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The Evalution of *Antibacterial* Activity of the (*E*)-(3-Methoxy-2-Nitroprop-1-Enyl)Benzene Compounds

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Abstract : A simple and convenient synthetic route for the synthesis of (*E*)-(3-methoxy-2-nitroprop-1-enyl)benzene using Baylis-Hillman chlorides in presence of potassium carbonate and hydroquinone. Baylis-Hillman adducts derived from aldehydes and nitroethylene except the initial report by Baylis and Hillman. This strategy opens new opportunities for the preparation of libraries of a wide variety of new nitro derivatives for biological screening.
Keywords : Baylis-Hillman reaction; O-alkylation, potassium carbonate, THF, nitro compound and methanol.

Introduction

During the past ten years the Baylis-Hillman reaction has seen enormous growth in terms of the components such as electrophile, activated olefin and catalyst.[1-3] A variety of activated olefins are explored by various research groups, however nitroolefins are not utilized much, as an activated olefinic component. So far there is no report available in the literature for the synthesis of Baylis-Hillman adducts derived from aldehydes and nitroethylene except the initial report by Baylis and Hillman. The reason for the nitroethylene to be unexplored may be due to its relatively more reactivity which would lead to polymerization.

Therefore, we have undertaken a research program for the synthesis and examining the possible applications of the trisubstitutedallyl halides derived from nitroolefins in various organic reactions.[4-6] We envisaged that the chloro derivative of Baylis-Hillman adducts derived from aldehydes and nitroethylene may be very useful starting material for a variety of applications in organic synthesis.[7]Baylis-Hillman adducts and its derived compounds are extensively utilized in the synthesis of biologically active molecules, heterocycles and manynatural products.[8-10] In particular chloro and acetate derivatives of Baylis-Hillman adducts are widely utilized for various organic transformations[11].

Antibacterial activity:

In vitro antibacterial inhibitory activities of the (E)-(3-methoxy-2-nitroprop-1-enyl)benzene compounds were determined by microdilution broth assay method using resazurin as an indicator. Nutrient-broth was used to culture the bacterial strains to a final inoculum size of 5×10^5 CFU/mL. The (*E*)-(3-methoxy-2-nitroprop-1-enyl)benzene compounds were dissolved in DMSO to a concentration of 10 mg/mL. Serially diluted these compounds solutions were added to successive wells in a 96-well microtitre plate and incubated with respective micro-organism for 18 h at 37°C. After the incubation period, 10 µL of 0.01% resazurin solution was added and incubated for 2 h. The color change was assessed visually. Growth of organism changed the color from blue to pink. Growth and sterility controls were also maintained during the experiment. Test compounds serially diluted

with DMSO were also kept in the 96-well microtitre plates (uninoculated dilution) to determine whether they precipitated out during the course of the experiments. One entire column had antibiotics as a positive control (Amphiciline). A blank assay with ethanol alone was taken into account to discount any possible effect of the solvent.

The minimum inhibitory concentration (MIC) of the (*E*)-(3-methoxy-2-nitroprop-1-enyl)benzene compounds were performed by microtitre dilution assay. The optical density was measured at 575 nm for all the tested human pathogenic bacteria. The MIC for all the six compounds was found at 0.625µg/ml against the test organisms. Interestingly, all the newly synthesized (*E*)-(3-methoxy-2-nitroprop-1-enyl)benzenecompounds showed excellent antibacterial activity against the Gram negative organism *E. coli*. Moreover, the methoxy compounds (**1a-f**) moderately inhibited the growth of *P aeruginosa.* Among the ten compounds, **1a, 1b** and **1d** were showed good antibacterial activity against all the test pathogens. (Table 1)

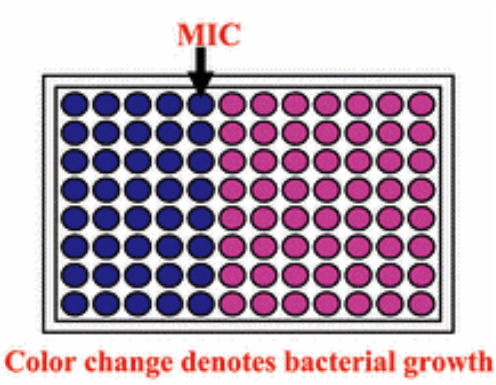
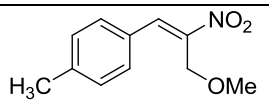
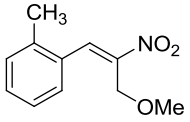
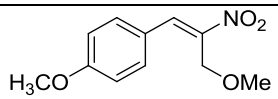
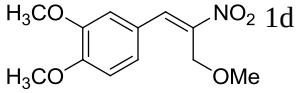


Figure 1. Antibacterial evaluation by two folds dilution method using resazurin dye

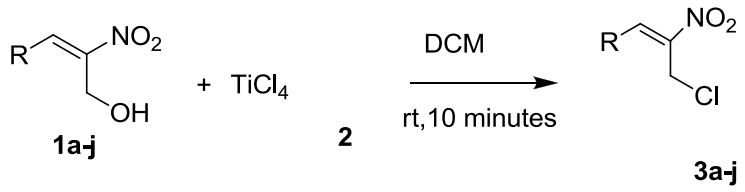
Table 1. Antibacterial activity (Minimum inhibitory concentration µg/ml) of methoxy compounds (in µM):

Entry	(*E*)-(3-methoxy-2-nitroprop-1-enyl)benzene	Antibacterial activity		
		Staphylococcus aureus	***Pseudomonas aeruginosa***	***Escherichia coli***
	Control/DMSO	**0.6731**	**0.8141**	**0.9316**
1	 1a	**0.1870**	**0.6684**	**0.1675**
2	 1b	**0.1551**	**0.6213**	**0.1559**
3	 1c	**0.5815**	**1.1627**	**0.1451**
4	 1d	**1.0916**	**0.2728**	**0.1360**

In the literature survey we found that the tricyclic chromeno [4,3-*b*] pyrrolidine frameworks are known to be non-competitive antagonists of the muscular nicotin receptor.[12] It is well documented in literature that the Baylis-Hillman adducts have been utilized very well for the synthesis of various heterocyclic compounds.[13-21] We envisaged that the *O*-allylicmethoxy derivatives prepared from the Baylis-Hillman Chlorides.

We envisaged that the synthesized compound, namely (*E*)-2-nitro-3-phenylprop-2-en-1-ol (1a), can be conveniently transformed into the corresponding chloro derivative 3a by treatment with chloroneting agents.Accordingly, the Baylis–Hillman adduct 1a, derived from nitroolefin and formaldehyde, was treated with titanium(IV) chloride, dichloromethane as the solvent to yield successfully (*E*)-(3-chloro-2-nitroprop-1-enyl)benzene (3a) in 62% yield according to the scheme 1

Scheme 1



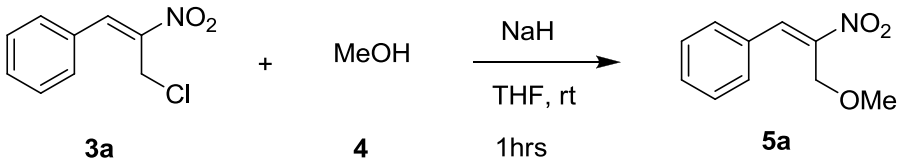
1a-j **2** **3a-j**

R = 2-Me-C_6H_4, 4-Me-C_6H_4, 2-MeO-C_6H_4, 4-MeO-C_6H_4, 3,4-$(MeO)_2$-C_6H_3, 3,4-(OCH_2O)-C_6H_3, 2-Cl-C_6H_4, 3-Cl-C_6H_5, 4-Cl-C_6H_5, 3,4-Cl-C_6H_5

Encouraged by this result, we prepared a variety of Baylis Hillman adducts derived from nitroolefins and successfully converted them into the desired chloro derivatives **3a**–**j** in very good yields.

We decided to synthesize the O-alkylation derivatives from the corresponding Baylis Hillman adducts under mild reaction conditions. The treatment of Baylis–Hillman adduct **3a** with with methanol in the presence of sodium hydride in tetrahydrofuran (THF) at room temperature, over a period of one hours successfully provided the desired (E)-(3-methoxy-2-nitroprop-1-enyl)benzene **5a** in 64% yield according to the scheme 2

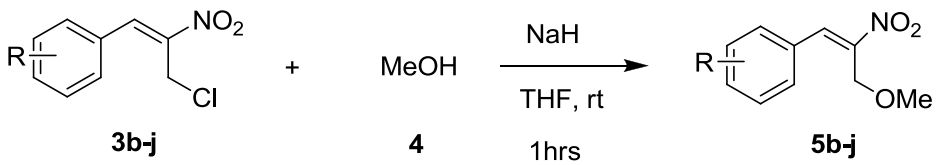
Scheme 2



3a **4** 1hrs **5a**

Encouraged by this results we prepared variety of Baylis-Hillman adducts and successfully transformed them into their corresponding methoxy derivatives **5b-j,** according to scheme 3.

Scheme 3



3b-j **4** 1hrs **5b-j**

Table 1. Synthesis of (E)-(3-methoxy-2-nitroprop-1-enyl)benzene compounds from Baylis-Hillman derivatives

S.No	Allyl Chloride	Methoxy	Yield
3a	C_6H_5	5a	64
3b	2-Me	5b	67
3c	4-Me	5c	62
3d	2-MeO	5d	60
3e	4-MeO	5e	59
3f	3,4-$(MeO)_2$	5f	54
3g	3,4-(OCH_2O)	5g	62
3h	2-Cl	5h	56
3i	3-Cl	5i	52
3j	4-Cl	5j	61

[a]All reactions were carried out with 4 mmol scale of allyl chloride (5a-j), [b]All products gave satisfactory IR, ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), mass spectral data and elemental analyses. [c]Yields of the pure products (5a-j) obtained after column chromatography (silica gel, (5a-j) 5% EtOAc in hexanes,

Typical experimental procedure for the synthesis of(*E*)-2-nitro-3-o-tolylprop-2-en-1-ol(1a)

To a stirred solution of 1-methyl-2-((*E*)-2-nitrovinyl)benzene (1 mmol) in THF (2 mL) at room temperature, was added imidazole (68 mg, 1eq) followed by the addition of DABCO (11.2 mg, 10 mol %) and 38 % aqueous formaldehyde, (2 mL, excess). The reaction mixture was stirred at room temperature for about 24 hours. After completion of the reaction (confirmed by TLC analysis), the reaction mixture was acidified with dill HCl (5 mL). The reaction mixture was diluted with ethyl acetate and the organic layer was extracted (3×10 ml). The combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Then the organic layer was evaporated and crude liquid thus obtained was purified by silica gel column chromatography (eluting with 10 % ethyl acetate in hexanes) to afford pure 1a (0.90 g, 50%) as a yellow oil.

IR (KBr): 3423, 1653, 1522, 1326, 1023, 695 cm–1.
1H NMR (300 MHz, CDCl3): d = 2.61 (s, 1 H), 4.71 (d, *J* = 4.2 Hz,2 H), 7.48–7.58 (m, 5 H), 8.22 (s, 1 H).
13C NMR (75 MHz, CDCl3): d = 56.62, 129.14, 130.19, 130.96,131.31, 137.67, 149.44.
MS: *m*/*z* = 179 (M+).
Anal.Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.37; H, 5.08; N, 7.80.

Synthesis of (*E*)-(3-chloro-2-nitroprop-1-enyl)benzene

To a stirred solution of ((*E*)-2-nitro-3-phenylprop-2-en-1-ol (3a) (1.00 gm, 5.55 mmol) in DCM (20 mL), $TiCl_4$ was added at room temperature. Then the reaction mixture was stirred well at room temperature for about 1 hours. After the completion of reaction (confirmed by TLC analysis), the reaction mixture was poured into water and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and solvent was evaporated. The crude product thus obtained was purified by column chromatography (2%, EtOAc / hexanes) to provide 3a in 62% (0.85 gm) yield, as a pale white crystalline solid

IR (KBr): 1637, 1519, 1328 cm–1.
1H NMR (300 MHz, CDCl3): δ = 4.79 (s, 2 H), 7.45–7.59 (m, 5 H),8.28 (s, 1 H).
13C NMR (75 MHz, CDCl3): δ = 61.65, 129.15, 130.24, 131.10, 131.38, 138.99, 147.36.
MS: *m*/*z* = 197 (M+), 199 (M+ + 2).
Anal.Calcd for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09. Found: C,54.61; H, 4.04; N, 7.13.

Procedure for *O*-alkylation of BH derivatives:

To a solution of methanol (4) in THF, sodium hydride (0.5g, 1.46mmol) was added and stirred well for few minutes at room temperature. To this solution, (*E*)-(3-chloro-2-nitroprop-1-enyl)benzene (3a) (0.178g, 1.46mmol) in THF (10mL) was added dropwise and stirred well for 1hr. After the completion of the reaction (confirmed by TLC analysis), the reaction mixture was poured into water and the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The combined organic layer was washed with brine (20 mL), and dried over anhydrous Na_2SO_4 and solvent was evaporated. The crude product thus obtained was purified by column chromatography (EtOAc / hexanes) to provide the compound 5a in 64% (0.21 g) yield, as a pale yellow crystalline solid.

Yield : 64 %
Time : 1 hr
mp : 110 – 112 ^oC
^1H NMR : δ 3.49 (s, 3H), 5.14 (s, 2H), 6.96 - 7.90 (m, 5H), 8.29 (s, 1H)
^{13}C NMR : δ = 57.41, 61.65, 129.15, 130.24, 131.10, 138.99, 147.36.
MS: *m*/*z* = 193
Anal.Calcd for $C_{10}H_{11}ClNO_3$: C, 62.17; H, 5.74; N, 7.25, Found: C, 61.15; H, 5.71; N, 7.23.

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