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Chemoselective protection of thiols versus alcohols and phenols. The Tosvinyl group

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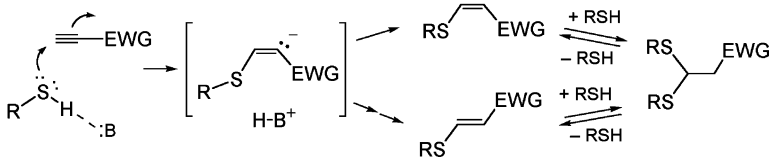
Abstract—The conjugate addition of aliphatic and aromatic thiols to ethynyl *p*-tolyl sulphone (tosylacetylene) has been managed to afford Tosvinyl derivatives chemoselectively (in the presence of oxygen nucleophiles) and stereoselectively (isomers *Z*) in practically quantitative yields. The conditions of choice are: catalytic amounts of Et_3N (only 0.5–1.0 mol%), a reaction temperature around 0°C and, for the less acidic thiols, CF_3CH_2OH or CH_3CN/CF_3CH_2OH as the solvent. Thus, *N*-Boc-Cys-OMe has been quantitatively protected as its *S*-Tosvinyl derivative in the presence of *N*-Boc-Ser-OMe and *N*-Boc-Tyr-OMe. This novel protecting group is stable to several basic and acidic conditions; its removal is achieved at rt by treatment with an excess of pyrrolidine or at 0°C with alkanethiolate ions.

Protection of thiol groups is sometimes troublesome.[1] Conjugate, hetero-Michael addition of thiols to triple bonds activated by electron-withdrawing groups (HC≡C–EWG) to afford the one-to-one adduct is a well-known possibility, but it has a limited scope. This is due to the harsh conditions reported for the protection or deprotection steps, unknown chemoselectivity, formation of *Z*/*E* mixtures, and/or double addition to give dithioacetals (see Scheme 1).[2,3] We posed ourselves the challenge of protecting quantitatively the thiol groups of a polyfunctional molecule, in the presence of oxygen nucleophiles, by using equimolar amounts of an appropriate alkyne.

Apparently, for the first step of the addition of thiols to these triple bonds only a trace of base (or minute amounts of thiolate ions) should be required to start the reaction. Appropriate Brönsted or Lewis bases (:B in Scheme 1), including any electron-donating heteroatom or group of the substrate, reagent or solvent involved, could catalyze these conjugate additions (general base catalysis). In practice, it is known from classical works[2a–f] and it is understandable on stereoelectronic grounds that the first conjugate addition tends to give rise to *trans* additions of RS and H, thus affording *Z* derivatives. This rule is violated, however, if the EWG can delocalise the negative charge by resonance and/or an intermediate species may equilibrate via its allenol, ketene hemiacetal, etc. (EWG = CO, COOR, etc., respectively) or if there are nucleophiles in the medium that can catalyze the double bond isomerisation via a second conjugate addition and elimination (this includes reaction with thiolate excess, through a double addition[2a]). *Z*/*E* mixtures are then obtained, with the *E* isomers as the major compounds, as it could be expected. Obviously, stereoisomerically pure and stable protecting groups are required in the synthesis of complex, polyfunctional molecules (e.g. in



Scheme 1.

Keywords: addition reactions to triple bonds; thiol protecting group; 1-(ethynylsulfonyl)-4-methylbenzene (tosylacetylene).
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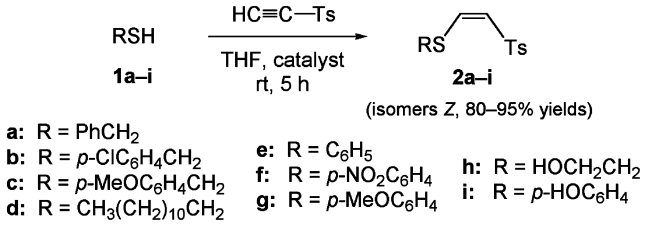
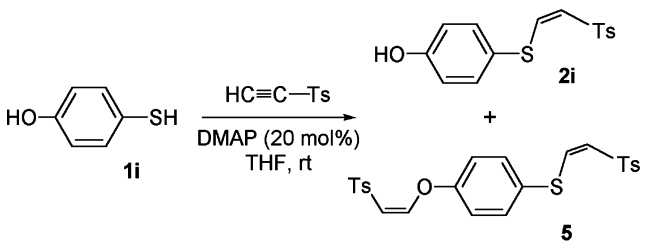
peptides with several cysteine units). Since in preliminary experiments we observed that reaction of benzenemethanethiol (phenylmethanethiol, **1a**) with an acetylenecarboxyl derivative (methyl propynoate, HC≡C-COOMe) affords always mixtures of *Z* and *E* isomers,[4] we moved to HC≡C-SO_2Ar, specifically to ethynyl *p*-tolyl sulphone (tosylacetylene, HC≡C-Ts), a commercially available compound that could react with a higher stereoselectivity. Moreover, in competition experiments, we noted that it reacted more rapidly with nucleophiles than methyl propynoate.

Trial reactions of tosylacetylene with equimolar amounts of C(sp^3)-linked thiol groups (**1a–d**), with benzenethiols (**1e–g**), and with hydroxy groups-containing thiols (**1h** and **1i**) were performed in THF at rt for 5 h, as shown in Scheme 2. In the presence of 10–20 mol% of 4-dimethylaminopyridine (DMAP), triethylamine (Et_3N) or trialkylphosphines (Me_3P, Bu_3P), the reactions were complete,[5] affording the 1:1 thiol–alkyne adducts in excellent yields;[6] *Z*/*E* ratios were ca. 85:15 (mainly RSH) or higher (mainly ArSH), in general. We confirmed that the major adducts were always the corresponding (*Z*)-tosylvinyl derivatives, **2a–i** (for **2a**, δH 6.98 and 6.18, $^3J_{HH}$ = 10.3 Hz, NOE, δC 127.8 and 123.4), and the minor ones had *E* configurations (for isomer *E* of **2a**, δH 7.70 and 6.19, $^3J_{HH}$ = 14.4 Hz, no NOE, δC 128.0 and 122.9). Isomers *Z* could be readily separated by column chromatography from isomers *E*, which were eluted first with 10:1 hexane–EtOAc.

The exception to the above general results or rules was the case of 4-mercaptophenol (**1i**) with DMAP (Scheme 3). Apart from ca. 60% of **2i**, disubstituted compound **5** was isolated in ca. 20% yield; only the major product, (*ZZ*)-**5**, is drawn in Scheme 3, but the crude product was indeed a 85:15 *ZZ*/*ZE* mixture.[7] Thus, use of DMAP is not appropriate when only the protection of thiol groups is desired.[8] With Et_3N and Me_3P, by using exactly 1.0 equiv. of tosylacetylene, byproduct **5** was hardly detected.



Scheme 2.



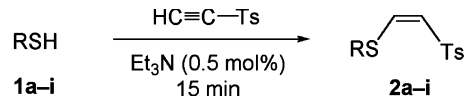
Scheme 3.

These preliminary experiments showed that, for a chemo- and stereoselective protection of thiols with a *Z*-tosylvinyl group (Ts–CH=CH, henceforward 'the Tosvinyl group'), strong nucleophilic catalysts such as DMAP are sometimes counterindicated, since they enhance the relative reactivity of other functional groups such as phenols. Moreover, the amount of base, reaction times and temperature should be controlled,[5] otherwise the equilibria depicted in Scheme 1 may give rise to a complex outcome. A relative excess of thiol with regard to tosylacetylene (e.g. a slow addition of the reagent to the thiol and base mixture) also has to be avoided; despite the fact that the second conjugate addition is much slower,[2m] the presence of a strong base may favor the formation of dithioacetals. Quick protonation of the first anionic intermediate,[6] to minimize the *Z*-to-*E* conversion through this anion, was also taken into account.

In the light of these ideas, a series of experiments were undertaken (see Table 1 for the most relevant results) until reaching the following optimum conditions:[9] (i) a reaction temperature maintained at 0°C (or between 0 and 15°C); (ii) addition of very minute amounts of Et_3N (from a 0.04 M stock solution of Et_3N in CH_3CN); (iii) reaction times as short as possible; and (iv) *CF_3CH_2OH or CH_3CN/CF_3CH_2OH (1:1 v/v) as the best solvents for the less acidic thiols (aliphatic thiols)*, see entries 1–5 and 12 of Table 1. In fact, CF_3CH_2OH and CH_3CN/CF_3CH_2OH yielded practically identical results (95±1% of *Z*) in all the examples investigated, where CH_3CN had given rise to 85±2% of isomers *Z* and CH_3CN/MeOH or EtOH had given 90±2% of isomers *Z* (data not included in Table 1 for the sake of simplification). On the other hand, *for the aromatic thiols **1e** and **1f**, addition of CF_3CH_2OH*, looking for a more acidic protic medium, *was not required* (compare entries 6 and 7 as well as entries 8 and 9), since the stereoselection was almost complete already in CH_3CN. This also occurred in the case of the mercaptophenol **1i** (see entry 13). We explain these facts by the higher trend of these thiols to give *Z* isomers (related, in our above-mentioned working hypothesis, with the known stronger acidity of aromatic thiols or the presence of another appropriate proton source in the substrate). An intermediate case was that of **1g** (aromatic thiol, electron-donating substituent), for which the differences between an aprotic medium and a protic medium were still noted (compare entries 10 and 11).

In short, under selected conditions of Table 1, with addition of a protic cosolvent, CF_3CH_2OH, in the cases of the less acidic substrates, a practically quantitative and stereoselective protection was achieved. *E* isomers were hardly detected by NMR, so that they did not disturb the characterisation of the resulting products. *In practice, it can be considered that only Z isomers are obtained.*

Table 1. Reaction of thiols **1a–i** with tosylacetylene, catalyzed by Et_3N[a]

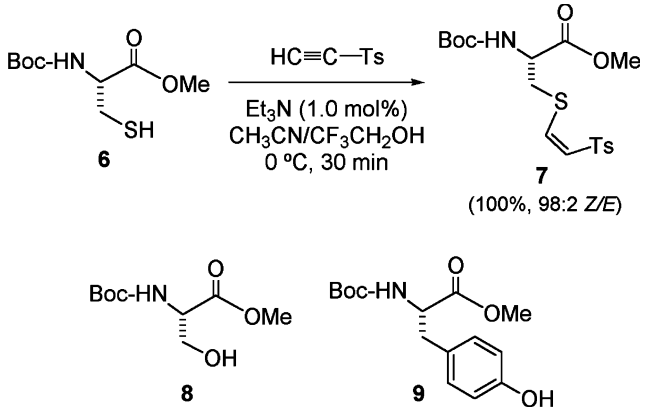


Entry	Thiol	Solvent	Temp. (°C)	Yield of **2a–i** (% $Z+E$)	Z/E ratio
1	**1a**	CF_3CH_2OH	15	100	95:5
2	**1a**	CH_3CN/CF_3CH_2OH	0[b]	100	95:5
3	**1b**	CF_3CH_2OH	0	98	95:5
4	**1c**	CF_3CH_2OH	0	100	94:6
5	**1d**	CH_3CN/CF_3CH_2OH[c]	15	100	96:4
6	**1e**	CH_3CN	0	99	98:2
7	**1e**	CH_3CN/CF_3CH_2OH	0	99	100:0
8	**1f**	CH_3CN	0	99	100:0
9	**1f**	CH_3CN/CF_3CH_2OH	0	100	100:0
10	**1g**	CH_3CN	0	98	91:9
11	**1g**	CH_3CN/CF_3CH_2OH	0	98	100:0[d]
12	**1h**	CH_3CN/CF_3CH_2OH	0	100	96:4
13	**1i**	CH_3CN	0	95	100:0

[a] All the reactions were performed with a 10% molar excess (1.10 equiv.) of tosylacetylene (except in entry 13, in which 1.00 equiv. were employed), at ca. 0.1 M concentrations (for a typical procedure, see Ref. 9).
[b] The result was identical at −20°C. Also by using 1 mol% of DMAP instead of Et_3N.
[c] Use of CH_3CN/CF_3CH_2OH is specially appropriate here as **1d** is not miscible with CF_3CH_2OH.
[d] In this case, the result was practically identical in absolute EtOH (>98% Z).

Chemoselective protection of the side chain of cysteine versus those of serine and tyrosine. The high chemoselectivity obtained in the protection of thiols versus alcohols and phenols prompted us to apply the procedure to derivatives of natural α-amino acids. First of all, *N*-Boc-Cys-OMe (**6**) was submitted to the conditions summarised in Scheme 4 (see also Table 1), to give Tosvinyl derivative **7** in 100% yield (ca. 90:10 Z/E in CH_3CN, ca. 98:2 Z/E in CH_3CN/CF_3CH_2OH). Later, equimolar amounts of identically protected cysteine **6**, serine **8** and tyrosine **9** (0.30 mmol each) were treated with only 0.30 mmol of tosylacetylene (Scheme 4).

The Tosvinyl derivative of cysteine, **7**, was obtained (ca. 100%, 100:0 Z/E) while unreacted Ser and Tyr derivatives **8** and **9** were fully recovered. This result shows the potential of the Tosvinyl group in peptide chemistry.



Scheme 4.

Stability of the Tosvinyl group. The stability of Tosvinyl derivatives was checked in basic and acidic media. Compound **2a** was recovered unchanged, when treated overnight with Et_3N/THF or LiOH/MeOH/H_2O at 25°C and with DMAP/CH_3CN at 25°C or at reflux. Also, **2a**, **2b**, **2e** and **2g** turned out to be stable against AcOH/H_2O, HCl/THF or TFA/CH_2Cl_2 overnight at rt. With a large excess of TFA/CH_2Cl_2 or with TFA as the solvent only a partial Z-to-E isomerization was observed.

Deprotection. The deprotection step can be accomplished with pyrrolidine, via an addition–elimination mechanism, in CH_3CN at rt (>95% isolated yields, by using 10 equiv. of pyrrolidine). Alternatively, cleavage of the sulphur–vinyl bond was simply achieved by a thiolate exchange. Thus, deprotection of aromatic thiol derivatives (e.g. **2e**) was readily performed by using 2.2 equiv. of sodium dodecane-1-thiolate (from **1d** and NaH)[10] in CH_3CN at 0°C, for 15 min, which afforded **1e** and the expected dithioacetal, $(C_{12}H_{25}S)_2CH–CH_2Ts$, in excellent yield.[11] For the deprotection of aliphatic thiols, an excess of propane-1,3-dithiolate ion may be used,[12] as an alternative to pyrrolidine.

In summary, significant improvements have been disclosed that can allow one to use Tosvinyl group as the protecting group of choice for thiols, even for polyfunctional molecules containing hydroxy groups. Chemoselective reaction of the Cys side chain in front of the Ser and Tyr side chains has been demonstrated indeed, which may give rise to practical applications.

Acknowledgements

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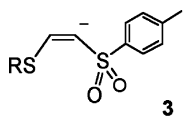
4. In our hands, benzenemethanethiol (**1a**) reacts completely, in CH_3CN at 0°C, within 15 min in the presence of 20 mol% of Et_3N or DMAP, with an equivalent amount of methyl propynoate (HC≡C-COOMe) to afford ca. 65:35 ratios of the Z/E adducts (isomer Z, δ 7.07 and 5.82, $J=10.0$ Hz; isomer E, δ 7.70 and 5.81, $J=15.2$ Hz). No significant changes in these Z/E ratios were obtained by performing the reaction of **1a** and HC≡C-COOMe in the presence of only 1 mol% of Et_3N and/or by using absolute EtOH or THF instead of CH_3CN. Without Et_3N or DMAP, the reaction was very slow (several days of reaction were required for its completion). On the other hand, by heating a 65:35 Z/E adduct mixture with a small amount of benzenemethanethiolate ion ($NaSCH_2Ph$, 10 mol%) for few hours, a new ratio of 18:82 (Z/E) was obtained; this ratio could not be modified in favor of the E isomer by prolonged heating or by adding larger amounts of thiolate (which caused only an increase of the double addition product, the dithioacetal). We assume, therefore, that the Z/E equilibrium position for most RS–CH=CH–COOMe adducts is nearly the above-mentioned 18:82 ratio. In sharp contrast, for RO–CH=CH–COOR and R_2N–CH=CH–COOR, Z/E ratios of ca. 0:100 are observed (for a classical review, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press: Oxford, 1992).
5. In the absence of a base (catalyst), the reactions were much slower and poor yields of adducts were generally obtained after 5 h of reaction, unless the solutions were concentrated or heated. Stereoselectivities of 90:10 or higher were usually obtained. It is worth noting that in the base-catalyzed additions too long reaction times were detrimental. Thus, with DMAP a dismutation took place in some cases (e.g. in the case of **1a**, stirring for 20 h afforded a mixture of **2a**, starting material **1a** and dithioacetal in a 2:1:7 ratio) and a retroaddition occurred mainly in others (e.g. in the case of **1e**, stirring for 4 days gave only a 40% of **2e** with recovery of starting material). With 20 mol% of Et_3N, the Z/E ratios decreased to 68:32 in two experiments. With Me_3P, too long reaction times caused a stereoselectivity loss (e.g. after 20 h, a 86:14 Z/E mixture of **2a** was converted to a 75:25 mixture).
6. DMAP and R_3P may act as basic catalysts (B of Scheme 1), to afford intermediates **3**, and/or as nucleophilic catalysts (Nu), with previous conjugate addition to the triple bond, followed by proton transfer from thiol to give intermediate **4**. Complex adduct mixtures might be expected. However, even in the case of Nu = Me_3P, which could be prone to give byproducts arising from the attack of RS^- at position α of **4**, we did not observe these byproducts (probably because our reaction conditions are very mild).



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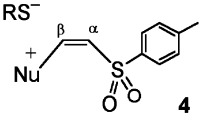

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For 'anomalous' reactions of 2-alkynoates catalyzed by Bu_3P or Ph_3P (α- or γ-addition instead of β-addition), see: (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167; (b) Alvarez-Ibarra, C.; Csáky, A. G.; Oliva, C. G. *Tetrahedron Lett.* **1999**, *40*, 8465; (c) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595, and refs. cited therein; (d) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535; (e) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677. Also see: (f) Back, T. G.; Wehrli, D. *Tetrahedron Lett.* **1995**, *36*, 4737, and Ref. 2c.
7. That the *S*-Tosvinyl group had always configuration Z whereas the *O*-Tosvinyl group was a 85:15 Z/E mixture could be confirmed by allowing **1i** to react with 210 mol% of tosylacetylene in the presence of 20 mol% of DMAP. The *O*,*S*-diprotected derivative **5** was formed quantitatively and could be easily analyzed by NMR to be the above-mentioned mixture of only two stereoisomers (the ZZ one as the major compound).
8. The DMAP-catalyzed (largely Nu-catalyzed) protection of phenols and catechols with alkyl propynoates is known: Ariza, X.; Pineda, O.; Vilarrasa, J.; Shipps, G. W.; Ma, Y.; Dai, X. *Org. Lett.* **2001**, *3*, 1399.

9. Typical procedure: To a solution of 1-(ethynylsulfonyl)-4-methylbenzene (ethynyl *p*-tolyl sulphone, tosylacetylene, 60 mg, 0.33 mmol) in CF_3CH_2OH (1.5 ml), stirred at 0°C or 15°C (see Table 1), was added a solution of the thiol (0.30 mmol) in CH_3CN and/or CF_3CH_2OH (1.5 ml) and then a stock solution of Et_3N in CH_3CN (40–45 μL of 0.04 M solution, i.e. 0.5–0.6 mol%). After stirring for ca. 15 min, the reaction was quenched at 0°C with 0.5 M HCl or with 7% aqueous citric acid, and partitioned between water and CH_2Cl_2. The organic extracts were collected and dried over $MgSO_4$, filtered and concentrated under reduced pressure, without heating. The crude reaction product was sometimes (although it was not generally required) purified by column chromatography, with 10:1 hexane–EtOAc. In the case of long-chain aliphatic thiol **1d**, a white precipitate was formed almost immediately, so that **2d** can also be isolated by filtration.
10. The advantage of thiol **1d** is that it is odorless. For a relevant comparison of the smelling of thiols, see: Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett*. **2001**, *42*, 9207.
11. Typical example: **1d** (180 μL, 152 mg, 0.75 mmol) was added to a stirred suspension of NaH (30 mg of a 60% suspension in mineral oil) in anhydrous THF (4 mL). After 15 min, a solution of **2e** (100 mg, 0.34 mmol) in anhydrous THF (4 mL) was added at 0°C, under N_2. Fifteen minutes later the crude mixture was treated with brine (10 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated at reduced pressure to yield 200 mg (ca. 100%) of the expected dithioacetal as a white solid. Addition of 0.1 M HCl to the aqueous phase and extraction with CH_2Cl_2 afforded after the usual workup 34 mg (ca. 90%) of **1e**.
12. The foul smell of this dithiol is, however, a practical disadvantage. Sodium dodecane-1-thiolate cannot be recommended in these cases (deprotection of derivatives of aliphatic thiols), as a large excess of **1d** is required to shift the equilibria toward the desired side; this large excess makes later cumbersome the isolation of the desired thiol.