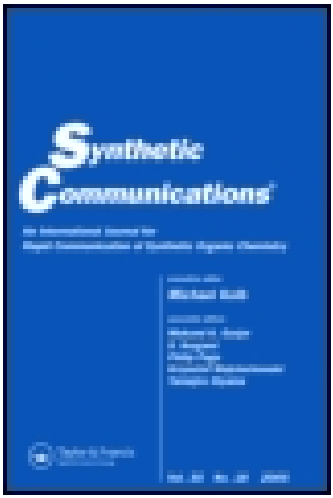

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Surface-Mediated Solid Phase Reaction. PART 7.[1] A Simple and Convenient Procedure for the Methoxymethylation of Alcohols with Methoxymethyl Chloride on the Surface of Alumina

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SURFACE-MEDIATED SOLID PHASE REACTION. PART 7.[1] A SIMPLE AND CONVENIENT PROCEDURE FOR THE METHOXYMETHYLATION OF ALCOHOLS WITH METHOXYMETHYL CHLORIDE ON THE SURFACE OF ALUMINA

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ABSTRACT : A variety of alcohols react with methoxymethyl chloride on the surface of alumina without any solvent to afford the corresponding methoxymethyl ethers in good yields.

The protection of hydroxyl group as methoxymethyl ether (MOM ether) is a frequently used process in organic synthesis.[2] Although a number of methods are available in the literature employing dimethoxymethane and expensive catalysts,[2,3] simple and direct methods using methoxymethyl chloride are very few.[2,4] As a part of our continuing efforts to utilize surface-mediated reaction for useful synthetic transformations,[5] we have achieved a very simple and convenient procedure for methoxymethylation of alcohols through a solvent free reaction on the surface of alumina under sonication.[6]

$$ROH \xrightarrow[Al_2O_3,\ \text{ultrasound}]{ClCH_2OCH_3} ROCH_2OCH_3$$

In a typical general procedure, methoxymethyl chloride was added dropwise to the alcohol adsorbed on the surface of alumina (activated) at 0-5°C with stirring. The whole solid mass was then sonicated in an ultrasonic cleaner. The progress of the reaction was monitored by TLC. After the reaction was complete, the product was isolated by simple extraction of solid mass with methylene chloride followed by evaporation of solvent.

Several structurally varied alcohols were treated under this procedure to furnish the protected MOM ethers. The results are summarized in Table. The reactions are, in general, reasonably fast and high-yielding. The reaction condition is mild enough not to induce any isomerization of double or triple bond in case of allylic and propargylic alcohols. The reaction is also very smooth for molecules like cholesterol and tetrahydrofurfuryl alcohols. Tertiary alcohols are inert to this procedure; thus this methodology can be employed to protect primary and secondary hydroxyl groups selectively in presence of tertiary ones. It is also noteworthy that alumina can be recycled after being washed with methanol and activated.

In conclusion, the present procedure on the solid surface of alumina provides a very convenient methodology for the methoxymethylation of alcohols. The operational simplicity, mild condition, good yield and low cost make this procedure a useful and attractive alternative to the currently available methods.

Table. Methoxymethylation of Alcohols on the Surface of Alumina

Entry	Alcohols	Reaction Time (h)	Yields (%) of MOM ethers
1	Cyclopentanol	6	83
2	Cyclohexanol	15	82
3	3-Methylcyclohexanol	6	92
4	Isopropanol	6	77
5	n-Hexanol	24	85
6	Benzyl alcohol	1	84
7	Tetrahydrofurfuryl alcohol	4	72
8	Allyl alcohol	1	68
9	Propargyl alcohol	2	74
10	Cholesterol	5	80
11	t-Butanol	12	-

EXPERIMENTAL

General Procedure for Methoxymethylation : Methoxymethyl chloride (2 mmol) was added dropwise through a syringe to the alcohol (1 mmol) adsorbed on alumina (1 g, acidic, Brockmann activity grade 1, activated by heating at 200°C for 4 h in vacuo and cooled under nitrogen) at 0-5°C (ice-water bath)

under mild shaking. The white solid mass was then sonicated in an ultrasonic cleaner (Julabo USR-3, manufactured by Julabo Labortechnik, Germany, 50 Hz) for a certain period of time as required to complete the reaction (The progress of the reaction was monitored by TLC). The solid mass was then eluted with methylene chloride and the extract was evaporated to furnish the product as methoxymethyl ether. The product was further purified by quick column chromatography over silica gel. The MOM ethers were easily identified by comparison with authentic samples (IR and ^{1}H NMR).

Though the results shown in Table were obtained from milligram scale reactions, gram-scale reactions also afforded the corresponding products in analogously good yields.

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6. Without sonication the reaction was very slow.

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