p-tolyl)methylacrylate.

RESULT:

Yield = 70%

PREPARATION OF METHYL-2-((4-ETHYLPHENYL)(HYDROXY)METHYL) ACRYLATE

REACTION:

CHEMICALS REQUIRED:

- 4ETHYLBENZALDEHYDE.
- METHYLACRYLATE.
- DABCO.

PROCEDURE:

A mixture of 4-ethylbenzaldehyde (1g), methylacrylate (0.76g) and DABCO (0.16g) was kept at room temperature for few days. The reaction mixture was then diluted with ethylacetate (100ml) and added 100ml of 2N HCl solution washed with water (100ml) and aqueous saturated brine solution (75ml). The organic layer extracted was then dried over anhydrous Na_2SO_4. The solvent was then evaporated. The crude product thus obtained was purified by column chromatography (silica gel in 2% of ethyl acetate in hexane) to provide the desired 2-((4-ethylphenyl)(hydroxy)methyl)acrylate.

RESULT:

Yield = 75%

PREPARATION OF (Z)-METHYL-2-(BROMOMETHYL)-3-PHENYLACRYLATE

REACTION:

CHEMICALS REQUIRED:

- METHYL-2-(HYDROXY(PHENYL)METHYL)ACRYLATE

- CONC. H_2SO_4
- HYDROBROMIC ACID
- DICHLOROMETHANE

PROCEDURE:

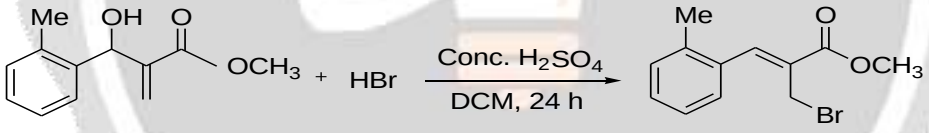
A stirred solution of methyl 3-hydroxy-2-methylene-3-phenyl propanoate (10 mmol, 1.92g) in DCM (15 ml) was added hydrobromic acid (15 mmol, 3 ml) followed by dropwise addition of Conc. H_2SO_4 (0.2ml). After stirring overnight at room temperature, the reaction mixture was poured into ice cold water and then extracted with ethylacetate (3×15 ml). The combined organic layer was dried over Na_2SO_4 and then solvent was evaporated. The crude product thus obtained was purified by Column Chromatography (silica gel, 2% ethylacetate in hexane) to provide (Z)-methyl-2-(bromomethyl)-3-phenylacrylate.

RESULT:

Yield = 2.32g (91%)

PREPARATION OF (Z)-METHYL-2-(BROMOMETHYL)-3-o-TOLYLACRYLATE

REACTION:



CHEMICALS REQUIRED:

- METHYL 2-(HYDROXY(o-TOLYL)) METHYL ACRYLATE
- CONC. H_2SO_4
- HYDROBROMIC ACID
- DICHLOROMETHANE

PROCEDURE:

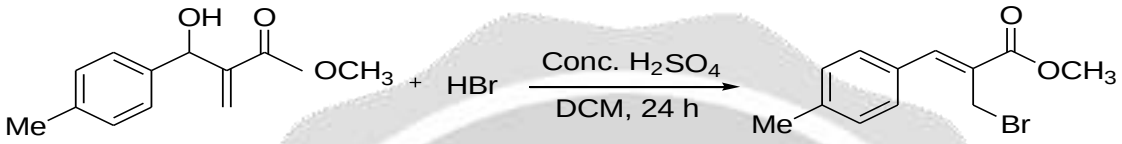
A stirred solution of methyl-2-(hydroxyl(o-tolyl))methylacrylate (10 mmol, 2.06g) in DCM (15 ml) was added hydrobromic acid (15 mmol, 3 ml) followedby dropwise addition of Conc. H_2SO_4 (0.2ml). After stirring overnight at room temperature, the reaction mixture was poured into ice cold water and then extracted with ethylacetate (3×15 ml). The combined organic layer was dried over Na_2SO_4 and then solvent was evaporated. The crude product thus obtained was purified by Column Chromatography (silica gel, 2% ethylacetate in hexane) to
Provide (Z)-methyl-2-(bromomethyl)-3-o-tolylacrylate.

RESULT:

Yield = 2.37g (86%)

PREPARATION OF (Z)-METHYL-2-(BROMOMETHYL)-3-p-TOLYLACRYLATE

REACTION:



CHEMICALS REQUIRED:

- METHYL2-(HYDROXY(p-TOLYL))METHYLACRYLATE
- CONC. H_2SO_4
- HYDROBROMIC ACID
- DICHLOROMETHANE

PROCEDURE:

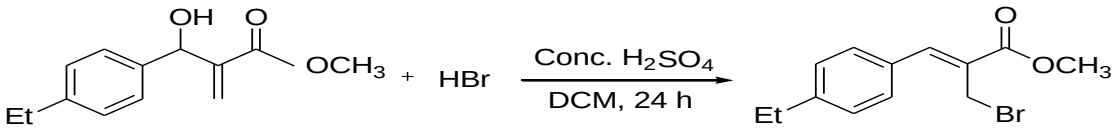
A stirred solution of methyl-2-(hydroxyl(p-tolyl))methylacrylate (10 mmol, 2.06g) in DCM (15 ml) was added hydrobromic acid (15 mmol, 3 ml) followedby dropwise addition of Conc. H_2SO_4 (0.2ml). After stirring overnight at room temperature, the reaction mixture was poured into ice cold water and then extracted with ethylacetate (3×15 ml). The combined organic layer was dried over Na_2SO_4 and then solvent was evaporated. The crude product thus obtained was purified by Column Chromatography (silica gel, 2% ethylacetate in hexane) to provide (Z)-methyl-2-(bromomethyl)-3-p-tolylacrylate.

RESULT:

Yield = 2.30g (86%)

PREPARATION OF (Z)-METHYL-2-(BROMOMETHYL)-3-(4-ETHYLPHENYL) ACRYLATE

REACTION:



CHEMICALS REQUIRED:

- METHYL-2-((4ETHYLPHENYL(HYDROXY))METHYLACRYLATE
- CONC. H_2SO_4
- HYDROBROMIC ACID
- DICHLOROMETHANE

PROCEDURE:

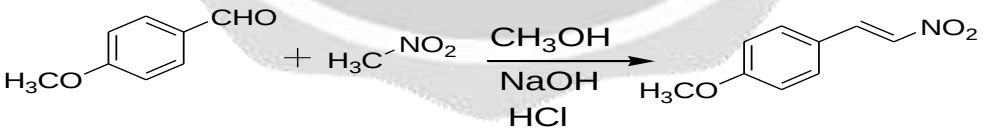
A stirred solution of methyl-2-((4-ethylphenyl)(hydroxyl))methylacrylate (10 mmol, 2.20g) in DCM (15 ml) was added hydrobromic acid (15 mmol, 3 ml) followed by dropwise addition of Conc. H_2SO_4 (0.2ml). After stirring overnight at room temperature, the reaction mixture was poured into ice cold water and then extracted with ethylacetate (3×15 ml). The combined organic layer was dried over Na_2SO_4 and then solvent was evaporated. The crude product thus obtained was purified by Column Chromatography (silica gel, 2% ethylacetate in hexane) (Z)-methyl-2-(bromomethyl)-3-(4-ethylphenyl)acrylate.

RESULT:

Yield = 2.35g (83%)

PREPARATION OF p-METHOXY NITROSTYRENE

REACTION:



CHEMICALS REQUIRED:

- P-methoxybenaldehyde
- Nitromethane
- Methanol
- Sodiumhydroxide
- Hydrochloric acid

PROCDURE:

To a solution of nitromethane (4.48ml) and p-methoxybenzaldeyde (10ml) in methanol (5ml) added a solution of sodium hydroxide (3g in 10ml water) with vigorous stirring. After 30 minutes of stirring the reaction mixture was acidified with dil HCl resulting in a pale yellow precipitate, which was filtered and dried. The crude p-methoxy nitrostryene was recrystallised with ethylacetate and hexane solvent to provide pale yellow crystalline solid.

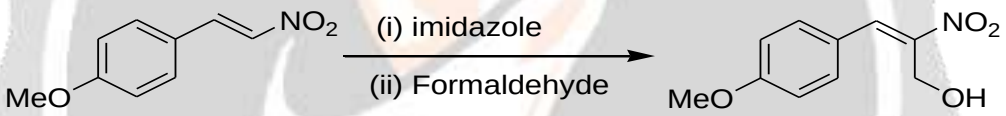
RESULT:

Yield = 5.2g

IR = 1608, 1508, 1426, 1310, 1252

PREPARATION OF (*E*)-3-(4-METHOXYPHENYL)-2-NITROPROP-2-EN-1-OL

REACTION:



CHEMICALS REQUIRED:

THF

PROCEDURE:

Stirred solution of nitroalkene (1mmol) in THF (2ml) at room temperature was added imidazole (68mg, 1equiv) followed by 38% aqueous formaldehyde (2ml, more). After completion of the reaction (confirmed by TLC analysis), the reaction mixture was acidified with 5N HCL (5ml) and the aqueous layer was extracted with ethyl acetate (3x10ml). The combined organic layers were washed with brine (10ml), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with EtOAC-Hexane (0-25%, gradient elution) to afford pure.

RESULT:

Yield = 71%

CONCLUSION

Within the short span of time I have learned various techniques like TLC, Column chromatography, Solvent purification, work-up procedures and conducting reaction. After learning the above said skills I have prepared variety of Baylis-Hillman Adducts and its derivatives using various aldehydes with different types of activated olefins

I also characterized the Baylis-Hillman adduct by IR and ^{1}H NMR. Hence I have successfully prepared variety of Baylis-Hillman Adducts which is potential starting materials for variety of organic transformations

REFERENCES

1) Baylis, A. B.; Hillman, M. E. D. *German Patent*,**1972**, 2155113; *Chem. Abstr*. **1972**, … *77*, 34174q.
2) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
3) Basavaiah, D.; Dharma Rao, P; Suguna Hyma, R. *Tetrahedron*, **1996**, 52, 8001.
4) Ciganek, E. Organic Reactions, Paquette, L.A. (Editor), John Wiley & Sons, New York, **1997**, 51, pp201.
5) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem.Rev.* **2003**, *103*, 811-891.
6) Kataoka, T.; Iwama, T.; Tsujiyama, S.I. *Chem. Commun*. **1998**, 197.
7) Basavaiah, D.; Pandiaraju, S.; Sarma, P.K.S. *Tetrahedron Lett*. **1994**, *35*, 4227.
8) Lee, H. J.; Seong, M. R.; Kim, J. N. *Tetrahedron Lett*. **1998**, *39*, 6223.
9). Basavaiah, D.; Bakthadoss, M.; Jayapal Reddy, G., *Synthesis* **2001**, *6*, 919
10) Yadav, J. S.; Subba Reddy, B. V.; Basak, A.K.; Narsaiah, A. V.; Prabhakar, A; Jagadeesh, B. *Tetrahedron Lett*. **2005**, *46*, 639.
11) Bauchat, P.; Le Rouille, E,; Foucaud, A. *Bull. Soc. Chim. Fr*. **1991**, *128*, 267.
12) Kumareswaran, R.; Vankar, Y. D. *Synth. Commun.* **1998**, *28*,2291.
13) Yoshimatsu, M.; Timura, Y. *J. Org. Chem.* **2002**, *67*, 5678.
14) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commn*. **1998**, 1639.
15) Basavaiah, D.; Reddy, R. M.; *Tetrahedron Lett*. **2001**, *42*, 3025.