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Synthesis Of Poly Functionalized Tricyclic Nitro Chromenopyrazole Frameworks Via Intramolecular Cycloaddition Reactio Derived From Nitroolefins

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Abstract
A simple and novel protocol for the easy synthesis of complex angle-substituted tricyclic frameworks including the IA 3a-nitro-2,3-diphenyl-2,3a,4-tetrahydrochromeno[4.3-C]pyrazole ring system. This reaction leads to a new class of merged merges and tetra cycles, creating two new rings, three coherent steer centers and a carbon center that replaces tetras in a unique way. The angle-substituted nitro compounds were highly stereoselectively conserved in high yields.
Keywords:- *Baylis-Hillman adducts, Chromenopyrazole and O-allylated salicylaldehyde, (E)-2-nitro-3-phenylprop-2- en-1-ol, Conc. HCl and ethanol.*

INTRODUCTION

The practical and efficient structure of highly functionalized and diversified molecules made from simple starting materials is highly desirable and remains a major challenge. In fact, the formation of heterocyclized compounds is one of the largest classical sectors of organic chemistry. Furthermore, heterocycling is more important for biological and industrial applications. Participation in various fields cannot be underestimated. Heterocycles are found in most biologically active drugs. For this reason, chemists are ongoing searches to design and produce better medicines, pesticides, rodents and pesticides by following natural models2. Heterocycles are an important part of the biochemical process and are also the time group of the most representative and most important components of living cells. Other important practical applications from these dies. The connection can also be determined as additives and modifiers for various industries, such as, for example, reproduction, information storage, plastics, solvents, antioxidants, vulcanization accelerators[3]. After all, heterocyclic chemistry as applied science is an endless resource of new connections. Many combinations of carbon, hydrogen and heteroatoma can be designed, providing connections with the most diverse physical, chemical and biological properties. Of the 20 million compounds recognized since the end of the 4th Millennium, more than three-thirds are fully or partially aromatic, almost heteroaromatic. The synthesis of complex heterocyclized compounds remains important in the realm of synthetic organic chemistry[6].

MATERIAL METHODS

To carry out our idea, we wanted to synthesize various Baylis Hillman adducts by treatment of (E)-(2-nitrovinyl)-alene (A-P) with paraformaldehyde using imidazole and antran phosphate as a catalytic system. Connection 1A was characterized by IR, 1H and ^{13}C-NMR spectroscopy, mass spectroscopy, and basic analysis. The ^{1}H-NMR spectra of connection 1A showed singlets of hydroxyl protons at ROH 2.61, and doubles were observed in O-CH_2 protons at ROH 4.71. Aromatic protons appeared as multiples in the region 7.48-7.58. Olefin protons were observed as single at 8.22.

All reactions were performed using 10 mmol nitrogen containing formaldehyde in THF at room temperature. Barr products provided satisfactory IR, 1H-NMR, 13C-NMR, and mass spectral data. Site-Erd of pure product (1A-P) obtained according to column chromatography (pebble, 10-20% ETOAC in hexane). Over the past decade, Baylis Hillman's reaction has recorded enormous growth in relation to components such as electropathy, activated olefins, and catalysts.[7] Various activated olefins are examined

by different research groups, but nitrolfins are not used as olefin components[8]. So far, with the exception of the first report by Baylis and Hillman, there are no reports in the literature[9] on the synthesis of Baylis-Hillman adducts derived from aldehydes and nitroethylene. The reason nitroethylene is unexplored can be due to its relatively large reactivity, which can lead to polymerization. So far, nitrolefins have still been reported in the literature, and it is necessary to investigate the application of this Tris-Stituted Allyl Halogenidal. Therefore, we conducted a research program for synthesis and investigated possible applications of Tris-Stituted Allyl Halogenids derived from nitrolefins in various organic reactions. The Baylis-Hillman adduct and its derived connections have been used in detail for the synthesis of biologically active molecules, heterocycles, and many natural products. For example, Basavaiah et al.[10] Bond Serine - Méti Letters synthesized.

Based on these reports, we envisaged that the bromo compounds derived from nitroolefins will also serve as excellent building blocks for the synthesis of a wide variety of useful compounds. Triggered by this idea, we have decided to prepare the bromo compound derived from nitroolefins which will open new avenues for several synthetic transformations. In continuation of our ongoing research in our laborotory in the field of Baylis-Hillman chemistry,[11-13] we planned to synthesize 1-((*E*)-3-bromo-2-nitroprop-1-enyl)benzene, which is a very useful starting material for various transformations.

It occurs to us that the target compound *i.e.* 1-((*E*)-3-bromo-2-nitroprop-1-enyl)benzene can be easily synthesized directly by treating α-methylnitrostyrene with NBS under allylic radical bromination condition. Unfortunately we did not obtain the desired bromo compound. The abundance of oxygen and nitrogen containing cyclic compounds in pharmaceuticals and agrochemicals continues to ensure that they are important synthetic targets for organic chemists.[14-15] Azomethine ylide involved [3+2] cycloaddition is a concerted cycloaddition process that represents a powerful tool for the construction of various types of complex polyheterocyclic frameworks.[16-20] In recent years the azomethine ylide has gained a vital place in the field of heterocyclic chemistry as it serves as an important building block for the construction of nitrogen containing five-membered heterocycles, which are often an integral part of many natural products and bioactive molecules such as tocopherol, (+) Haematoxyline, tocotrienols, martinelline, etc [21].

Some of the representative natural products possessing this heterocyclic ring

Utilizing this [3+2] cycloaddition chemistry variety of tricyclic chromeno pyrrolidine frameworks have also been reported in the literature. Due to the interesting and important biological properties of these tricyclic pyrrolidines, development of simple and convenient routes for the construction of tricyclic chromeno pyrrolidine derivatives with various substituents represents an attractive and interesting endeavor in synthetic organic chemistry and medicinal chemistry. In fact, a number of methodologies/strategies are reported in the literature for the synthesis of these molecules with different functionalities[22]. For example, Bashiardes *et al*[23] developed a new method for the synthesis of tricyclic pyrrolidines and pyrroles *via* the microwave-assisted intramolecular [3+2] cycloaddition reaction of azomethine ylides to the activated and nonactivated alkenes and alkynes.

RESULT AND DISCUSSION

Literature survey reveals that Chromenopyrazole and O-allylated salicylaldehyde frameworks constitutes an important structural assembly owing to the presence of these structural units in various molecules of historical importance. Hence the development of new, simple and efficient methodologies for the synthesis of tricyclic Chromenopyrazole frameworks represents an important endeavor in the area of organic chemistry. To achieve our idea towards the building of these chromenone fused pyrazole tricyclic frameworks, we have chosen O-allylated salicylaldehyde derived from bromo derivative of Baylis-Hillman adduct and phenyl hydrazine (2 a) as our model substrates and subjected them under various conditions to identify the optimum reaction condition. The target Chromenopyrazole frame works, we treated the Baylis-Hillman adducts (**1a-l**) with O-allylated salicylaldehyde and phenyl hydrazine without using Conc. HCl and ethanol at reflux 5 hrs, which successfully provided the desired 3a-nitro-2,3-diphenyl-2,3,3a,4-tetrahydrochromeno[4,3-c]pyrazole (**4a-l**) in 65-85% yields with high regioselectivity as shown in the scheme 1

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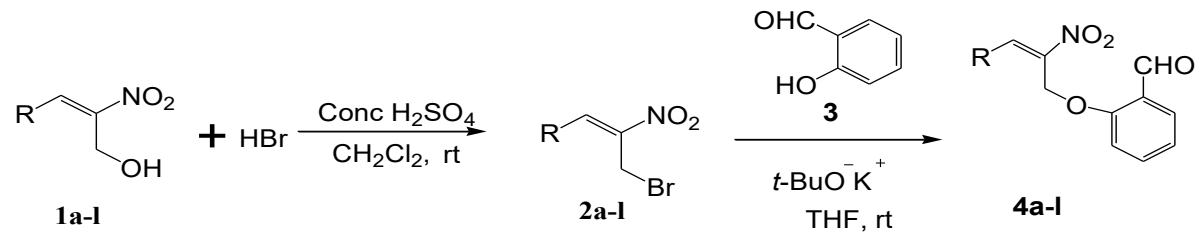
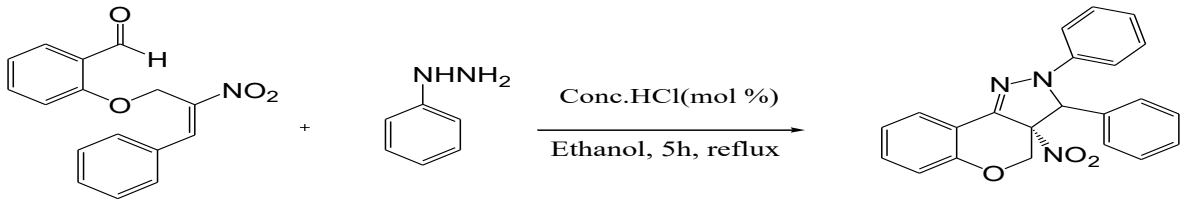
Scheme-1



1a-l **2a-l** **4a-l**

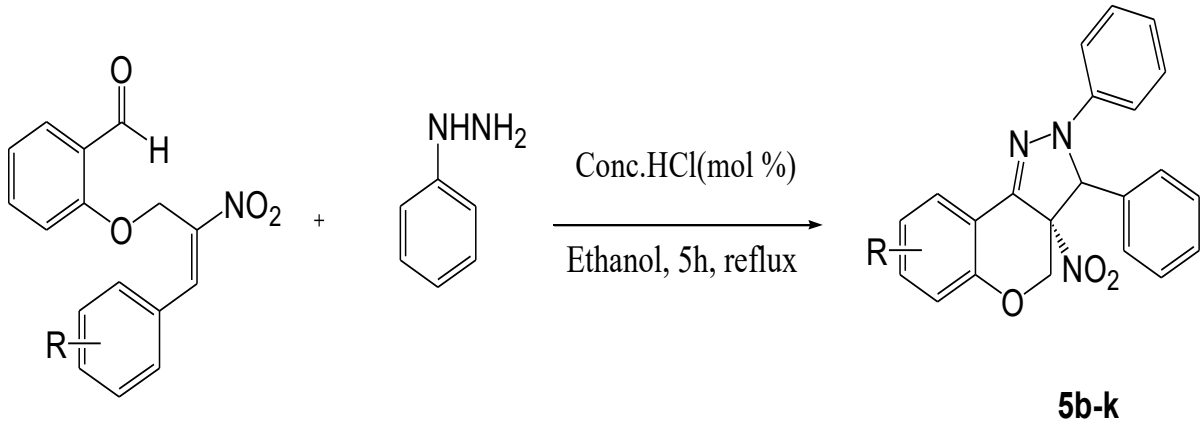
R = 2-Me-C_6H_4, 4-Me-C_6H_4, 2-MeO-C_6H_4, 4-MeO-C_6H_4, 3,4-$(MeO)_2$-C_6H_3, 3,4-(OCH_2O)-C_6H_3, 2-Cl-C_6H_4, 2-furyl, 2-thienyl



4a **5a**

The structure of the compound **5a** was confirmed by IR, ^1H and ^{13}C NMR, mass spectral data and elemental analyses. The IR spectrum of the compound **5a** exhibited absorption at 1726 cm^{-1} for lactone carbonyl (C=O) group and 1618 cm^{-1} for alkene group. The ^1H NMR spectrum of the compound **5a** showed one singlet for the CH_2 protons at δ 4.08 ppm and CH olefinic proton was observed as sharp singlet at δ 7.98 ppm and the aromatic protons appeared as multiplets in the region of δ 7.07-7.46 ppm. In the ^{13}C NMR spectrum of the compound, CH_2 carbon appeared at δ 28.89 ppm, lactone carbonyl (C=O) carbon appeared at δ 164.43 ppm. The mass spectrum peak at 237 (M^++1) of the compound also evidences the formation of the product.

Encouraged by this result, we have synthesized a variety of Chromenopyrazole compounds (**5b-m**) utilizing Baylis–Hillman adducts with phenyl hydrazine (**5a**) (**5b**) under similar reaction condition in good yields (69-84%) according to scheme 2. The structures of the compounds (**5b-m**) were confirmed by ^1H & ^{13}C NMR, IR and mass spectral analyses. (Scheme 2). **Scheme 2**



4b-k **5b-k**

R = 2-Me-C_6H_4, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-*i*-Pr-C_6H_4, 2-MeO-C_4H_4, 4-MeO-C_6H_4, 3,4-$(MeO)_2$-C_6H_3, 3,4-(OCH_2O)-C_6H_3, 4-F-C_6H_4, 2-Cl-C_6H_4,

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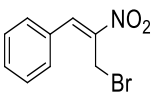
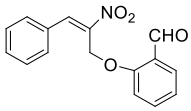
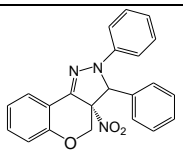
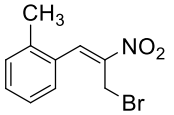
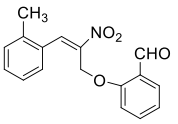
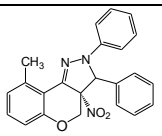
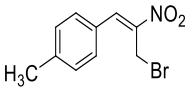
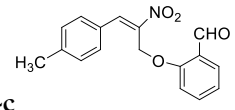
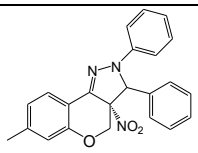
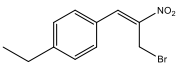
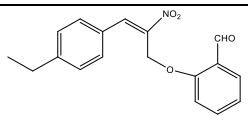
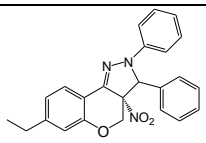
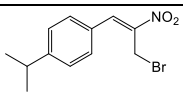
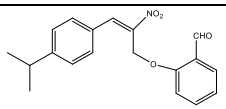
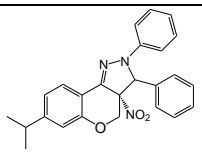
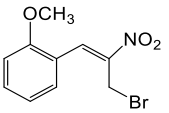
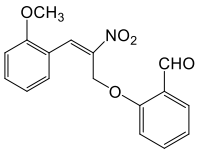
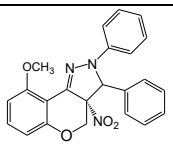
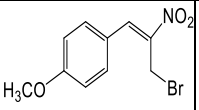
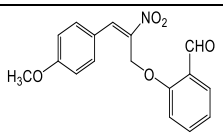
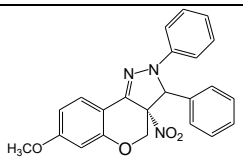
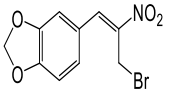
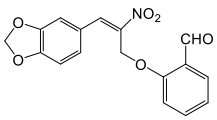
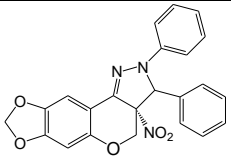
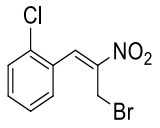
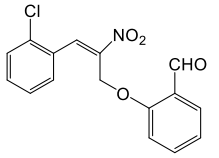
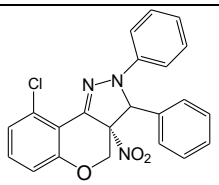
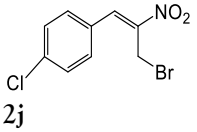
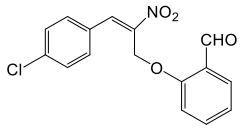
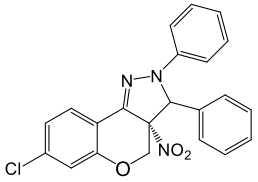
Table 1. Synthesis of fused 1-methyl-3a-nitro-3-phenyl-1,2,3,3a,4,9b-hexahydro chromeno [4,3-b]pyrrole from Baylis-Hillman derivatives

S.No	Allyl bromides	Salicyaldehyde derivatives[a, b]	Yield (%)[c]	Chromenopyrrolidines	Yield (%)
1	 **2a**	 **4a**	65	 **5a**	76
2	 **2b**	 **4b**	72	 **5b**	85
3	 **2c**	 **4c**	74	 **5c**	73
4	 **2d**	 **4d**	72	 **5d**	70
5	 **2e**	 **4e**	71	 **5e**	70
6	 **2f**	 **4f**	82	 **5f**	72
7	 **2g**	 **4g**	70	 **5g**	75
8	 **2h**	 **4h**	67	 **5h**[e]	80

9	 **2i**	 **4i**	72	 **5i**	73
10	 **2j**	 **4j**	78	 **5j**	71

[a]All reactions were carried out with 2 mmol scale of allyl bromide and 2-hydroxybenzaldehyde (2 mmol) in 10 ml of THF for 10min at room temperature. [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** and **5a-j**) obtained after column chromatography (silica gel, (**5a-j**) 2% EtOAc in hexanes, (**5a-j**) 5% EtOAc in hexanes). [d]All reactions were carried out using 2 mmol of intermediate (**5a-j**) with *N*-methyl glycine (2 mmol) in 10 mL of CH_3CN under reflux for 6 h.

CONCLUSION

We have successfully developed a simple and novel protocol for the facile synthesis of complex angularly substituted tetracyclic frameworks containing a chromenopyranpyrazole ring system *via* an intramolecular domino Knoevenagel hetero Diels-Alder reaction using Baylis-Hillman derivatives. This new protocol leads to a novel class of angularly substituted fused tetracyclic frameworks which creating two new rings, three contiguous stereocentres and one tetrasubstituted carbon center in a unique fashion. Angularly substituted tetracyclic compounds were obtained in a highly stereoselective fashion with excellent yields.Gratifyingly, these heterocyclic frameworks were developed in solvent and catalyst free conditions, this method not only minimize the generation of wastes but also simplify the work-up procedure.

Experimental procedure and characterization data for the synthesis of tricyclic chromenopyrazoles 3 having nitro at the angular position. Methyl-2,3- nitro-diphenyl-2,3- dihydrochromeno[4,3-c]pyrazole-3a(4H) (5a)

To a mixture of O-allylated salicylaldehyde derivatives (**4a**) (1 mmol) in EtOH (5mL), phenylhydrazine (1.1 mmol) was added in a round bottomed flask, followed by addition of 10 mol% conc. HCl. Then, the reaction mixture stirred at 80 ℃ for 5h. After cooled to room temperature, EtOH was removed under reduced pressure. The residue was diluted with water (15 mL) and washed using ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give fused tricyclic chromenopyrazoles (**5a**) Yellow Color Solid, Yield: 83%; mp: 168-170 °C; IR (KBr): 1714, 1541, 1323, cm^{-1} 1H NMR (300 MHz, CDCl3): δ 3.35 (d, J= 10.9 Hz, 1H), 3.72 (s, 3H), 4.35 (d, J= 10.8 Hz, 1H), 5.62 (s, 1H), 6.76- 8.02 (m, 13H), 8.01 (d, J= 6 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 53.62, 60.34, 70.15, 113.46, 117.38, 119.40, 122.17, 124.80, 126.45, 128.79, 129.19, 129.41, 130.55, 134.26, 140.86, 143.09, 154.67; HRMS (m/z) Calcd. For $C_{22}H_{17}N_3O_3$ [M + 1] + 371.152, Found 371.139.

COMPETING INTERESTS: We have no competing interests**.**

AUTHORS' CONTRIBUTIONS:

Author-1,2 Reaction are carried out and Data collection

Author-3,4 Paper writing

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