

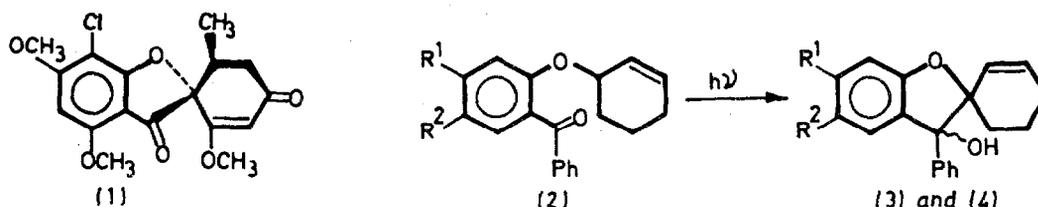
A Photochemical Entry to Spirobenzofurans

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Abstract : Synthesis of spirobenzofurans based on photochemical δ^1 hydrogen abstraction is reported.

Spirobenzofurans and their derivatives have received considerable attention in the field of pharmacology as most of these have been found to be biologically active¹. In particular, there has been a revival of interest in griseofulvin (1), an antifungal antibiotic isolated from Penicillium griseofulvum². Many syntheses are known in literature for this compound and its derivatives, based on Diels-Alder reaction³, double Michael addition⁴, oxidative coupling⁵ and intra-ester condensation⁶. Surprisingly, methodologies based on photochemical transformations have not been exploited so far. Recently, we reported a photochemical route for the construction of 2-ethenyl and 2-ethynylbenzofurans⁷. In continuation of our work in this area, we were interested in exploring the potential of this photochemical reaction for building up the spirobenzofuran system constituting the framework of griseofulvin. Herein we report a simple and direct entry into spirobenzofurans based on photochemical spiroannulation as depicted in Scheme-I.

Scheme-I



The photosubstrates (2a-d) required for this purpose were prepared by the Williamson ether synthesis (Scheme-II). Compounds (2a-d) are pale yellow viscous liquids and have been thoroughly characterised.

Scheme-II

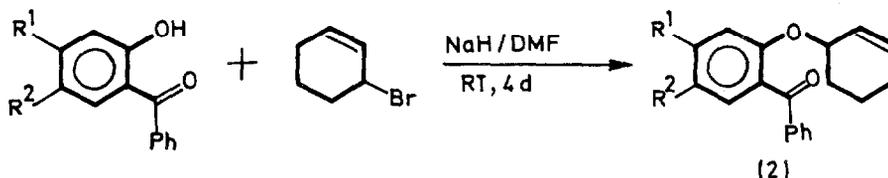
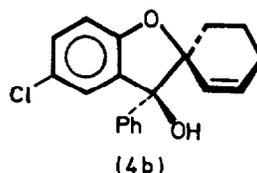
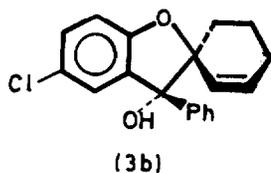


Table - I

Entry	Compound	R ¹	R ²	Yield (%)
1	(2a)	H	CH ₃	60
2	(2b)	H	Cl	60
3	(2c)	H	OCH ₃	70
4	(2d)	OCH ₃	H	80

Irradiation of ether (2b) in benzene (10^{-3} M) using 350 nm lamps in a Rayonet photoreactor in an atmosphere of argon for four hours afforded a viscous liquid (80%) after evaporation of the solvent under reduced pressure which was found to be a mixture of diastereomeric spirobenzofuranols namely 5-chlorospiro[benzofuran-2(3H), 1'-[2]cyclohexene]-3-phenyl-3-ols, (3b) and (4b) as revealed by spectral data⁸. The crude photolysate exhibited 32 lines in its ¹³C nmr spectrum⁹. The 400 MHz ¹H nmr spectrum showed three signals in the olefinic region viz. δ 5.3(d), δ 5.6 (m) and δ 6.2, the signal at δ 6.2 being a closely spaced unresolved multiplet. The IR spectrum showed a band at 3600 cm^{-1} (-OH) while the band at 1660 cm^{-1} (C=O) had disappeared. Though the tlc analysis of this liquid showed only a single spot, hplc analysis¹⁰ clearly revealed it to be a 1 : 1.1 mixture showing two peaks. Preparative hplc separation of this mixture afforded the pure diastereomers. ¹H nmr spectrum of one of the isomers (3b) had a signal at δ 5.3(d, 1H, J = 8.8 Hz) and another at δ 5.65 (m, 1H) indicating olefinic protons while the signal at δ 6.2 seen in the spectrum of the crude product had totally disappeared. The ¹³C nmr of this compound displayed 17 lines.¹¹ The ¹H nmr of the other isomer (4b) showed a signal at δ 6.2 due to the two olefinic protons and the signals at δ 5.3 and δ 5.65 were clearly absent. The ¹³C nmr of this isomer also exhibited 17 lines as expected in its broad band decoupled spectrum¹². Both these compounds showed the molecular ion at 312 in their mass spectra.



The stereochemistry assigned to (3b) is based on its ¹H nmr spectral data as well as from its NOESY spectrum which revealed the spatial interaction between the olefinic proton signal at δ 5.3 and the aromatic proton signal at δ 7.38¹³. Irradiation of the ethers (2a) and (2d) likewise afforded the respective spirobenzofuranols as a mixture of two diastereomers which were separated by preparative hplc and characterised by spectral data (Table II). In contrast, ether (2c) was inert under

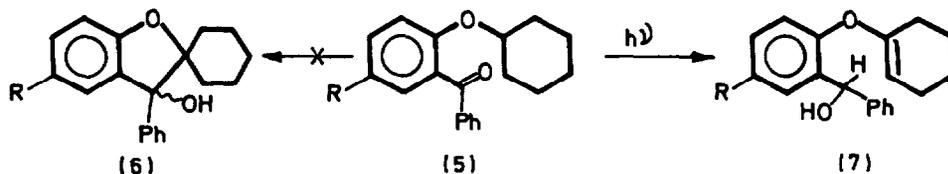
the above irradiation conditions. Even after irradiating for ten hours, there was no appreciable reaction¹⁴. This remarkable retarding effect exhibited by the methoxy group in (2c), which is meta to the benzoyl group, has also been observed in a similar attempted δ hydrogen abstraction reaction¹⁵.

Table - II

Compound	Product	Yield (%) ¹⁶
(2a)	(3a) + (4a)	90
(2d)	(3d) + (4d)	80
(2c)	(3c) + (4c)	10

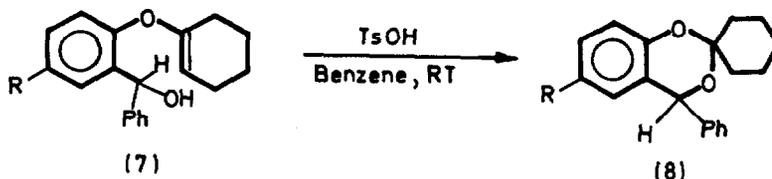
As it is known that the ease of δ hydrogen abstraction by the excited carbonyl group in *o*-alkoxybenzophenones is governed by the structure of *O*-alkyl moiety¹⁷, it was of interest to study the photochemical behaviour of the saturated analogues of ethers (2a) and (2b) namely *o*-cyclohexyloxybenzophenones (5a) and (5b) respectively. Irradiation of ethers (5) under UV light for thirty minutes led not to the product of δ hydrogen abstraction and cyclisation viz. (6) but to the formation of the respective 2-(cyclohex-1-enyloxyphenyl)phenyl carbinols (7) in 60-70% yield (Scheme III).

Scheme-III



The ¹H nmr spectrum of the product (7) showed a signal at δ 5.87 and a signal at δ 4.76 along with an exchangeable proton signal at δ 2.7. The IR spectrum showed a band at 3600 cm⁻¹ (-OH) and also a band at 1665 cm⁻¹ (C=C). The absorption band at 300-350 nm in the UV spectrum was absent, as expected. The assigned structures have been supported further by the following observation. Treatment of (7) with a catalytic amount of *p*-toluenesulfonic acid in dry benzene gave rise to the respective spiroketals (8) in 90-95% yield (Scheme IV).

Scheme-IV



The ^1H nmr spectrum of (8) revealed the absence of the signal at δ 4.76 due to the olefinic proton. The signal due to hydroxyl proton was also not seen. The IR spectrum showed the absence of bands at 1665 cm^{-1} and 3600 cm^{-1} as expected.

In summary o-(2-cyclohexenyloxy)benzophenones have been found to undergo a facile photochemical cyclisation to give the corresponding spirobenzofurans. We are currently engaged in exploring the scope of this annulation reaction for the synthesis of griseofulvin and other condensed spirobenzofuran systems.

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- The ratio of the two isomers based on ^1H nmr spectrum was found to be 1:1.5.
- The ^{13}C nmr signals for the crude photolysate are as follows: 157.71, 157.45, 139.63, 139.49, 136.53, 134.77, 133.98, 131.61, 130.52, 130.26, 128.03, 127.89, 127.84, 127.30, 127.094, 126.092, 125.62, 125.591, 125.394, 122.981, 112.386, 112.143, 92.364, 91.818, 85.473, 85.200, 31.08, 27.429, 24.92, 24.45, 19.26, 18.50.
- HPLC analysis was carried out using Zorbax ODS column with 80% aqueous methanol as eluent.
- The ^{13}C nmr signals for the isomer (3b) are : 157.76(s), 139.5(s), 134.0(s), 131.7(d), 130.6(d), 127.9(d), 127.89(d), 127.34(d), 126.08(d), 125.64(d), 125.47(s), 112.2(d), 92.39(s), 85.27(s), 27.47(t), 24.48(t), 19.29(t).
- The ^{13}C nmr signals for (4b) are 157.51(s), 139.69(s), 136.71(d), 134.91(s), 130.36(d), 128.11(d), 127.92(d), 127.12(d), 125.71(s), 125.38(d), 123.01(d), 112.48(d), 91.89(s), 85.55(s), 31.10(t), 24.98(t), 18.55(t).
- The three aromatic protons of the trisubstituted benzene ring is discernable and appear in the upfield region δ 6.8-7.28.
- The spirobenzofuranols were obtained in 8-10% with 30% of cleavage leading to 5-methoxy-2-hydroxybenzophenone, with the rest being unreacted.
- 2-propynyloxybenzophenone having methyl substituent at 5-position underwent complete photocyclisation in one hour while methoxy substituent at 5-position did not lead to efficient photocyclisation even after ten hours. (Unpublished results)
- The yields are after four hours irradiation in the cases of (2a) and (2d) and after ten hours in the case of (2c)
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