The Efficient Synthesis of 3-Arylsydnones Under Neutral Conditions

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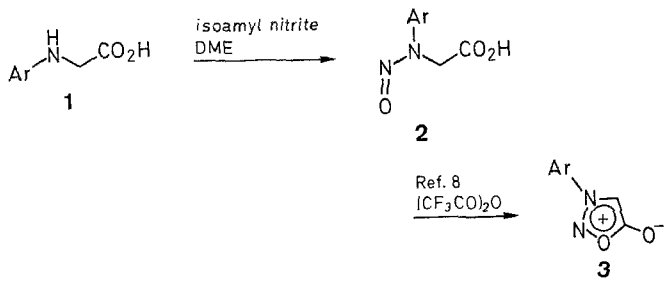
Various substituted aryl sydnones can be prepared in high yield under mild, neutral conditions by nitrosation of the appropriate aryl glycine with isoamyl nitrite in dimethoxyethane followed by cyclization with trifluoroacetic anhydride.

Sydnones **3** are unique, dipolar heterocycles first prepared by Earl and Mackney in 1935.[2] Since that time a considerable body of data concerning their chemical, physical and biological properties has been amassed and this is summarized in several reviews.[3-6] The only viable route to the sydnone ring system involves treatment of an *N*-alkyl or arylglycine with nitrous acid to form the corresponding *N*-nitroso species followed by cyclization with acetic anhydride[7] or trifluoroacetic anhydride.[8]

This method has been used to prepare a large variety of sydnones in reasonable yields. However, difficulties associated with the synthesis of 3-(2-acetylphenyl) sydnone **(3i)** stimulated our search for a milder method. We had first prepared this compound in 1986[9] using the nitrous acid route. However, subsequent attempts to do so led only to the formation of the *C*-nitroso glycine rather than the *N*-nitroso species. It appeared likely that nitrosation under neutral conditions would circumvent these difficulties and we chose to examine the use of isoamyl nitrite for this purpose. Indeed, reaction of *N*-(2-acetylphenyl)glycine **(1i)** with isoamyl nitrite in dimethoxyethane (DME) at 25 °C for 9 h gave the corresponding *N*-nitrosoglycine **2i** in high yield. No *C*-nitrosoglycine could be detected. Cyclization with trifluoroacetic anhydride in dichloromethane gave the sydnone **3i** in 78% overall yield (average of 3 runs).



1 2 3

1–3	Ar	1–3	Ar
a	Ph	**f**	2-$CH_3OC_6H_4$
b	2-$(NC)C_6H_4$	**g**	2-$NO_2C_6H_4$
c	2-$(H_3CO_2C)C_6H_4$	**h**	2-BrC_6H_4
d	2-$(HO_2C)C_6H_4$	**i**	2-$CH_3COC_6H_4$
e	2-$CH_3C_6H_4$		

Table. Preparation of Sydnones **3** Under Neutral Conditions

Product	Overall Yield[a] (%)	Reaction Time for Nitrosation (h)	mp (°C)	Lit. mp (°C)
3a	80	5	132-3	134-5[2]
3b	85	44	119-21	121-2[9]
3c	79	25	107-8	104-6[10]
3d	90	40	204-5	205-6[11]
3e	76	5	98-9	100-1[12]
3f	48	4	98-9	96-7[13]
3g	74	50	148-9	147-8[13]
3h	70	44	78-9	–[b]
3i	78	9	111-13	113-15[9]

[a] The yields given are for the 2 step conversion of the glycine to the sydnone and represent the average for 3 runs.

[b] $C_8H_5BrN_2O_2$ (241.1) calc. C 39.80 H 2.09 N 11.62
found 39.85 1.99 11.37
IR (KBr): $\nu = 3120, 1765, 1743, 1453, 935, 757\ cm^{-1}$.
^1H-NMR ($CDCl_3$/TMS): $\delta = 6.63$ (s, 1H); 7.57 (m, 3H); 7.80 (m, 1H).

The generality of this process for the preparation of other *ortho*-substituted aryl sydnones was explored. The results are presented in the Table and, as can be seen, the yields for the 2 step nitrosation–cyclization process are good to excellent in the presence of a variety of functional groups.

Electron-donating groups apparently speed up the process, cf. **3e** and **3f**, and here it proved helpful to run the reaction at ca. 15 °C. For all glycines, after the appropriate reaction time, the solvent was removed *in vacuo* (or under a stream of nitrogen) at room temperature and the oily product was washed with a mixture of ether/petroleum ether (bp 30–60 °C) (1:15). After decanting or filtering off the solvent, the crude nitrosamine was dissolved in dichloromethane and cyclized at 10 °C with a 1.5–2 times excess of trifluoroacetic anhydride.

Overall, we have shown that a variety of substituted aryl sydnones can be prepared in good yield using mild, neutral conditions. This approach is successful even in those cases where the conventional methods fails, cf. **3h** and **3i**. The former was obtained as one of a complex mixtures of compounds using the sulfuric acid/sodium nitrite route, whereas with isoamyl nitrite a 70% yield of the sydnone was achieved.

Conversion of *N*-Arylglycines to 3-Arylsydnones; General Procedure:
To a stirred solution (or suspension) of the glycine **1** (0.02 mol) in DME (20 mL) is added isoamyl nitrite (0.03 mol). After the reaction is complete (TLC, solvent: EtOH), the solvent is removed *in vacuo* (or under a stream of nitrogen). The resultant oil or semi-solid is digested with petroleum ether (bp 30–60 °C)/ether mixture (15:1, 24 mL). The crude *N*-nitroso intermediate **2** is isolated either by filtration or by decanting off the supernatant. The resultant product is dissolved in CH_2Cl_2 (40 mL) and cyclized to the sydnone **3** with trifluoroacetic anhydride (0.04 mol) at 10 °C as previously described.[8]

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