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Solid-Phase Photochemical C-S Bond Cleavage Of Thioethers-A New Approach To The Solid-Phase Production Of Non-Peptide Molecules.

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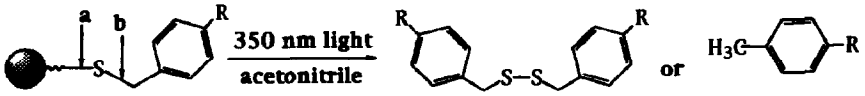
Abstract: Thioethers can readily be used as a method for attachment of organic molecules to solid supports and can undergo light induced heterogeneous C-S bond cleavage upon irradiation with 350 nm light.

There is increasing interest in carrying out organic chemistry on a solid support.[1] Traditional methods rely heavily on ester and amide functionality for attaching the growing organic compound to the support.[2] While this may be suitable in some specific cases, in other cases it may be advantageous to have a non-reactive functional group remaining after cleavage from the resin.

This paper reports the solid-phase photochemical cleavage of a C-S bond to give as the major products either the resulting disulfide **3** or the tolyl derivative **4**. While the disulfide **3** is produced by the literature predicted C-S bond cleavage at site "a",[3-10] the tolyl derivative comes from the unexpected and novel C-S bond cleavage at site "b"(Scheme 1).

Scheme 1



1, R=H
2, R=phenyl

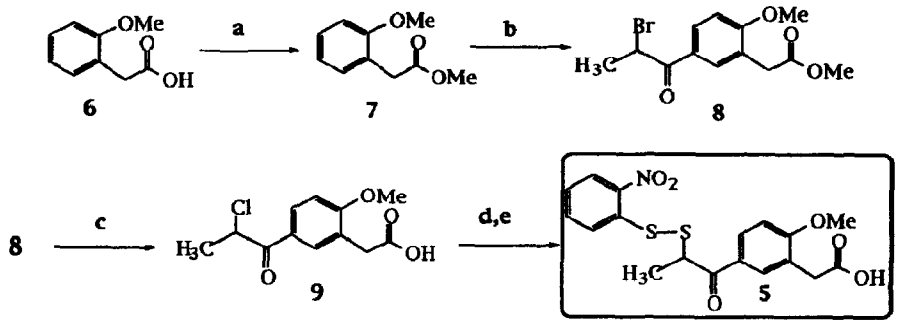
3, R=H

4, R=phenyl

This later cleavage route presents many advantages over existing methods. In the case where R= phenyl (**2**), the cleaved product **4** contains no vestigial functional groups such as a carboxylic acid or an amide bond. The deprotection conditions are mild, involving only de-oxygenated solvent and light; conditions easily lending this method to automation. Although this chemistry has been examined in combination with a commercially available polyethylene glycol-polystyrene support (TentaGel), other types of composite supports can be used.[11,12] The expansion properties of this polyethylene glycol containing support allow for the possibility of photochemical cleavages in aqueous solvents and therefore show potential for in-situ cleavage and biological testing of the synthesized product in water.

The photosensitive linker that allows scaffold attachment and cleavage from the support is an alpha-mercapto substituted phenyl ketone (**5**) which is protected as the disulfide (Scheme 2). The (+-)-2-methoxy-5-[2-[(2-nitrophenyl)dithio]-1-oxopropyl)phenyl acetic acid (**NpSSMpact**) linker **5** is attached to an amine containing support through an amide bond.

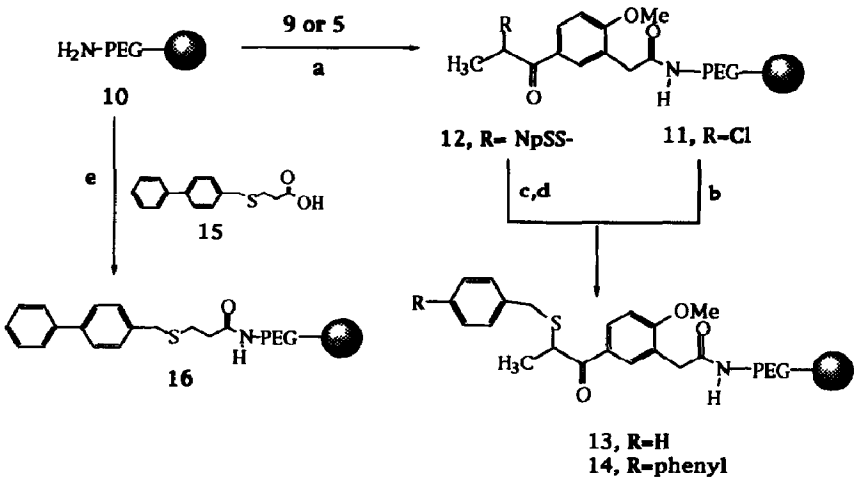
The synthesis of the **NpSSMpact** linker **5** begins with treatment of 2-methoxyphenylacetic acid with methanol and sulfuric acid to give the corresponding phenylacetate **7** in 83% yield (Scheme 2). The phenylacetate is then treated with 2-bromopropionyl chloride in the presence of aluminum trichloride to give the corresponding Friedel-Crafts acylation product **8** in 66% yield. The phenylacetate **8** is then refluxed in acetone and aqueous HCl to give the alpha-chloro derivative **9** in 64% isolated yield.[13-15] The alpha-chloro derivative **9** is then treated with the sodium salt of 2-methyl-2-propanethiol in tetrahydrofuran to give the corresponding thioether which is then treated without any further purification with 2-nitrobenzenesulfenyl chloride to give the **NpSSMpact** linker **5** in 59 % yield.[16]



Scheme 2 Reagents: (a) MeOH, H^+; (b) 2-Bromopropionyl chloride, $AlCl_3$, 50 °C ; (c) HCl, H_2O, acetone, reflux; (d) 2-Methyl-2-propanethiol sodium salt, NaH, THF; (e) 2-nitrobenzenesulfenyl chloride, acetic acid, dimethylformamide, H_2O.

The methoxy group at the 6-position serves not only to enhance the photolytic cleavage but also to direct the Friedel-Crafts acylation reaction to give only one isomer.[17] X-ray crystallographic analysis of the **NpSSMpact** linker **5** shows the positional selectivity to be para to the methoxy group.[18]

Both the **NpSSMpact** linker **5** and its precursor (**ChloroMpact** linker) **9** were coupled to a polyethylene glycol-polystyrene (TentaGel) support using standard diisopropylcarbodiimide coupling methods (Scheme 3).[14,15] The substitution of support **11** was determined by quantitative ninhydrin analysis of the free amines remaining after amide formation.[19] The substitution of support **12** was determined using a modified Ellman-type assay for free thiol.[16] Support **11** was treated with benzylmercaptan and diisopropylethylamine (DIEA) to give the resulting benzylthiolether derivative **13**. Support **12** was first treated with β-mercaptoethanol (BME) and DIEA to give the free thiol form of the linker (HSMpact), which was then alkylated with 4-phenylbenzylbromide to give the resulting biphenylthioether adduct **14**. As a comparison, support **10** was coupled with the biphenyl acid compound **15** to give the biphenyl ether support **16**. To each support was then added acetonitrile, which was de-oxygenated by the freeze-thaw method. The reaction mixtures were then irradiated at 350 nm, under a nitrogen atmosphere, using a Rayonet photochemical reactor. The cleaved products of the photochemical reaction were analyzed using reversed-phase HPLC, GC mass spectrometry and ^1H NMR spectroscopy. The cleaved support was analyzed by gel-phase carbon NMR.[20-22]



Scheme 3 Reagents: (a) Diisopropylcarbodiimide, CH_2Cl_2; (b) benzylmercaptan, DIEA, DMF; (c) BME, DIEA, DMF; (d) 4-phenylbenzylbromide, DIEA, DMF; (e) DIC, CH_2Cl_2.

Irradiation of the β-keto-sulfide **13** (R=H), produces, as the sole product, disulfide **3**.[5] Irradiation of resin **14** (R=phenyl) yields biphenyl compounds **15** and **4** exclusively (Table 1). The reason for this is most likely electronic. Fleming and Jensen have shown that the rate of homolytic photocleavage of the benzyl-sulfur bond is affected by substituents on the aryl ring.[23] It is reasonable to believe that in the case of support **13** (R=H), the rate of homolytic benzyl sulfur bond cleavage is much slower than the rate for a Norrish type II cleavage to give, after oxidation of the resulting thiocarbonyl, a disulfide. When R= phenyl, the rate of homolytic benzyl sulfur bond cleavage is much faster than other competing photochemical reactions. When one compares the resin containing the **Mpact** linker (**14**) versus the

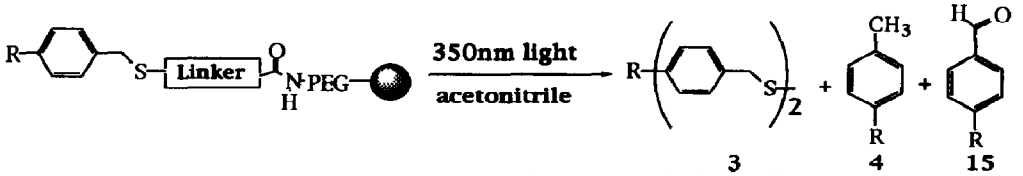


Table 1: Photochemical Cleavage of Thioethers

Linker	R	Solvent Conditions/Rxn Time	Mass Ratios (a)/ Yield (b) %3	%4	%15
16	phenyl	non-deoxygenated/ 1.5 h	0	15/0.4	85/6.2
16	phenyl	deoxygenated/ 2h,17min	0	69/32	31/15
16	phenyl	deoxygenated/ 5h	0	75/30	25/7.4
13	H	deoxygenated/ 2h,30min	100/26	0	0
14	phenyl	deoxygenated/ 2h	0	95/33	5/2
14	phenyl	deoxygenated/ 5h	0	94/58	6/0.7

(a) % Mass ratios by proton NMR before isolation from CD_3CN. (b) % Yields by mass after rotary evaporation; volatility of products contributing to low recoveries.

3-mercaptopropionic acid linker (16), one finds the production of aldehyde (15) to be much greater in the later case. The production of aldehyde is most probably due to dissolved oxygen. Preliminary experiments in our laboratory have shown that when using dry acetonitrile, the amount of aldehyde containing product is dramatically reduced. A greater efficiency in deoxygenation in the absence of residual water may be a factor.

In order to measure the relative rates of cleavage between supports **14** and **16**, the release of 4-phenyltoluene was measured as a function of time.[24] The rate of production of biphenyl **4** was found to be much higher ($t_{1/2} \approx 30$ min.) in the resin containing the **Mpact** linker (**14**) than the linker containing the 3-mercaptopropionic acid group (**16**) ($t_{1/2} \approx 4$ h). The higher rate of biphenyl cleavage from support **14** could be due to intramolecular single electron transfer or simply to a weaker C-S bond as compared to support **16**.

In conclusion, the solid-phase photochemical cleavage of a thioether is a useful new method for producing non-amide containing compounds. The mild conditions and simple procedure employed by this method should rapidly facilitate its use in the preparation of non-peptide molecules.

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References and Notes

1. Moos, W.H.; Green, G.D.; Pavia, M. R. *Annual Reports in Medicinal Chemistry* (Bristol, J.A. ed.), **1993**, *28*, 315.
2. Fréchet, J.M.J. in *Polymer-supported Reactions in Organic Synthesis*, **1980**, (Edited by Hodge, P. and Sherrington, D.C.), John Wiley & Sons, *Chapter 6*, 294.
3. Schönberg, A. Fateen, A.K.; Omran, S.M.A.R. *J. Am. Chem. Soc.* **1956**, *78*, 1224.
4. Hobeveen, H.; Smit, P.J. *Recueil*, **1966**, *85*, 489.
5. Collier, J.R.; Hill, J. *Chem. Commun.* **1968**, 700.
6. Collier, J.R.; Hill, J. *Chem. Commun.* **1969**, 640.
7. Caserio, M.C.; Lauer, W.; Novinson, T. *J. Am. Chem. Soc.* **1970**, *92*, 6082.
8. Padwa, A.; Pashayan, D. *J. Org. Chem.* **1971**, *36*, 3550.
9. Vedejs, E.; Perry, D.A. *J. Org. Chem.* **1984**, *49*, 573.
10. Lumma, W.C.; Berchtold, G.A. *J. Am. Chem. Soc.* **1967**, *89*, 2761.
11. Bayer, E.; Rapp, W. in *Chemistry of Peptides and Proteins*, **1986**, *2*, 3.
12. Bayer, E.; US 4,908,405, **1990**, 5 pages.
13. Tjoeng, F.S.; Heavner, G.A. *Tetrahedron Lett.*, **1982**, 23, 4439.
14. TJoeng, F.S.; Heavner, G.A. *J. Org. Chem.*, **1983**, 48, 355.
15. Uggeri, F.; Giordano, C.; Brambilla, A.; Annunziata, R. *J. Org. Chem.* **1986**, 51, 97.
16. Sucholeiki, I.; Lansbury, P.T. *J. Org. Chem.*, **1993**, *58*, 1318.
17. Chamberlin, J.W. *J. Org. Chem.* **1966**, *31*, 1658.
18. The pure NpSSMpact linker **5** was recrystallized from a chloroform-methanol solution to give crystals suitable for x-ray crytallographic analysis.
19. Sarin, V.K.; Kent, S.B.H.; Tam, J.P.; Merrifield, R.B. *Anal. Biochem.* **1981**, *117*, 147.
20. In a typical experiment, 100 mg of the support was added to a 5 mm NMR tube and sufficient deuterated chloroform added to solvate the resin. Number of transients = 15000. AQ = 1.3 s. FIDRES = 0.36 Hz.
21. Giralt, E.; Rizo, J.; Pedroso, E. *Tetrahedron*, **1984**, *40*, 4141.
22. Giralt, E.; Albericio, F.; Bardella, F.; Eritja, R.; Feliz, M.; Pedroso, E.; Pons, M.; Rizo, J. In: *Innovation and Perspectives in Solid Phase Synthesis*, (Epton, R. editor), **1990**, Hartnolls Ltd, Bodmin, Cornwall, 111-120.
23. Fleming, S.A.; Jensen, A.W. *J. Org. Chem.* **1993**, *58*, 7135.
24. The release of 4-phenyltoluene was measured using RPHPLC and 254 nm detection.

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