

Microwave assisted synthesis of some isoxazoles

Manoj Kumar¹ and Nagendra Prasad²

Associate Professor, Department of Chemistry, Raja Singh College, Siwan

²Research Scholar, J.P. University, Chapra

Email-kumarmanoj1921990@gmail.com, prasadnagendra985@gmail.com

Manuscript received online 03 March 2022, accepted on 18 July 2022

Abstract : A pair of isoxazole derivatives A and B has been prepared by reacting 6-(4-fluorophenyl)-3-cyano-4-methylsulfanyl-2H-pyranon-2-one with hydroxylamine hydrochloride. A is 3-amino-6-(4-fluorophenyl)pyrano[4,3-c]isoxazol-4-one and B is [3-(4-fluorophenyl)isoxazol-5-yl]acetonitrile. The starting material has two positions susceptible to nucleophilic attack. The first position is at C-4 and the second at C-6. The attack at C-4 leads to formation of A by usual ring closure. The attack at C-6 leads to ring opening followed by decarboxylation and cyclisation to an intermediate which eliminates methanethiol to produce B.

(Keywords : isoxazole derivatives, microwave assisted synthesis)

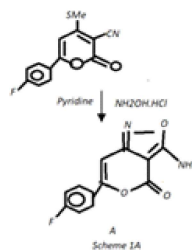
Introduction

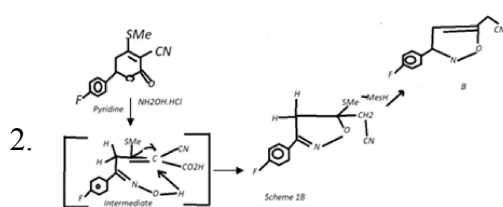
The synthesis of a wide range of functionalized heterocyclic scaffolds is important to medicinal chemists because it allows them to increase the amount of drug-like chemical space that may be used to bind to biological targets based on chemical diversity. To speed up the drug development procedure, it is also highly desirable to create reliable synthetic methods for the production of a varied array of heterocyclic compounds. The five-membered heterocyclic pharmacophore isoxazole is a key component of many drug discovery studies. The biological effects of functionalized isoxazole scaffolds include anticancer, putative HDAC inhibitors, antioxidant, antibacterial, and antimicrobial action. Evidently, the core structure of isoxazole has been found in a variety of medications, including sulfamethoxazole^{3a} A, which has antibiotic properties, muscimol^{3b} B, which has GABAA

properties, ibotenic acid^{3c} C, which has neurotoxin properties, parecoxib^{3d} D, which has COX₂ inhibitor properties, and leflunomide^{3e} E, which has immunosuppressive properties (Fig. 1). Additionally, isoxazole derivatives play a significant role in the tiny chemical entities found in synthetic everyday items. Isoxazole moiety is one of the most extensively studied scaffold which has wide applications as drugs¹⁻⁵. We have also prepared a pair of isoxazole derivatives whose preparation and characterization are being reported in the present communication.

Experimental

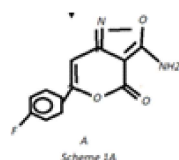
A mixture of 6-(4-fluorophenyl)-3-cyano-4-methylsulfanyl-2H-pyran-2-one (5mmol) and hydroxylamine hydrochloride (5mmol) in pyridine (6 ml) was irradiated with microwave at 40% (320 W) level. Pyridine was removed and residue was taken up in chloroform. It was washed with water, dried and chromatographed on a silica gel column. Three products were obtained. The structure assignments were based on their spectroscopic and analytical data. Scheme 1 represents the reaction taking place.





Results and Discussion

Compound -A



M.P.: 294°C

Yield: 33%

Microanalysis:

Found: C, 58.52%, H, 2.97%, N, 11.36%

C₁₂H₇FN₃O₃ requires, C, 59.53%, H, 2.84%, N, 12.38%.

IR: 9_{MAX}/CM⁻¹: 3376(NH₂), 1701 (C=O)

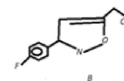
NMR: 0H (CDCl₃ + [2H6]-DMSO)

6.58 (1H, s, 7-H), 7.59 (2H, d, J 10Hz, 3'-, 5'-H),

7.62 (2H, d, J 10Hz, 2'-, 6'-H)

Mass: M/z (71 eV) 245(M⁺), 201

Compound B



Gummy mass

Yield: 21%

Microanalysis:

Found: C, 58.48%, H, 5.55%, N, 12.28%

B-requires, C, 58.6%, H, 4.4%, N, 12.2%.

IR: 9_{max}/cm⁻¹: 2226 (CN)

NMR: 5ΔH (CDCl₃) 2.26 (3H, s, S-CH₃),

2.17, 3.33 (1H each, d, J 14 Hz, CH₂CN),

3.76, 3.68 (1H each, d, J 18 Hz, 4a-, 4b-H),

6.58 (2H, d, J 9 Hz, 3'-, 5'-H),

7.94 (2H, d, J 9 Hz, 2'-, 6'-H)

Mass: m/z (69 eV) 250(M⁺), 204, 161

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An International Peer Reviewed Research Journal of Chemistry

Abstracted / Indexed in : Chemical Abstract U.S.A.

JC- 1495/2K22 (ISSN:0973-239X), INDIA

Journal Chemtracks Vol. 24 (1&2), 99-100, January to December 2022