SYNTHESIS OF HETEROACYL-1,4-QUINONES AS PRECURSORS FOR HETEROANTHRACYCLINONES

R.T. Pardasani[a]*, P. Pardasani[a], S. Muktawat[a], R. Ghosh[a], and T. Mukherjee[b]
[a] Department of Chemistry, University of Rajasthan, Jaipur -302004, India
[b] Chemistry Division, Bhabha Atomic Research Centre, Mumbai-400085, India

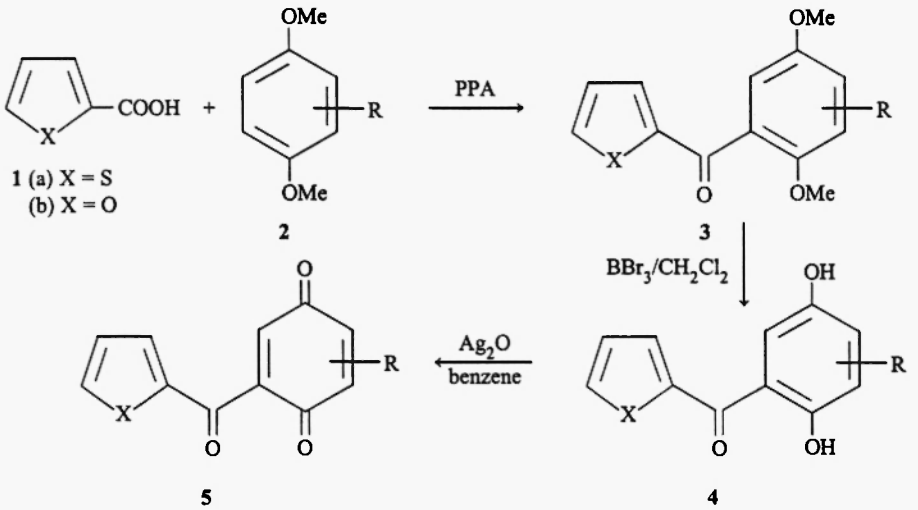
Abstract : A facile three step synthesis of heteroacyl-1,4-benzoquinones such as 2-(2'-furanoyl/thienoyl)-1,4-benzoquinone, 2-(3'-furanoyl/thienoyl)-1,4-benzoquinone and derivatives *via* readily available starting materials is described.

Introduction

Quinones represent an important class of versatile organic compounds endowed with rich and fascinating chemistry (1-3). A pronounced antileukemic activity has been shown by aziridino-1,4-benzoquinones (4). Ostenhof (5) described the antibacterial property of benzoquinones. Anthracyclinones and heteroanthracyclinones are valuable drugs for the treatment of certain human cancers (6). Since quinones can form the foundation upon which new medicinal agents including anthracyclinones and heteroanthracyclinones can be constructed (7), this fact has provided the impetus for the creation of new and facile synthetic routes for substituted quinones (8). Keeping these observations in mind and in pursuing our interest on quinone studies (9), a number of heteroacyl-1,4-benzoquinones have been synthesized. These quinones may work as good dienophiles in Diels-Alder cycloaddition reactions i.e. these may be good precursors for the Diels-Alder reaction with various dienes and this approach may be extended to the synthesis of heteroanthracyclinones.

Results and Discussion

Our approach towards the synthesis of quinones employ three steps to secure the target molecules from readily available precursors :



The first step involved condensation of a suitable dimethoxybenzene derivative **2** with an excess of appropriate heteroyl acid (furan or thiophene-2-or-3-carboxylic acid) **1**, in the presence of polyphosphoric acid at 70-80°C for 7 hours to afford dimethoxyketones **3** in 50-72% yield. Their IR spectra exhibited a strong band in the region 1690-1660 cm^{-1} due to νC=O. In the PMR spectra, the methoxy protons appeared at δ 3.7-3.86 as two separate sharp singlets; aromatic 3-,4- and 6-H at δ 7.1-7.4 and heteroprotons 2'-,3'-,4'-and 5'-H at δ 7.6-8.1 ppm, a singlet at δ 2.3-2.4 was assigned to methyl protons.

Demethylation of ketones **3** was carried out by stirring their solution in dichloromethane with an excess of boron tribromide at 0°C for 5-7 hrs. The hydroquinones **4** were obtained as yellow-orange crystals in 56-87% yield. The formation of hydroquinones was easily ascertained by disappearance of methoxy singlet in PMR and appearance of a broad singlet at δ 11-0-12.0 ppm for hydrogen bond OH as well as by appearance of a medium band in IR around 3350-3330 cm^{-1} due to νOH.

The quinones **5** were prepared by the oxidation of the corresponding hydroquinones **4** using 5-8 fold excess of silver oxide at room temperature in benzene in 50-84% yield. The absence of broad peaks in the region 3350-3330 cm^{-1} in the IR spectra of these quinones shows the disappearance of hydroxyl group whereas the quinonoid carboxyl stretching bands appeared at 1690-1630 cm^{-1}. In the PMR spectra, the hydroxy signals in the range δ 11.0-12.0 ppm were absent and the quinonoid protons appeared at δ 6.7-7.1 either as multiplet or as broad singlet with some fine structure. The aromatic protons appeared in the range δ 6.65-8.0 ppm. In addition all the compounds showed satisfactory elemental analysis. The characteristic data are given in Table I.

In summary, a convenient and high yielding synthesis of heteroacyl-1,4-benzoquinones has been accomplished from readily available starting materials and their application to the synthesis of heteroanthracyclinones is currently under progress.

Experimental

Melting points, determined on a Swastika melting point appararatus (capillary method) are uncorrected. The purity of synthesized compounds was tested by thin layer chromatography on silica gel in various non-aqueous solvents. IR spectra were recorded in KBr on a Nicolet Magna IR^{TM} spectrometer model 550 (ν_{max} in cm^{-1}). PMR spectra were taken in $CDCl_3$ on Jeol FX90Q (89.55 MHz) using TMS as internal standard.

The following procedure is representative. A mixture of an appropriate acid **1** (0.011 mol), suitable dimethoxybenzene derivative **2** (0.01 mol) and polyphosphoric acid (25 ml) was heated at 70-80° C with vigorous mechanical stirring on an oil bath for 6-7 hrs. A slow colour change of the reaction mixture from yellow to red was observed. The reaction mixture was poured into 250 ml hot water with stirring and allowed to cool. It was then extracted with diethyl ether (4 x 25 ml), washed the ether layer with sodium bicarbonate solution (2 x 25 ml) to remove excess of acid and finally with water (2 x 25 ml) and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent then afforded the dimethoxyketones **3** which were purified by column chromatography using petroleum ether-chloroform (5:1) as eluent.

To a solution of the ketone **3** (0.01 mol) in dry methylene chloride (10 ml) at 0°C was added dropwise a solution of boron tribromide (BBr_3) (0.03 mol) in dry methylene chloride (15 ml). The resultant red solution was stirred for 5-7 hrs. and then decomposed with cold water (25 ml). After separating aqueous layer, the organic layer was washed with water (3 x 25 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **4** as yellow orange crystalline solid in 56-87% yield.

A mixture of hydroquinone **4** (0.005 mol), silver oxide (0.02-0.04 mol), anhydrous sodium sulfate (1.8 gm) in dry benzene (25 ml) was shaken at room temp. for six hrs. under aluminium foil cover. The products **5** in benzene were filtered through celite, concentrated and crystallised from pet. ether-chloroform as yellow orange crystalline solid, yield 50-84%.

The analytical and spectral data of the quinones **5** are given in Table I.

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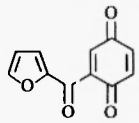
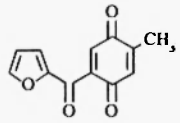
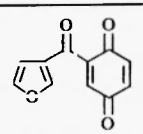
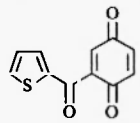
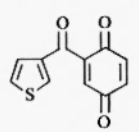
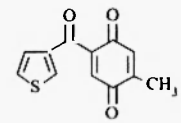
TABLE I : Characterisation data for Heteroacyl-1,4-benzoquinones **5**

Compound	M.P.°C	% yield	Molecular Formulae	Analysis Found/Calcd (%)		PMR (δ ppm)
				C	H	
	106-107	80	$C_{11}H_6O_4$	65.27 (65.34)	2.94 (2.97)	6.65(m H-4'), 6.98(bs, H-3+5+6), 7.35(d, J=4Hz H-5') 7.78(d J=1.5Hz, H-3')
	122-23	81	$C_{12}H_8O_4$	66.62 (66.66)	3.64 (3.70)	2.09(d, J=1.7Hz, 5-CH_3), 6.67(dd, J_1=4.0Hz, J_2= 1.5Hz H-4'), 6.78(q, J=1.7Hz, H-6), 5.95(s H-3), 7.30(d, J=4Hz, H-5'), 7.72(d, J= 1.5Hz, H-3')
	103	78	$C_{11}H_6O_4$	65.28 (65.34)	2.95 (2.97)	7.1(m H-3+5+6+4'), 7.89(m, H-5'), 8.2(d, J=1.5Hz H-2')
	85	84	$C_{11}H_6O_3S$	60.48 (60.55)	2.70 (2.75)	6.9(s with fine structure, H-3+5+6), 7.19(dd, J_1=4.0Hz, J_2=1.5Hz, H-4'), 7.58(d, J=4.0Hz H-5'), 7.91(d J=1.5Hz H-3')
	118	77	$C_{11}H_6O_3S$	60.49 (60.55)	2.70 (2.75)	7.09(bs H-3+5+6) 7.5(m H-4'+5'), 7.9 (d, J=1.5Hz H-2')
	95	50	$C_{12}H_8O_3S$	62.59 (62.06)	3.40 (3.44)	2.2(d J=1.7Hz 5-CH_3), 6.7(q, J=1.7Hz, H-6), 6.9(s, H-3), 7.4(m, H-4'), 7.6(dd, J_1=3.5Hz J_2=1.5Hz, H-5'), 8.0(d, J=1.5Hz, H-2')