

Synthesis of some isoxazole derivatives by ring transformation of pyrone-2

Anita Sharma¹, Anamika² and S. R. Kumar³

¹Research scholar, Kolhan University, West Singbhum, Chaibasa, Jharkhand

²Department of Chemistry, Jamshedpur Women's College, Jamshedpur, Jharkhand

³Department of Chemistry, Lalit Narayan Mithila University, Darbhanga (Bihar)

Email : anitajsr2@gmail.com

Manuscript received online 22 March 2018, accepted on 19 June 2018

Abstract : Heterocyclic compounds containing nitrogen and oxygen as hetero atoms are an important class of compounds largely employed in pharmaceutical and therapeutic field. The present paper deals with the synthesis of 3,5-disubstituted isoxazoles from substituted phenyl pyrone-2 on treatment with hydroxyl amine hydrochloride on irradiation in microwave. This method of ring transformation is a deviation from the classical synthetic procedures.

(Key words: Heterocyclic compounds, pharmaceutical, pyrone- 2, hydroxylamine hydrochloride, irradiation, isoxazole)

Introduction

Heterocyclic compounds are woven into life processes. A variety of compounds are naturally occurring. Heterocyclic Chemistry has its origin in organic synthesis, natural products chemistry and medicinal chemistry. These are present in more than 90 percent of the novel drugs. The isoxazole moiety is present in insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and anti-ulcerogenic drugs. Many general methods of synthesis of substituted isoxazoles are known. Condensation- cyclisation of α , β - diketones with hydroxylamine yields isoxazoles. Ring transformation reactions include ring contraction, ring retention or ring expansion. Pyrones are taken as the starting material for the synthesis in the given research work. There are two pyrones to be known 2H-pyrone and 4H-pyrone. These compounds do not possess an aromatic sextet. Studies show that 2-pyrones bear higher order of activity. It is found that a number

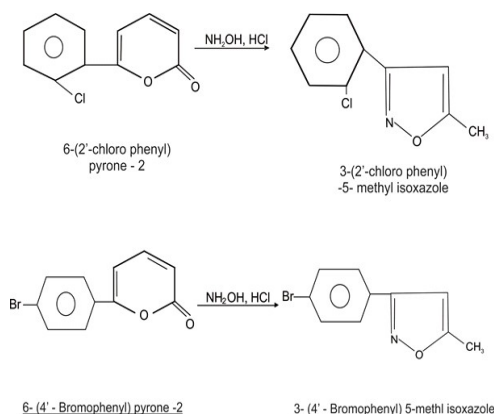
of nucleophilic centres in 2-pyrone could alone or in combination be exploited for the generation of a variety of new heterocyclic products. These are present at C2, C4 and C6 centres. It is also found that in contrast to electrophilic substitution, pyrones are easily attacked by nucleophilic reagents. Weak nucleophiles add at 2-position while strong ones at 6-position. The present work involves the treatment of 6-(substitutedphenyl) pyrone-2 with hydroxylamine hydrochloride under microwave irradiation for 5 minutes at 320W. The reaction proceeds via opening of the ring between N and C of carbonyl group after attack of the nucleophile on C atom followed by recyclisation to 3,5-disubstituted isoxazole derivatives. The substituent initially at position 6 in pyrone-2 is retained at position 3 of the isoxazole nucleus.

Experimental

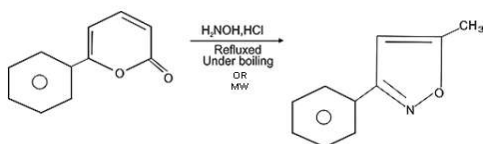
Melting points were uncorrected. Elemental analysis was carried out by elemental analyser Vario EL III, IR spectra (KBr) was performed by IR-Prestige 21 FTIR spectrum. The visible absorption spectra were recorded on UV-visible spectrophotometer, Perkin Elmer Lambda-25 and NMR spectra (CDCl_3) on Varian A- 60 spectrophotometer with TMS as an internal standard. Mass spectra were measured on JEOL JMS D-300 spectrometer. Silica gel used for chromatography was 60-120 mesh. Reactions were carried out in Samsung CE74JD (800W) unmodified domestic oven.

General method for the synthesis of 3-(substitutedphenyl)-5-methylisoxazoles

A mixture of 6-(o-chlorophenyl)pyrone-2 or 6-(p-bromophenyl)pyrone-2 (6g), hydroxylamine hydrochloride (1.7g) and pyridine (5ml) was taken in a conical flask and homogenous solution was prepared by shaking. It was allowed to irradiate in a microwave for 5 minutes at 320W. After completion of the reaction pyridine was evaporated and to the residue chloroform was added, washed with water several times. It was dried and finally passed through column of silica gel and was eluted with benzene-ethylacetate and double run. The compound obtained was recrystallized from methanol and chloroform to furnish pure crystals of 3-(substitutedphenyl)-5-methylisoxazole. The 6-substitutedphenyl pyrones were earlier synthesized by Van Pechmann condensation. The following isoxazole derivatives were prepared by the above method



In general the reaction will be given as



3-(2¹-chlorophenyl)-5-methylisoxazole

Yellow crystals

Yield = 70%

Melting point : 122°C

Found N = 7.10%

Calculated N = 7.19%

I.R V_{max} (KBr disc.) :

1660 cm^{-1} (for C=N stretching frequencies), 940 cm^{-1} (for N-O group), 3340 cm^{-1} (phenyl substituted isoxazole ring), 3600 cm^{-1} (for C=N-O- grouping), 740 cm^{-1} (for aromatic C-Cl group), 720 cm^{-1} (for C-H bending for 1,2-disubstituted benzene ring)

¹H.N.M.R. δ H(CDCl_3): (80, MHz) 1.84 (1H, s), 7.27 (2H, d, J 8.1, Hz, ArH), 7.54 (2H, d, J 8.1, Hz, ArH), 1.58 (1H, s, -CH), 6.62 (1H, s, 8H)

Mass spectrum

(m/z) = 193.5

3-(4¹-bromophenyl)-5-methylisoxazole

Yellow crystals

Yield = 2.8g

Melting point = 182°C

Found N = 5.84%

Calculated N = 5.88%

I.R V_{max} (KBr disc) 1665 cm^{-1} (for C=N- stretching frequency) 950 cm^{-1} (for N-O group), 3340 cm^{-1} (for aryl substituted isoxazole), 3360 cm^{-1} (for C=N-O group), 750 cm^{-1} (for C-H bending for 1,2-disubstituted benzene), 820 cm^{-1} (for aromatic C-Br group)

¹H.N.M.R. δ H(CDCl_3), (80MHz)

1.84 (1H, S), 7.26 (2H, d, J 8.1, Hz, Ar-H), 7.62 (2H, d, J 8.1, Hz, Ar-H)

1.54 (1H, s, -CH), 6.54 (1H, S, 8H)

Mass spectrum (700ev) (m/z)⁺ = 238, 223

Conclusion

The 3 and 5 di-substituted isoxazole derivatives were obtained by the transformation of corresponding substituted 2- pyrones in the presence of hydroxylamine hydrochloride which were further characterised by spectral studies. The IR range of the synthesized compounds falls between 700-1670 cm^{-1} which is within the range of isoxazole molecule. The values for substituted

benzene ring is also in accordance with the actual range. The obtained NMR data helps in building the structure of the compound thus suggesting that values obtained are correct. Some deviations in the values may occur due to substitution at 3 and 5. These spectral studies help in revealing and identifying the structures of the synthesized isoxazoles derivatives.

References

1. H.C.Vander Plas and H.J.Den Hertog. *Rec. trav Chem* **81**, 841 (1996)
2. The Chemistry of Heterocyclic compounds, R.C. Elderfield (Ed.) Vol. V John Wiley and Sons New York (1956).
3. K.M. Johnson and R.G. Schotter. *J.Chem. Sockl* **1774**, (1960).
4. R. Justoni and R.Pesia, *Gazz, Chim etal.* **85**, **34**, (1955).
5. W.J. Wakefield, and D.J. Wright. *Adv. Heterocycl Chem.* **25**, 147 (1979).
6. T. Shimizu, Y. Hayashi, N. Furukawa and K. Teramura *Bull.Chem. Soc. Japan* **64**, 318 (1991).
7. K. Shravan kumar. V. Chandrashekhar, V. Ravinder "N- Heterocyclic carbon catalysed 1,3- dipolar cycloaddition reaction" *Org. biomole* **9**, 7869, (2011)
8. Ajay Kumar, M. Govindraju and Vasant kumar "synthesis of isoxazole via 1,3 – dipolar cycloaddition reaction and their antimicrobial activity *Ind. J. Het. chem.* **20**, 183, 184, (2010).
9. P. Jayroopa, Vasantkumar, N. Renuka and Ajay kumar " synthesis of new 3,5- diaryl dipolar cycloaddition reaction " *IQSR. J, APP. Chem.* **14**, 20, (2011)
10. Ajay kumar K.Govindraju M.Jayarupa P.and Vasanth Kumar G., Nitrile Oxides; A key intermediate in organic synthesis. *Int. J. Chem. Bio Sci.* **3(1)**, 91 (2013)
11. V.S. Jamode, H.S. Chandak, P.R Bhagat, D.H. Tambekar *Indian J. Heterocyclic Chem.* **12**, 323, (2003).
12. Vasant kumar, P. Jayaroopa "synthesis of 3,5- diarylisoxazolo-4-carbonitriles and their efficacy as antimicrobial agents" *Org. pharma chem.*, 4161, 2283 (2012)
13. J.P Waldo and R.C. Larock. "synthesis of isoxazoles via electrophilic cyclisation. " *Org. lett* **7**, 5203 (2005).
14. J. Fried in Heterocyclic compounds R.C. Elderfield (Ed.) Vol-I willy New York. Page 343, (1950).

