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Synthesis and photochemical reactivity towards the Paternó–Büchi reaction of benzo[*b*]furan derivatives: their use in the preparation of 3-benzofurylmethanol derivatives

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Abstract

4-Amino-2,7-dimethylbenzo[*b*]furan and 4-chlorobenzo[*b*]furan have been synthesized. The irradiation of 4-amino-2,7-dimethylbenzo[*b*]furan in the presence of benzaldehyde gave the corresponding *endo* adduct. The adduct can be hydrolysed to the corresponding 3-benzofurylmethanol derivative. The irradiation of the same compound in the presence of benzophenone gave the corresponding adduct. 4-Chlorobenzo[*b*]furan did not react with benzaldehyde while, in the presence of benzophenone, gave the corresponding adduct. The hydrolysis of this adduct gave the corresponding 3-benzofurylmethanol derivative.

Keywords: Benzofuran derivatives; Photochemistry; Paternò–Büchi reaction

1. Introduction

The Paternò–Büchi reaction is a photochemical [2 + 2] cycloaddition reaction between a carbonyl compound and an alkene. Recently we reported some applications of the Paternò–Büchi reaction on furan derivatives in the realization of diastereoselective syntheses [1–10]. We showed that the presence of a hydroxyl group on the side chain on the furan ring can induce a high diastereoselectivity when the reaction is performed in the presence of benzaldehyde or benzophenone. Furthermore, diastereoselective reaction can be obtained if the carbonyl compounds used in the reaction have a chiral auxiliary (i.e. the alcoholic part of an ester) in the structure, or if the carbonyl compounds are chiral (i.e. β-hydroxyketones). The Paternò–Büchi reaction on furan has been used in the past in the synthesis of several biological active natural compounds, such as perillaketone, asteltoxin, oxetanocin, and avenaciolide [11,12].

The possible use of substituted benzofuran derivatives in the treatment of osteoporosis (**1**) [13,14], as anaesthetic agent (**2**) [15,16], as inhibitors of platelet aggregations (**3**) [17], as inhibitors of xanthyn oxydase (**4**) [18], as antiarrythmycs (**5**) [19], as anti-HIV agents (**6**) [15], as agonist of the benzodiazepines [20], as inhibitors of ATPase (**1**) [21] has been described (Fig. 1).

Most of these compounds are benzofuran derivatives substituted in position 3 with a side chain containing in α position an alcoholic function or a carbonyl group.

The Paternò–Büchi reaction has been performed on benzofuran [7,22,23] but no synthetic use of reaction was described. Furthermore, the acid treatment of the oxetanes obtained in the reaction between ketones and furan derivatives converted them into 3-furylmethanol derivatives [24–26] (Scheme 1), but the use of this methodology on the oxetanes obtained from benzofuran derivatives does not seem to have large synthetic utility. In fact, the use of treatment of the oxetanes obtained from the reaction between benzofuran and 1-acetylisatine gave a mixture of products, where chloro substituted dihydrobenzofuran derivatives were present [27]. In this paper we want to report the results of our study devoted to improve the synthetic utility of the Paternò–Büchi reaction on benzofuran derivatives: our goal was to obtain compounds with a structure similar to that of the biologically active compounds described above. Here we describe the synthesis of suitable benzofuran derivatives, the results of the oxetane formation reaction of these substrates and

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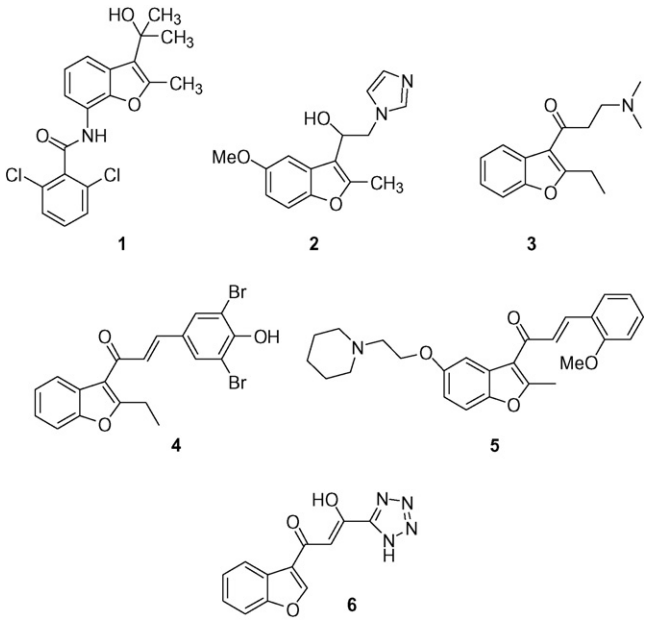
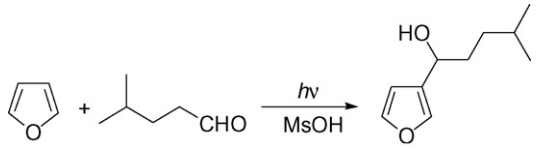


Fig. 1. Pharmacological active benzofuran derivatives.



Scheme 1. Synthesis of 3-furylmethanol derivatives using a photochemical approach.

the conversion of these substrates in the 3-benzofurylmethanol derivatives through acidic treatment.

2. Experimental procedures

Column chromatography was carried out on Merck silica gel (0.063–0.200 mm particle size). ^{1}H and ^{13}C NMR spectra were normally carried out in $CDCl_3$ solutions on a Bruker AM 300 MHz or on a Varian Inova 500 instrument operating at 499.60 MHz. IR spectra were carried out on a Perkin-Elmer 883. Mass spectra were obtained with a Hewlett-Packard 5971 mass-selective detector on a Hewlett-Packard 5890 gas chromatograph (OV-1 capillary column between 70 and 250 °C (20 °C/min)). Elemental analyses were obtained using a Carlo Erba Elemental Analyzer 1106.

Caution: while performing the NMR spectra of cycloadducts we observed that deuterated chloroform purchased from Aldrich induced a retro-cycloaddition reaction giving, within an hour, the starting material. We did not observe this behaviour using deuterated chloroform from Fluka or Carlo Erba. We asked Aldrich about the presence of metals or some other trace impurities in deuterated chloroform which could give this type of reaction. Until now, we have not had a reply from Aldrich and we think we should advise readers of this possible problem.

*2.1. 4-Methyl-1-nitro-3-propargyloxybenzene (**8**)*

To a solution of 2-methyl-5-nitrophenol (**7**) (8.3 g, 54.4 mmoles) in anhydrous acetone (200 ml) propargyl chloride (6.1 g, 81.6 mmoles) and anhydrous K_2CO_3 (25 g) were added. The mixture was refluxed for 72 h. The reaction mixture was filtered and the evaporation of the solvent gave a crude product that was chromatographed on silica gel. The elution with 9:1 hexanes–Et_2O gave pure 4-methyl-1-nitro-3-propargyloxybenzene (9.1 g, 88%): ^{1}H NMR ($CDCl_3$) δ: 7.83 (s, 1H, 2-H), 7.82 (d, 1H, J = 7 Hz, 6-H), 7.24 (d, 1H, J = 7 Hz, 5-H), 4.82 (s, 2H, 1′-H), 2.59 (s, 1H, 3′-H), and 2.34 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 155.6, 151.9, 134.5, 130.9, 119.1, 106.30 (aromatic carbons) 77.5 (CH_2**C**≡CH), 76.4 (CH_2C≡**C**H), 56.2 (**C**H_2C≡CH), and 16.6 ppm (CH_3); MS, *m/z*: 191 (100%), 144 (68), 115 (84), 39 (100); elemental analysis: found: C, 62.85; H, 4.70; N, 7.28. $C_{10}H_9NO_3$ requires: C, 62.82; H, 4.74; N, 7.33%.

*2.2. 2,7-Dimethyl-4-nitrobenzo[b]furan (**9**)*

To a solution of 4-methyl-1-nitro-3-propargyloxybenzene (**8**) (7.7 g, 40.4 mmoles) in *N*,*N*-diethylaniline (20 ml) CsF (4.1 g, 26.8 mmoles) was added. The mixture was refluxed for 7 days. The mixture was diluted with ethyl acetate (100 ml) and washed with a diluted hydrochloric acid solution (3× 50 ml). The organic layer was dried (Na_2SO_4). The evaporation of the solvent yielded a crude product that was chromatographed on silica gel. The elution with 8:2 hexanes/Et_2O gave pure 2,7-dimethyl-4-nitrobenzo[*b*]furan (5 g, 65%): ^{1}H NMR ($CDCl_3$) δ: 8.05 (s, 1H, 2-H), 7.06–7.02 (m, 2H, 5-H, 6-H), 2.60 (s, 3H, CH_3), and 2.57 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 154.1, 153.0, 142.2, 127.4, 127.0, 126.3, 119.0, 106.1 (aromatic carbons), 15.5 (CH_3), and 13.8 ppm (CH_3); MS, *m/z*: 191 (100%), 161 (36), 145 (25), 115 (43); elemental analysis: found: C, 62.78; H, 4.78; N, 7.36. $C_{10}H_9NO_3$ requires: C, 62.82; H, 4.74; N, 7.33%.

*2.3. 4-Amino-2,7-dimethylbenzo[b]furan (**10**)*

2,7-Dimethyl-4-nitrobenzo[*b*]furan (**9**) (3 g, 16.1 mmoles) in ethanol (100 ml) was treated with hydrogen in the presence of catalytic amounts of 10% Pd/C for 24 h. The mixture was filtered and the solvent was evaporated. The crude product was chromatographed on silica gel. The elution with 9:1 hexanes–Et_2O gave pure 4-amino-2,7-dimethylbenzo[*b*]furan (1.8 g, 68%): ^{1}H NMR ($CDCl_3$) δ: 6.80 (d, 1H, J = 5 Hz, 5-H), 6.40 (d, 1H, J = 5 Hz, 6-H), 6.29 (s, 1H, 2-H), 3.65 (br s, 2H, NH_2), 2.47 (s, 3H, CH_3), and 2.38 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 153.4, 152.4, 146.4, 126.6, 118.4, 116.6, 109.1, 99.4 (aromatic carbons), 30.3 (CH_3), and 29.7 ppm (CH_3); MS, *m/z*: 161 (93%), 160 (100), 146 (9), 131 (3), 130 (7); elemental analysis: found: C, 74.55; H, 6.82; N, 8.75. $C_{10}H_{11}NO$ requires: C, 74.51; H, 6.88; N, 8.69%.

*2.4. 1-(2,2-Dimethoxyethyl)-2,6-dichlorobenzene (**12**)*

Trimethylorthoformate (3.2 g, 30 mmoles) and a catalytic amount of *p*-TsOH were added to a suspension of 2,6-dichlo-

rophenylacetaldehyde (**11**) (1 g, 5.29 mmoles) in methanol (80 ml). The mixture was refluxed for 4 h. The mixture was treated with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (250 ml). The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give pure 1-(2,2-dimethoxyethyl)-2,6-dichlorobenzene (1.2 g, 95%): ^{1}H NMR ($CDCl_3$) δ: 7.22 (d, 2H, $J = 7$ Hz, 3-H, 5-H), 7.05 (dd, 1H, $J_1 = J_2 = 7$ Hz, 4-H), 4.68 (t, 1H, $J = 6$ Hz, $CH(OMe)_2$), 3.32 (s, 6H, CH_3), and 3.23 ppm (d, 2H, $J = 6$ Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ: 136.2, 128.8, 128.5, 128.1 (aromatic carbons), 103.6 (CH), 54.0 (CH_3), and 35.3 ppm (CH_2); MS, *m/z*: 234 (1%), 203 (24), 159 (11), 75 (100); elemental analysis: found: C, 51.13; H, 5.10. $C_{10}H_{12}Cl_2O_2$ requires: C, 51.09; H, 5.14%.

2.5. 4-Chlorobenzo[b]furan (*13*)

A mixture of $Pd(OAc)_2$ (13 mg, 0.06 mmoles), P(*t*-Bu)$_3$ (36 mg, 0.18 mmoles), 1-(2,2-dimethoxyethyl)-2,6-dichlorobenzene (**12**) (470 mg), *t*-BuONa (211 mg, 2.2 mmol) and xylene (5 ml) were maintained at 120 °C for 4 h under nitrogen. The mixture was treated with water and extracted with ethyl acetate (3 × 50 ml). The solvent was evaporated. The residue was treated with hydrochloric acid (4.5 g) and the mixture was stirred for 30 h at r.t. The mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The crude product was chromatographed on silica gel. The elution with 95:5 hexanes–Et_2O gave pure 4-chlorobenzo[*b*]furan (243 mg, 80%): ^{1}H NMR ($CDCl_3$) δ: 7.50 (d, 1H, $J = 5$ Hz, 3-H), 7.45 (dd, 1H, $J_1 = J_2 = 6$ Hz, 6-H), 7.25 (d, 1H, $J = 6$ Hz, 5-H), 7.24 (d, 1H, $J = 6$ Hz, 7-H), and 7.05 ppm (d, 1H, $J = 5$ Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ: 170.9 (C-8), 145.5 (C-1), 125.5 (C-6), 124.8 (C-4), 122.7 (C-3), 110.0 (C-5), 105.2 (C-7), and 95.0 ppm (C-2); MS, *m/z*: 152 (100%), 117 (7); elemental analysis: found: C, 63.04; H, 3.27. C_8H_5ClO requires: C, 62.97; H, 3.30%.

2.6. 1-Methyl-6-phenyl-(3-amino-6-methyl)benzo[1,2-b]-2,7-dioxabicyclo[3.2.0]heptane (*14*)

4-Amino-2,7-dimethylbenzo[*b*]furan (**10**) (160 mg, 1 mmol) and benzaldehyde (150 mg, 1.5 mmoles) were dissolved in benzene. The mixture was flushed with nitrogen for 30 min. and then irradiated for 51 h in an immersion apparatus with a 125 W high pressure mercury arc (Helios-Italquartz, Milan, Italy) surrounded by a Pyrex water jacket connected to a Haake F3 thermostat to maintain the mixture at 8 °C. The removal of the solvent yielded a crude mixture that was chromatographed on silica gel. The elution with 8:2 hexanes–Et_2O gave pure 1-methyl-6-phenyl-(3-amino-6-methyl)benzo[1,2-*b*]-2,7-dioxabicyclo[3.2.0]heptane (176 mg, 66%): ^{1}H NMR ($CDCl_3$) δ: 7.25–7.21 (m, 5H), 7.0 (d, 1H, $J = 6$ Hz, 4-H aromatic), 6.98 (d, 1H, $J = 6$ Hz, 5-H aromatic), 5.96 (d, 1H, $J = 5$ Hz, 6-H), 4.18 (d, 1H, $J = 5$ Hz, 5-H), 3.52 (s, 2H, NH_2), and 1.29 ppm (s, 6H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ: 151.0, 142.5, 137.7, 130.0, 128.1, 126.8, 125.5 (aromatic carbons), 117.08 (C-1), 60.40 (C-6), 56.95 (C-5), 19.71 (CH_3), and 14.12 ppm (CH_3); elemental analysis: found: C, 76.42; H, 6.37; N, 5.30. $C_{17}H_{17}NO_2$ requires: C, 76.38; H, 6.41; N, 5.24%.

2.7. 4-Amino-2,7-dimethyl-3-(1-hydroxybenzyl)-benzo[b]furan (*15*)

1-Methyl-6-phenyl-(3-amino-6-methyl)benzo[1,2-*b*]-2,7-dioxabicyclo[3.2.0]heptane (**14**) (100 mg) was dissolved in Et_2O (100 ml) and treated with a catalytic amount of *p*-TsOH. The mixture was stirred at r.t. for 21 h. The reaction mixture was neutralized adding a saturated solution of $NaHCO_3$. The reaction mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a crude product that was chromatographed on silica gel. Elution with 9:1 hexanes–Et_2O gave pure 4-amino-2,7-dimethyl-3-(1-hydroxybenzyl)benzo[*b*]furan (77 mg, 77%): ^{1}H NMR ($CDCl_3$) δ: 8.73–7.27 (aromatic proton), 7.01 (d, 1H, $J = 6$ Hz, H-5), 6.90 (d, 1H, $J = 6$ Hz, H-6), 6.61 (s, 1H, CHOH), 4.21 (br s, 1H, OH), 3.65 (s, 2H, NH_2), and 2.46 ppm (s, 6H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ: 159.8 (C-2), 131.2 (C-7a), 130.9 (C-4), 129.2 (CH_{arom}), 128.8, 128.7 (aromatic carbons), 128.6 (C-6), 124.4 (C-3a), 117.1 (C-5), 112.2 (C-7), 101.2 (C-3), 68.1 (CHOH), 14.1 (CH_3), and 10.9 ppm (CH_3); MS, *m/z*: 267 (2%), 249 (100), 234 (3), 204 (4), 145 (13); elemental analysis: found: C, 76.35; H, 6.44; N, 5.29. $C_{17}H_{17}NO_2$ requires: C, 76.38; H, 6.41; N, 5.24%.

2.8. 1-Methyl-6,6-diphenyl-(3-amino-6-methyl)benzo[1,2-b]-2,7-dioxabicyclo[3.2.0]heptane (*16*)

4-Amino-2,7-dimethylbenzo[*b*]furan (**10**) (160 mg, 1 mmol) and benzophenone (150 mg, 1.5 mmoles) were dissolved in benzene. The mixture was flushed with nitrogen for 30 min and then irradiated for 60 h in an immersion apparatus with a 125 W high pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water jacket connected to a Haake F3 thermostat to maintain the mixture at 8 °C. The removal of the solvent yielded pure 1-methyl-6,6-diphenyl-(3-amino-6-methyl)benzo[1,2-*b*]-2,7-dioxabicyclo[3.2.0]heptane (322 mg, 94%): ^{1}H NMR ($CDCl_3$) δ: 7.83–7.80 (m, aromatic protons), 7.55 (d, 1H, $J = 5$ Hz, 5-H aromatic), 7.45 (d, 1H, $J = 5$ Hz, 6-H aromatic), 4.11 (s, 1H, 6-H), 2.44 (s, 2H, NH_2), 2.00 (s, 3H, CH_3), and 1.25 ppm (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 151.07 (C-3), 142.57 (C–NH_2), 130.04 (C_{arom}–C–CH_3), 122.91–128.91 (aromatic carbons), 117.78 (C_{arom}–CH_3), 115.27 (C-4), 110.65 (C-1), 110.61 (C_{arom}–C–NH_2), 76.53 (C-6), 55.20 (C-5), 19.65 (CH_3) and 15.46 ppm (CH_3).

2.9. 6,6-Diphenyl-3-chlorobenzo[1,2-b]-2,7-dioxabicyclo[3.2.0]heptane (*17*)

4-Chlorobenzo[*b*]furan (**13**) (150 mg, 1 mmol) and benzophenone (150 mg, 1.5 mmoles) were dissolved in benzene. The mixture was flushed with nitrogen for 30 min and then irradiated for 60 h in an immersion apparatus with a 125 W high pressure mercury arc (Helios-Italquartz) surrounded by

a Pyrex water jacket connected to a Haake F3 thermostat to maintain the mixture at 8 °C. The removal of the solvent yielded a crude mixture that was chromatographed on silica gel. The elution with 8:2 hexanes–Et_2O gave pure 6,6-diphenyl-3-chlorobenzo[1,2-*b*]-2,7-dioxabicyclo[3.2.0]heptane (134 mg, 40%): ^{1}H NMR ($CDCl_3$) δ: 7.64–7.42 (aromatic protons), 7.08 (dd, 1H, $J_1 = J_2 = 6$ Hz, 5-H aromatic), 6.84 (d, 1H, $J = 6$ Hz, 4-H aromatic), 6.66 (d, 1H, $J = 6$ Hz, 6-H aromatic), 6.54 (s, 1H, 1-H), and 5.13 ppm; ^{13}C NMR ($CDCl_3$) δ: 155.1 (C-3), 146.9 (C-6), 135.3 (C_{arom}-5), 129.7 (C-4), 128.9 (C-1), 128.6, 128.0, 122.7 (aromatic carbons), 122.8 (C_{arom}-4), 111.5 (C_{arom}-3), 106.1 (C_{arom}-6), and 78.1 ppm (C-5); elemental analysis: found: C, 75.40; H, 4.44. $C_{21}H_{15}ClO_2$ requires: C, 75.34; H, 4.52%.

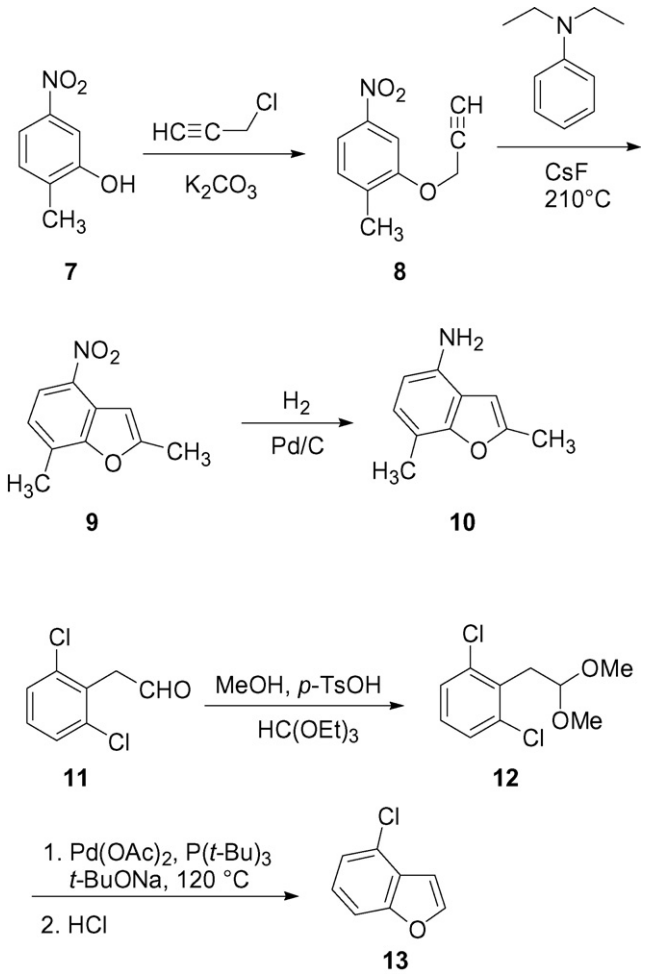
*2.10. 4-Chloro-3-(1-hydroxy-diphenylmethyl)-benso[b]furan (**18**)*

6,6-Diphenyl-3-chlorobenzo[1,2-*b*]-2,7-dioxabicyclo[3.2.0] heptane (**17**) (134 mg) was dissolved in Et_2O (100 ml) and treated with a catalytic amount of *p*-TsOH. The mixture was stirred at r.t. for 72 h. The reaction mixture was neutralized adding a saturated solution of $NaHCO_3$. The reaction mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a crude product that was chromatographed on silica gel. Elution with 9:1 hexanes–Et_2O gave pure 4-chloro-3-(1-hydroxydiphenylmethyl)benzo[*b*]furan (88 mg, 66%): ^{1}H NMR ($CDCl_3$) δ: 7.64–7.43 (aromatic proton), 7.38 (d, 1H, $J = 6$ Hz, H-5), 7.28 (dd, 1H, $J_1 = J_2 = 6$ Hz, H-6), 7.15 (d, 1H, $J = 6$ Hz, H-7), 6.98 (s, 1H, H-2), and 3.67 ppm (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 160.0 (C-7a), 148.1 (C-2), 147.0 (C_{arom}), 133.3 (C-6), 130.2, 129.6, 128.8, 126.4 (aromatic carbons), 125.9 (C-3a), 122.3 (C-5), 118.8 (C-3), 105.3 (C-7), and 81.9 ppm (COH); elemental analysis: found: C, 75.28; H, 4.55. $C_{21}H_{15}ClO_2$ requires: C, 75.34; H, 4.52%.

3. Results and discussion

In order to synthesize benzofuran derivatives with potential biological properties we used as starting material 4-amino-2,7-dimethylbenzo[*b*]furan (**10**) and 4-chlorobenzo[*b*]furan (**13**) (Scheme 2). The selection of these substrates was due to our intention to give an answer to two questions in the field of the Paternò–Büchi reaction. First, we want to verify if the presence of both photolabile substituents, such as chlorine, and substituents able to induce electron transfer reactions, such as the amine, was able to modify the photochemical behaviour of the furan ring. Then, we wanted to verify if the Paternò–Büchi reaction on benzofuran could be used in the synthesis of potential biological properties. In fact, the amine group is present (as an amide) in compound **1** [13,14,21] while the chlorine substituent is present in some compounds claimed for their anaesthetic properties [15].

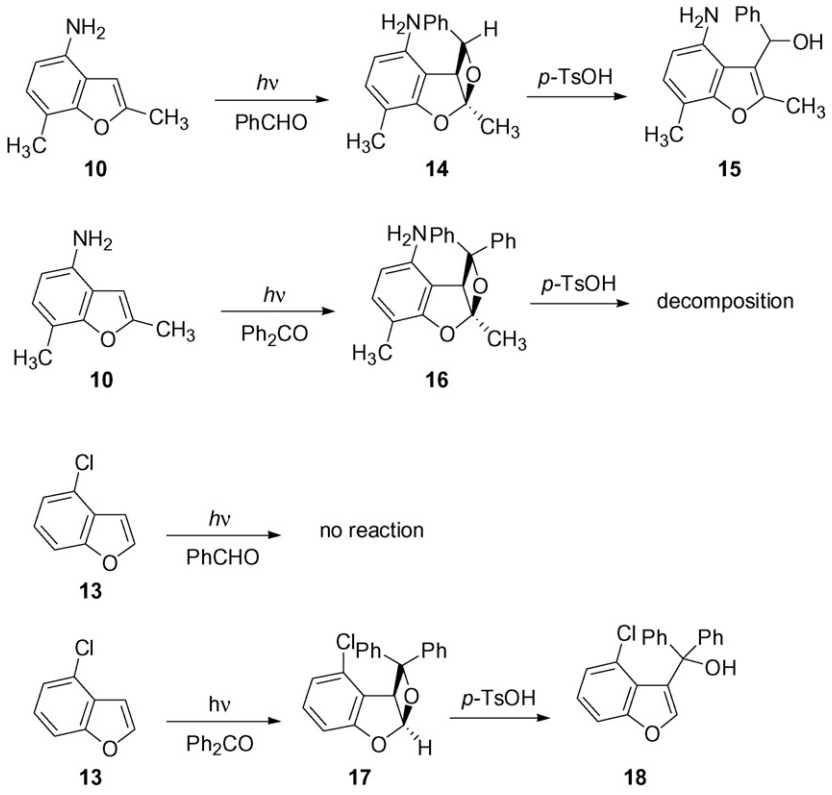
The synthesis of **10** started from 2-methyl-5-nitrophenol that was alkylated with propargyl chloride in basi medium: the resulting ether **8** was converted in the benzofuran derivative **9** through reaction with CsF in the presence of *N*,*N*-diethylaniline. The reduction of the nitro group afforded **10** (Scheme 2). The synthesis of **13** was performed starting from 2,6-dichlorophenylacetaldehyde (**11**) that was converted in the corresponding acetal through reaction with methanol in acidic condition and in the presence of triethylorthoformate; the acetal **12** gave 4-chlorobenzo[*b*]furan (**13**) via a condensation reaction in basic conditions in the presence of palladium(0) (Scheme 2).



Scheme 2. Synthesis of **10** and **13**.

The irradiation of **10** in the presence of benzaldehyde in benzene gave the corresponding adduct **14** in good yields (Scheme 3, Table 1).

It is interesting to note that the reaction allowed the formation of the *endo* isomer. The reaction between benzo[*b*]furan and benzaldehyde gave an adduct whose stereochemistry has not been described [22]. However, in the NMR spectrum the chemical shift of the proton at C-6 (5.45 ppm) was in agreement with an *exo* stereochemistry [26]. In our case, we observed that the proton at C-6 had a chemical shift at 5.96 δ while the proton at C-5 showed a chemical shift of 4.18 δ. These data are in agreement with an *endo* stereochemistry: in fact, in the *endo* adduct between furan and benzaldehyde, the proton at C-6 had a chemical shift at 6.07 δ while the proton at C-5 showed an peak at 4.21 δ [28].



Scheme 3. Synthesis of 3-benzofuryl derivatives by using the Paternò–Büchi reaction.

The hydrolysis of the adduct **14** was performed in ethyl ether in the presence of a catalytic amount of *p*-TsOH. This way, the 3-benzofurylmethanol derivatives **15** was obtained in good yields (Scheme 3, Table 1). The reaction of **10** with benzophenone gave the corresponding adduct **16** in very good yields (Scheme 3, Table 1). Unfortunately, this compound was labile and after a night at 5 °C it was completely decomposed. Compound **13** did not react with benzaldehyde (Scheme 3), while it reacted with benzophenone to give the corresponding adduct **17** (Scheme 3, Table 1). This compound, treated with *p*-TsOH, gave the 3-benzofurylmethanol derivative **18** (Scheme 3, Table 1).

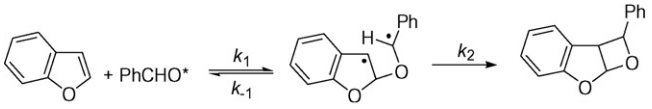
The lack of reactivity of **13** towards benzaldehyde has to be explained. We assume that the Paternò–Büchi reaction occurs following the scheme reported by Scharf [29] and depicted in Scheme 4.

Table 1
Paternò–Büchi reaction on benzofuran derivatives and acid hydrolysis of the oxetanes

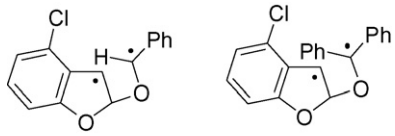
Benzofuran	Carbonyl compound	Oxetane	3-Benzofurylalcohol	Yield [%]
10	Benzaldehyde	**14**	–	66
10	Benzophenone	**14**	**15**	77
		16	–	94
		16	–	–
13	Benzaldehyde	–	–	–
13	Benzophenone	**17**	–	40
		17	**18**	66

In this scheme we have a reversible addition of the carbonyl compound to the double bond to give the corresponding biradical, followed by an irreversible ring closure reaction. The lack of the reactivity observed in the case of the reaction between **13** and benzaldehyde cannot be attributed to an inefficient attack of the excited triplet state of the benzaldehyde on the benzofuran double bond (k_1). There is not significant difference between the benzophenone and benzaldehyde triplet energy (286 and 301 kJ mol^{-1}, respectively) to explain the observed photochemical behaviour. We think that the observed lack of reactivity can be due to the relative rate between the retrocleavage (k_{-1}) and ring closure (k_2) reactions. We investigated on the presence of some features able to explain the different reactivity in the biradical intermediates **19** and **20** (Fig. 2) obtained in the reaction of **13** with benzaldehyde and benzophenone, respectively.

We performed some DFT calculations with hybrid functional B3LYP and using 6-31G + (d,p) basis set [30]. The biradicals are very similar: the only difference we found is in the charge on the radical carbon deriving from the carbonyl compound. The charge on the radical carbon on the benzofuran ring is −0.2. In the case of **19** the benzylic radical carbon has a charge of −0.1 while, in the case of **20**, the charge on the diphenylmethyl radical



Scheme 4. Mechanism of the Paternò–Büchi reaction in the scheme of Scharf [29].



19 20

Fig. 2. Biradical intermediates in the reaction of benzaldehyde and benzophenone with **13**.

carbon is 0.00. The repulsion between to similar charge can be responsible of the low k_2 value, driving the reaction towards the retrocleavage.

In conclusion we showed that the Paternò–Büchi reaction between benzofuran and carbonyl compounds can be used in the synthesis of oxetanes also in the presence of substituents able to interfere with the reaction. In some cases the oxetanes can be converted into the corresponding 3-benzofurylmethanol derivatives, giving a building block for the synthesis of potential pharmacological active compounds.

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