Photochemical synthesis and antimicrobial activity of dihydrobenzofuranols from 2-alkoxy substituted benzophenones and ethyl-2-aroyl aryloxy acetates[1]

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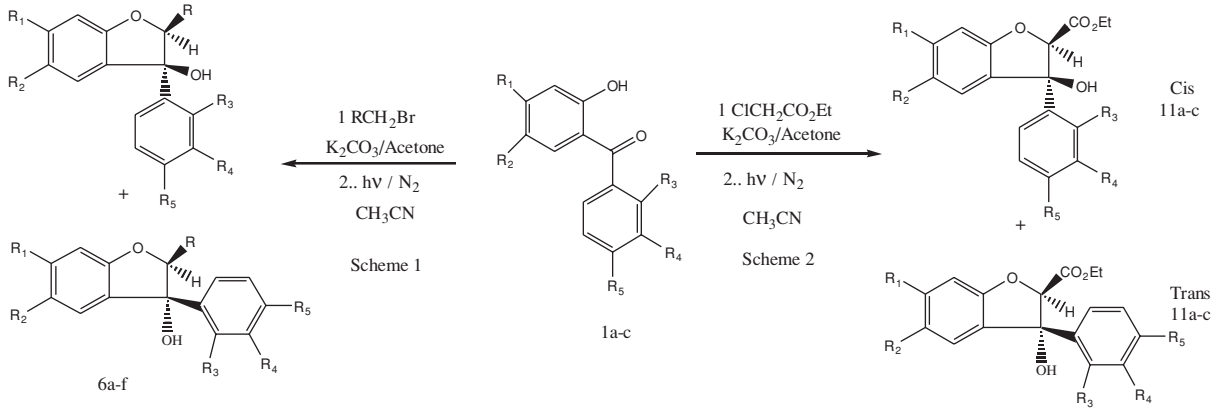
Upon UV irradiation 2-alkoxy substituted benzophenones **2a–f** and ethyl-2-aroyl aryloxy acetates **7a–c**, in acetonitrile under went intramolecular δ hydrogen abstraction and led to synthesis of solely dihydrobenzofuranols **6a–f** and **11a–c** in excellent yield with potent antimicrobial activity.

Keywords: photocyclisation, dihydrobenzofuranols, antimicrobial activity.

The chemistry of dihydrobenzofurans has recently received considerable attention.[2–4] Though there are several methods for the construction of dihydrobenzofuranols system, none of these can be used for a direct synthesis of *cis* and *trans* dihydrobenzofuranols. Intramolecular hydrogen abstractions are among some of the best studied reactions in organic photochemistry. Higher forms of hydrogen abstraction such as δ and ε, have attracted interest, not only because they provide useful insight into ketone photochemistry and biradical behaviour, but also because of their potential synthetic utility in the construction of five and six membered rings.[7] One example of a δ hydrogen abstraction, which has found applications in synthesis, is the photocyclisation of 2-alkoxy substituted benzophenones and ethyl-2-aroyl aryloxy acetates to dihydrobenzofuranols. The photocyclisation reaction of *ortho* substituted hydroxy ketones is considered to proceed via 1,5-biradical intermediates which are formed through δ hydrogen abstraction by carbonyl group. Wagner *et al*. has reported that photocyclisation of 2-benzyloxybenzophenone and 2-benzyloxyacetophenone derivatives in nonpolar benzene revealed high stereoslectivity of *cis* isomer. However, in the presence of a Lewis acid solvent the stereoselectivity decreased markedly.[8]

The photo substrates, 2-alkoxy substituted benzophenones **2a–c** and **2d–f** were synthesised by the reaction of **1a–c** (0.02 mol) with bromomethane (0.02 mol) and bromoethane (0.02 mol) respectively, in presence of anhydrous potassium carbonate (0.02 mol) and dry acetone (50 ml). (Scheme 1). Under similar condition **1a–c** (0.02 mol) reacted with ethyl chloroacetate (0.02 mol) in dry acetone (50ml) to give the corresponding esters **7a–c** in excellent yield[11] (Scheme 2). Irradiation of degassed solution of **2a–f** (2 mmol) and **7a–c** (2 mmol) in acetonitrile (25 ml) was conducted at ambient temperatures (~ 33°C) and 365 nm, 400 W high-pressure mercury lamp with Pyrex filter (Scheme 1 and 2). The irradiation was stopped when the reactant had almost disappeared (15–20 h).

The photocylisation reaction pathways of 2-alkoxy-benzophenones and ethyl-2-aroyl aryloxy acetates are similar to each other. Irradiation of **2a–c** produced a racemic mixture of **6a–c**, where as irradiation of **2d–f** and **7a–c** produced a mixture of *cis* and *trans* isomers **6d–f** and **11a–c** respectively. The respective ratio of **6a–f** and **11a–c** are given with regard to R and hydroxyl group and ester and hydroxyl group (Table 3 and 4). The stereochemistry of *cis* and *trans* isomers was determined.[8] On the basis of anisotropic effect of C_3-phenyl group and C_2–R of **6d–f** and C_3-phenyl group and C_2-ester of **11a–c**, in the ^{1}H NMR spectra. The C_3-phenyl group shields C_2–R protons in **6d–f** and C_3-phenyl group shields C_2-ethyl ester protons in **11a–c** in the *cis* position. Hence the C_2-R and C_2-ethyl ester protons resonate at a higher magnetic field than that of *trans* position. As a result of to the intersystem crossing process (ISC), irradiation of **2a–f** and **7a–c** produces (n, π^*) excited triplet state. 1,5-Biradicals are obtained by the abstraction of δ hydrogen of the carbonyl group of **3a–f**.[8,12] The 1,5-biradical cyclises directly or after solvation of the hydroxyl group to dihydrobenzofuranols **6a–f** and **11a–c**. The ratio of *cis* and *trans* dihydrobenzofuranols would be controlled by the steric effect of Ph, R and OH in **6d–f**



a: R_1=R_5=CH_3, R_2=Cl, R=R_3=R_4=H; b: R_1=CH_3, R_2=R_4=Cl, R=R_3=R_5=H;
c: R=R_1=R_5=H, R_2=R_3=R_4=Cl; d: R=R_1=R_5=CH_3, R_2=Cl, R_3=R_4=H;
e: R=R_1=CH_3, R_2=R_4=Cl, R_3=R_5=H; f: R=CH_3, R_1=R_5=H, R_2=R_3=R_4=Cl

a: R_1=R_5=CH_3, R_2=Cl, R_3=R_4=H;
b: R_1=CH_3, R_2=R_4=Cl, R_3=R_5=H;
c: R_1=R_5=H, R_2= R_3=R_4=Cl

Schemes 1 and 2

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Table 3

Comp.	Yield/% (*Cis:trans*) ratio	M.p./°C	
		Cis	*Trans*
6a	77%	–	–
6b	80%	–	–
6c	76%	–	–
6d	74% (2.2:1.8)	130–132	128–130
6e	75% (3:1.9)	125–123	121–123
6f	72% (2.9:1.4)	135–137	130–132

Table 4

Comp.	Yield/% (*Cis:trans*) ratio	M.p./°C	
		Cis	*Trans*
11a	74% (2.4:1)	120–22	117–19
11b	85% (2.6:1)	125–27	120–22
11c	71% (1.7:1)	118–20	115–13

and Ph, CO_2Et and OH during the cyclisation of 1,5-biradicals. *Cis* isomer would be produced preferentially when 1,5- biradicals cyclise directly. In acetonitrile the hydroxyl group in 1,5-biradicals would be solvated by acetonitrile by intermolecular hydrogen bonding. Hence the hydroxyl group becomes bulkier than free hydroxyl group. The solvated 1,5-biradicals would give a mixture of *cis* and *trans* isomers. The hydrogen bonding lowers the stereoselectivity of *cis* and *trans* isomers.[7]

Compounds **6a–f** and **11a–c** were screened for their antimicrobial activity against two pathogenic bacteria viz., *Bacillus cereus and Escherichia coli* and two fungal cultures viz., *Aspergillus fumigatus and Fusarium solani*. The standard drugs used were Norfloxacin and Griseofulvin respectively. The tests were carried out with the title compounds by the cup plate method[13] with 20 µg of the substance in 0.1 ml of dimethylformamide. The meta chloro substituted **6b**, **6c**, *cis* **6e** and *cis* **6f** have shown growth inhibition equal to that of the standard, where as **6a**, *cis* and *trans* **6d,** *trans* **6e**, *trans* **6f** and *cis* and *trans* isomers **11a, 11b** and **11c** have shown weak to moderate activity against both strains. The antifungal activity of **6b, 6c**, *cis* **6e** and *cis* **6f** is more than that of the standard, **6a**, *cis* **6d,** *cis* and *trans* **11a**, **11b** and **11c** showed activity equal to that of standard and for *trans* isomers **6d**, **6e** and **6f** it is weak against both strains. These are examples, which shows how the biological properties are influenced by even minor structural modifications. In general, these compounds are found to possess more antifungal than antibacterial activity.

In summary, photocyclisation reactions of alkoxybenzophenone and ethyl aroyl aryloxy acetate are useful methods for preparation of dihydrobenzofuranols, which gave *cis* isomers preferentially as a result of intramolecular hydrogen bonding between hydroxyl and carbonyl groups in 1,5-biradical. Chloro substituent at *meta* position in benzophenone moiety favoured 1,5-cyclisation and gave highest yield when compared to chloro substituent at *ortho* and *para* position and also methyl substituent at *meta* and *para* positions.

Techniques used: FTIR, ^{1}H NMR and ^{13}C NMR spectrometry.

Table 1: Reaction of **1a-c** with bromo methane and bromo ethane in the presence of anhydrous potassium carbonate.

Table 2: Reaction of **1a-c** with ethyl chloroacetate in the presence of anhydrous potassium carbonate.

Table 5: IR, ^{1}H NMR and ^{13}C NMR spectral data of all the compounds prepared.

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