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A RESEARCH ARTICLE ON SYNTHESIS OF BROMOMETHYLATED NITROALKENES AS AN INTERMEDIATE FOR THE SYNTHESIS OF ANTICANCER AGENTS

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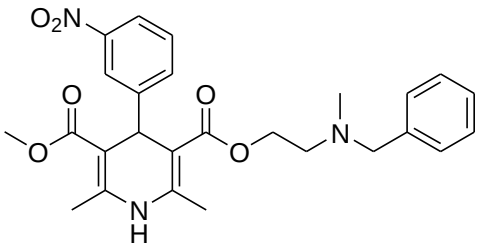
ABSTRACT

Bromomethylatednitroalkenes were prepared from nitroalkenesby **Baylis–Hillman reaction.** These bromomethylatednitroalkene can be convereted into aromatic nitro compounds which are investigated to have toxic effects on bacteria, parasites, or tumor cells and can be developed as chemotherapeutic agents. **Baylis–Hillman reaction** is a carbon-carbon bond forming reaction between the α-position of an activated alkene and a carbon electrophile such as an aldehyde in presence of nucleophilic catalyst such as a tertiary amine and phosphine. We have planned to synthesize novel 3-nitro substituted 1-aryl naphthalenes and 6-nitro substituted 4-arylbenzofuran and benzothiophene, aziridines from bromomethylatednitroalkenes via aziridines. Aromatic Nitro compounds can be used as anticancer agents due to selective toxicity on tumor cells.

KEYWORDS: Baylis-Hillman, nitroalkene, THF, anthranillic acid, anticancer, tumor.

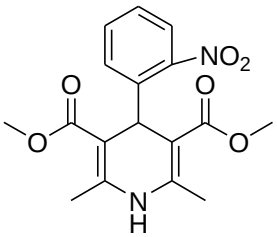
INTRODUCTION

Aromatic nitro compounds are of great importance to a variety of disciplines. They can be found in an array of pharmaceuticals[1] such as calcium channel blockers Nicardipine **1** and Nifedipine **2 (Figure 1)**, dyes,[2] and materials.[3]



Nicardipine

1



Nifedipine

2

Figure 1

Moreover, they are important entities in synthesis and can participate in a range of useful transformations.[4]

The nitro group plays an important role in the action of several drugs. Although the detailed mechanism of action of many nitro aromatic drugs is unknown, it is quite clear that several of these drugs are exceedingly valuable materials for the treatment of diseases. The nitro group is a unique functional group with a diversity of chemical and biological actions. It's very strong electron attracting ability creates localized electron deficient sites within molecules. When such compounds interact with living systems these electrophilic sites may then react with a variety ofintra and extracellular biological nucleophiles, i.e., proteins, amino acids, nucleic acids, enzymes, etc., to produce biological changes. On a molecular level the interaction may be a nucleophilic addition or displacement, an electron transfer involving oxidation and reduction, or molecular complexation without formation of a formal covalent bond. The biological changes which result can be deleterious to the organism as a whole, but in many cases the toxicity is selective; that is, it can result in poisoning the bacteria, parasites, or tumor cells without harming the host organism or normal cells. Such selective toxicity is the basis for chemotherapy.[5]

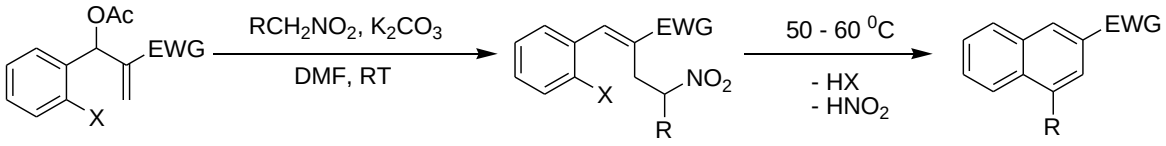
To the best of our knowledge, 3-nitro substituted 1-aryl-naphthalenes have never been tested for their biological responses. Considering the importance of substituted biaryl's biological activities combined with the peculiar nature of the nitro group, we decided to synthesize nitro substituted 1-aryl naphthalenes, benzofurans and benzothiophenes.

Although diverse synthetic approaches toward naphthalene compounds have been developed,[6] versatile and efficient methodologies to construct these compounds with selective control of substitution patterns using readily accessible building blocks are still needed. Unsymmetrically substituted arylnaphthalene derivatives are attracting much attention as a synthetic target,[7] because they serve as the basic skeleton of several biologically active natural products.

The preparation of unsymmetrical biaryls is generally allowed by Stille reaction, Suzuki reaction and Grignard cross-coupling reaction.[8,9] These methods despite their efficiency, involve the use of a stoichiometric amount of organometallic intermediates. Also, the traditional protocol for the Suzuki-Miyaura reaction prescribes a palladium species with phosphine ligand as the catalyst. However, many phosphines, which are necessary to stabilize the catalytically active palladium species, are toxic and/or expensive. Also, some phosphines are sensitive to air and moisture with conversion to phosphine oxide species. Consequently, the development of phosphine free catalytic systems to overcome these difficulties is considered to be one of the most challenging fields in organic chemistry.[10]

Morita-Baylis-Hillman (MBH) reaction is an atom-economic green reaction that allows coupling of an activated alkene with an electrophile to result in a multi-functional product for exploitation by synthetic organic chemists.[11–13]

Recently, Kim and co-workers reported the synthesis of naphthalenes **8** from the reaction of the Baylis–Hillman acetates **6** derived from *o*-halobenzaldehydes and primary nitroalkanes via the successive S_N2'–S_NAr-elimination strategy **(Scheme 1)**.[14]



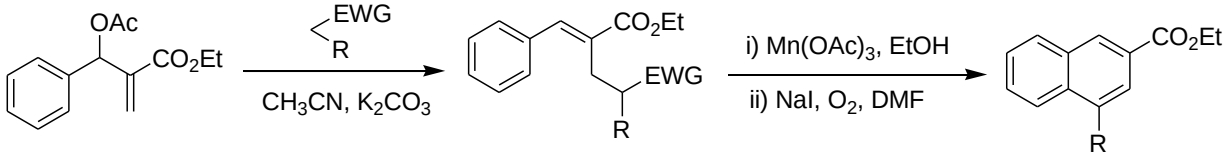
3 **4** **5**

EWG: CO_2Et, $COCH_3$

R: Me, Et, *n*-Bu, Ph, CO_2Et

Scheme 1

Later the concept was extended to a more general one by using the Mn(III)-assisted radical cyclization protocol **(Scheme 2)**.[15]



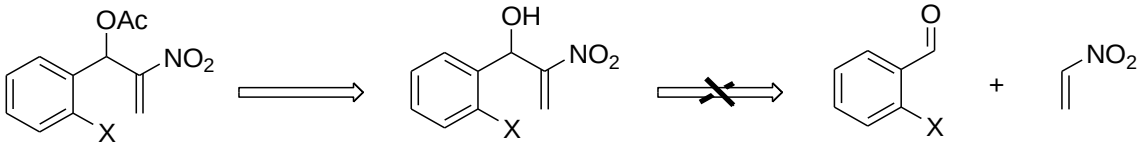
6 **7** **8**

EWG: CO_2Et, CO_2CH_3, NO_2

R: CO_2Et, CO_2CH_3, CH_3

Scheme 2

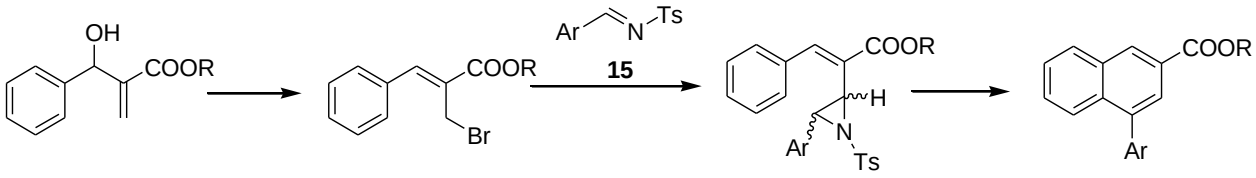
However, both the methods cannot be applied for the synthesis of corresponding nitro substituted aromatics because the required Baylis-Hillman adduct **10** of the corresponding aldehyde **9** and nitroethylene**12** could never been synthesized owing to the unstability of nitroethylene **(Scheme 3)**.



9 **10** **11** **12**

Scheme 3

However, more recently, Kim and co-workers reported the synthesis of 1-arylnaphthalene derivatives **17** via the intramolecular ring-opening reaction of *N*-tosylaziridines **16** derived from Baylis–Hillman adducts **14** and tosylimines**15 (Scheme 4)**.[16]



13 **14** **16** **17**

Scheme 4

We envisioned that this protocol if applied to the MBH adducts of nitroalkenes would lead to the synthesis of 1-aryl-3-nitro-naphthalenes. Also, because the hydroxymethlated MBH adducts of nitrovinyl furan and nitrovinyl thiophenes can easily be synthesized in high yields, this methodology would be useful for the synthesis of corresponding nitro substituted benzofurans and benzothiophenes.

MATERIAL AND METHODS

General: Following general procedures were employed in all reactions unless otherwise stated. Air and moisture sensitive reactions were carried out in flame-dried glassware under nitrogen atmosphere using standard vacuum line techniques. Sensitive liquids and solutions were transferred by syringe through the rubber septum. All the organic extracts were dried over anhydrous Na_2SO_4.

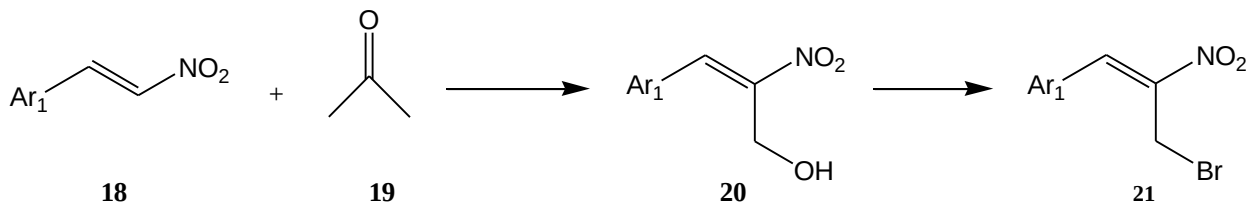
Reagents and Solvents: Solvents used for all reactions were purified/dried by standard procedures.[17] Reagents such as nitromethane, aldehydes (used for the preparation of nitroalkenes and tosylimines), *p*-toluene sulfonamide etc were purchased from their respective commercial sources and were used as obtained.

Chromatography: Thin layer chromatography (TLC) was performed on aluminium plates coated with silica gel 60 GF254, supplied by E. Merck (India) Limited. Visualization of spots on TLC plates was achieved either by exposure to UV light or suitable stain such as iodine vapour, $KMnO_4$ etc. Flash chromatography was performed on silica gel (100-200 mesh). The elution was done with petroleum ether (60-80 ^{0}C)-ethyl acetate mixture.

Physical Properties and Spectroscopic Measurements: Melting points were recorded on RAMI melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin Elmer's RX I FTIR spectrophotometer. Solid samples were recorded as KBr wafers and the liquid films were made on CsBr or NaCl plates and analyzed. 1H NMR was recorded on Bruker DPX- 300 MHz FT spectrometers. ^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield from a TMS internal standard (0.00 ppm). To describe spin multiplicity, standard abbreviations such as s, d, t, q, m, dd referring to singlet, doublet, triplet, quartet, multiplet, double doublet respectively, are used. The ESMS were recorded on MICROMASS Quadro-II LCMS system.

SCHEME OF WORK

As the synthesis of hydroxymethylated MBH adducts of the nitroethylenes have not been reported, we utilized the MBH adducts of *β*–substituted nitroalkenes[18]**20** and converted them into the corresponding bromo derivatives **21**.[19]



18 **19** **20** **21**

Scheme 5

The scheme was initiated with the synthesis of several *β*-substituted aromatic and heteroaromaticnitroalkenes**18a-j(Figure 2)**.

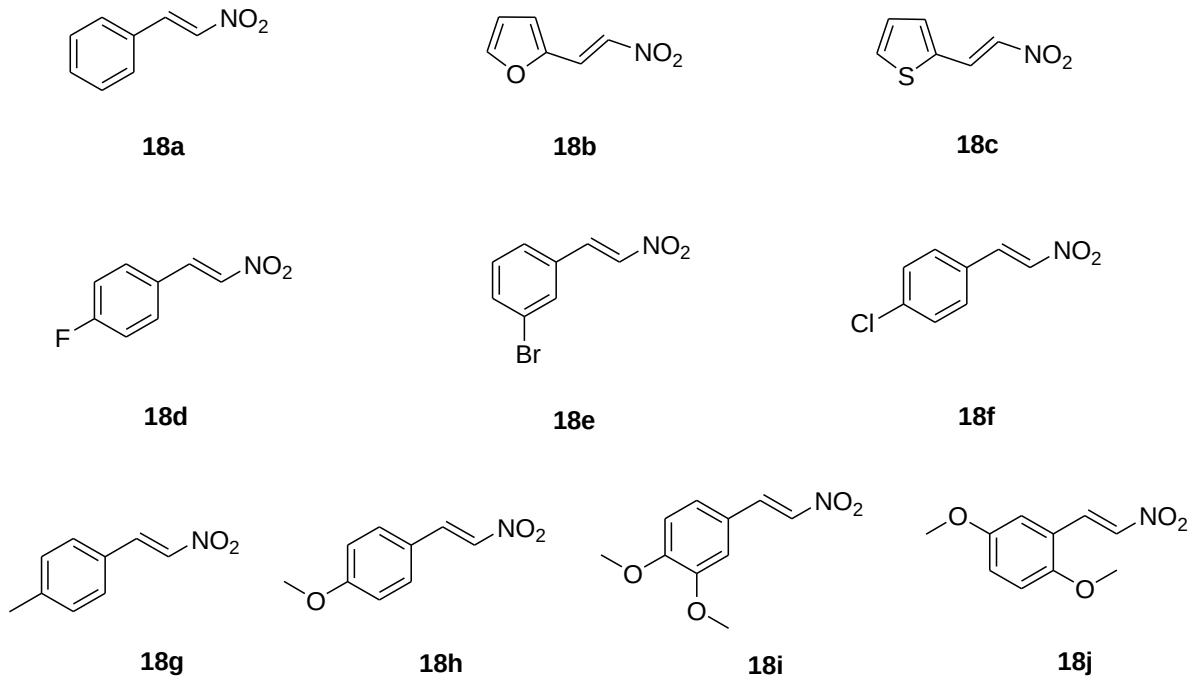
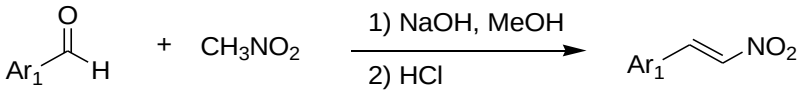


Figure 2.

The choice of nitroalkenes was such that it included both electron withdrawing as well as electron releasing substituents on the aromatic ring in order to ascertain the effect of electronic properties of various functional groups on the reaction.

General procedure for the synthesis of nitroalkenes 18a-j

Aromatic nitroalkenes**18a-j** were prepared by the method described by Worrall and co-workers **(Scheme 6)**.[20]

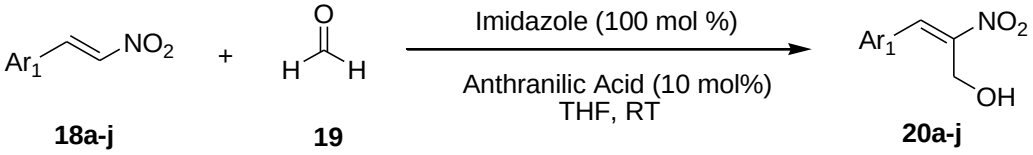


Scheme 6

To an ice-cold solution of the aldehyde**16** (10 mmol) and nitromethane**17** (0.54 ml, 10 mmol) in MeOH (5 ml), an aqueous solution of NaOH (420 mg or 10.5 mmol of NaOH in 2 ml cold water) was added dropwise with stirring, while maintaining the internal temperature of the reaction mixture at 0-10 °C. Thick precipitate which is formed in some cases was dissolved by adding MeOH into the reaction mixture and stirring was continued at low temperature till the disappearance of the aldehyde **16** (TLC). The reaction mixture was then diluted with cold water (5 ml) and poured into cold aqueous solution of concentrated HCl (1 ml HCl in 1.5 ml water). The solid formed was collected by suction filtration and washed with cold water. The crude product thus obtained was recrystallized from hot ethanol to obtain the pure nitroalkenes**18**.

General procedure for the synthesis of hydroxymethylatednitroalkenes 20a-j

Hydroxymethylation of nitroalkenes**18a-j** was carried out via Morita-Baylis-Hillman reaction as described by Namboothiri and co-workers **(Scheme 7)**.[16]



Scheme 7

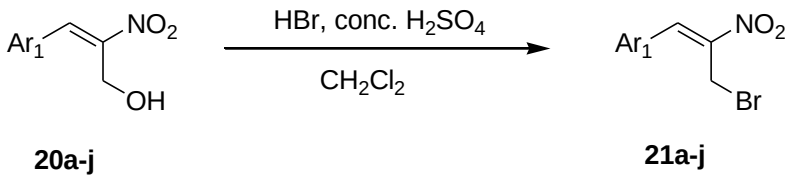
To a stirred solution of nitroalkene**18** (1 mmol) in THF (2 ml) at room temperature was added imidazole (68 mg, 1 mmol, 1 equiv.) followed by anthranilic acid (14 mg, 0.1 mmol, 10 mol %). 38 % aqueous formaldehyde **19** (2 ml, excess) was then added and the reaction mixture was stirred at room temperature for the period specified in **Table 1**. After the completion of the reaction (confirmed by TLC analysis), the reaction mixture was acidified with 5 N HCl (5 ml) and the aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography by eluting with ethyl acetate/hexane mixture to afford pure **20**.

Table 1.

Entry	20	Ar_1	Time (h)
1	**20a**	Ph	24
2	**20b**	2-Furyl	84
3	**20c**	2-Thienyl	15
4	**20d**	4-F-Ph	30
5	**20e**	3-Br-Ph	62
6	**20f**	4-Cl-Ph	78
7	**20g**	4-Me-Ph	24
8	**20h**	4-MeO-Ph	15
9	**20i**	3,4-$(MeO)_2$-Ph	36
10	**20j**	2,5-$(MeO)_2$-Ph	34

General procedure for the synthesis ofbromomethylatednitroalkenes 21a-j

Conversion of Morita-Baylis-Hillman products **20a-j** into corresponding bromomethylatednitroalkenes**21a-j** was carried out by following the procedure described by Bakthadoss and co-workers **(Scheme 8)**.[17]



20a-j **21a-j**

Scheme 8

To a stirred solution of hydroxymethylatednitroalkene**20** (1 mmol) in DCM (5 ml), 48% aq HBr (0.2 mL) was added at room temperature. The mixture was cooled to 0 ^{0}C and concentrated H_2SO_4 (0.02 mL) was added dropwise. The mixture was stirred well at room temperature for 12 -24 h. On completion of the reaction (confirmed by TLC analysis), the mixture was poured into H_2O and the aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product thus obtained was purified by silica gel column chromatography by eluting with ethyl acetate/hexane mixture to afford pure **21**.

(3-Bromo-2-nitro-propeny1)-benzene (21a)

Yellow crystalline solid; Yield 55 %; mp 86 ^{0}C (obs); 87-89 ^{0}C (rep); IR (KBr) cm^{-1} 1643 (m), 1527 (m), 1328 (m), 1218 (m), 766 (s); ^{1}H NMR ($CDCl_3$) δ 4.65 (s, 2H), 7.54-7.57 (m, 3H), 7.64-7.65 (m, 2H), 8.26 (s, 1H).

2-(3-Bromo-2-nitro-propeny1)-furan (21b)

Yellow crystalline solid; Yield 90 %; mp 98 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); 94-96 ^{0}C(rep); IR (KBr) cm^{-1} 1632 (m), 1505 (w), 1308 (m), 1217 (s), 767 (s), 670 (w); ^{1}H NMR ($CDCl_3$) δ 4.98 (s, 2H), 6.70 (d, *J* = 3.0 Hz, 1H), 7.09 (d, *J* = 6.0 Hz, 1H), 7.82 (s, 1H), 7.97 (s, 1H).

2-(3-Bromo-2-nitro-propeny1)-thiophene (21c)

Yellow crystalline solid; Yield 92 %; mp 100 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); 96-98 ^{0}C (rep); IR (KBr) cm^{-1} 1631 (m), 1521 (m), 1424 (w), 1309 (m), 1217 (s), 766 (s); ^{1}H NMR ($CDCl_3$) δ 4.83 (s, 2H), 7.28 (s merged with $CDCl_3$ peak, 1H), 7.64 (d, *J* = 3.0 Hz, 1H), 7.85 (d, *J* = 6.0 Hz, 1H), 8.44 (s, 1H).

1-(3-Bromo-2-nitro-propeny1)-4-fluoro-benzene (21d)

Yellow crystalline solid; Yield 75 %; mp 125 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); 120-122 ^{0}C (rep); IR (KBr) cm^{-1} 1744 (s), 1657 (m), 1601 (m), 1526 (s), 1331 (s), 1225 (s), 1029 (m), 838 (m), 763 (s); ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 2H), 7.18 (dd collapsed to t, *J* = 9.0 and 6.0 Hz, 2H), 7.61 (dd collapsed to t, *J* = 6.0 Hz, 2H), 8.30 (s, 1H).

1-Bromo-3-(3-bromo-2-nitro-propeny1)-benzene (21e)

Pale yellow crystalline solid; Yield 50 %; mp 115 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); IR (KBr) cm^{-1} 1746 (m), 1532 (s), 1334 (m), 1217 (s), 1029 (w), 762 (s), 672 (m);

^{1}H NMR ($CDCl_3$) δ 5.22 (s, 2H), 7.44 (s, 2H), 7.67 (s, 2H), 8.29 (s, 1H).

1-(3-Bromo-2-nitro-propeny1)-4-chloro-benzene (21f)
Yellow crystalline solid; Yield 60 %; mp 135 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); IR (KBr) cm^{-1} 1745 (s), 1653 (w), 1530 (s), 1331 (m), 1219 (s), 1093 (w), 1028 (w), 763 (s);^{1}H NMR ($CDCl_3$; ethyl acetate peaks visible) δ 5.22 (s, 2H), 7.50 (two d appearing as dd, *J* = 12.0 and 9.0 Hz, 4H), 8.32 (s, 1H).

1-(3-Bromo-2-nitro-propeny1)-4-methyl-benzene (21g)
Pale Yellow crystalline solid; Yield 74 %; mp 110 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); 110-112 ^{0}C (rep); IR (KBr) cm^{-1} 1752 (w), 1641 (m), 1526 (m), 1324 (m), 1218 (s), 766 (s).

1-(3-Bromo-2-nitro-propeny1)-4-methoxy-benzene (21h)
Orange crystalline solid; Yield 92 %; mp 106 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); 102-104 ^{0}C (rep); IR (KBr) cm^{-1} 1601 (s), 1513 (s), 1313 (s), 1258 (s), 1176 (m), 1026 (s), 837 (s); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 4.70 (s, 2H), 7.08 (d, *J* = 9.0 Hz, 2 H), 7.65 (d, *J* = 12.0 Hz, 2H), 8.25 (s, 1H).

4-(3-Bromo-2-nitro-propeny1)-1,2-dimethoxy-benzene (21i)
Dark Yellow crystalline solid; Yield 90 %; mp 128 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); 130-132 ^{0}C (rep); IR (KBr) cm^{-1} 1637 (w), 1520 (w), 1319 (w), 1270 (w), 1218 (m), 768 (s); ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 6H), 4.70 (s, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 7.26 (t, *J* = 6.0 Hz, 2H), 8.21 (s, 1H).

2-(3-Bromo-2-nitro-propeny1)-1,4-dimethoxy-benzene (21j)
Orange crystalline solid; Yield 64 %; mp 117 ^{0}C (obs); (CH_2Cl_2-hexane 1:3); IR (KBr) cm^{-1} 1640 (s), 1525 (s), 1498 (s), 1219 (s), 1044 (s), 860 (w), 760 (s), 670 (s); ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 6H), 4.65 (s, 2H), 6.93 (d, *J* = 9.0 Hz, 1H), 7.07 (d, *J* = 6.0 Hz, 1H), 7.28 (s, 1H), 8.49 (s, 1H).

DISCUSSION

Marketed Anticancer agents had anumerous adverse effects thus; there is a continuous need to discover new and effective anticancer drugs with more effectiveness and minimum adverse effects. According to literature review, aromatic nitro compounds have a variety of medicinal properties and can be potential anticancer agents in future. Therefore, wehave planned to synthesizesome compounds (MBH adducts) using Morita-Baylis-Hillman reaction. The compounds obtained were in exemplary yield specially 1-(3-Bromo-2-nitro-propeny1)-4-methoxy-benzene and 4-(3-Bromo-2-nitro-propeny1)-1, 2-dimethoxy-benzene. The MBH adducts can be further used to synthesize 3-nitro substituted 1-aryl-naphthalenes, 6-nitro substituted 4-aryl benzofuran and benzothiophene.MBH adducts wereplanned to convert into 1-arylnaphthalene derivatives via the intramolecular ring-opening reaction of *N*-tosylaziridines derived from Baylis–Hillman adducts and tosylimines.

CONCLUSION

In our attempt to synthesize novel 3-nitro substituted 1-aryl naphthalenes and 6-nitro substituted 4-aryl benzofuran and benzothiophene, we prepared several nitroalkenes and subjected them to Morita-Baylis-Hillman reaction with formaldehyde as electrophile. The resulting MBH adducts were successfully converted into the corresponding bromo derivatives. Our initial attempts to synthesize aziridines from bromomethylated nitroalkenes were unsuccessful but efforts to modify the reaction conditions are underway in our laboratory.

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