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Synthesis of Ethyl 4,6-Dichloro 2-Methyl Nicotinate from 2,4,6-Trichlorophenol

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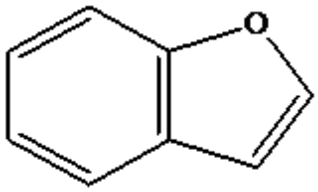
ABSTRACT

The present work on the preparation and trapping of Furo [3,4-c] pyridine inspired us to study the scope and limitations of this work. Beside this it was decided to work and study Tandem pummerer-Diels-Alder reaction on keto Sulphoxide. With these keto sulphoxides we turned our attention to the formation of some azalignans via the standard sequential pummerer Diels-alder reaction.The treatment of keto Sulphoxide with acetic unhydried.P-toluene sulphonic acid in presence of dimethyl maleate in refluxing toluenegave the bridged product.

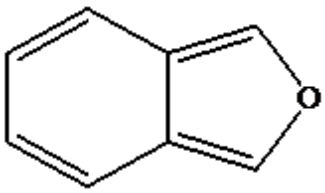
Keywords: Isobenzofuran ,Diels-Alder reaction.

I. INTRODUCTION

Isobenzofuran is a heterocyclic compound consisting of fused benzene and furan rings.Itis isomeric with benzofuran .



Benzofuran



Isobenzofuran

The IUPAC name of isobenzofuran is 2-benzofuran. Science these isobenzofurans and highly reactive and their ability to polymerizes rapidly. They can be prepared by thermolysis by using some suitable precursors and can be trapped at low temperature.Isobenzofurans represented by benzo[c] furan have for a long timeserved as an interesting ciass of reactive intermediates in organic synthesis.As a functional derivative of o-xylylenes. They take part in both inter and intramolecular Diels-Alder reactions leading to a veriety of polycyclic rings

systeams including natural products of biological significance(1).In contrast, heteroanalogues of isobenzofurans have received much less attention ,although this situation is changing in recent years(2,3).Unlike isobenzofurans,heteroisobenzofurans have not found as much as use in the synthesis of natural products.However,the limited work published in the literature is summerisedhere.One of the most interesting application of heteroisobenzofurans is found in a synthesis of the potent anticancer pyridocarbazole alkaloid ellipticine.

II. EXPERIMENTAL DETAILS

2, 4, 6 -Trichlorophenol

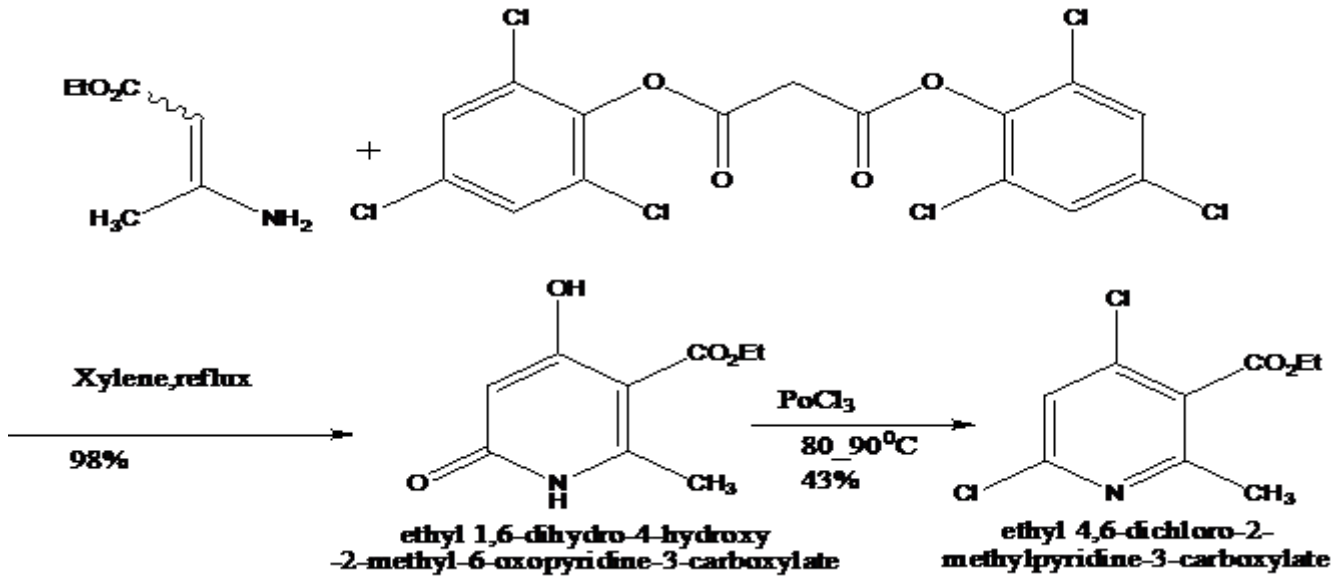
To a vigorously stirred solution of phenol (9.6 g,0.1 mol) in conc. HCl(150 ml) was addede 30% H_2O_2 (40 ml) dropwise at 0^0c over a period of 30 minute. The reaction mixture was heated at 60^0c for 4^{th} during which orange solid was formed. After filtration, washing and drying 19.8 g (98%) of titlecompound was obtained
MP 68^oc (lit[81]71^0c)

Bis 2,4,6-trichlorophenyl malonate[71]

To mixture of molanoic acid (3g.28.84 mmol),2,4, 6 – trichlorophenol (9.11 g 46.14 mmol) was added $POCl_3$ (10 ml) at 0^0c dropwise. Then the reaction mixture was allowed to come to room temperature and heated at 120-130^0c over a period of 6-7 hours. The resulting black solution was poured into ice-cold water slowly and stirred for 5 min. During which a brown precipitate was formed. The precipitate was filtered and repeatedly washed with water (5 times) and then dried in oven for 5h (keeping oven temperature below 800c) to give 8.5 g (63.6%) of the title compound. Bis2, 4, 6 -trichlorophenyl malonate.
M.P. 138-139^0 c

Ethyl 4, 6 – dichloro -2-methyl nicotinate

A stirred solution of 3- aminocrotonate(1.29 g,10 mmol) and bis -2, 4, 6 -trichloro phenyl malonate71 (4.63 g,10 mmol) in xylene (10 ml) was heated at reflux for 7-8 hours. Then the reaction mixture was cooled to room temperature and kept for overnight during which a brown precipitate was formed filtration and washing with benzene 3-4 time to remove any 2, 4, 6-trichlorophenol gave 1.93g of ethyl 4 – hydroxy-2-methyl-6-oxo- 1, 6-dihydropyridine-3- carboxylate,mp 225-228^0c (lit[72] 232^0c) in 98% yield, which was used for next step without further purification.
To the pyridone (1.9 g , 9.6 mmol) was added $POCl_3$(3.67 ml,40 mmol) at 0^0c and then heated on an oil bath keeping bath temperature fixed at 80-90^oc. After 70 hrat that temperature the resulting back solution was cooled to room temperature,pouredinto 50 ml of ice -cold water and extracted with CH_2Cl_2(3-4 times). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solutiondried over anhydrous Na_2SO_4, concentratedand purified by column chromatography to give 980 mg (43% of the title compound. Ethyl 4, 6-dichloro-2-methylnicotinate, as a yellow liquid).



III. CONCLUSION

In conclusion, a synthesis of constrained nicotine analogues 84 a and 90 has been achieved.Furthermore,the importance of electron withdrawing group on the pyridine ring and of the phenylsulfanyl group in the pyridine sidearm has been demonstrated as in the earlier work reported from our laboratory. Although the structure of 84 a is evident from extensive NMR, HRMS dataand transition state analysis,further investigation may be needed to confirm its stereochemistry via preparation of a solid derivative and x-ray crystal structure determination of the latter.

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