



Sulfenylation of nitroalkanes and hydroxyaryls

Guillermo A. Blanco, Maria T. Baumgartner*

INFIQC, Dpto. Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, Córdoba 5000, Argentina

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ABSTRACT

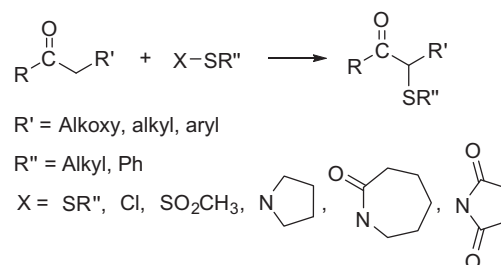
The sulfenylation of nitroalkanes and hydroxyaryls in DMSO using aryl disulfides as sulfenylating reagents was studied. The corresponding arylthionitroalkanes and arylthiohydroxyaryls were obtained in moderate to good yields in very mild conditions, thus improving the reported procedures for the synthesis of these compounds.

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The sulfur atom behaves as an electrophile when it is present in a species in which it has electron deficiency. These type of compounds are widely used as sulfur transfer agents to introduce a sulfur moiety into nucleophilic species like ketones, 1,3-diketones, β -keto esters, amides, etc. in basic conditions. There has been developed a wide range of sulfur transfer agents, some of them are disulfides,¹ sulfenyl chloride,² methylmethanethiosulfate,³ sulfenamides,⁴ *N*-phenylthiocaprolactam,⁵ and *N*-phenylthiosuccinimide⁶ (Scheme 1). However, disulfides are often preferred because of their stability, low cost, and commercial availability.

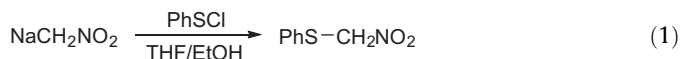
Many sulfur-containing compounds are particularly useful as synthetic intermediates and have biological activity. For instance, α -sulfenylated carbonyl species are especially interesting since they can be used in numerous organic transformations,⁴ thus, many protocols to obtain these species have been widely studied.^{1–6} Recently, the enantioselective synthesis of α -sulfenylated carbonyl compounds has received much attention.⁷ Many studies concerning the sulfenylation of other species like indoles,^{8,9} phosphonates,¹⁰ β -amino esters,¹¹ and nitriles¹² have also been developed.

On the other hand, less research has been reported on the sulfenylation of nitroalkanes and hydroxyaryls. For instance, the preparation of phenylthionitromethane was carried out by the reaction of nitromethane anion with sulfenyl chloride (Eq. 1),¹³ from the nitration of the dianion derived from phenylthio acetic acid,¹⁴ or from ethyl nitroacetate and *N*-phenylthio morpholine.¹⁵ All of



Scheme 1. Common sulfur transfer agents.

these procedures are highly complex and require non commercial, unstable starting materials.



To our knowledge, no research has been reported about the sulfenylation of nitroalkanes with stable commercial sulfenylating reagents as disulfides. As it was said, these latter compounds are desirable but constitute weaker electrophiles than the other sulfur transfer agents mentioned.⁴ Some sulfenylated nitroalkanes are important synthetic intermediates.¹³

In the case of hydroxyaryls, the electrophilic reaction of a hindered phenol with sulfenyl chloride to give the corresponding arylthiolated phenol in good yield was reported.¹⁶ Additionally, a series of 4-arylthio-2,6-dialkylphenols have been prepared with aryl disulfides in basic media, with long periods of reaction at high temperatures.¹⁷ However, the only report about the synthesis of

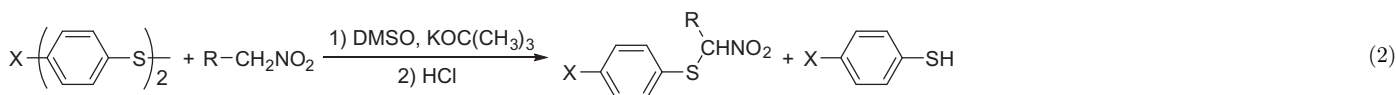
* Corresponding author. Tel.: +54 351 4334170/73; fax: +54 351 4333030.

E-mail addresses: tere@mail.fcq.unc.edu.ar, tere@fcq.unc.edu.ar (M.T. Baumgartner).

1-sulfenylated-2-naphthols involves a different protocol in which these compounds are obtained in moderate yields with a vanadium-catalyzed reaction, using thiols as sulfenylating reagents.⁹ These products may be used as agricultural chemicals for powdery mildew.⁹

In this work, a sulfenylation protocol in mild conditions is described for nitroalkanes and hydroxyaryls with stable and cheap commercial reagents as disulfides.

Table 1 summarizes the results obtained from the study of the reactions of nitroalkanes and disulfides in basic media. Firstly, the reaction of nitromethane anion formed by deprotonation of nitromethane (**1**) with potassium *t*-butoxide, and diphenyldisulfide (**2**) was analyzed. When a mixture of **1**, **2**, and base (ratio 10:1:10.5) was allowed to react for 2 h in DMSO, phenylthionitromethane (**3**) in 82% yield was obtained (Eq. 2) (Table 1, entry 1).



In order to improve the synthetic conditions of the reaction, the nitroalkane concentration was decreased by a factor of 5. Thus, when a mixture of **1**, **2**, and base (ratio 2:1:2.5) was allowed to react for 22 h, a 45% yield of product **3** was obtained (Table 1, entry 2). In addition, di-(phenylthio)methane (**4**) was observed in these conditions in 46% yield. Product **4** may be formed by disubstitution of nitromethane anion with subsequent loss of the nitro group.

With the aim of improving product yield, the effect of the reaction time (Table 1, entries 3–5) was analyzed. The best result, 65% yield of **3**, was obtained in 5 h, product **4** not being observed.

When the nitroalkane concentration was decreased even more to a ratio **1**:**2**:base of 1:1:1, a 30% yield of product **3** was observed in a 5 h reaction.

The procedure was extended to other disulfides, thus with di-(*p*-methylphenyl)disulfide (**5**) and di-(*p*-chlorophenyl) disulfide (**6**) the corresponding products, *p*-methyl-phenylthionitromethane (**7**) and *p*-chlorophenylthio-nitromethane (**8**), were obtained with yields of 80% and 55%, respectively (Eq. 2) (Table 1, entries 7 and 9).

Additionally, di-(2-naphthyl)disulfide (**9**) reacted with **1** (ratio **1**:**9**:base = 10:1:10.8) affording 2-naphthylthionitromethane (**10**) in 84% yield (Fig. 1).

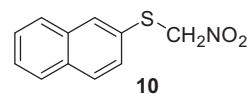


Figure 1. 2-Naphthylthionitromethane.

In order to explore the use of disulfides as sulfenylating reagents for nitroalkanes, the behavior of other nitroalkanes in this system was also examined. Therefore, under analogous conditions, the reactions of 1-nitropropane (**11**) with disulfides **2**, **5**, and **6** were tested, in which the corresponding products (**12–14**) were obtained with moderate to good yields (Eq. 2) (Table 1, entries 11–13).

However, the reaction of 2-nitropropane with disulfide **2** afforded a very low yield (approx. 10%) of 1-phenylthio-2-nitropropane, characterized by CG-MS.

On the other hand, 1-nitropentane (**15**) reacted with disulfide **2** affording 1-phenylthio-1-nitropentane (**16**) in 99% yield (Table 1, entry 14).

In all reactions the thiol formed (Eq. 2) dimerized to the corresponding disulfide after the work-up. This latter product may be recovered easily, for further use, in the purification process. The equivalents of disulfide recovered in each reaction are also in agreement with the expected values taking into account the equivalents of disulfide coming from thiol dimerization and unreacted disulfide.

The effective sulfenylation of nitroalkanes with disulfides in basic media may be possible because of the enhanced nucleophilicity of nitroanions in DMSO compared with other solvents like water or alcohols.¹⁸ This solvent is not much desirable in large-scale synthetic procedures, however, it can be removed easily from the reaction crude since it stays in the water phase in a dichloromethane/water extraction.

Thus, this is the first study about the sulfenylation of nitroalkanes with disulfides with synthetic purpose, which shows important advantages from the procedures reported for the synthesis of sulfenylated nitroalkanes.

Table 1
Reactions of nitroalkanes with disulfides in DMSO

Entry	Nitroalkane RCH ₂ NO ₂	Disulfide (<i>p</i> -X-C ₆ H ₄ S) ₂	Ratio nitroalkane:disulfide	Reaction time (h)	Product <i>p</i> -X-C ₆ H ₄ S-CH(R)NO ₂	Yield ^a (%)
1	1 , R = H	2 , X = H	10:1 ^b	2	3 , R = H, X = H	82 ^c
2			2:1 ^d	22		45 ^e
3			2:1	8½		51 ^e
4			2:1	5		65 ^e
5			2:1	2		47 ^e
6			1:1	5		30 ^e
7		5 , CH ₃	10:1	2	7 , R = H, X = CH ₃	80 ^c
8			2:1	5		46 ^e
9		6 , Cl	10:1	2	8 , R = H, X = Cl	55 ^c
10			2:1	5		45 ^e
11	11 , R = CH ₂ CH ₃	2 , X = H	10:1	2	12 , R = CH ₂ CH ₃ , X = H	46 ^c
12		5 , CH ₃	10:1	2	13 , R = CH ₂ CH ₃ , X = CH ₃	71 ^c
13		6 , Cl	10:1	2	14 , R = CH ₂ CH ₃ , X = Cl	84 ^c
14	15 , R = (CH ₂) ₃ CH ₃	2 , X = H	2:1	5	16 , R = (CH ₂) ₃ CH ₃ , X = H	99 ^c

^a Yields refer to initial moles of disulfide.

^b [**1**] = 0.82 M, [**2**] = 0.08 M.

^c Quantified by gas chromatography with the internal standard method.

^d [**1**] = 0.16 M, [**2**] = 0.08 M.

^e Isolated yield.

Table 2
Reactions of 2-naphthol (**17**) with **2** in DMSO

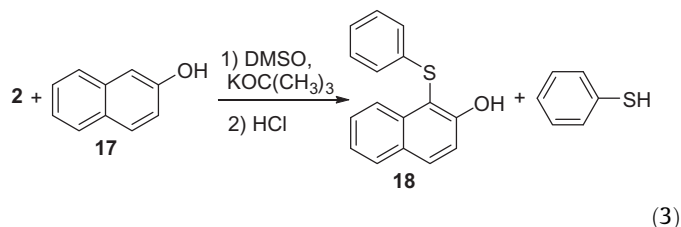
Entry	Ratio 2 : 17	Reaction time (h)	Yield ^a of 18 (%)
1	1:6 ^b	2	75
2	1:2 ^c	2	56
3	1:2	7	72

^a Determined by gas chromatography using the internal standard method and refer to initial moles of disulfide.

^b [**2**] = 0.08 M, [**17**] = 0.48 M.

^c [**2**] = 0.08 M, [**17**] = 0.16 M.

The use of disulfides as sulfenylating reagents was also tested with hydroxyaryls. The reaction of 2-naphthol (**17**) and disulfide **2** (ratio **2**:**17** = 1:6), in the presence of potassium *t*-butoxide, afforded 1-phenylthio-2-naphthol (**18**) in 75% yield (Eq. 3) (Table 2, entry 1). When a smaller concentration of **17** was used (ratio **2**:**17** = 1:2), product **18** was obtained with yields of 56% and 72% at different reaction times, 2 and 7 h, respectively (Table 2, entries 2 and 3).

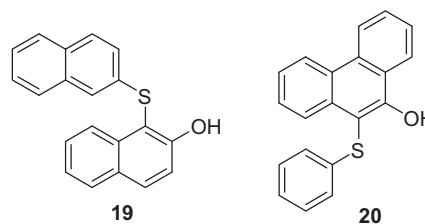


In analogous conditions, **17** reacted with disulfide **9** to give 1-(2-naphthylthio)-2-naphthol (**19**) in 84% isolated yield. Moreover, the reaction of 9-phenanthrol with disulfide **2** afforded 1-phenylthio-9-phenanthrol (**20**) in 65% isolated yield (Fig. 2). In both cases the hydroxyaryl/disulfide ratio used was 2:1 with a reaction time of 5 h. These latter results show the applicability of this methodology to the sulfenylation of hydroxyaryls.

In recent years there have been new studies on sulfenylation processes using more specific reagents, and the traditional methods have been restudied. We present here the sulfenylation of nitroalkanes and hydroxyaryls using stable commercial sulfenylating reagents as disulfides, under conditions with low environmental impact. The synthesis of arylthionitroalkanes and arylthiohydroxyaryls was achieved in moderate to good yields in very mild conditions, improving the reported procedures to obtain these compounds.

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**Figure 2.** 1-(2-Naphthylthio)-2-naphthol and 1-phenylthio-9-phenanthrol.

Supplementary data

Supplementary data (general methods, materials, experimental procedures and ¹H NMR, ¹³C NMR and MS of products 4, 7, 8, 10, 12, 13, 14, 16, 18, 19 and 20) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.053.

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