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Synthesis of Isobenzofuran Derivative {2, 6- Dichloro-4-[(Phenylthio) Methyl] Pyridine-3-Yl} (4-Methyl Phenyl) Methanol from 2, 6-Dichloro -4-[(Phenylthio) Methyl] Nicotinonitrite

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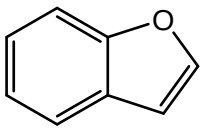
ABSTRACT

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

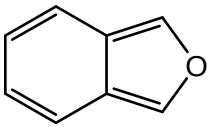
Keywords: - Isobenzofuran, Diels- Alder reaction.

I. INTRODUCTION

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



Benzofuran



Isobenzofuran

The IUPAC name of isobenofuran is 2-benzofuran. Since these isobenzofurans are highly reactive and their ability to polymerise rapidly. They can be prepared by thermolysis by using some suitable precursors and can be trapped at low temperature.

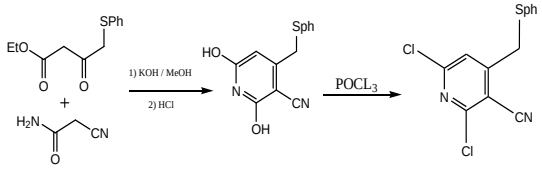
Isoenzofurans represented by benzo [c] Furan have for a long time served as an interesting class if reactive intermediates in organic synthesis. As a functional derivatives of o-xylylenes. They take part in both inter and intramolecular Diels- Alden reactions leading to a variety of polycyclic ring systems including natural products of biological significance(1). In contrast, heteroanaloguesof isobensofurans have received much less attension, 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 and non-natural products. However, the limited work published in the literature is summerised here. One of the most interesting application of

heteroisobenzofurans is found in a synthesis of the potent anticancer pyridocarbazole alkaloid ellipticine.

II. EXPERIMENTAL DETAILS

A]. Preparation of 2,6 –dichloro – 4- [(phenylthio) methyl] nicotinitrile: [A]

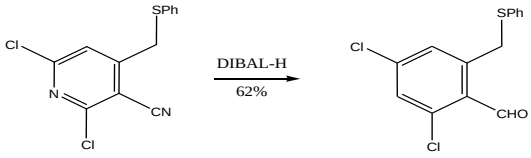
A mixture containing cyanoacetamide (5.60 gm, 60.21 mmol) and ethyl 4-(phenylthiol) acetoacetate (14.33 gm, 60.21 mmol) in 50 ml of methanol was warned to attain solution and potassium hydroxide (4.14 gm, 73.82 mmol) dissolved in 20 ml of methanol was added dropwise with stirring. The mixture was heated reflux : after 2 hours a brown PPT formed and heating was continued for an additional 5 hours. Then the reaction mixture was cooled and 2,6 – dihydroxy -4-(phenylthiol) methyl nicotiononitrate monopotassium salt'so formed was separated by filteration, dissolved in warm, cooled and acidified with concentrated hydrochloric acid. The product was separated by filtration, washed with cold methanol dried in air and finally further dried at 120-130^{0}C for 5 hours to give 8.4 gm of 2,6-dihydroxy-4-[(phenylthio)methyl] nicotinonitrile as of white solid : chars at 268^{0}C.



[A]

B]. Preparation of 2,6 – dichloro-4- [phenylthiol) methyl] nicotinonitrile :

A mixture containing 2,6-dihydroxy-4- [phenylthiol) methyl] nicotinonitrile. (4 gm , 15.5 mmol) and Pocl$_3$(5.8 ml, 62.0 mmol) was heated in a sealed tube at 150^{0}C for 9 hours. It was then cooled to room temperature and transferred into 100 ml of ice cold water. The mixture was filetered with repeated washings with was obtainedwater. The residue was dissolved in hot methanol, heated for 10 min with activated charcoal, filtered and concentrated. The resulting brown oil was purified by chromatography (EtOAc: Petroleum ether 1 : 99) to give 2.45 g (54%) of A as a yellow solid. A purer sample was obtained by recrystallization from petroleum ether to give colorless needles : mp 117^{0}C (mp 118-119^{0}C, reported by Dr. S. Basak from this laboratory).



[B]

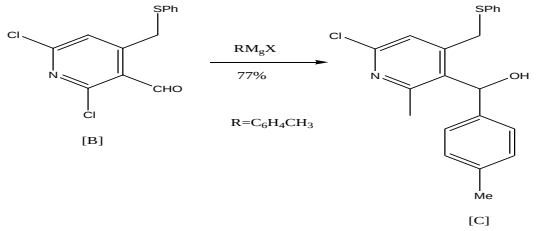
C]. Preparation of 2, 6 – Dichloro-4- [(phenylthio) methyl] nicotinaldehyde [B] from 2, 6- Dichloro -4- [(phenylthio) methyl] nicotinonitrile [A]

To a stirred solution of A(4 g, 13.56 mmol) in 60 ml of CH_2Cl_2 cooled to -78^{0}C was added 15 ml of DIBAL-H(1.0 M solution in toluene) dropwise over a period of 1 h. The resulting mixture was allowed to attain room temperature. After 2h of stirringat room temperature the solution was quenched with saturated aqueous NH_4Cl at 0^{0}C stirred for another 1h at that temperature and then acidified with 3N HCl. The organic layer was separated and the aqueous $NaHCO_3$. brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by chromatography (EtOAc : petroleum ether 1 : 99) to give 2.7g (67%) of the titled compound B as white crystalline solid : mp. 59-60^{0}C (mp. 61-62^{0}C, reported by Dr. S. Basak from this laboratory).

D]. Preparation of {2,6 – Dichloro -4- [(phenylthio) methyl] pyridine -3- yl} (4- methylphenyl) methanol from 2, 6 Dichloro-4-[(phenylthiol) methyl] nicotinaldehyde [A]

Toa stirred solution of aldehyde B (1g, 3.5 mmol) in 20 ml of dry THF was added dropwise a tolymagnesium bromide solution (16.8 ml, 0.4M)

[Prepared from P-bromo toluene(1.23 ml, 10 mmol and Mg (480 mg, 20 mmol) in 24 ml of THF] over a period of 10 min at -78^{0}C. During addition a blood red color was formed. After 1h of stirring the mixture was slowly warmed to 0^{0}C and the quenched with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was dried over anhydrous Na_2SO_4. Concentrated under reduced pressure, and purified by chromatography (EtOAc : petroleum ether 10 : 90) giving 950 mg (73%) of 120 as a white crystalline solid : mp – 129-131^{0}C.



IR.(KBr)3371, 1575, 1524, 1104, cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$: CCCl4 7 : 3) δ2.36 (S, 3H) 3.46 (S,1H), 3.84 (d,1H. J_{AB}= 15.3 Hz), 6.57(br S, 1H), 6.82-7.41 (m,10H).

^{B}C NMR (50 MHz, $CDCl_3$:$CCL_4$7 : 3) δ21.1(q), 35.4(t) 70.9 (d) 125.0 (d), 125.2 (d), 127.0 (d), 129.0(d), 129.3(d), 130.1(d), 134.3(S), 134.4(S), 137.2(S), 137.6(S), 149.5(S), 149.8(S), 152.9(S)

FAB Ms m/z(rel intensity) 390 ($[M+H)]^+$, 100) 372 [(M-H_2O] H^+ 26), 279(31), 264(42), 227(10), 219(S), 188(4), 120(10)

HRMS (FAB) Calcd for $C_{20}H_{17}Cl_2NOS$ (M+H) + m/z 390.0486, found 390.0486

Anal Calcd for $C_{20}H_{17}C_{12}NOS$: C, 6.56: H, 4.38; N, 3.58

Found: C. 61.34; H, 4.19: N, 3.85

III. CONCLUSION

In conclusion, we have demonstrated that the sequential pummerer – Diels – Alder reaction sequence is situated to efficient synthesis of a variety of heterocyclic ring systems including some 1 arylnapthalene lignans. The key intermediates in this cascade process are α-thiosubstitued furo [3,4 -C] pyridines, which in some cases can be isolated and independently reacted with a suitable dienophile to give [4+2]- cycloadducts. However we found it to be most conveninent to carry out these reactions in an all tandem fashion. In addition intramolecular trapping of the insitu generated furo [3, 4 -C] pyridine is an efficient route for the rapid access to annulated isoquinoline derivatives. Our results clearly indicate that this methodology provides rapid entry into heteroaroamtlc O-quinodimethanes.

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