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A CONVENIENT METHOD FOR THE PREPARATION OF UNSYMMETRICAL ETHERS AND IT'S APPLICATION TO THE SYNTHESIS OF ROSE OXIDE AND DIHYDRO ROSE OXIDE

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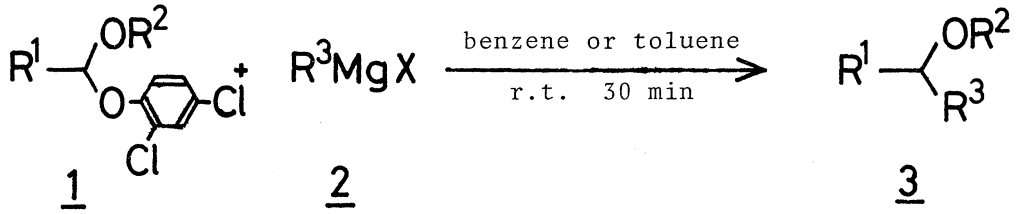
Alkyl 2,4-dichlorophenyl acetals react with Grignard reagents in aromatic hydrocarbons such as benzene or toluene at room temperature to afford the corresponding unsymmetrical ethers in good yields. The utility of this new procedure is demonstrated by the synthesis of rose oxide and dihydro rose oxide.

In the preceding paper[1] dealing with the $TiCl_4$-promoted reaction of mixed acetals as alkyl 2,4-dichlorophenyl acetals (1) with Grignard reagents in tetrahydrofuran at -78°C, it was shown that 2,4-dichlorophenoxy group of the acetals was replaced by an alkyl or aryl group originated in the Grignard reagents to form the corresponding unsymmetrical ethers in high yields.

In the present experiment, it was established that unsymmetrical ethers (3) were prepared in good yields by the treatment of 1 with Grignard reagents (2) in aromatic hydrocarbons such as benzene or toluene at room temperature without any assistance of $TiCl_4$.[2]



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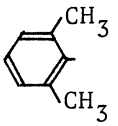
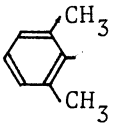
The typical procedure of the present experiment is described for the reaction of 2-(2,4-dichlorophenoxy)tetrahydropyran (1a) with phenethylmagnesium bromide (2a): To a benzene solution (4 ml) of 2a (4 mmol)[3] was added a benzene solution (2 ml)

of 1a (2 mmol) under an argon atmosphere at room temperature, and the reaction mixture was stirred for 30 min. After quenching with water, the product was extracted with ether. The organic layer was washed with 10% aqueous sodium hydroxide and condensed under reduced pressure. The residue was chromatographed on silica gel, and 2-phenethyltetrahydropyran was isolated in 88% yield.[4] In a similar manner, various unsymmetrical ethers were obtained in good yields as shown in the Table.

Table. Reaction of Alkyl 2,4-Dichlorophenyl Acetals with Grignard Reagents

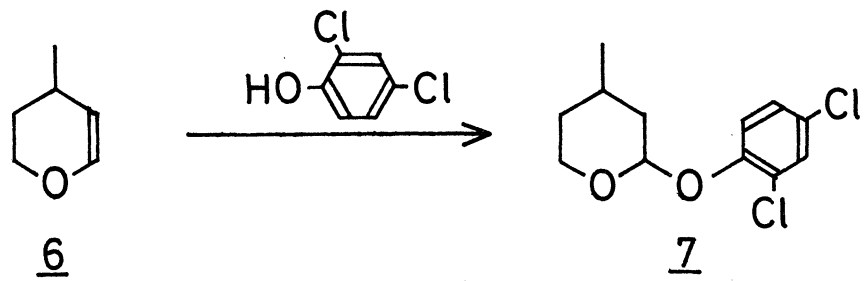
Acetal (1)		Grignard Reagent (2)	Unsymmetrical Ether (3)
R^1	R^2	R^3	Yield(%)
$-(CH_2)_4-$		$n\text{-}C_3H_7$	67[a]
		$n\text{-}C_8H_{17}$	85[b]
			60[a]
		C_6H_5	84[b]
			79[b]
		$C_6H_5CH_2CH_2$	88[b],[c]
CH_3	C_2H_5	$n\text{-}C_8H_{17}$	87[b]
			49[a]
		C_6H_5	83[b]
			76[b]
		$C_6H_5CH_2CH_2$	88[b]

a) Isolated by distillation
b) Isolated by silica gel chromatography
c) The unsymmetrical ether was obtained in 82% yield when the reaction was carried out in toluene.

The utility of this new procedure is illustrated by synthesis of rose oxide, cis- and trans-2-(2-methyl-1-propenyl)-4-methyltetrahydropyran (4), and dihydro rose oxide, cis- and trans-2-isobutyl-4-methyltetrahydropyran (5). There have been reported a number of synthetic routes to rose oxide, because it is a minor but important olfactive ingredient of rose otto and geranium oil.[5)]

The key intermediate 2-(2,4-dichlorophenoxy)-4-methyltetrahydropyran (7) was prepared by the addition of 2,4-dichlorophenol to 4-methyl-2,3-dihydro-4H-pyran (6)[6)] in 81% yield. The following experiment is detail of the procedure employed for the preparation of 4: To a benzene solution (30 ml) of 2-methyl-1-propenyl-magnesium bromide (30 mmol) was added a benzene solution (15 ml) of 7 (15 mmol) under an argon atmosphere at room temperature, and the reaction mixture was stirred for 1 hr and then at 50°C for 30 min. After the similar work-up, 4 was isolated by distillation (bp 86-88°C/22 mmHg) in 86% yield. An analytical sample gave the following data: The composition of the mixtrue as determined by glpc analysis, comparing with the authentic sample, was 32% cis and 68% trans isomer; mass spectrum (20 eV) m/e 155(p+1) 140.

Similarly, dihydro rose oxide was synthesized by the reaction of 7 with isobutylmagnesium bromide, (bp 63-64°C/10 mmHg), in 79% yield.



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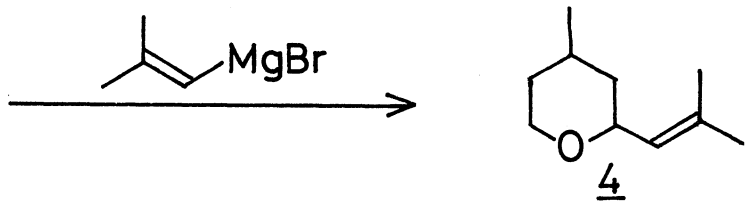

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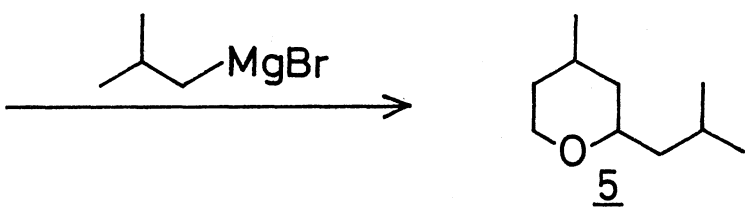

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3) A benzene or toluene solution of various Grignard reagents was prepared by replacing ether used in the formation of Grignard reagents.

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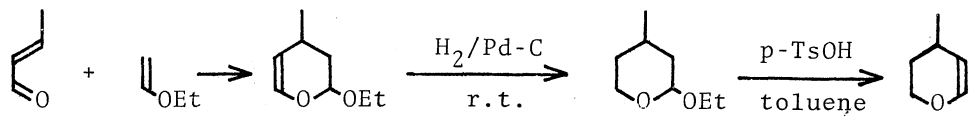
6) This was prepared according to Julia's procedure[5i)] with some modifications depicted below.



80% 92% 74%

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