An alternative synthetic path to 1-substituted 2-naphthol†

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The photoinduced substitution of the 2-naphthoxide anion was carried out using diethylphosphite, benzenethiolate or 2-naphthalenethiolate anions in the presence of an electron acceptor. The corresponding products were afforded in good yield. This is a simple and convenient approach, which involves the use of 2-naphthol without a leaving group for the synthesis of C_1-substituted derivatives.

Introduction

Nucleophilic substitutions can be achieved through processes that involve electron transfer steps. Radical nucleophilic substitution or $S_{RN}1$ has been previously used for the elaboration of complex molecules from simple starting materials. A great variety of unactivated aromatic compounds with appropriate leaving groups have been shown to react by this mechanism.[1]

$$\mathrm{ArX} + \mathrm{Nu}^- \xrightarrow{h\nu} [\mathrm{ArNu}]^{\bullet -} \xrightarrow{\mathrm{ET}} \mathrm{ArNu} \qquad (1)$$

An important step of this reaction is the coupling between the nucleophile and the radical of the substrate, which affords the radical anion of the substitution product, and later, the final product after an electron transfer (ET) step.[1]

Furthermore, it is well known that excited 2-naphthoxide anion **1** is a good electron donor.[2] This species easily transfers one electron to *N*,*N*-di-(*n*-butyl)-*p*-toluenesulfonamide (**2**), affording 2-naphthoxyl radical **3** and the radical anion of **2** (Scheme 1).[3] This reaction is used to easily remove the tosyl group in protected amines. However, it may also be an alternative method to generate intermediate **3** from excited anion **1**.

In this work, we report a study of the photoinduced reactions of **1** in the presence of an electron acceptor with nucleophiles as a method for the synthesis of arylphosphonates and diaryl sulfides from a substrate without a leaving group.

The synthetic value of organophosphonates, as well as their applications as biologically active compounds, have attracted considerable attention.[4] Although the Michaelis–Arbuzov reaction is the most common method for the synthesis of organophosphonates $RP(O)(OR')_2$, it fails in the preparation of arylphosphonates $ArP(O)(OR)_2$.[4f] However, several other reactions have been developed in order to prepare these compounds. For instance, the free radical phosphonation of aromatic compounds with diethylphosphite and *t*-butylperoxide as a radical initiator has been reported.[5] Also, the catalytic phosphonation of arenes with dialkyl phosphites, carried out under the influence of an $Mn(OAc)_2/Co(OAc)_2/O_2$ redox couple, has recently been developed.[6] Trialkyl phosphates react with aryl radicals obtained by the photolysis of iodobenzenes,[7] or by classical thermal AIBN/n-Bu_3SnH generation.[4e] A great variety of arylphosphonates have been prepared by photoinduced $S_{RN}1$ reactions of diethylphosphite anion with haloarenes.[1] Nevertheless, despite the large number of reactions to prepare these compounds that have been explored, there are few examples of the phosphonation of aromatic alcohols.[7]

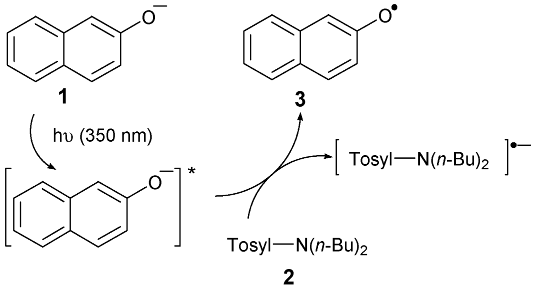
Results and discussion

The results obtained in the experimental study of the photoinduced reactions of anion **1** and diethylphosphite anion **4** in the presence of an electron acceptor (Scheme 2) are summarized in Table 1 and Table 2.

The general procedure for the above mentioned reactions is as follows: To a solution of anion **1**, obtained by deprotonation of 2-naphthol with an excess of KBuO-*t* in DMSO, was added first the diethylphosphite[8] and then the appropriate electron acceptor. Following this approach, the reaction of anions **1** and **4** in the presence of **2** (ratio **4**:**2**:**1** = 10:1:6) afforded 1-(2-naphthoxyl)diethylphosphonate (**5**) in 66% yield with respect to moles of **2** (Table 1, entry 1).

The yield of the product decreased by half in the absence of **2**, and was not observed in the dark (Table 1, entries 2 and 3). The substitution products between **2** and **1** or **4** were not detected.

In order to find the best synthetic conditions for the reaction, different ratios of **4**:**2**:**1** were investigated (see



Scheme 1

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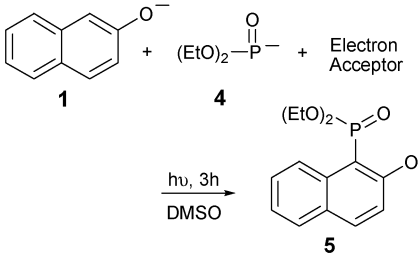
† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR and MS spectra of compounds **5**, **7** and **9**. Table of energy differences between relevant points of the PES for the coupling of radical **3** with anion **4**.



Scheme 2

Table 1 Photoinduced reactions of anions **4** and **1** in the presence of **2**[a]

Entry	Ratio **4** : **2** : **1**	Yield of **5** (%)[b]
1	10 : 1 : 6[c]	66
2	10 : 0 : 6	31
3[d]	10 : 1 : 6	—
4	10 : 1 : 2	51
5	10 : 1 : 1	40
6	5 : 1 : 1[e]	45

[a] Irradiation for 3 h under a nitrogen atmosphere in DMSO. [b] Determined by GC using the internal standard method with respect to moles of **2**. [c] **4**, 0.20 M; **2**, 0.02 M, **1**, 0.12 M. [d] In the dark. [e] **4**, 0.20 M; **2**, 0.04 M, **1**, 0.04 M.

Table 2 Reactions of anions **4** and **1** in the presence of different electron acceptors[a]

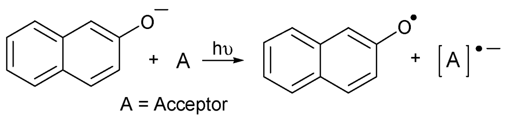
Entry	Acceptor	Product yield (%)[b]	Reduction potential/V[c]
1	Benzophenone	90	−1.77
2	Sulfonamide (**2**)	66	
3	Naphthalene	64	−2.53
4	Chlorobenzene	44	−2.78

[a] Irradiation for 3 h under a nitrogen atmosphere in DMSO. **1**, 0.24 M; **4**, 0.40 M; acceptor, 0.04 M. [b] Determined by GC using the internal standard method with respect to moles of acceptor. [c] DMF *vs.* SCE.

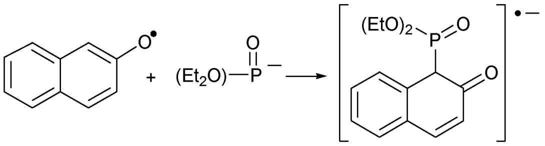
Table 1). When concentrations were decreased by half for anion **4** and by six times for **1**, a decay in the yield of product **5** from 66 to 45% was observed (Table 1, entry 6). These results show that the substitution works very well without a large excess of reactants being necessary.

The effects of the acceptor were studied in the reaction of ion **1** with **4**. When other electron acceptors, different from **2**, were used, product **5** was also obtained in yields that correlate with their reduction potentials (see Table 2). The best acceptor used, benzophenone, gave rise to the highest yield of **5** (90%), while chlorobenzene produced the smallest (44%) (Table 2, entries 1 and 4).

These latter results, concerning the reaction in the dark and the reaction in the absence of an electron acceptor, suggest a photoinduced electron transfer mechanism. The best electron donor in the reaction medium is anion **1**; therefore, it may have transferred an electron to the acceptor, thus generating radical **3** (eqn (2)). This latter species, coupled with anion **4**, affords the corresponding radical anion (eqn (3)). Further electron transfer and re-aromatization gives rise to final product **5** (eqn (4)).



(2)



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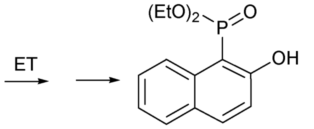


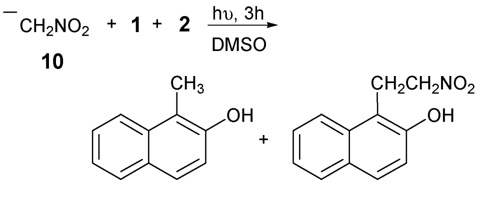
(4)

Based on these promising results obtained with the diethylphosphite anion, we investigated this experimental strategy as an alternative procedure to the synthesis of substituted 2-naphthol systems. In this analysis, we studied the reaction of **1** with sulfur nucleophiles.

Benzenethiolate anion **6** reacted with **1** in the presence of **2**, affording a 92% yield of 1-phenylthio-2-naphthol (**7**) (Fig. 1).‡ This was considerably better than the yield reported by a vanadium-catalyzed reaction.[9] However, in the reaction of the 2-naphthalenethiolate anion **8**, a 44% yield of 1-(2-naphthylthio)-2-naphthol (**9**) was observed, showing its lower reactivity. These products may be used as agricultural chemicals for powdery mildew.[10]

Product **7** was not observed in a reaction in the dark. The photoinduced reaction of **1** with thiolate anions is a "one-pot" method for the synthesis of unsymmetrical diaryl sulfides.

The photoinduced methodology has been extended to carbanion nucleophiles.[1] The anions of acetophenone and pinacolone did not react with **1**, whereas in the reaction of nitromethane anion **10** and **1** in the presence of **2**, traces of 1-methyl-2-naphthol and 1-(2-nitroethyl)-2-naphthol were observed (eqn (5)). These products are presumably formed by the fragmentation of radical anion intermediates.



(5)

In order to compare this methodology with the radical nucleophilic substitution of the substrate with an adequate leaving group (ArX), photoinduced reactions of 1-bromo-2-naphthol (**12**)[11] (eqn (6)) with anions **4** or **6** were performed

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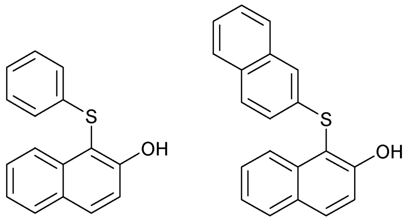
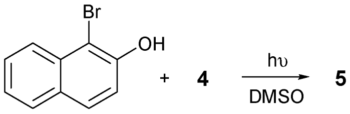
‡ In the photoinduced conditions, the phenylthiyl radical was not formed.



7 **9**

Fig. 1

(ratio **4** (or **6**) : **12** : KBuO-*t* = 10 : 1 : 11.5). Products **5** and **7** were obtained in yields of 6 and 23%, respectively.



12 (6)

Theoretical calculations

In order to clarify the mechanism of the reactions mentioned above, a theoretical study was performed.[12]

First, the tautomers **3** and **13** (Fig. 2) were considered as the two possible intermediates involved in the reaction mechanism. An energy difference of 36.8 kcal mol^{-1} between them demonstrated that **3** is the more probable reaction intermediate.

The spin density and SOMO coefficients[13] of radical **3** are higher at C_1 and the oxygen atoms, showing that this species is an ambident radical that may react with a nucleophile *via* these two positions.

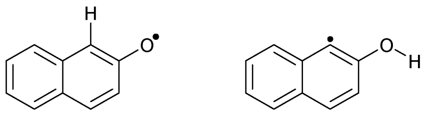
Thus, the potential energy surface (PES) for the coupling of radical **3** with anion **4** was inspected. The energy differences between the critical structures of the PES indicated a preference for the coupling at C_1 in the gas phase and taking into account the solvent effect (polarized continuum model)[14] (Table 3) (see the ESI†). These results agree with the experimental observations of the present work and the proposed mechanism.

Conclusions

Summing up, the photoinduced reaction of the 2-naphthoxide ion with nucleophiles in the presence of an electron acceptor provides a good alternative for introducing a sulfur or phosphorous functionality at the C_1 position of the naphthyl moiety. The 2-naphthol ring without the leaving group being substituted by nucleophiles.

Experimental evidence and theoretical calculations agree with an electron transfer mechanism, in which radical **3** is an intermediate.

Several reactions were performed with different electron acceptors. The use of a commercially available, easy to handle, inexpensive compound, together with very mild conditions, makes this process a simple and convenient approach for obtaining 2-naphthol derivates.



3 **13**

Fig. 2

Table 3 Energy differences between relevant points of the PES for the coupling of radical **3** with anion **4** in DMSO

Position of **3**	ΔE_a/kcal mol^{-1a}	ΔE_r/kcal mol^{-1b}
C1	0.72	−10.23
O	1.46	−4.12

[a] ΔE_a = Energy difference between transition states and reactants (radical **3** + anion **4**). [b] ΔE_r = Energy difference between radical anions and reactants (radical **3** + anion **4**).

Various studies are now in progress in order to extend this methodology to the functionalization of aromatic alcohols without leaving groups.

Experimental section

General procedure for reactions of 2-naphthoxide anion 1 with nucleophiles

The reactions were carried out in a 50 mL three-necked round-bottomed flask equipped with a nitrogen inlet and a magnetic stirrer. To 5 mL of dry and de-gassed dimethylsulfoxide was added potassium *tert*-butoxide (203 mg, 1.81 mmol). After total dissolution of the base, 2-naphthol (87 mg, 0.60 mmol), diethylphosphite (141 mg, 1.02 mmol) and *N*,*N*-di-(*n*-butyl)-*p*-toluenesulfonamide (29 mg, 0.10 mmol) were added. The reaction mixture was irradiated with two 400 W lamps emitting maximally at 350 nm (air and water refrigerated) for 3 h. The reaction was quenched with an excess of ammonium nitrate and 30 mL of water was added. After that, it was extracted three times with dichloromethane (portions of 10 mL), and the organic layer obtained was washed twice with water (portions of 15 mL) to eliminate traces of dimethylsulfoxide. It was then dried with $MgSO_4$, filtered and concentrated to give a residue, which after radial chromatography on silica gel 60 (petroleum ether : acetone 98 : 2) gave 1-(2-naphthoxyl)diethylphosphonate (**5**) as a slightly yellow oil. ^1H NMR (200 MHz, CCl_4 with a capillary tube with $(CD_3)_2CO$ inside): δ 1.26–1.33 (6H, t), 3.85–4.25 (4H, m), 7.01–7.08 (1H, dd, J_1 = 5.84 Hz, J_2 = 9.12 Hz), 7.21–7.29 (1H, m), 7.37–7.45 (1H, m), 7.65 (1H, d, J = 8.04 Hz), 7.80 (1H, d, J = 9.12 Hz), 7.98 (1H, d, J = 8.76 Hz), 11.68 (1H, s, OH); ^{13}C NMR (50 MHz, CCl_4 with a capillary tube with $(CD_3)_2CO$ inside): δ 16.3, 16.4, 61.9, 62.0, 100.5, 119.9, 120.2, 123.2, 124.8, 124.9, 127.5, 128.1, 128.3, 128.7, 133.7, 135.7, 164.7, 167.9; HRMS calculated for $C_{14}H_{17}O_4P$ 280.08645, found 280.08633. The yield of product **5** was quantified by gas chromatography by the internal standard method.

1-Phenylthio-2-naphthol (7)

White solid, mp = 61.5–63.5 °C (lit.[9] 61.5–62.5 °C); ^1H NMR (200 MHz, CCl_4 with a capillary tube with $(CD_3)_2CO$ inside): δ 6.93–7.17 (6H, m), 7.25–7.33 (2H, m), 7.38–7.47 (1H, m), 7.73 (1H, d, J = 7.68 Hz), 7.83 (1H, d, J = 9.12 Hz), 8.14 (1H, d, J = 8.40 Hz); ^{13}C NMR (50 MHz, CCl_4 with a capillary tube with $(CD_3)_2CO$ inside): δ 107.9, 117.0, 123.8, 124.8, 128.8, 126.3, 127.9, 128.6, 129.2, 129.5, 132.7, 135.6, 157.3.

1-(2-Naphthylthio)-2-naphthol (9)

White solid, mp = 99–100 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.20–7.23 (1H, dd, J_1 = 8.64 Hz, J_2 = 1.88 Hz), 7.38–7.45 (4H, m), 7.49–7.52 (2H, m), 7.63 (1H, d, J = 7.76 Hz), 7.76 (1H, d, J = 8.68 Hz), 7.81 (1H, d, J = 7.20 Hz), 7.93 (1H, d, J = 8.08 Hz), 8.06 (1H, d, J = 8.96 Hz), 8.33 (1H, d, J = 8.52 Hz), 8.66 (1H, s, OH); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 109.5, 119.6, 125.3, 125.6, 126.1, 126.4, 127.1, 128.3, 128.4, 129.3, 129.4, 130.3, 131.2, 133.3, 134.4, 135.5, 136.2, 137.6, 159.9. HRMS calculated for $C_{20}H_{14}OS$ 302.0765, found 302.0763. 1-(2-Naphthylthio)-2-naphthol was synthesized by another route from di-(2-naphthyl)-disulfide and 2-naphthol and isolated from this reaction to verify the proposed structure of **9**.

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