Efficient Synthesis of *N*-Allylated 2- Nitroiminoimidazolidine Analogues from Baylis-Hillman Bromides

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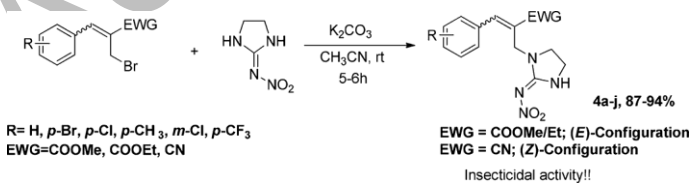
Abstract

Various Baylis-Hillman derived new *N*-allylated 2-nitroiminoimidazolidine analogues were efficiently prepared using potassium carbonate as base. Simple workup procedure, excellent yields and mild reaction conditions are the salient features of this method. All the synthesized compounds are screened for their larvicidal activity on fourth instar mosquito larvae, a *culex quinquefasciatus*.



KEYWORDS: Baylis-Hillman bromides, 2-nitroiminoimidazolidines, *N*-cinnamyl nitro imino imidazole derivatives, Insecticidal activity

1. INTRODUCTION

Discovery of new insecticides is an ongoing process and challenging area for organic chemists worldwide.[1] Earlier generation of insecticides include nicotine, a most well known and widely used alkaloid containing pyridine as a basic moiety. Analogue molecules were introduced into market as most potent insecticides include imidacloprid, acetamprid, thiacloprid etc. When the structures of these compounds are compared with nicotine, it appears that only minor changes were made on pyridine moiety of nicotine and major changes incorporated in the side chain heterocyclic moiety (Fig 1).

Imidacloprid[2] is a relatively new insecticide, first registered for use as a pesticide in the U. S. in 1994, and was the first insecticide in its chemical class to be developed for commercial use. The neonicotinoid imidacloprid is currently one of the most widely used insecticides in the world.[3] Imidacloprid, and other insecticides in the nicotionid chemical family, are "similar to and modeled after the natural nicotine [a tobacco toxin]." Because of their molecular shape, size, and charge, nicotine and nicotinoids fit into receptor molecules in the nervous system that normally receive the molecule acetylcholine. Acetylcholine carries nerve impulses from one nerve cell to the tissue that a nerve controls. Imidacloprid and other nicotinoids irreversibly block acetylcholine receptors.[4]

The nicotinoids are a newer class of insecticides with a new mode of action. Imidacloprid is a systemic insecticide, used as a soil, seed or foliar treatment in cotton, rice cereals, peanuts, potatoes, vegetables, pome fruits, pecans and turf, for the control of sucking insects, soil insects, whiteflies, termites, turf insects and the Colorado potato beetle, with long residual control. Like nicotine, it acts on the nervous system. It has wide diversity of applications in agriculture. The development of resistance to imidacloprid by pest insects is a significant concern,[5] so there is a need to synthesize new insecticides, to show better results than earlier reported. Motivated by these findings, and in continuation of our ongoing efforts endowed with the discovery of nitrogenated heterocycles with potential chemotherapeutic activities,[6] herein we report the facile synthesis and larvicidal activity of various Baylis-Hillman derived *N*-cinnamyl substituted nitro imino imidazole derivatives.

2. RESULTS AND DISCUSSION

Baylis–Hillman reaction[7] is a standard C–C bond formation reaction generally used in synthetic organic chemistry. The reaction has been greatly studied and various applications are reported in the literature.[8] Various Baylis-Hillman bromides were prepared from respective Baylis-Hillman adducts by using the literature procedure.[9] Present work deals with the synthesis of new *N*-allylated 2-nitroiminoimidazolidine analogues derived from Baylis-Hillman bromides. The target compounds (**4a-j**) can be obtained by the reaction between Baylis-Hillman bromides and 2-nitro imino imidazole moiety in acetonitrile solvent using K_2CO_3 at room temperature. Variety of new *N*-

allylated 2-nitroiminoimidazolidines are synthesized and analyzed for their insecticidal activity.

This invention relates in essence to cinnamyl substituted-nitro imino imidazoline derivatives. Baylis-Hillman derived *N*-cinnamyl substituted nitro imino imidazole derivatives were effectively prepared by the reaction between Baylis-Hillman bromides **2a-j** and 2-nitro imino imidazole **3,** the starting materials Baylis-Hillman bromides **2a-j** were synthesized according to the literature procedure.[9] 2-nitro imino imidazole was treated with Baylis-Hillman bromide, **2a** in acetonitrile solvent in the presence of K_2CO_3 at room temperature for 5 h, the desired product was obtained in very good yield. The sequence of synthetic methodology is depicted in **Scheme 1**.

During the optimization studies, the reaction was carried out in different bases such as NaH, K_2CO_3, NaOMe in MeOH, NEt_3, and also with hindered amine DABCO. Compared with other bases, it was observed that with K_2CO_3, the imino derivative was obtained at ambient temperature in excellent yield. To demonstrate the general utility of the method, we applied these conditions to a variety of Baylis-Hillman bromides having ester and nitrile functionality (**2a-j**). In all the cases, the reactions occurred smoothly, affording products in very good yields (**Table 1**). All the synthesized products were characterized well by spectroscopic data.

The preparation of another half of heterocyclic moiety of the target molecule (nitro imino imidazole) can be synthesized under different experimental conditions.[10, 11] The nitro

imino imidazole **3** is conveniently and efficiently prepared from ethylenediamine and nitroguanidine in presence of hydrochloric acid (**Scheme 2**).[12]

The present study was carried out to determine the insecticidal (larvicidal) activity of compounds 4(a-j). Larvae mortality was recorded after 24 hours. Toxicity or activity was reported as LC_{50} and LC_{90} that is ppm of compound 4(a-j) that killed 50% and 90% larvae respectively in 24 hours. This calculation was carried out using probit analysis software. The detail results are presented in Table 2. Mosquito larvicidal test was performed according to the standard methodology (WHO, 1978). Fourth instar mosquito larvae, a *Culex quinquefasciatus* were reared under laboratory conditions (temperature 25 ± 3° and relative humidity 75 ± 5%). The insecticidal (larvicidal) activity was compared with a standard insecticide imidacloprid whose LC_{50} is 0.1 ppm against fourth instar larvae of *Culex quinquefasciatus*.

3. CONCLUSION

In conclusion, Baylis-Hillman derived *N*-cinnamyl substituted nitro imino imidazole derivatives were prepared in an efficient manner. The prepared compounds were tested for their larvicidal activity on fourth instar mosquito larvae, a *culex quinquefasciatus* and compared with a standard insecticide imidacloprid.

4. EXPERIMENTAL SECTION

4.1 General Methods

All the chemicals used were of reagent grade obtained from local suppliers, Aldrich and Fluka. All reactions were performed in oven-dried glassware under nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed on silica gel plates and TLC visualization was carried out with UV, using TLC aluminium sheets precoated with silica gel 60 F_{254} to a thickness of 0.25 mm (Merck). Flash column chromatography was done using silica gel (Merck, 60-120 mesh). Melting points were determined on a Mettlers-Temp apparatus and are uncorrected. IR Spectra were recorded using a Perkin-Elmer FT-IR spectrometer; ν in cm^{-1}. ^{1}H and ^{13}C-NMR spectrum ($CDCl_3$/DMSO-d_6) was recorded with Gemini-200 and Bruker-Avance-300 instruments; chemical shifts δ in ppm relative to $SiMe_4$ as an internal standard, couplings in Hz. Mass spectra were recorded on VG Micromass 7070 H (EI), Thermofinnigan ESI ion trap mass spectrometer. HRMS (ESI) data were recorded on a QSTAR XL High resolution mass spectrometer; in *m/z* (rel. %).

4.2 General Procedure For The Synthesis Of {(Substituted Cinnamyl)-] Tetrahydro-1*H*-2-Imidazolyliden}-1-Hydraziniumolate (4a-J): 2-{1-[(*E*)-2-(Methoxycarbonyl)-3-Phenyl-2-Propenyl] Tetrahydro-1*H*-2-Imidazolyliden}-1-Oxo-1-Hydraziniumolate (4a):

To a solution of 2-nitro imino imidazole (**3**) (156 mg, 1.2 mmol) in acetonitrile (3 mL) was added K_2CO_3 (165 mg, 1.2 mmol), Baylis-Hillman bromide (**2a**) (254 mg, 1 mmol) sequentially at room temperature and the reaction mixture was stirred for 5 h at room temperature. After complete consumption of starting material as monitored by TLC, the reaction mixture was filtered and the filtrate was washed with water and extracted with ethyl acetate (2 x 15 mL), dried (Na_2SO_4), concentrated under reduced pressure and the

residue was purified by silica gel column chromatography using EtOAc:hexane (1:1) as eluent to afford pure product (280 mg, 92%) as white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.41-3.47 (t, *J* = 9.1 Hz, 2H), 3.58-3.64 (t, *J* = 9.1 Hz, 2H), 3.83 (s, 3H), 4.44 (s, 2H), 7.34-7.43 (m, 5H), 7.92 (s, 1H), 8.05 (s, NH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 41.2, 41.4, 45.2, 52.5, 127.3, 129.1, 129.3, 129.8, 135.4, 142.9, 160.9, 167.1. IR (KBr): 3411, 2923, 1711,1561, 1434, 1285, 1251. Mass (ESI): m/z 305 $[M+H]^+$ HRMS (ESI) *m/z* calcd for $C_{14}H_{17}N_4O_4$: $[M+H]^+$ 305.1249; found: 305.1263.

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SUPPLEMENTARY INFORMATION

The supplementary information includes all experimental procedures, characteristic data and spectra of new compounds (**4a-j**). This material can be found via the "Supplementary Content" section of this article's webpage.'

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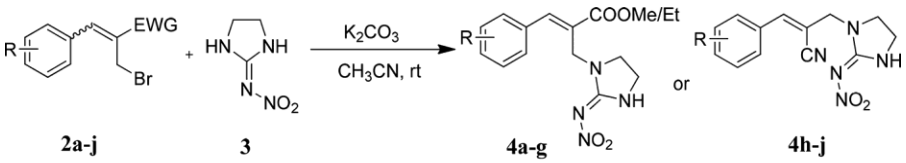
Table 1: /V-Cinnamyl nitro imino imidazole derivatives from Baylis-Hillman bromides



2a-j **3** **4a-g** **4h-j**

EWG = COOMe, COOEt, CN when EWG =COOMe/Et EWG = CN

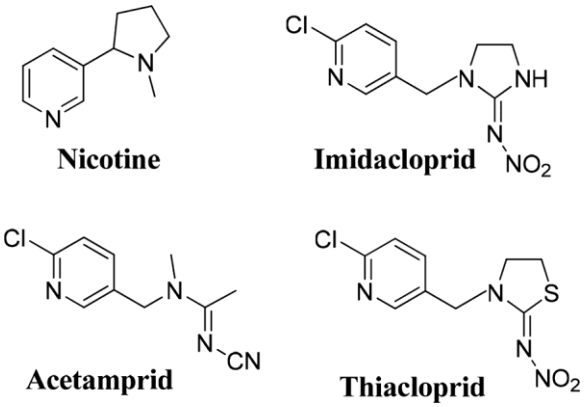
S.No.	Product	Time (h)	Yield (%)[a]	Mp (°C)
1	4a; R = H; EWG = COOMe	5	92	146-148
2	4b; R = p-Br; EWG =	5.5	91	98-100
3	4c; R = p-CI; EWG =	6	90	Viscous
4	4d; R = p-CH_3; EWG =	5	92	106-108
5	4e; R = m-CI; EWG =	5.5	91	118-120
6	4f; R = p-CF_3; EWG =	6	94	182-184
7	4g; R = H; EWG = COOEt	5.5	90	126-128
8	4h; R = H; EWG = CN	5.5	87	116-118
g	4i; R = p-CH_3; EWG = CN	6	88	110-112
10	4j; R = p-CI; EWG = CN	6.5	87	122-124

[a]isolated yield

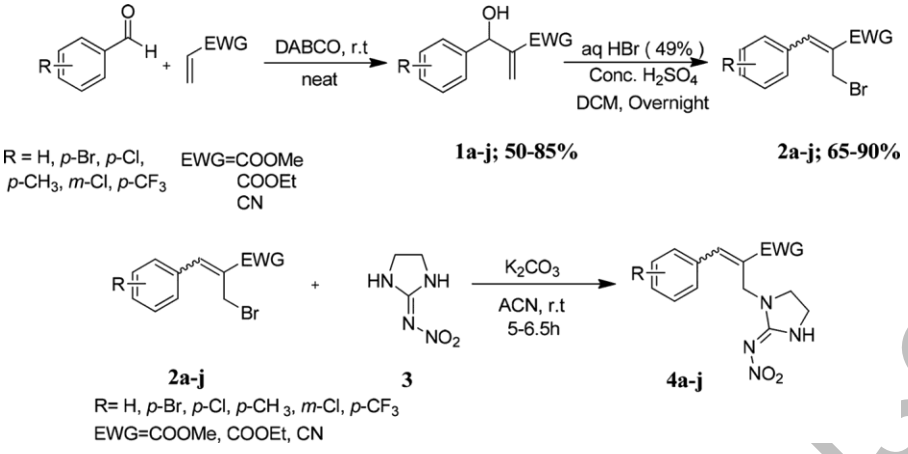
Table 2:Larvicidal activity of compounds 4a-j on mosquito larvae

S. No	Compound	LC_{50} Values	LC_{90} Values
1	4a	41.22	118.48
2	4b	92.37	287.24
3	4c	38.56	119.38
4	4d	95.45	412.58
5	4e	12.49	108.21
6	4f	72.16	252.04
7	4g	> 100	> 100
8	4h	> 100	> 100
9	4i	> 100	> 100
10	4j	> 100	> 100

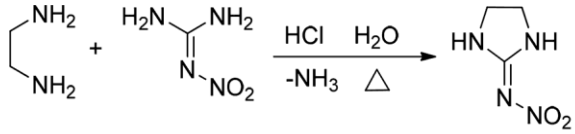
Figure 1: Potent insecticides available in the market



Scheme 1: Synthesis of *N*-allylated 2-Nitroiminoimidazolidines analogues from Baylis-Hillman bromides



Scheme 2: Synthesis of Nitro imino imidazole



3, 62%