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Direct Synthesis of DI-and Trimethoxybenzyl Thiols from the Corresponding Alcohol

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SYNTHETIC COMMUNICATIONS, 28(17), 3219-3223 (1998)

DIRECT SYNTHESIS OF DI- AND TRIMETHOXYBENZYL THIOLS FROM THE CORRESPONDING ALCOHOL

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Abstract: An efficient and reliable procedure for the one-pot synthesis of di- and trimethoxybenzyl thiols from the corresponding benzyl alcohol is described.

We wish to report a new, convenient and efficient strategy for the synthesis of di- and trimethoxy substituted benzyl thiols directly from the corresponding benzyl alcohol.

We esterify di- and trimethoxybenzyl thiols to the C-terminal carboxylic group of peptides synthesized by solid phase peptide synthesis. Whether the free C-terminal thiocarboxylic acid or the peptide thioester is obtained after sidechain deprotection and cleavage of the peptide from the resin can be controlled by the substitution pattern of the methoxybenzyl thiol and the conditions used for the cleavage. Peptidic thioacids and thioesters have been used for the chemoselctive ligation of unprotected peptide fragments [1] and the chemical synthesis of proteins as described by Kent and Tam [2].

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We synthesized a range of methoxy substituted benzyl thiols starting from commercially available di- and trimethoxybenzaldehydes. The benzyl alcohols were obtained in quantitative yield by reduction of the aldehydes with sodium borohydride in ethanol. The alkylation of sulfur is the key step in the synthesis of thiols and benzyl halides (bromides and chlorides) or sulfonates are usually used in general procedures for the alkylation of hydrogen sulphide or thiourea [3]. However, di and trimethoxybenzyl bromides can not be obtained by simple esterification using hydrobromic acid. The methoxy substituted aromatic rings are activated for electrophilic substitutions and react in a non-controllable way to polymeric products when the benzylic cation is liberated from the alcohols upon treatment with an acid. The formation of the benzyl bromides under neutral condition e.g. by reaction with PPh_3/CBr_4 presents an alternative [4] but was found to be avoidable by the method described below.

The readily formation of benzylic cations from di- and trimethoxy substituted benzyl alcohols was recognized as an advantage. When the benzylic cation is generated in the presence of thiourea as a nucleophile, then the corresponding methoxybenzyl isothiouronium salts are directly obtained. The isothiouronium salts can be isolated when they are the products of interest or can be directly hydrolyzed yielding the benzyl thiols [Scheme 1].

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Scheme 1

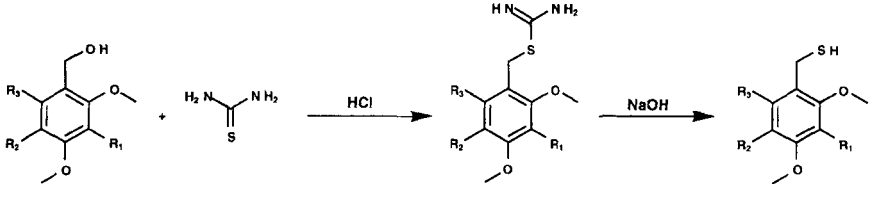

Table 1

Product	R_1	R_2	R_3	Yield	Purity [a]
3a	H	H	H	97%	>98%
3b	OMe	H	H	95%	>96%
3c	H	OMe	H	94%	>97%
3d	H	H	OMe	95%	>97%

a: purities were determined for the crude products by C-18 RP HPLC-analysis using UV absorbance at 260 nm.

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Methoxy benzylisothiouronium salts are nearly quantitatively obtained, when diluted hydrochloric acid is added dropwise to a well stirred mixture of the methoxybenzyl alcohols and an excess of thiourea in an aqueous solution. A simple washing step with diethyl ether removes traces of side products and unreacted starting material. The isothiouronium salts are directly hydrolyzed by adding NaOH and refluxing under an inert atmosphere in order to obtain the benzyl thiols. The thiol separates and is easily extracted. The synthesis of several methoxybenzyl thiols following this protocol was examined in detail.

All thiols were isolated in high yield and good purity, therefore further purification was not necessary [Table 1].

The method reported herein has several advantages compared to reported methods involving benzyl halides or sulfonic acid esters for the alkylation of thiourea. The acid induced *in situ* formation of the highly reactive benzylic cation and direct quenching by alkylation of thiourea is most straightforward. Only inexpensive and readily to handle reagents (thiourea, HCl, NaOH) as well as simple reaction conditions are required. The entire reaction sequence is performed in aqueous solution, therefore problematic solvent wastes are not produced, which makes this protocol particularly useful for large scale synthesises.

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Typical Procedure

The methoxybenzyl alcohol **(1a-b)** (0.1 mol) and 2 equivalents thiourea (0.2 mol, 15.2 g) were dissolved in 200 ml water/acetone (1:1 - 1:2 v:v). 30 ml of 5N HCl was added dropwise and the acidic solution was stirred at room temperature overnight. The mixture was extracted with Et_2O (2x50 ml) and the aqueous phase was then brought to alkaline pH by careful addition of NaOH (0.3 mol,12 g) under an inert atmosphere and heated to reflux for 3 hours. The reaction was followed by TLC (hexane:ethyl acetate 1:1) and HPLC. The thiol **(5a-d)** was isolated after acidification with HCl by extraction with EtOAc (4x50 ml). The combined organic phases were dried ($Mg(SO_4)$). The thiols were obtained as colorless liquids or white solids after removal of the solvent.

Analytical Data

2,4-dimethoxybenzyl thiol **(5a)** [$C_9H_{11}O_2S$]; colorless liquid
microanalysis: found (calculated) C 58.88% (58.67 %) H 6.62% (6.56%) S 17.54% (17.40%) MS (TEI) m/z: found 184.046; calculated 184.056 ^1H NMR (200MHz, $CDCl_3$) δ 7.18 (d, J=7.8 Hz, 1H), δ 6.48 (d, J=7.8Hz, 1H), δ 6.45 (s, 1H), δ 3.80 (s, 3H), δ 3.85 (s, 3H), δ 3.67 (s, 2H)

2,3,4-trimethoxybenzyl thiol **(5b)** [$C_{10}H_{13}O_3S$];
microanalysis: found (calculated) C 56.32% (56.05 %) H 6.46% (6.58%) S 14.82% (14.96%) MS (TEI) m/z: found 214.053; calculated 214.066 ^1H NMR (200MHz, $CDCl_3$) δ 6.96 (d, J=7.6 Hz, 1H), δ 6.63 (d, J=7.6 Hz, 1H), δ 3.96 (s, 3H), δ 3.83 (s, 3H), δ 3.81 (s, 3H), d 3.70 (s, 2H)

2,4,5-trimethoxybenzyl thiol **(5c)** [$C_{10}H_{13}O_3S$]; white solid, mp. 53-55 °C
Microanalysis: found (calculated) C 56.12% (56.05 %) H 6.50% (6.58%) S 14.87% (14.96%) MS (TEI) m/z: found 214.126; calculated 214.066 ^1H NMR (200MHz, $CDCl_3$) δ 6.83 (s, 1H), δ 6.53 (s, 1H), δ 3.89 (s, 3H), δ 3.85 (s, 3H), δ 3.83 (s, 3H), δ 3.71 (s, 2H)

2,4,6-trimethoxybenzyl thiol **(5d)** [$C_{10}H_{13}O_3S$]; white solid, mp. 60-62 °C Mircoanalysis: found (calculated) C 56.12% (56.05 %) H 6.72% (6.58%) S 14.89% (14.96%) MS (TEI) m/z: found 214.027; calculated 214.066 ^1H NMR (200MHz, $CDCl_3$) δ 6.11 (2H), δ 3.85 (s, 3H), δ 3.83 (s, 3H), δ 3.79 (s, 3H), δ 3.71 (s, 2H)

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