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Diastereoselectivity in the Paternò–Büchi reaction on furan derivatives

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Abstract—The reaction of benzoin, 4,4′-dimethoxybenzoin and benzoin ethyl ether with furan gave the corresponding adduct with high diastereoselectivity (71–100%). The diastereoselectivity was explained considering the relative stability of the biradical intermediates. Benzofuran reacts with (*S*)-1-methylpropylbenzoylformate to give the corresponding adduct with de = 58%. The diastereoselectivity was explained considering the relative stability of the biradical intermediates.

The Paternò–Büchi reaction is a photochemical 2 + 2 cycloaddition reaction between a carbonyl compound and an olefin.[1–7] Several synthetic applications have been described.[8] Attempts to have a diastereoselective reaction did not give good results in several reported articles. The reaction of furan with acyl cyanides yields the corresponding oxetanes but both diastereoisomeric *endo*- and *exo*-oxetanes are formed. When chiral acyl cyanides are used low asymmetric induction is observed.[9] Furan reacts also with chiral ketones. In this case, an α-cleavage reaction before the 2 + 2 cycloaddition modifies the expected products. When (−)-menthone was used as a substrate a chiral product was obtained as 2:1 diastereoisomeric mixture where the most abundant product has 1*R*,3*R* configuration.[10] When the reaction was performed on a carbohydrate, a complex reaction mixture was obtained.[11,12]

Attempts to obtain stereoselective Paternò–Büchi reactions were performed carrying out the reaction between 3,4-dimethylfuran and *R*-isopropylidene glyceraldehyde. The coupling products were obtained with an overall yield of 35% as a 1.2:1 mixture of diastereoisomers. Furthermore, the product was obtained with 54% ee.[13,14] This behaviour suggests the operation of a mechanism that is insensitive to the substitution pattern of chiral aldehydes. Reaction between an excited aldehyde (singlet or triplet state) and furan proceeds with initial carbon–oxygen bond formation to produce either of the two biradical species. The stereocentre adjacent to the carbonyl is now in a 1,4-relationship to the newly formed stereocentre at the acetal carbon and is expected to exert little influence as a stereocontrol device.[13] The extensive racemisation observed probably reflects the photolability of the aldehydes towards racemisation under the conditions of the reaction.[14]

In a previous work we performed some diastereoselective reaction on furan derivatives using chiral phenylglyoxylate derivatives on furan and substituted furans.[15] The observed diastereoselectivity was explained on the basis of relative stability of the possible biradical intermediates. In this letter we show that (a) the first stereo-selective reaction can be obtained using benzoin as carbonyl compound, (b) good stereoselectivity can be obtained performing a reaction between a chiral phenylglyoxylate and benzofuran, both in solution and in organised media and (c) all the results can be rationalized on the basis of the relative stability of the biradical intermediates.

We used benzoin as substrate in a reaction with furan. Benzoin (1 mmol) was dissolved in furan (70 mL) and irradiated with a 125 W high-pressure mercury arc (Helios–Italquartz) surrounded with a Pyrex water jacket for 15 h. The solvent was evaporated and the residue extracted with ether. The removal of the solvent yielded a crude product that was chromatographed on silica gel. The elution with 85:15 petroleum ether/Et_2O gave the pure product.[16] The adduct was obtained in 56% yield (Scheme 1, Table 1).

Keywords: Photochemistry; Furan; Benzoin; Benzofuran; Paternò–Büchi reaction.

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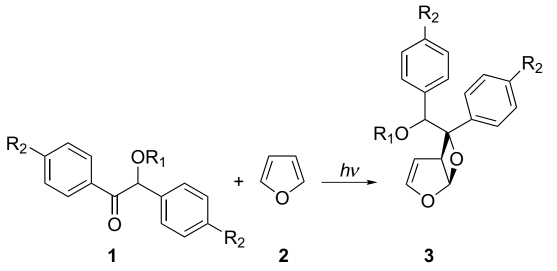


a: $R_1 = R_2 = H$
b: $R_1 = H$, $R_2 = OCH_3$
c: $R_1 = OC_2H_5$, $R_2 = H$

Scheme 1.

Table 1. The Paternò–Büchi reaction between benzoin derivative and furan

Substrate	Product	Exp. cond.	Yield (%)	De (%)
1a	**3a**	Solution	56	100
1b	**3b**	Solution	72	100
1c	**3c**	Solution	54	71
1a	**3a**	Zeolite	20	100

NMR data are in agreement for an *exo* configuration for the phenyl group at C-6. Chiral HPLC (Chiralcel OD, $\lambda = 235$ nm, 98:2 *n*-hexane/isopropanol) showed a de = 100%.

On the basis of the NMR data we were not able to assign the exact configuration to the product. The same result was obtained using the benzoin derivative **1b** (Scheme 1, Table 1): we observed a de = 100% (Chiralcel OD, 98:2 *n*-hexane/isopropanol).[16] When benzoin ethyl ether (**1c**) was used as substrate the corresponding adduct was obtained but, in this case, a de of 71% (Chiralcel OJ, 99.5:0.5 *n*-hexane/isopropanol) was observed (Scheme 1, Table 1).

Recently the diastereoselectivity of photochemical reactions has been improved performing these reaction in a zeolite in the presence of a chiral compound adsorbed.[17] We used this procedure in the reaction with phenylglyoxylates.[15] When benzoin reacted with furan in NaY in the presence of (−)-ephedrine, the yields of the product were lower and the stereoselectivity was maintained.

In order to explain the observed diastereoselectivity we performed some calculations of the stability of the possible biradical intermediates. As reported above the relative stability of these intermediates is strictly related to the diastereoisomeric excess. If the energy gap is high we can wait for a large diastereoisomeric excess. On the contrary, if the energies of the possible intermediates are quite similar, low diastereoselectivity was expected. We performed some ab initio calculations using 6–31G** basis set on GAUSSIAN 03, using UHF method. The calculations were usually done using Møller–Plesset perturbations (MP2).[18] The Polak–Ribiere algorithm with gradient calculations was adopted for geometry optimizations. The open-shell states were treated at the same level of accuracy as the closed state states. We verified that the obtained structures were minima on the potential energy surfaces calculating the frequencies of the optimised structures.

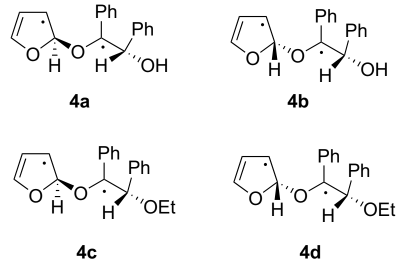


Figure 1. Possible biradical intermediates in the reaction of **1a** and **1c** with furan.

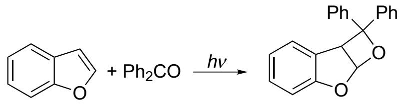
We calculated the total energy of the intermediates in the reactions of **1a** and **1c** with furan. The structures of these compounds (**4a**–**d**) are reported in Figure 1.

The biradical **4a** is more stable than **4b** for 3.66 kcal mol^{-1} in agreement with the observed stereoselectivity. In the case of the biradical **4c** and **4c** we expected a lower energy gap: in fact **4c** is more stable than **4d** for 1.55 kcal mol^{-1}. All these results are in agreement with the experimental results.

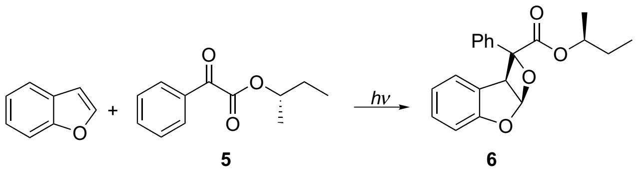
We have shown the first diastereoselective Paternò–Büchi reaction on a furan derivative using an asymmetric ketone as reagent; we confirmed our approach where the diastereoselectivity can be rationalised on the basis of the relative stability of all the possible biradical intermediates. Finally, on the basis of our calculation we can affirm that the compound **3a** is (1*RS*,5*SR*,6*RS*,6′*RS*)-6-phenyl-6-(hydroxybenzyl)-2,7-dioxa-bicyclo[3.2.0]hept-3-ene.

Schenck reported the reaction of some aromatic carbonyl compounds (benzophenone, benzaldehyde) with benzofuran (Scheme 2); he showed that when high triplet energy compounds were used, dimers of benzofuran were obtained, while oxetanes were the products of the reaction when low triplet energy carbonyls were used.[19] As in the case of furan, he obtained only one product showing that the reaction has a high regioselectivity. Reinvestigation of the reaction of benzofuran with acetophenone or propiophenone showed that, also in this case, oxetanes were obtained.[20]

No attempts to have diastereoselective reactions with this reagent have been performed.



Scheme 2.



Scheme 3.

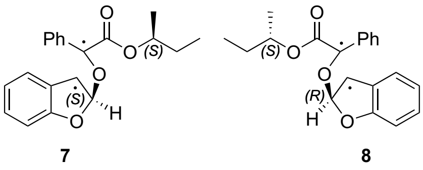


Figure 2. Possible biradical intermediates in the reaction of benzofuran with **5**.

We used as carbonyl compound (*S*)-1-methylpropylbenzoylformate (**5**). The main product of the reaction was the dimer of benzofuran; however, the cycloadduct **6** was obtained in 20% yield (Scheme 3).[21]

The adduct **6** was obtained with a de = 58% (Chiralcel OJ, $\lambda = 235\,\text{nm}$, 98:2 *n*-hexane/2-propanol). This diastereoisomeric excess is higher that that obtained when furan was the substrate (15%).[15] We examined the reason of this difference studying the relative stability of the possible biradical intermediates **7** and **8** (Fig. 2).

Calculations showed that **7** is more stable than **8** for $1.48\,\text{kcal}\,\text{mol}^{-1}$, in agreement with the observed diastereoisomeric excess.

In conclusion, we have shown the first diastereoselective Paternò–Büchi reaction of benzoin with furan. The high observed diastereoisomeric excess can be explained on the basis of the relative stability of the possible biradical intermediates. Also the reaction of benzofuran with a chiral phenylglyoxylate gave a product with a good diastereoisomeric excess. Also in this case the observed de can be explained considering the stability of the possible biradical intermediates. These results confirm the utility of calculations on the stability of the biradical intermediates as instrument to predict the diastereoselectivity of the Paternò–Büchi reaction.

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16. Compound **3a**: ^{1}H NMR (CDCl$_3$, δ): 7.4–7.3 (m, 10H, aromatic protons), 6.73 (d, 1H, $J = 3$ Hz, 1-H), 6.56 (d, 1H, $J = 4$ Hz, 3-H), 5.58 (d, 1H, $J = 3$ Hz, 4-H), 5.49 (dd, 1H, $J_1 = J_2 = 3$ Hz, 5-H), 3.69 (m, 1H, –C*H*(OH)Ph) and 1.59 ppm (s, 1H, –OH); ^{13}C NMR (CDCl$_3$, δ): 148.5 (C-3), 141.1 (aromatic C$_q$), 128.7 (aromatic C$_p$), 125.3 (aromatic C$_{o,m}$), 108.2 (C-1), 104.2 (C-4), 92.7 (C-6), 76.6 (–COH), 52.2 (C-5). Found: C, 77.2; H, 5.6%. $C_{18}H_{16}O_3$ requires: C, 77.12; H, 5.75%. Compound **3b**: ^{1}H NMR (CDCl$_3$, δ): 7.85 (d, 2H, $J = 9$ Hz, aromatic protons), 7.38 (d, 2H, $J = 9$ Hz, aromatic protons), 7.02 (d, 2H, $J = 9$ Hz, aromatic protons), 6.95 (d, 2H, $J = 9$ Hz, aromatic protons), 6.72 (d, 1H, $J = 2$ Hz, 1-H), 6.56 (d, 1H, $J = 4$ Hz, 3-H), 5.53 (m, 1H, 4-H), 5.47 (m, 1H, 5-H), 3.90 (s, 3H, –OCH$_3$) and 1.27 ppm (s, 1H, –OH); ^{13}C NMR (CDCl$_3$, δ): 162.5, 159.8 (*C*–OCH$_3$ aromatic C), 148.6 (C-3), 133.5, 132.3, 130.2, 127.3, 114.6 (aromatic C), 108.4 (C-1), 104.5 (C-4), 93.05 (C-6), 55.8, 55.6 (–OCH$_3$) and 52.7 ppm (C-5). Found: C, 70.5; H, 6.0%. $C_{20}H_{20}O_5$ requires: C, 70.57; H, 5.92%. Compound **3c**: ^{1}H NMR (CCl$_3$, δ): 7.4–7.3 (m, 10H, aromatic protons), 7.28 (m, 1H, 1-H), 6.48 (m, 1H, 3-H), 6.12 (d, 1H, $J = 3.5$ Hz, 4-H), 5.41 (s, 1H, –CH(OEt)Ph), 4.40 (dd, 1H, $J_1 = 7$ Hz, $J_2 = 5$ Hz. 5-H), 3.69 (m, 2H, –CH$_2$CH$_3$) and 1.59 ppm (m, 3H, –CH$_2$CH$_3$). Found: C, 77.8; H, 6.6%. $C_{20}H_{20}O_3$ requires: C, 77.90; H, 6.54%.
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21. Compound **6**: $[\alpha]_D$ −23.1 (*c* 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$ δ): 7.3–6.6 (m, 9H, aromatic protons), 7.95 (d, 1H, $J = 7.5$ Hz, 5-H), 5.15 (d, 1H, $J = 7.5$ Hz, 1-H), 5.01 (m, 1H, $–CO_2CH(CH_3)–$), 1.60 (m, 3H, $CO_2CH(CH_3)–$) and 1.25 ppm (m, 5H, $–CH_2CH_3$); ^{13}CNMR ($CDCl_3$, δ): 171.0 (CO_2), 160.1 (C-3), 129.7–121.6 (aromatic carbons), 127.8 (C-6), 106.2 (C-2), 54.1 (C-5), 74.5, 28.5, 19.1 and 9.5 ppm.