A general synthesis of benzofuran-2-thiolates *via* intramolecular addition of phenolates to alkynethiolates

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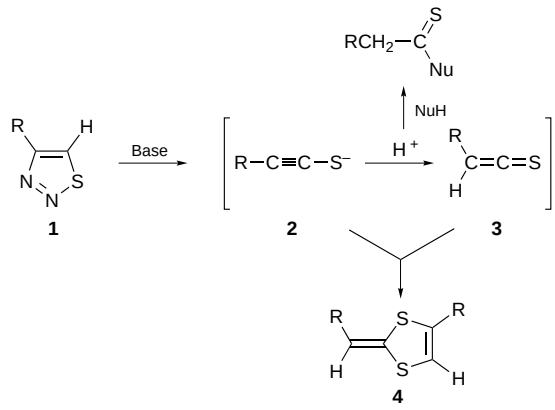
4-(*ortho*-Hydroxyaryl)-1,2,3-thiadiazoles can be transformed into benzofuran-2-thiolates *via* an intramolecular cyclization.

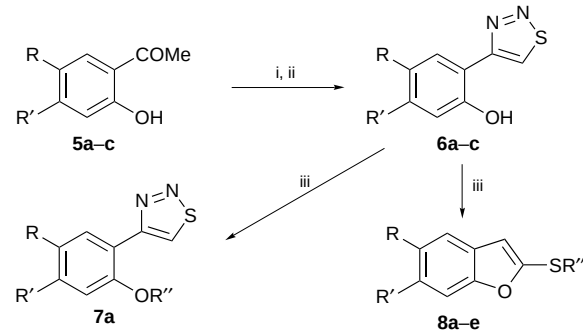
1,2,3-Thiadiazoles **1**, unsubstituted at the 5-position, are cleanly decomposed into alkynethiolates **2** under the influence of strong bases such as organolithium reagents, sodamide, sodium hydride and potassium *tert*-butoxide.[1] These alkynethiolates are interesting reagents which have been alkylated and acylated at sulfur, and converted with nucleophiles into derivatives of the thioketenes **3** which result from protonation at carbon of **2**.[1,2] Another possibility is the combination of alkynethiolate **2** with thioketene **3** to give a dithiafulvene **4**. The dimer **4**[2] will be formed in protic solvents or when no efficient nucleophile is present to trap the thioketene **3** (Scheme 1).

The method of Hurd and Mori[3] gives access to 5-unsubstituted 1,2,3-thiadiazoles **1**, and consists of reacting methyl ketones successively with ethyl carbazate (or tosylhydrazide) and thionyl chloride. This procedure was used to obtain 4-(orthohydroxyaryl)-1,2,3-thiadiazoles **6a–c** from the acetophenones **5a–c** in 37–74% overall yield.[4] We wanted to use the alkylation of phenol **6a** as a means to attach the 1,2,3-thiadiazole group to other molecules.[5] However, the thiadiazole **6a** proved to be susceptible to relatively weak bases, such as potassium carbonate, and in the presence of alkylating agents the unexpected thioethers **8a–c** were formed in high yields instead of the *O*-alkylated thiadiazoles **7**. Only with the very reactive methyl iodide is some *O*-alkylated product **7a** formed. The formation of **7a** can be suppressed by adding the alkylating agent after the decomposition is completed. (Scheme 2, Table 1).

The mechanism of this unusual reaction was elucidated by following the decomposition of **6a** by ^{1}H NMR (400 MHz) spectroscopy. Thus, a solution of compound **6a** in CD_3CN was treated with aqueous tetrabutylammonium hydroxide at room temperature. Initially, the phenolate **9** was present as indicated by the disappearance of the phenolic OH at δ_H 9.69 (as compared to the spectrum without base) and the downfield shift of the thiadiazole 5-H from δ_H 9.20 to 9.76. In addition, the



Scheme 1



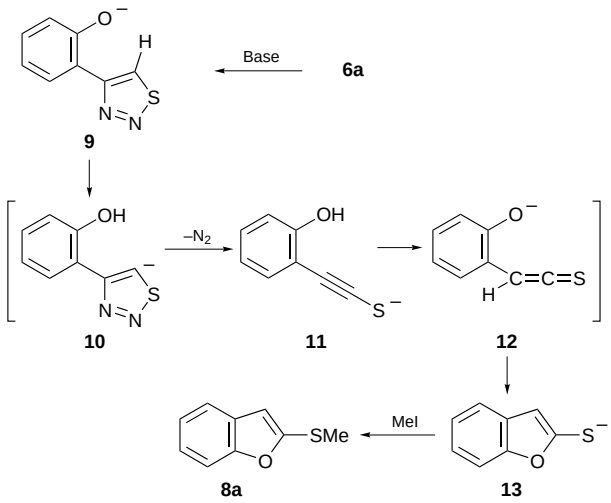
Scheme 2 *Reagents and conditions*: i, EtO_2CNHNH_2; ii, $SOCl_2$; iii, base, R″X, acetone, reflux

phenyl protons at the 3, 4 and 5 positions moved upfield by 0.42, 0.34 and 0.64 ppm, respectively, whereas the 6-H was little affected (Δδ +0.17 ppm). Slow nitrogen evolution was observed, and after a period of 21 h the ^{1}H NMR spectrum corresponded to a 1 : 1 mixture of compounds **9** and **13**. The 5-H of the 1,2,3-thiadiazole ring of **9** was partially deuterated under these conditions, proving the intermediacy of the 1,2,3-thiadiazol-5-yl anion **10**. After 93 h the reaction was completed and the NMR spectrum showed a clean absorption pattern of benzofuran-2-thiolate[7] with δ_H 5.98 (3-H), 6.81, 6.90 (5-H and 6-H) and 7.06 (4-H and 7-H), with no detectable impurities present. When the same reaction was followed by NMR spectroscopy in [$^2H_6$]DMSO, the alkynethiolate **11** (48%) was observed after 15 min, together with the phenolate **9** (35%) and benzofuran **13** (17%). Compound **11** showed peaks in the ^{13}C NMR spectrum at δ 71.8 (d) and 101.2 (s) for the alkyne carbons (respectively β and α to sulfur). After 3 h the phenolate **9** had disappeared and the spectrum showed a 1 : 1 mixture of **11** and **13**. The ^{13}C NMR spectrum of thiolate **13** had peaks at 173.9 (d, $^2J_{CH}$ 9 Hz) and 99.1 (d, $^1J_{CH}$ 173 Hz) for the C-2 and C-3 carbons of the benzofuran, respectively. After one week, the transformation to benzofuranthiolate **13** was complete and the reaction could be treated with methyl iodide to give an immediate and quantitative reaction, affording the sulfide **8a**. From this it follows that an alternative pathway where, in the first step, the alkynethiolate **11** is alkylated, followed by

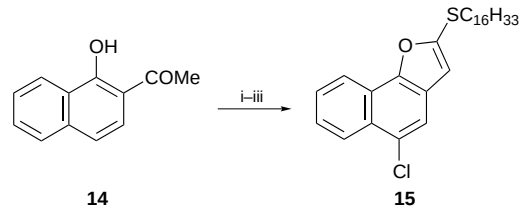
Table 1 Products and yields from the reactions of **6a–c** with base and alkylating agents

Starting material	R	R′	R″X	Products	Yield (%)[a] 7	8
6a	H	H	MeI	**7a** + **8a**	43	56
6a	H	H	BnCl	**8b**	0	91
6a	H	H	$C_{16}H_{33}Br$	**8c**	0	97
6b	OH	H	$C_{16}H_{33}Br$	**8d**	0	92
6c	H	OH	$C_{16}H_{33}Br$	**8e**	0	46

[a] Isolated yields after chromatographic separation.



Scheme 3



Scheme 4 *Reagents and conditions*: i, EtO_2CNHNH_2; ii, $SOCl_2$; iii, K_2CO_3, $C_{16}H_{33}Br$, acetone, reflux

intramolecular phenolate addition,[8] can be excluded (Scheme 3).

It is most unusual that a weak base such as phenolate would be capable of abstracting the 5-thiadiazole hydrogen. We found that the decomposition reaction to alkynethiolate **2** also occurs, although at a much slower rate (several days), when equal amounts of phenol and 4-phenyl-1,2,3-thiadiazole **1** are reacted in refluxing acetone in the presence of equivalent amounts of potassium carbonate and benzyl chloride. There is no observable reaction when only **1**, potassium carbonate and benzyl chloride are present, proving the intermediacy of the phenolate anion. Here, the major products are the known[2] dimeric dithiafulvalene **4** and benzyl phenyl ether. It is interesting to note that no dimers have been detected in the reactions starting from **6a**–**c**. Apparently, intramolecular phenolate addition is much more effective than the intermolecular dimerization process.

The generality of the reaction was investigated by reacting the 2,4-dihydroxyphenyl- and 2,5-dihydroxyphenyl-thiadiazoles **6b** and **6c** with hexadecyl bromide under the same reaction conditions. In the presence of one equivalent of alkylating agent, only the *S*-monoalkylated products **8d** and **8e**, respectively, were formed in fair to excellent yields (Scheme 1, Table 1). The chloronaphthofuran **15** was produced following a similar strategy from 2-acetyl-1-naphthol **14**. The chlorine was introduced on the electron rich naphthol at the stage of the Hurd–Mori reaction (Scheme 4).[3]

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Footnote and References

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