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Non-Acidic Cleavage of Wang-Derived Ethers From Solid Support: Utilization of a Mixed-Bed Scavenger For DDQ

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Abstract: Ethers derived from ArgoGel®-Wang-Chloride resin have been prepared and evaluated in both trifluoroacetic acid and DDQ-mediated cleavage protocols. DDQ cleavage of resin-bound *p*-alkoxy benzyl ethers has been found to circumvent problems associated with trifluoroacetylation of alcohol products during TFA treatment. In order to facilitate the removal of excess DDQ and DDQH from cleaved products, a mixed-bed ion exchange scavenger has been developed. © 1997 Elsevier Science Ltd.

Solid-phase organic synthesis strategies have become increasingly important in drug discovery.[1] Following solid-phase synthesis operations, elaborated core structures remain bound to polymer supports through attached "linkers." Many linkers which are currently used for small molecule applications were originally developed for use in biopolymer synthesis and generally require trifluoroacetic acid in order to release ester, amide, or amine products. There continues to be a great need for new linker systems to anchor other functionalities, including alcohols. Attachment of alcohols to solid supports has been accomplished using trityl and chlorotrityl resins,[2] carbonate resins,[3] a dihydropyran-functionalized resin[4] (acid cleavage), or silyl chloride resins[5] (acid or fluoride-mediated cleavage). In this article, we present an alternative approach to acid-mediated cleavage of ethers from solid support involving stoichiometric, oxidative cleavage of ArgoGel Wang ethers (**2**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[6]

ArgoGel-Wang-Chloride resin[7,8] (**1**) was prepared by treatment of ArgoGel®-Wang-OH resin with thionyl chloride in toluene (80 °C, 12 h). Resin-bound ethers **2** were formed by treatment of resin **1** with the appropriate sodium alkoxide (3 equiv., DMF, 60 °C, 12 h, **Scheme 1**).[9] Displacement reactions were monitored using gel-phase ^{13}C

Scheme 1

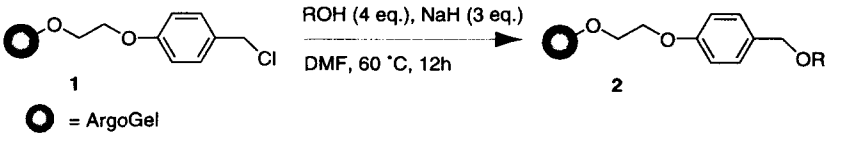
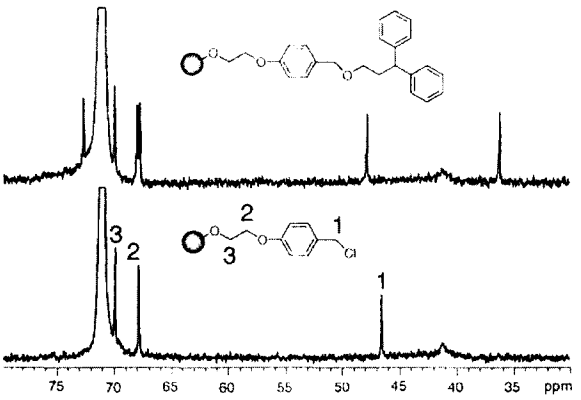


Figure 1



NMR by observing the shift in the benzylic carbon (δ 45.5 ppm) to the 60-70 ppm range (*cf.* **Figure 1**). Alternatively, reactions could be monitored colorimetrically by incubation of a small sample of beads with a solution of benzylamine in DMSO. After washing with DMF, the beads may be stained with either bromophenol blue or chloranil to test for the presence of secondary amine.[9]

Initial studies were focused on the cleavage of ArgoGel Wang-bound ethers using 20 % TFA/ DCM. It was found that ethers could be cleaved under these conditions (2 h), but released alcohol products were contaminated with variable amounts of the corresponding trifluoroacetate esters (20-30 %). Although the desired alcohols could be recovered by subsequent treatment with NH_3/MeOH, we were interested to find an alternative cleavage protocol which circumvented reprocessing of TFA-cleaved samples.

The oxidative cleavage of the *p*-alkoxy benzyl ether system using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was next examined as a mild and neutral alternative to TFA cleavage.[6] In order to facilitate the removal of excess DDQ and DDQH from cleaved products, a mixed-bed ion exchange scavenger was developed which would reduce excess DDQ to DDQH, and subsequently scavenge DDQH from the cleavage solution.[10] A reducing "bed" was prepared by ion-exchange of Amberlyst® A-26[11] (OH^- form) with ascorbic acid.[12,13] Amberlyst A-26 (HCO_3^-) form was utilized as the DDQH scavenging bed.[14] Results for the DDQ cleavage/scavenger protocol are provided in **Table 1**.[15] For the ether systems evaluated, cleavage yields are >70 % and purities of alcohol products high, with no evidence of ascorbate or DDQ-derived impurities by HPLC analysis.

Finally, we tested the ability to perform sub-stoichiometric, staged-release of alcohol products by examining the DDQ oxidation of a representative ether (**Table 1**,

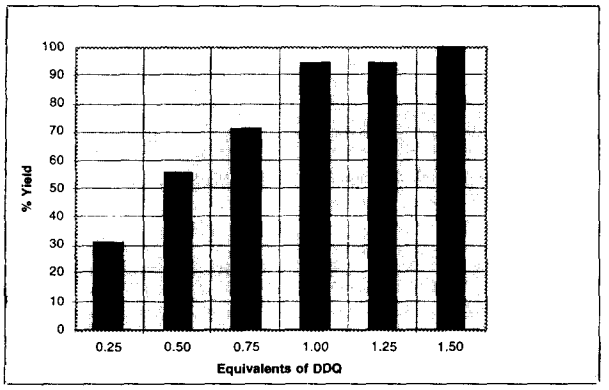
Table 1: DDQ cleavage of resin-bound ethers

R-OH	Yield (HPLC Area %)[1]
S-1,2-methoxybenzoyl-2-pyrrolidinemethanol	100% (>99%)
3,3-diphenylpropanol	98.1% (86.0%)
1-(2-benzylphenoxy)-2-propanol	82.7% (83.1%)
2-(4-bromophenoxy)ethanol	86.0% (>99%)
1-(4-methoxyphenoxy)-2-propanol	70.1% (>99%)

[1]HPLC method: 2-90% Acetonitrile-water (9 minutes, Microsorb MV C18 column)

entry 1) using a range of equivalents of DDQ (**Figure 2**). Preliminary data showed that sub-stoichiometric cleavage with DDQ could be performed in aliquots and correlated well with the amount of DDQ that was introduced. Such reagent-based cleavage may be a useful alternative to other staged release protocols (*e.g.* photochemistry, multiple linkers, *etc.*)[16] if combined with the appropriate scavengers or other non-invasive protocols.

Figure 2: Sub-stochiometric DDQ cleavage



In summary, DDQ oxidation of ArgoGel-Wang-derived ethers, in combination with a mixed-bed scavenger resin for DDQ, has been utilized as an alternative strategy to acid-mediated cleavage. Byproducts were efficiently removed by use of a mixed-bed scavenger providing pure compounds. The use of a stoichiometric, reagent-based cleavage strategy also provided a means to release aliquots of product from the resin for biological analysis and/or structural determination, while preserving material on the bead for further chemical transformations or subsequent analysis of "actives." The development and use of other mixed-bed scavengers and alternative sub-stoichiometric cleavage strategies are in progress and will be reported in due course.

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References and Notes

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6. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021 and references cited therein.

7. ArgoGel-Wang-Cl resin is commercially available from Argonaut Technologies, San Carlos, CA.

8. For a recent paper on the preparation of Wang halide linkers for sulfonamide formation/cleavage see: Ngu, K.; Patel, D.V. *Tetrahedron Lett.* **1997**, *38*, 973.

9. *Representative procedure for ether formation*: 2.0 g of ArgoGel-Wang-Cl (0.37 mmol/g, ~0.75 mmol) was weighed into a dry 50 mL 2-neck round bottom flask equipped with a mechanical stirrer and purged with nitrogen. Sodium hydride (100 mg, 2.25 mmol, 3 equiv. of a 60% suspension in mineral oil), 1-(4-methoxyphenoxy)-2-propanol (550 mg, 3.0 mmol, 4 equiv.), and DMF (10 mL/g) were added sequentially. The reaction was stirred for 30 minutes at 25 °C and then heated to 60 °C overnight. An aliquot of resin was transferred to a test tube, washed 10 X DMF, and treated with 1.0 mL of 1.0 M benzylamine/DMSO. After 30 minutes, the aliquot was washed with 8 X DMF, 8 X MeOH, and treated with bromophenol blue indicator which indicated the absence of a secondary amine. The resin was subsequently washed with 5 X DMF, 5 X 1:1 DMF-H_2O, 5 X H_2O, 5 X 0.1 N HCl, 5 X H_2O, and 5 X THF (10 minute agitations). The resin was washed further with 4 X DCM, 4 X MeOH, and dried in a high-vacuum desiccator overnight.

10. For the use of resins as scavengers, see: (a) Gayo, L.M.; Suto, M.J. *Tetrahedron Lett.* **1997**, *38*, 513. (b) Kaldor, S.W.; Siegel, M.G.; Fritz, J.E.; Dressman, B.A.; Hahn, P.J. *Tetrahedron Lett.* **1996**, *37*, 7193.

11. Amberlyst® A-26 is a registered trademark of the Rohm and Haas Company.

12. For the reduction of excess DDQ with ascorbic acid, see: Fukase, K.; Yoshimura, T.; Kotani, S.; Kusumoto, S. *Bull. Chem. Soc. Jpn.*, **1994**, *67*, 473-482

13. *Preparation of Amberlyst-26 Ascorbate Resin*: 20 g Amberlyst A-26 (Cl^- form, Aldrich) was washed with 15 X 1 L water, 6 X 1 L methanol, and 6 X 1 L acetone, and dried under vacuum (60 °C, 12 h). The beads were subsequently transferred to a glass column, flushed with nitrogen, and washed with 3 X 1 L 1.0 *N* NaOH for 1 h. The resin was washed with water until a neutral pH was obtained (4 X 1 L). 0.4 *N* Ascorbic Acid was passed through the column for 2 h (3 X 1 L), and the beads finally washed with 4 X 1 L water, 4 X 1 L MeOH, and 4 X 1 L acetone. The ascorbate beads were dried in a high vacuum desiccator for 72 h and stored under nitrogen.

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15. *Representative DDQ cleavage*: 200 mg of ether-derived ArgoGel-Wang resin (0.35 mmol/g, 0.07 mmol, 1.0 equiv.) was added to a 8 mL glass vessel. Solid 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (32 mg, 0.14 mmol, 2.0 equiv.) was added followed by 2.0 mL of 20:1 DCM-H_2O. The reaction was agitated for 2 hours at 25 °C. The mixed-bed scavenger resin (Amberlyst A-26 Ascorbate resin (200 mg, ~3.8 mmol/g, 0.70 mmol, 5.0 equiv relative to DDQ)) and Amberlyst A-26 HCO_3^- resin (400 mg, ~3.8 mmol/g, 1.40 mmol, 10 equiv. relative to DDQ)) was weighed into a 12 mL polypropylene cartridge. The cleavage solution and 3 X 2 mL DCM washes were then filtered onto the mixed-bed resin. The filtrate was agitated with the mixed-bed resin for 1 hour at 25 °C. The solution and 3 X 2 mL DCM resin washes were collected by filtration and concentrated.

16. For a discussion of linkers that utilize staged-release, see Ref 1 (a) and refs. cited therein.

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