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ARYL VINYL SULFONES AS THIOL PROTECTIVE GROUP

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Abstract : Phenyl vinyl sulfone and p-tolyl isobutenyl sulfone are convenient reagents for protecting SH groups via the Michaël adduct. Protection and deprotection can be achieved in high yields under mild basic conditions, in protic or aprotic solvents.

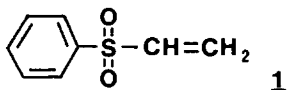
Protection of the thiol group is an important problem in many areas and the synthetically useful protective groups have been reviewed (1). Among them, some Michaël type adducts have been proposed for protection in mild basic conditions in the case of aromatic thiols (2a), cysteine and glutathion (2b, 2c); however, all of them suffer from limitations :

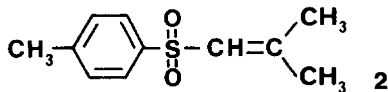
- an adduct with a chalcone (2a) does not allow any subsequent reduction with most reducing agents.
- diethyl methylene malonate (2b) is a too unstable reagent.
- with nitrostyrene, diastereoisomeric adducts can be formed (2c).

Aryl vinyl sulfones present a priori some advantages over these groups (3, 4) and 2-Arylsulfonyl ethyl derivatives have been previously used to protect alcohols (18a), amines (18b) and carboxylic acids (18c). However, the Michaël reaction of thiols with vinylic sulfones has been thoroughly studied only with the above-mentioned aromatic thiols (5), cysteine (4, 6) or glutathion (4),that is with rather acidic SH groups (pK_A = 7.7-8.5) (7, 8). Only a few examples of simple aliphatic thiols (pK_A = 11-14) (7a, 7b) have been reported (3, 4, 9).

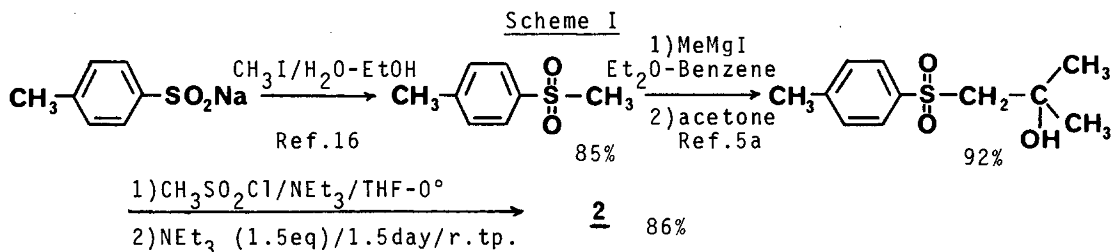
For all the Michaël acceptors (2, 4), the reported deprotection conditions of the thiol adducts always use an excess of aqueous or alcoholic base (0.5-1N) (2b, 2c, 4, 9), or less basic media but with added lead (2a) or silver (6) salts, with a very low yield in the latter case.

In the present note, we develop an initial study using phenyl vinyl sulfone 1 (3) and we show that this reagent and p-tolyl isobutenyl sulfone 2 are convenient and efficient thiol protective groups. A large variety of aliphatic thiols of different pK_A and steric hindrance have been studied and, in each case, efficient protection and deprotection conditions have been found. The sulfones are either commercially available 1, or easily prepared 1 (10), 2 (Scheme I).





Scheme I



FORMATION OF MICHAEL ADDUCTS : (Table I)

Adducts are prepared generally in high yields in THF, at room temperature under Argon, with 1 (1.1 eq) or 2 (1.1-1.5 eq). Some previous Michaël reactions attempted with 2 failed due to the easy base-catalyzed deconjugation into the more stable β,γ-isomer (5a), deconjugation which is not observed in the conditions we describe.

The nature of the base catalysis is determined by the pK_A and (or) the steric hindrance of the thiol and of the Michaël acceptor, as already reported in other thiol Michaël additions (7b, 7c, 11) :

- triethylamine (0.1 eq) for low pK_A thiols with 1 (1.1 eq).
- more generally 0.2 eq CH_3OLi/CH_3OH 0.5 M or $LiOH/H_2O$ for most of the primary and secondary aliphatic thiols, whatever the sulfone 1 or 2.
- CH_3ONa/CH_3OH 0.25 M (0.1 eq) for the highest pK_A tertiary thiols with 1.

Noteworthy, with p-tolyl isobutenyl sulfone 2, adducts with hindered thiols are formed in very good yields. Only tertiary thiols do not add efficiently to 2 and methanol addition was observed to be quite competitive with that of tBuSH. However, tertiary thiols are protected in high yields with just 1.1 eq phenyl vinyl sulfone 1.

Table I - Formation of Michaël adducts

THIOL	φSH	φCH_2SH		nBuSH		nC_{12}SH	iPrSH	iBuSH	tBuSH	$φ_3$CSH
sulfone* base	1 a	1 a	2 b	1 b	2 b	2 b	2(1.5eq) b	2(1.5eq) b	1 c	1 b
conc. time (hr)	0.47M 4.5	0.47M 39	0.27M 5	0.20M <1	4	0.20M 18	0.18M 8	0.20M 6	0.58M 1	0.50M 2
yield	96%	quant.	84%	quant.	90%	97%	85%	89%	93%	86%

* 1.1eq sulfone, unless specified ; THF distilled over sodium ketyl ; r. tp.
a = NEt_3 (0.1eq) ; b= CH_3OLi/CH_3OH 0.5M (0.2eq) ; c = CH_3ONa/CH_3OH 0.25M (0.1eq)

DEPROTECTION

We have now found suitable conditions for high yield deprotection in relatively mild basic conditions, at room temperature, without addition of metallic salts (Table II). Conditions are totally different from those used for the formation of the adducts (3-10eq dilute base/adduct, dilution of the adduct) and always allow to keep the thiol in rigorously degassed oxygen-free solvents (12), under Argon; if desired, the symmetric disulfide can be prepared by stirring under air (or by oxidation with iodine for very hindered thiols). Conditions are mild enough to avoid alkaline decomposition of sensitive disulfides (i.e. $\varphi CH_2-S-S-CH_2\varphi$) (13, 14).

As shown in Table II, the cleavage is faster in DME than in THF, and much slower in protic solvents; it is much faster in tBuOH than in methanol or water. As anticipated, adducts with p-tolyl isobutenyl sulfone are deprotected much faster than those with phenyl vinyl sulfone; however, the latter are always cleaved in high yields (3, table II).

Table II - Cleavage of the adducts

$$RS-C(R')_2-CH_2-SO_2-Ar \xrightarrow[\text{solvent, r.tp.}]{\text{base}} RSH$$

R(thiol pK_A)	R'	adduct conc.	base/solvent	time(hr)	yield*
φ (8.5)	H	0.002 M	tBuOK/tBuOH 0.01 M	<1.5	99%
nBu (12.5)	H	0.003 M	tBuOK/THF 0.01 M	4	12%
			tBuOK/DME 0.01 M	<1	89%
	Me	0.002 M	tBuOK/tBuOH 0.01 M	<1	88%
nC_{12} (13.8)	Me	0.02 M	tBuOK/tBuOH 0.1 M	3	83%
φCH_2 (11.8)	H	0.085 M	CH_3ONa/CH_3OH 0.1 M	65	no deprot.
		0.01 M	tBuOK/tBuOH 0.1 M	8	80%
		0.002 M	tBuOK/THF 0.01 M	<0.5	51% ≠
	Me	0.005 M	CH_3ONa/CH_3OH 0.05 M	69	trace
		0.05 M	CH_3OLi/CH_3OH 0.5 M	66	54% ≠
			KOH/CH_3OH 0.5 M	32	61% ≠
		0.01 M	tBuOK/tBuOH 0.1 M	0.5	93%
iPr	Me	0.01 M	$NaOH/CH_3OH-H_2O$(1/1)0.1M	75	64%
		0.002 M	tBuOK/tBuOH 0.01 M	1	84%
iBu	Me	0.002 M	tBuOK/tBuOH 0.01 M	<1	79%
tBu (13.1)	H	0.01 M	CH_3ONa/CH_3OH 0.1 M	13 days	no deprot.
			tBuOK/tBuOH 0.1 M	<2	84%
φ_3C (11.1)	H	0.02 M	tBuOK/tBuOH 0.1 M	5.5	86%
		0.004 M	tBuOK/tBuOH 0.01 M	17.5	78%

* isolated yields ($nC_{12}SH$, φCH_2SH, φ_3CSH) or determined by iodometric titration or with Ellmann's reagent in oxygen-free phosphate buffer pH 7.0 (15); ≠ disulfide isolated after air oxidation.

Considering overall protection and deprotection, aromatic thiols and primary or secondary (even hindered) aliphatic thiols are at best protected with 2, tertiary thiols with 1. Due to the chemical inertness of the sulfone group, the adducts should be stable enough for many applications in synthesis. We observed that the adducts with 1 or 2 are quite convenient in a synthetic sequence, due to their stability in strong acidic media (CF_3COOH, HBr 40%) or mild basic conditions which for example allow selective saponifications of esters or thioesters, or use of Amberlite OH^-. The adducts are also stable during reductions with borohydrides, boranes or activated zinc (3, 17).

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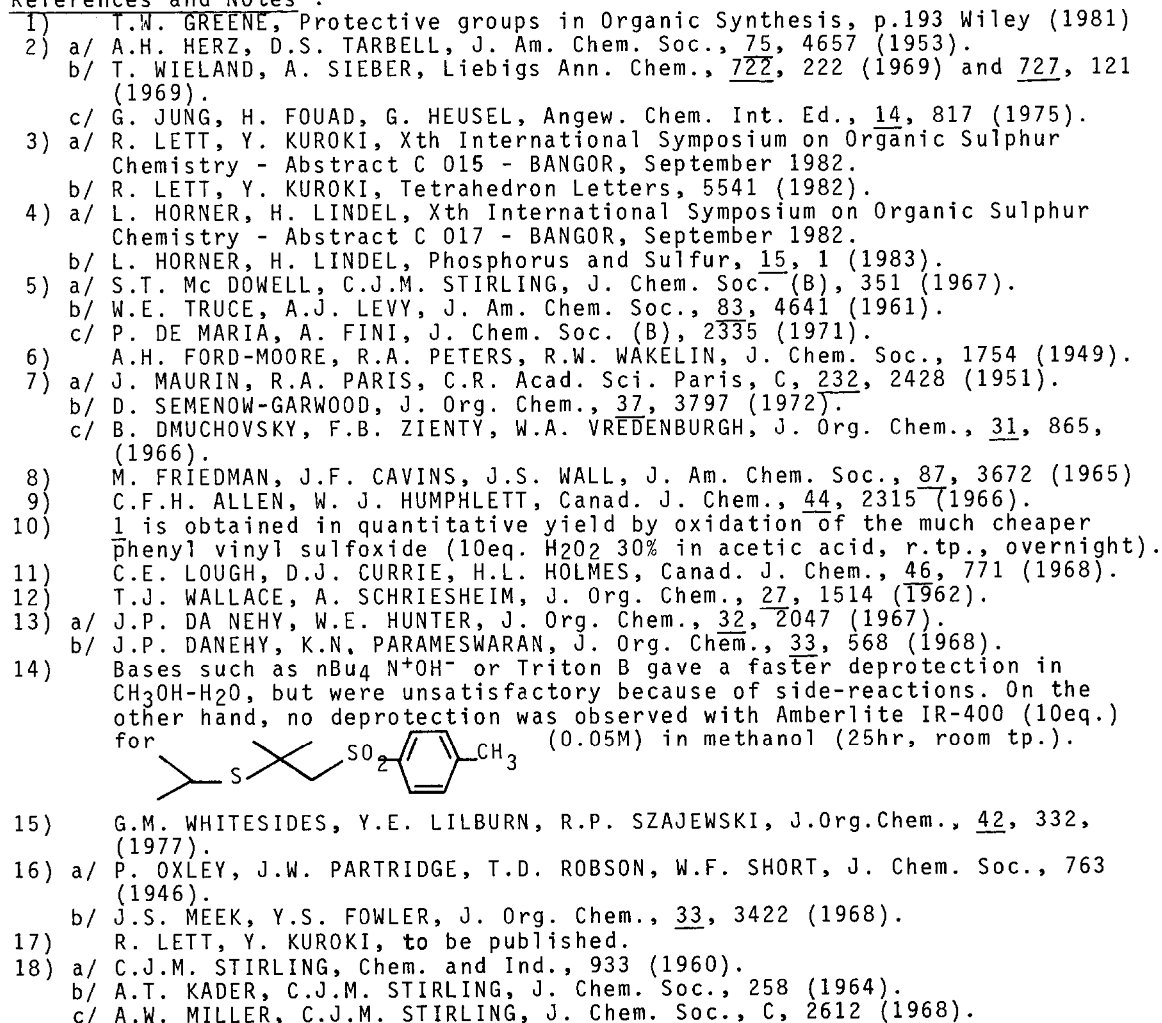
14) Bases such as $nBu_4N^+OH^-$ or Triton B gave a faster deprotection in CH_3OH-H_2O, but were unsatisfactory because of side-reactions. On the other hand, no deprotection was observed with Amberlite IR-400 (10eq.) for



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