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Synthesis of 5Z,5'Z,5''Z)-6,6',6''-(4,4',4''-NITRILOTRIS(BENZENE-4,1-DIYL))TRIS(5-NITROHEX-5-EN-2-ONE) and (4Z,4'Z,4''Z)-TRIETHYL 5,5',5''-(4,4',4''-NITRILOTRIS(BENZENE-4,1-DIYL))TRIS(4-NITROPENT-4-ENOATE) Derived From Baylis–Hillman Adduct and Evalution of Antibacterial Activity

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Abstract : we have successfully developed a simple methodology for the synthesis of **5z,5'z,5''z)-6,6',6''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one) and (4z,4'z,4''z)-triethyl 5,5',5''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(4-nitropent-4-enoate)** derivatives involving a tandem construction of C–C bonds through Prins-type reactions using Baylis–Hillman adducts with (TNVPA) 1 with MVK 2 under the influence of imidazole. We also demonstrated that this method is useful for making novel type of BH adducts.

Key Words : Nitrostyrene, Imidazole, MeOH, tris(4-((Z)-2-nitrovinyl)phenyl)amine, Methyl vinyl ketone, Baylis–Hillman adducts.

Introduction

The Baylis-Hillman reaction, in the present day version, is an atom-economic carbon-carbon bond-forming reaction between the α-position of the activated alkenes and carbon electrophiles under the influence of a catalyst or catalytic system providing diverse classes of densely functionalized molecules, which are generally referred to as the Baylis-Hillman adducts (scheme 1).[1-6] Most of the Baylis-Hillman reactions are catalyzed by organic compounds like tertiary amines and alkyl(aryl) phosphines, and thus these reactions are referred to as the "organocatalysis reactions".

It is a three-component carbon-carbon bond-forming reaction [activated alkenes (alkynes), electrophiles, and catalysts] providing molecule with diverse functionalities. This reaction creates a chiral center in the case of a prochiral electrophile thus offering challenges and opportunities for developing its asymmetric version. Since the Baylis-Hillman adducts are densely functionalized molecules and due to the proximity of functional groups, these adducts are highly useful as synthons in a number of synthetic processes and also in synthesis of interesting natural and unnatural products of medicinal relevance. If the substrate contains both the activated alkene and electrophile components in appropriate positions, there is the possibility of developing an intramolecular version of this reaction leading to the synthesis of carbocyclic or heterocyclic compounds, and thus this reaction offers challenges to design and synthesize of various substrates that can be

transferred into diverse classes of carbocyclic and heterocyclic compounds. Many variations of parameters present in this reaction, infact, generate wide spectra of mechanistic pathways, thereby making understanding the mechanism of this reaction an intellectual challenge.

The Morita–Baylis–Hillman (MBH) reaction[7] has emerged in recent years as an attractive strategy for the quick generation of multifunctional molecules and as a key step in syntheses of complex bioactive natural products and designed molecules.[8] The method involves introduction of a substituent at the α-position of an activated alkene in a one-pot, room-temperature, and atom-economical fashion through the Lewis base mediated reaction between an activated alkene and a carbon- or heteroatom-centered electrophile.[9] Various activated alkenes such as enones, enals, acrylates, acrylamides, acrylonitrile, and vinyl sulfoxides/sulfones/ sulfonates/phosphonates, as well as electrophiles suchas aldehydes, activated ketones/imines/alkenes/azo compounds, and iminium salts have been successfully employed in MBH reactions.[10]

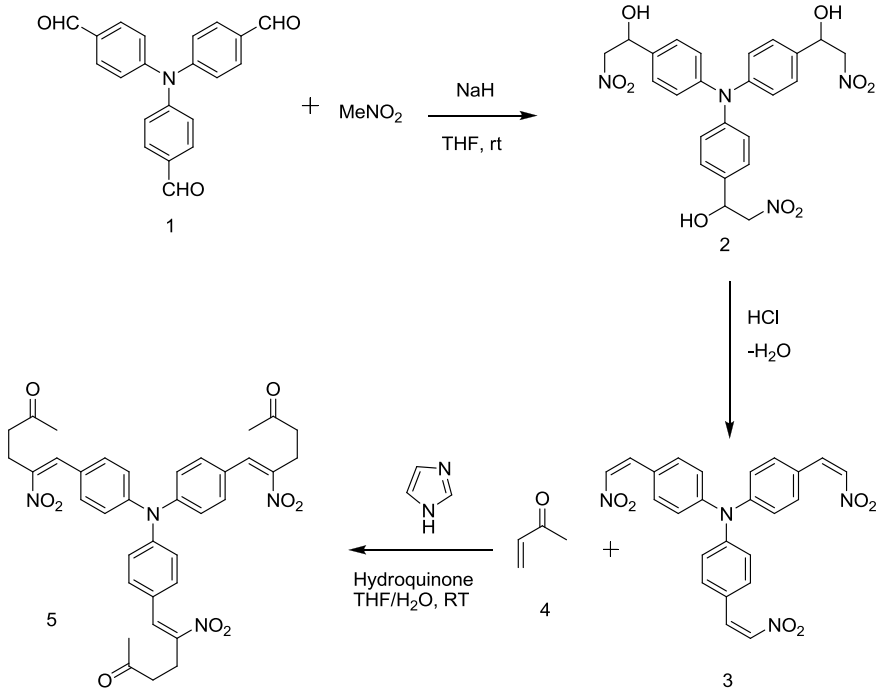
Although several activated alkenes, as mentioned above, have been employed as substrates in MBH reactions, conjugated nitroalkenes have not received much attention until recently. This is despite the fact that Baylis and Hillman, in their patent, reported the synthesis of α-hydroxyethylatednitroethylene through the reaction between nitroethylene and acetaldehyde in the presence of DABCO.[11] The fact that the superior Michael acceptor abilities of nitroalkenes have been extensively investigated in recent decades[12] and that the first step in the MBH reaction is the Michaeltypeaddition of the catalyst[13] has also not evoked sufficient interest for nitroalkenes to have become widely employed as substrates in MBH reactions.

The ability of nitroalkenes to exhibit important biological properties and function as key substrates and/or intermediates in the synthesis of many potent drugs and bioactive natural products makes them attractive molecules in the biological domain as well.[14]Among various biological properties, the anticancer properties of nitroalkenes have been scarcely investigated.[15]

There is a handful of reports in the literature where activated alkenes underwent self-condensation (dimerization) in the absence of another electrophile.[16] These include DABCO catalyzed dimerization of alkyl vinyl ketone and acrylonitrile,[17] and TDAP (tris-dimethylaminophosphine) or DABCO catalyzed dimerization of acrylate.[18] However, to our knowledge, there are only two reports where activated alkenes have been consciously used as electrophiles in the MBH reaction.[19-25]

The reaction of our substrate tris(4-((Z)-2-nitrovinyl)phenyl)amine (TNVPA) with MVK [26-29] was carried out in the presence of 10 mol% of imidazole. However, while imidazole andDMAP provided isolable amounts of the desiredMBH adduct, allothers failed to catalyze the reaction. Subsequently, the amount ofimidazole required to obtain the best yields of the MBH adductwas confirmed to be 100 mol%.Having optimized the amount of imidazole, the co-catalyticactivity of a variety of additives which are capable of (a) formingimine/iminium of the enone; (b) activating the enone via hydrogenbonding; and/or (c) inhibiting polymerization of the substrate(nitroalkene), was investigated.But, any appreciable improvement in the yield could be achievedonly when hydroquinone and (4-((Z)-2-nitrovinyl)phenyl)amine (TNVPA) were used inconjunction with imidazole in the reaction between (4-((Z)-2-nitrovinyl)phenyl)amine (TNVPA) and MVK 2for 24hrs at room temperature to provided successfully the desired (5Z,5'Z,5''Z)-6,6',6''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one) **4** in 53% yield after work up followed by column chromatography according to scheme 1.

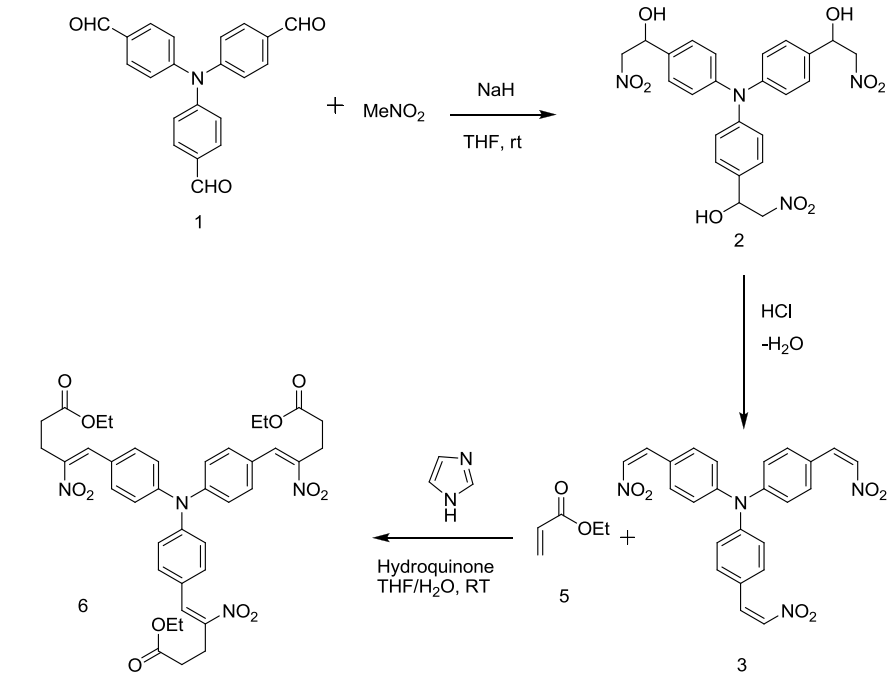
Scheme-1



The ^{1}H NMR spectrum of the compound **5**showed the CH_3 protons as a singlet at δ = 2.57 ppm, The CH_2 proton appears as two triplet at δ = 2.57 and 2.92 ppm, the olefinic proton as a singlet at δ = 8.27 ppm, and the aromatic protons as multiplets in the regionn of δ = 7.41–7.78 ppm.

Having established the experimental conditions for the reaction between nitroalkenes 1 and MVK 2, we explored the reactivity of other activated alkenes as electrophiles under these conditions. Thus, selected nitroalkenes were reacted with ethyl acrylate 4 which afforded the desired MBH products **6** respectively. All our attempts to use other activated alkenes such as acrolein, acrylonitrile, acrylamide and nitroethylene as terminal electrophiles have not been successful.

Scheme-2



The ^{1}H NMR spectrum of the compound **6**showed the OCH_3 protons as a singlet at δ = 3.71 ppm, The CH_2 proton appears as two triplet at δ = 2.72 and 3.25 ppm, the olefinic proton as a singlet at δ = 8.29 ppm, and the aromatic protons as multiplets in the regionn of δ = 7.51–7.83 ppm

The Evalution of Antibacterial Activity of the 5Z,5'Z,5''Z)-6,6',6''-(4,4',4''-NITRILOTRIS(BENZENE-4,1-DIYL))TRIS(5-NITROHEX-5-EN-2-ONE) AND (4Z,4'Z,4''Z)-TRIETHYL 5,5',5''-(4,4',4''-NITRI LOTRIS(BENZENE-4,1-DIYL))TRIS(4-NITROPENT-4-ENOATE) Derivatives

Biology

The effect of the MBH adducts are antibacterial activity of the newly synthesized compounds 5z,5'z,5"z)-6,6',6"-(4,4',4"-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one) and (4z,4'z,4"z)-triethyl 5,5',5"-(4,4',4"-nitrilotris(benzene-4,1-diyl))tris(4-nitropent-4-enoate) derivatives dissolved in 40% DMSO and waterwere evaluated for *in-vitro* antimicrobial activity studies against microorganisms and results are discussed. The bioactivity studies were carried out against bacteria, *Staphylococcus aureus, Bacillus Subtilis, Pseudomonosaeruginosa, Klebsiella pneumonia* and *Escherichia coli*.

Antibacterial activity of 5z,5'z,5''z)-6,6',6''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one) and (4z,4'z,4''z)-triethyl 5,5',5''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(4-nitropent-4-enoate) derivatives (agar diffusion assay)

The agar diffusion method was used for the determination of antibacterial activity of novel tris derivatives(**5-6**) against microorganism listed above. About 15 ml of nutrient agar media were poured into petri plates (9 cm in diameter) and inoculated with respective test organism. Wells are made with cork borer on the solid agar and loaded with 50, 75, 100 µg/well of the test compound with tetracycline as positive control and control served as 40% DMSO. Petri dishes were incubated at 37º C for 24 h and the average diameter of the inhibition zone surrounding the wells were measured after specified incubation period.

The percentage of inhibition zone was calculated by using following formula.

$$\% \text{ of Inhibition zone} = \frac{\text{Zone of inhibition (diameter in mm)}}{\text{Diameter of the Petri plate in mm}}$$

The antibacterial activity of the **5z,5'z,5''z)-6,6',6''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one) and (4z,4'z,4''z)-triethyl 5,5',5''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(4-nitropent-4-enoate) 5-6**were evaluated against five human pathogens namely *Bacillus subtilis, Klebsiella pneumonia, Staphylococcus aureus,Pseudomonas aeruginosa,*and *Escherichia coli*by the agar diffusion method. All the compounds were tested, each at 50 µg, 75 µg and 150 µg/well concentration to test their efficacy in inhibiting the growth of the tested pathogens (human pathogenic).

The tris derivatives are efficiently inhibited the growth of *Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas aeruginos, Staphylococcus aureus* and *Escherichia coli*(Table 1and 2). The benzoxepine derivatives system showed good antimicrobial activity against respective test bacteria using 100 µg/well concentrations. In addition of the compounds **5-6**were effectively inhibited the growth of the five human pathogenic bacteria.

The compounds **5& 6** showed good activity against gram(-) and gram(+) bacteria. The **5 & 6** compounds showed good activity against all bacterial pathogens.

Table 1. The minimum inhibitory concentration (MIC) µg/ml of Tris derivatives against human pathogens

Compound test using well diffusion methods	Human pathogens				
	Bacillus subtilis	***Staphylococcus areus***	***Escherichia coli***	***Pseudomonas argenosa***	***Klebciella pneumonia***
5	+++	+++	+++	-	++
6	+++	+++	+++	++	+++

Note:

+++ = Excelent
++ = Moderate
- = No activity

(**Figure 1**)

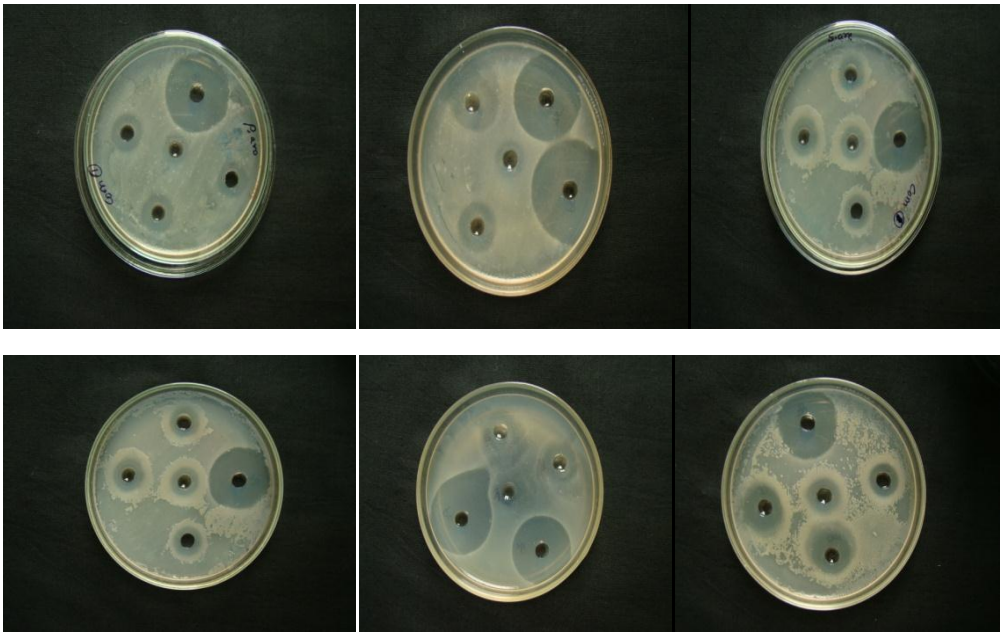


Table 2. Antibacterial activity of benzoxepines derivatives against human pathogens

Benzoxepines (µg/well)		***Bacillus subtilis* (mm)**	***Escherichia coli* (mm)**	***Staphylococcus aureus* (mm)**	***Pseudomonas argenosa* (mm)**	***Klebciella pneumonia* (mm)**
5	50	12	20	12	NA	4
	75	16	22	16	NA	7
	100	20	24	20	NA	9
Positive control		24	26	24	6	23
6	50	14	10	16	11	19
	75	14	12	18	13	21
	100	16	20	20	26	22
Positive control		24	26	24	26	24

- NA = No activity
- Positive control = tetracycline

Conclusion

In conclusion, we have successfully developed a simple methodology for the synthesis of **5z,5'z,5''z)-6,6',6''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one) and (4z,4'z,4''z)-triethyl 5,5',5''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(4-nitropent-4-enoate)** derivatives involving a tandem construction of C–C bonds through Prins-type reactions using Baylis–Hillman adducts with (TNVPA) 1 with MVK 2 under the influence of imidazole. We also demonstrated that this method is useful for making novel type of BH adducts.

Acknowledgments

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Experimental Section

Synthesis of ((5Z,5'Z,5''Z)-6,6',6''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one)(4):

To a stirred solution of tris(4-((Z)-2-nitrovinyl)phenyl)amine (0.35g, 2 mmol) and ethyl acrylate (1ml) in THF (10 mL), hydroquinone, imidazole(0.46g 2 mmol) was added at RT. The reaction mixture was stirred at RT for 24 h. After completion of reaction, the mixture was poured into water and aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (20 mL), and dried over anhydrous Na_2SO_4 and combined organic layer was evaporated. The crude product thus obtained was purified by column chromatography (5%, EtOAc/hexanes) to provide the desired compound **((5Z,5'Z,5''Z)-6,6',6''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(5-nitrohex-5-en-2-one)(4)** in good yield (53%) as a colorless liquid.

IR (KBr) : 1643, 1579, 1583, 1327, cm^{-1}
^{1}HNMR : δ 4.85 (s, 3H), 2.14(s, 3H), 7.37-7.63 (m, 14H), 8.14 (s, 1H)
^{13}C NMR : δ 30.67, 56.23, 126.70, 127.40, 130.01, 130.94, 131.44, 131.95, 132.37, 133.44, 135.23..
Chemical Formula: $C_{16}H_{15}NO_5S$
Molecular Weight: 333
Anal. Calcd for: C, 57.65; H, 4.54; N, 4.20.
Found: C, 57.68; H, 4.52; N, 4.23

Typical experimental procedure for the synthesis of (2E,2'E,2"E)-3,3',3"-(4,4',4"-nitrilotris(benzene-4,1-diyl))tris(2-nitroprop-2-ene-3,1-diyl) tris(4-methylbenzenesulfonate)

To a stirred solution of (2*E*,2'*E*,2"*E*)-3,3',3"-(4,4',4"-nitrilotris(benzene-4,1-diyl))tris(2-nitroprop-2-en-1-ol)(0.54g, 2 mmol) in THF (10 mL) and Tosyl (2)(0.48g, 2 mmol) was added at RT. After stirring for about 10 minutes K_2CO_3 added drop wise. The reaction mixture was stirred at RT for 2 h. After completion of reaction, the mixture was poured into water and aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (20 mL), and dried over anhydrous Na_2SO_4 and combined organic layer was evaporated. The crude product thus obtained was purified by column chromatography (20%, EtOAc/hexanes) to provide the desired compound **(2E,2'E,2''E)-3,3',3''-(4,4',4''-nitrilotris(benzene-4,1-diyl))tris(2-nitroprop-2-ene-3,1-diyl) tris(4-methylbenzenesulfonate)** in good yield (65%) pale yellow solid

IR (KBr) : 1645, 1569, 1573, 1354, cm^{-1}
Mass (m/z) : 1011 (M^+)
^{1}HNMR δ 4.92 (s, 3H), 2.74(s, 3H), 7.37-7.63 (m, 20H), 8.21 (s, 1H)
^{13}C NMR : δ 27.13, 56.13, 127.70, 127.40, 130.07, 130.94, 131.94, 131.99, 132.22, 123.41 135.23.
Anal. Calcd for $C_{23}H_{17}NO_2$: C, 57.02; H, 4.19; N, 5.54.
Found: C, 57.04; H, 4.15; N, 5.53.

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