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A NEW METHOD FOR THE PREPARATION OF UNSYMMETRICAL ETHERS. THE REACTION OF ALKYL 2,4-DICHLOROPHENYL ACETALS WITH GRIGNARD REAGENTS ACTIVATED BY $TiCl_4$

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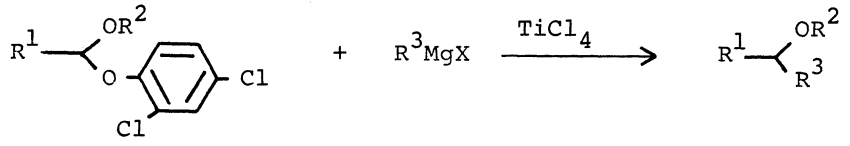
It was found that, in the presence of $TiCl_4$, alkyl 2,4-dichlorophenyl acetals react with Grignard reagents to give the corresponding unsymmetrical ethers in high yields.

In general, acetals, the most commonly encountered protective group for aldehydes and ketones, are stable to most alkaline reagents and inert to reactive species usually of the nucleophilic type, which normally affect a carbonyl function.

Many works have been reported on Grignard addition to steroidal cyclic acetals and cyclic acetals of halogenated saturated ketone in recent years.[1-5] However, no similar reactions have hitherto been known in the case of dialkyl and mixed acetals derived from various aldehydes and ketones.

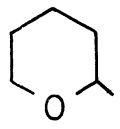
In the previous paper,[6] it was reported that allyl ethers are obtained in high yields by treating α,β-unsaturated acetals with Grignard reagents in the presence of $TiCl_4$ at low temperatures.

We wish to report the preparation of various unsymmetrical ethers by the $TiCl_4$-promoted reaction of some mixed acetals, namely alkyl 2,4-dichlorophenyl acetals[7] derived from acetaldehyde or dihydropyran, with Grignard reagents by replacing the 2,4-dichlorophenoxy group with an alkyl group[8] as shown in the following equation.



For example, to a mixture of 5 mmol of 2-(2,4-dichlorophenoxy)tetrahydropyran and 10 mmol of $TiCl_4$ in 20 ml of dry THF was added a THF solution of 10 mmol of phenethylmagnesium bromide at -78 °C for the period of 3 hr under an argon atmosphere, and the reaction mixture was stirred for additional 6 hr at -78°C. As 20 ml of 10% aqueous potassium carbonate was added to the solution, a dark brown precipitate appeared. After the usual work-up, 2-phenethyltetrahydropyran was isolated by thin layer chromatography in 98% yield. In a similar manner, various unsymmetrical ethers were obtained as shown in Table 1.

Table 1
Reaction of alkyl 2,4-dichlorophenyl acetals with Grignard reagents

Acetal R^1	Acetal R^2	Reaction Time (hr)	R^3	Yield % [2]
		9	$C_6H_5CH_2CH_2$	98
		9	$C_6H_5CH_2$	91
		6	C_6H_5	80
		9	C_8H_{17}	75
CH_3	CH_3CH_2	9	$C_6H_5CH_2CH_2$	87
		9	$C_6H_5CH_2$	77
		6	C_6H_5	82
		9	C_8H_{17}	71

In conclusion, it should be noted that the present process provides another new method for the preparation of the various unsymmetrical ethers from the corresponding acetals in high yields.

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7) Various alkyl 2,4-dichlorophenyl acetals were easily prepared by the addition of 2,4-dichlorophenol to vinyl ether derivatives.
8) Contrary to these results, a dialkyl acetal derived from an aliphatic aldehyde, such as β-phenylpropionaldehyde dimethyl acetal, was not alkylated by the coupled use of $TiCl_4$ and Grignard reagents to recover a considerable amount of the starting material.

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