

PREPARATION OF 3,5-DIARYLISOXAZOLES FROM CHALCONE DIBROMIDE AND HYDROXYLAMINE HYDROCHLORIDE.



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ABSTRACT:

The reaction of 2-acetylthiophene and 5-methyl-2-acetylthiophene with NaOH, and then with aromatic aldehyde, followed by treatment with molecular bromine in presence of chloroform, and subsequently with hydroxylamine provided the corresponding 3,5-diarylisoxazoles in moderate yields.

KEYWORDS: Chalcone dibromide, thiophene, 3,5-diarylisoxazoles, heterocycles.

1. INTRODUCTION:

Isoxazoles are well known five member heterocyclic compounds, receiving considerable importance both in advance organic material¹ and biological application in medicinal² and material science³. Isoxazoles and its derivatives have been studied for more than a century as an important class of five member heterocyclic compounds and have continued to attract considerable attention due to the broad range of biological activities including GABA antagonist⁴, antibiotic⁵, antipsychotic⁶, antidepressant⁷, novel inhibitors of cyclooxygenase-2 with analgesic and anti-inflammatory activities⁸, anti-inflammatory⁹, antagonist¹⁰, antinociceptive¹¹, antimicrobial¹², antifungal¹³, anti-cancer¹⁴ activities. The most representative synthetic strategies for the construction of isoxazole nucleus including (i) reaction of hydroxylamine with 1,3-dicarbonyl compounds¹⁵ (ii) [3 + 2] cycloaddition of alkynes/ alkenes and nitrile oxides¹⁶ (iii) intermolecular cyclization of oximes with C-C double/triple bonds¹⁷. However, these synthetic strategies generally require harsh reaction condition including strong bases, strong mineral acids, or high temperatures or provide modest regioselectivity and neither economic nor eco-friendly.

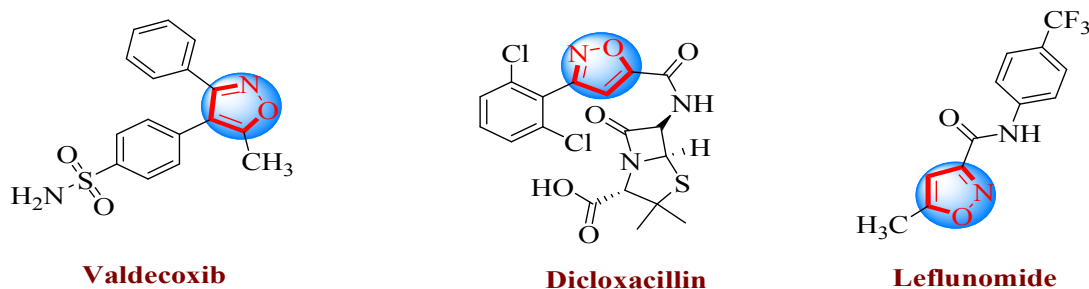


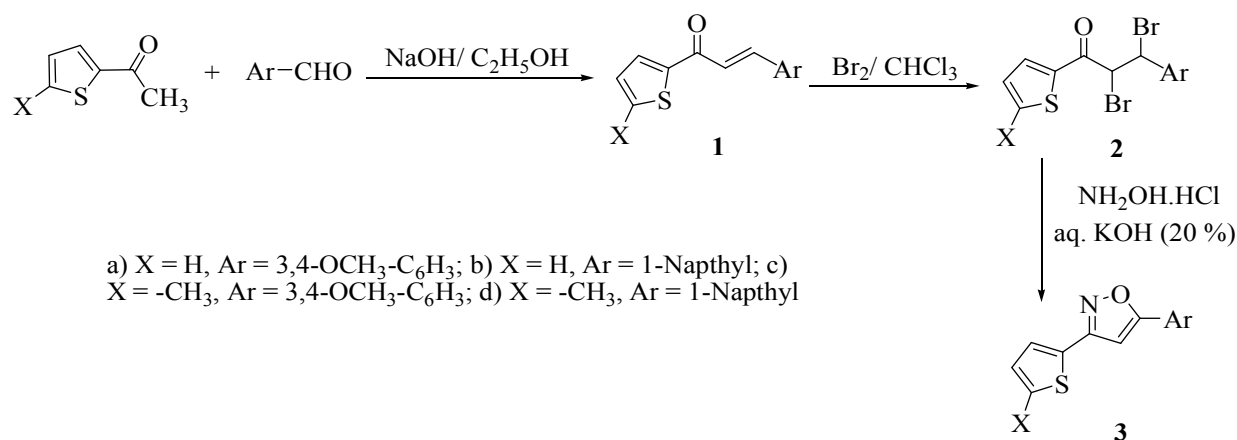
Fig:-1 Representative of biological active isoxazoles

From the literature survey, It was found that α,β -chalcone dibromide are also highly selective for preparation of isoxazoles¹⁸. Encourage by these results and with the aim to explore the potential of chalcone dibromide, four derivatives of 3,5-diaryl isoxazoles has been synthesized from chalcone dibromide having thienyl moiety.

2. RESULT AND DISCUSSION:

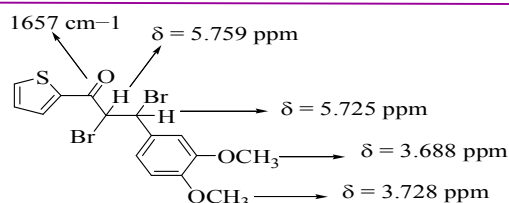
Chemistry:

The required starting material thienyl-containing chalcone (**1a**) obtained by treatment of 2-acetylthiophene with sodium hydroxide in ethanol under cold condition, followed by addition of 3,4-dimethoxybenzaldehyde. Then compound (**1a**) was treated with molecular bromine¹⁹ in presence of chloroform which results in the formation of corresponding chalcone dibromide (**2a**) in good yields (**Scheme 1**).



Scheme:-1 Synthesis of 3,5-diaryl isoxazoles

Compound (**2a**) gave agreeable analyses for the proposed structure, which is further confirmed by their spectral data. The ¹H NMR spectra(**Fig-1**) showed two doublets, one at δ 5.725 ppm (d, J = 10.4 Hz, 1H), and other at δ 5.759 ppm (d, J = 10.4 Hz, 1H), each peak integrating to one proton with a coupling constant of 10.4 Hz. These peaks can be ascribed for two methine protons of chalcone dibromide.



Remaining proton appear in aromatic region $\delta = 6.728-7.687$ ppm

Fig:-2 ¹HNMR spectra of 2, 3-dibromo-3-(3, 4-dimethoxyphenyl)-1-(thiophen-2-yl) propan-1-one

After refluxing of chalcone dibromide (**2a**) i.e 2, 3-dibromo-3-(3, 4-dimethoxyphenyl)-1-(thiophen-2-yl) propan-1-one with hydroxylamine hydrochloride in according to literature procedure²⁰ for 3-4 hours afforded 5-(3, 4-dimethoxyphenyl)-3-(thiophen-2-yl)isoxazole (**3a**) in moderate yield. Similarly, other isoxazole derivatives in moderate yields were synthesized by using similar approach.

Table:-1 Physical data of chalcone dibromide and 3,5-diarylisoxazoles according to scheme 1.

Entry	compound	X	Ar	M.pt(°C)	Yield(%)
1	2a	H	3,4-OCH ₃ -C ₆ H ₃	163-165	68
2	2b	H	1-Naphthyl	112-115	54
3	2c	CH ₃	3,4-OCH ₃ -C ₆ H ₃	140-142	60
4	2d	CH ₃	1-Naphthyl	155-158	71
5	3a	H	3,4-OCH ₃ -C ₆ H ₃	140-142	46
6	3b	H	1-Naphthyl	164-166	38
7	3c	CH ₃	3,4-OCH ₃ -C ₆ H ₃	151-153	54
8	3d	CH ₃	1-naphthyl	148-150	32

CONCLUSION:

Reactions of four different derivatives of chalcone dibromide were performed with hydroxylamine hydrochloride, which results in formation of 3,5-diarylisoxazoles in a regioselective manner.

3. EXPERIMENTAL

3.1. Chemical synthesis

Melting points were taken in open capillaries in electrical melting point apparatus and may be uncorrected. The IR (KBr) and ¹HNMR spectra were recorded on Perkin-Elmer IR1800 spectrophotometer and Bruker 300 MHz spectrophotometer, respectively. All the new compounds gave satisfactory analytical results (within ± 0.4 of the theoretical values). Chalcone dibromides were synthesized according to the literature procedure¹⁹.

3.2. Preparation of chalcone dibromide 2 (a-d).

To the cold solution of 1(a-d) (0.01 mol) in chloroform, a solution of bromine (0.01 mol) in chloroform was added drop-wise. The reaction mixture was stirred at room temperature for 2-3h. Then reaction mixture was diluted with petroleum ether and refrigerated for 3-4h. Then solid product was filtered and washed with petroleum ether and finally dried.

3.3. Preparation of 3, 5-diarylisoxazoles 3 (a-d).

Suspension of chalcone dibromides 2(a-d) (0.01 mol) was refluxed with hydroxylamine hydrochloride (0.02 mol) in 25-30 ml ethanol, and then solution of KOH (85 %) in water was added drop-wise. Then resulting mixture heated again for 20-25 min and then after cooling diluted with cold water. Then solid product was filtered, washes thoroughly with water and recrystallized with ethanol.

4. CHARACTERIZATION DATA OF 3,5-DIARYLISOXAZOLES

5-(3,4-dimethoxyphenyl)-3-(thiophen-2-yl)isoxazole (3a).

Yield 46 %; mp 140-142°C. IR (ν_{\max} , in KBr): No peak in CO region. ^1H NMR (CDCl_3 , 300 MHz, δ): 3.678 (s, 3H, OCH_3), 3.875 (s, 3H, OCH_3), 7.157-7.185 (m, 2H), 7.257-7.460 (m, 3H), 7.458 (s, 1H), 7.643 (s, 1H, isoxazolyl ring). ^{13}C NMR (CDCl_3 , 100Hz, δ): 56.98, 57.64, 102.24, 111.95, 112.69, 119.58, 123.01, 125.24, 127.98, 134.59, 144.68, 151.54, 152.00, 156.35, 173.25

5-(naphthalen-1-yl)-3-(thiophen-2-yl)isoxazole (3b).

Yield 46 %; mp 164-166°C. IR (ν_{\max} , in KBr): No peak in CO region. ^1H NMR (CDCl_3 , 300 MHz, δ): 7.227-7.369 (m, 3H), 7.435-7.560 (m, 3H), 7.658-7.829 (m, 4H), 7.694 (s, 1H, isoxazolyl ring). ^{13}C NMR (CDCl_3 , 100Hz, δ): 104.40, 122.95, 125.98, 126.00, 126.79, 127.08, 127.27, 127.41, 127.59, 128.15, 128.99, 130.05, 130.43, 130.56, 134.30, 156.99, 171.26.

5-(3,4-dimethoxyphenyl)-3-(5-methylthiophen-2-yl)isoxazole (3c).

Yield 54 %; mp 151-153°C. IR (ν_{\max} , in KBr): No peak in CO region. ^1H NMR (CDCl_3 , 300 MHz, δ): 2.459 (s, 3H, CH_3), 3.688 (s, 3H, OCH_3), 3.775 (s, 3H, OCH_3), 7.168-7.97 (m, 2H), 7.218-7.397 (m, 2H), 7.639 (s, 1H, isoxazolyl ring). ^{13}C NMR (CDCl_3 , 100Hz, δ): 21.04, 56.78, 56.98, 101.25, 110.59, 113.49, 118.78, 122.05, 125.85, 127.25, 134.46, 143.87, 151.04, 151.54, 155.39, 172.69

3-(5-methylthiophen-2-yl)-5-(naphthalen-1-yl)isoxazole (3d).

Yield 46 %; mp 148-150 °C. IR (ν_{\max} , in KBr): No peak in CO region. ^1H NMR (CDCl_3 , 300 MHz, δ): 2.448 (s, 3H, CH_3), 7.189-7.371 (m, 2H), 7.398-7.485 (m, 3H), 7.647-7.814 (m, 4H), 7.703 (s, 1H, isoxazolyl ring). ^{13}C NMR (CDCl_3 , 100Hz, δ): 20.83, 104.50, 125.92, 126.12, 126.24, 126.68, 127.15, 127.67, 125.15, 128.86, 130.49, 130.57, 133.60, 143.34, 155.36, 171.35

ACKNOWLEDGEMENT

The author Ravinder Kumar is thankful to the CSIR, New Delhi for award of Junior Research Fellowship and Kurukshetra University, Kurukshetra for providing lab facilities under the supervision of Dr. Raj Kamal.

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