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SYNTHESIS OF UNSYMMETRICAL DISULFIDES WITH THIOLSULFONATES IMMOBILISED ON A POLYSTYRENE SUPPORT

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Summary: Polystyrene sodium sulfinate reacted with thionitrites gave polystyrene thiolsulfonates. These immobilised thioalkylation reagents were used for an effective synthesis of mixed disulfides.

Unsymmetrical disulfides play an important part in diverse biochemical processes as regulatory hormones, drugs and enzyme activators or inhibitors. One of the best and most popular methods to prepare them is the thioalkylation of thiols with thiolsulfonates[1,2]. In many cases such syntheses are strongly limited by difficult and time-consuming separations of by-product sulfinic acid. In this work we describe the synthesis of polymer-attached thiolsulfonates with leaving sulfinate groups covalently bonded to the polymer matrix

$$\textcircled{P}-SO_2SR^1 + R^2SH \longrightarrow R^1SSR^2 + \textcircled{P}-SO_2H$$

Thus, undesired by-product, sulfinic acid, remains attached to the matrix and can be easily removed by simple mechanical filtration.

Chlorosulfonation of polystyrene and the reduction of sulfochloride with sodium sulfite yields sulfinated polystyrene. The reaction of sulfinated polystyrene with thionitrites formed "in situ" results in immobilised thiolsulfonates (Table 1).

$$\textcircled{P}-SO_2Na + O{=}N{-}S{-}R^1 \longrightarrow \textcircled{P}-SO_2SR^1 + NaNO$$

Table 1. Syntheses of polystyrene thiolsulfonates.

Polystyrene sodium sulfinate		Immobilised thiol	Thioalkylation conditions		Yield of R^1SSO_2P
$\frac{\text{mmol S}}{\text{g PS}}$	SO_2Na mmol/g PS	R^1SH	$ONSR^1/SO_2Na$ ratio	Reaction time hrs.	$\frac{\text{mmol}}{\text{g PS}}$
6,23	3,45	$HS(CH_2)_2SO_2Na$	1,3	36	0,87
6,43	3,38	– " –	2,5	24	0,97
6,43	3,38	– " –	2,5	38	1,61
8,30	3,30	N-Acetyl-L-Cys	1,0	32	1,86

The reactions of the polymer-attached thiolsulfonate reagents with thiols were performed in water under nitrogen atmosphere and followed by TLC or HPLC. A twofold excess of the thiolsulfonate was necessary to complete the reaction within few hours (Table 2).

Table 2. Syntheses of unsymmetrical disulfides.

Polystyrene thiolsulfonate		Thioalkylation conditions			Yield of crude prod.%	Mixed disulfide
R^1SH	R^1SSO_2P mmol/g PS	R^2SH	$\frac{R^2SH}{SO_2SR^1}$ ratio	Reaction time hrs.		R^1SSR^2
MESNA[a]	0,87	AcCys[b]	1,8	5	95	AcCys(MESNA)
– " –	1,61	– " –	0,56	20	92	– " –
– " –	1,61	– " –	0,41	8	95	– " –
– " –	1,61	Cys[d]	0,40	3,5	93	HCys(MESNA)
– " –	1,61	G[e]	0,32	3,5	95	G(MESNA)

a – MESNA = $HS(CH_2)_2SO_3Na$; b – AcCys = N–acethyl–L–Cys; d – Cys = L–Cysteine;
e – G = glutathione, reduced form

A good yield of formation of mixed disulfide of glutathione and 2-mercaptoethanesulfonic acid confirmed the possibility of syntesizing unsymmetrical disulfides of oligopeptide thiols using such immobilised thiolsulfonate reagents. We hope that this method of synthesis of mixed disulfides will be especially suitable for the thioalkylation of expensive and valuable thiols of biological importance which should be thioalkylated with high yield by means of less expensive low molecular thiols.

Experimental :

a. Polystyrene sodium sulfinate was prepared simlary to Komagawa at all.[5] (50 ml of $ClSO_3H$ for 5 g PS in 300 ml CH_2Cl_2, room temp., 30 min,. PS Fluka, 200–400 mesh, 1 or 2 % DVB).
b. Polystyrene thiolsulfonates: to a solution of thionitrite, obtained according to Hardt[3,4] procedure the sulfinated polystyrene was introduced. The suspension was stirred at room temperature until the red colour of the thionitrite disappeard, filtered, the polymer washed carefully with water and dried under vacuum.
c. Thioalkylation of thiols: to a solution of thiol in water (saturated with N_2) a twofold excess of thiolsulfonated polystyrene was added. The suspension was stirred or shaken under N_2 atmosphere until the starting thiol disappeard. The polymer was filtered off and carefully washed twice with small amount of water. The combined water filtrates were evaporated *in vacuo* below 30 °C or liophilised. Mixed disulfides mentioned in this paper were identical with those prepared earlier[6] by means of other methods.

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