776 © 1981 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 54, 776—780 (1981) [Vol. 54, No. 3

Reaction of Acetals with Grignard Reagents

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(Received June 10, 1980)

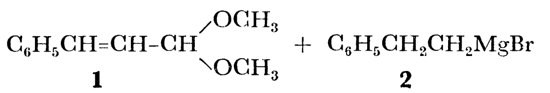
The reaction of dialkyl acetals derived from α,β-unsaturated aldehydes with Grignard reagents using $TiCl_4$ in THF afforded the cross coupling products, allyl ethers, in high yields. The $TiCl_4$-promoted reaction of alkyl 2,4-dichlorophenyl acetals, synthesized from 3,4-dihydro-2*H*-pyran or ethyl vinyl ether and 2,4-dichlorophenol, with Grignard reagents in THF at low temperature afforded the corresponding unsymmetrical ethers in high yields. When alkyl 2,4-dichlorophenyl acetals, synthesized from aromatic aldehyde or vinyl ethers and 2,4-dichlorophenol, were treated with Grignard reagents in benzene or toluene at room temperature in the absence of $TiCl_4$, the cross coupling reaction took place and the corresponding ethers were isolated in good yields.

We briefly reported in two previous papers[1-2] that the reaction of dialkyl acetals derived from α,β-unsaturated aldehydes with Grignard reagents using $TiCl_4$ and the reaction of alkyl 2,4-dichlorophenyl acetals, synthesized from 3,4-dihydro-2*H*-pyran or vinyl ether and 2,4-dichlorophenol, with Grignard reagents in benzene or toluene afforded the corresponding allyl ethers and ethers. In this report, the reactions are explained in detail and additional results are presented.

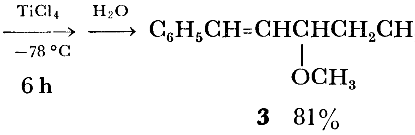
In general, acetals, the most commonly encountered protective group for aldehydes and ketones, are stable to most alkaline reagents and known to be inert toward various nucleophiles such as Grignard reagents and organolithium compounds except for cyclic acetals, steroidal cyclic acetals and cyclic acetals of halogenated saturated ketone.[3-7] No similar reactions have hitherto been know for dialkyl and mixed acetals derived from various aldehydes and ketones.

We have studied various synthetic reactions using $TiCl_4$ and have reported in the previous paper[8] that the reduction of dialkyl acetals derived from aromatic aldehydes and ketones with $TiCl_4$–$LiAlH_4$ in THF or diethyl ether at room temperature afforded the coupling products, pinacol ethers or olefins, in high yields. We also reported that various olefins were prepared in good yields by the treatment of allyl methyl ethers with $TiCl_4$–$LiAlH_4$ in THF or diethyl ether.[9]

In the present work, the reaction of various acetals with Grignard reagents in the presence and absence of $TiCl_4$ was tried; it was found that the various ethers were given in good yields. The $TiCl_4$-promoted reaction of dimethyl acetals derived from α,β-unsaturated aldehydes with Grignard reagents was examined in THF at −78 °C. For example, 1.5 molar amount of phenethylmagnesium bromide (**2**) was added to a mixture of an equimolar amount of cinnamaldehyde dimethyl acetal (**1**) and $TiCl_4$ in THF at −78 °C under argon atmosphere. After stirring at −78 °C for 6 h, the mixture was quenched with aqueous potassium carbonate. Purification by column chromatography (silica gel) gave 3-methoxy-1,5-diphenyl-1-pentene (**3**) in 81% yield.

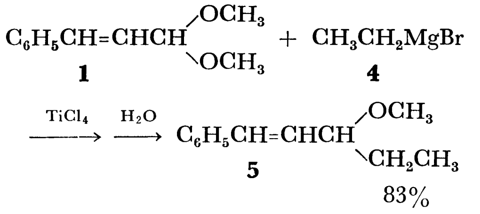


$$\underset{\mathbf{1}}{C_6H_5CH{=}CH{-}CH{<}^{OCH_3}_{OCH_3}} + \underset{\mathbf{2}}{C_6H_5CH_2CH_2MgBr}$$

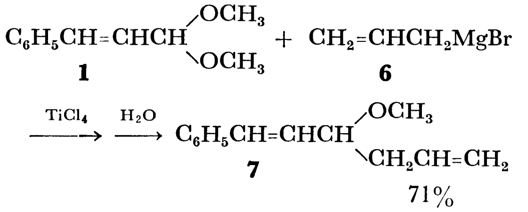


$$\xrightarrow[-78\,^{\circ}C,\ 6\,h]{TiCl_4}\xrightarrow{H_2O} \underset{\mathbf{3}\ \ 81\%}{C_6H_5CH{=}CH\underset{\substack{|\\OCH_3}}{CH}CH_2CH_2C_6H_5}$$

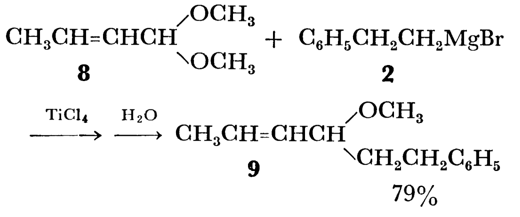
In a similar manner, the reactions of various acetals derived from α,β-unsaturated aldehydes in the presence of $TiCl_4$ were tried in THF at −78 °C, and the corresponding allyl ethers were obtained in high yields, as shown in the following equation:



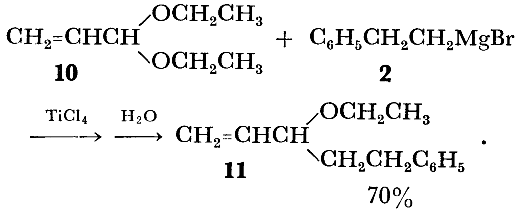
$$\underset{\mathbf{1}}{C_6H_5CH{=}CHCH{<}^{OCH_3}_{OCH_3}} + \underset{\mathbf{4}}{CH_3CH_2MgBr} \xrightarrow{TiCl_4}\xrightarrow{H_2O} \underset{\mathbf{5}\ \ 83\%}{C_6H_5CH{=}CHCH{<}^{OCH_3}_{CH_2CH_3}} \tag{1}$$



$$\underset{\mathbf{1}}{C_6H_5CH{=}CHCH{<}^{OCH_3}_{OCH_3}} + \underset{\mathbf{6}}{CH_2{=}CHCH_2MgBr} \xrightarrow{TiCl_4}\xrightarrow{H_2O} \underset{\mathbf{7}\ \ 71\%}{C_6H_5CH{=}CHCH{<}^{OCH_3}_{CH_2CH{=}CH_2}} \tag{2}$$



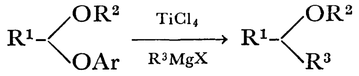
$$\underset{\mathbf{8}}{CH_3CH{=}CHCH{<}^{OCH_3}_{OCH_3}} + \underset{\mathbf{2}}{C_6H_5CH_2CH_2MgBr} \xrightarrow{TiCl_4}\xrightarrow{H_2O} \underset{\mathbf{9}\ \ 79\%}{CH_3CH{=}CHCH{<}^{OCH_3}_{CH_2CH_2C_6H_5}} \tag{3}$$

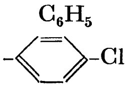
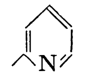
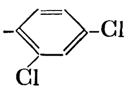
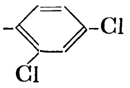


$$\underset{\mathbf{10}}{CH_2{=}CHCH{<}^{OCH_2CH_3}_{OCH_2CH_3}} + \underset{\mathbf{2}}{C_6H_5CH_2CH_2MgBr} \xrightarrow{TiCl_4}\xrightarrow{H_2O} \underset{\mathbf{11}\ \ 70\%}{CH_2{=}CHCH{<}^{OCH_2CH_3}_{CH_2CH_2C_6H_5}}\ . \tag{4}$$

It was found that γ-arylation took place to afford vinyl ethers when phenylmagnesium bromide (**12**) was employed in the above reactions. For example, 1-methoxy-3-phenyl-1-butene (**13**) was obtained in 42% yield by the reaction of crotonaldehyde dimethyl acetal (**8**) and phenylmagnesium bromide (**12**) in the presence

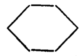
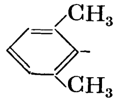
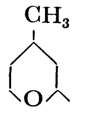
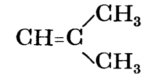
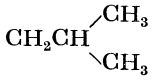
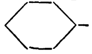
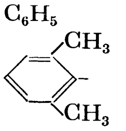
Table 1. $TiCl_4$-promoted reaction of alkyl aryl acetals with Grignard reagents in THF



Acetal R¹	Acetal R²	Acetal Ar	Grignard reagent R³	Ether yield[a]/%	Bp (°C/mmHg)[b,c]	
$-(CH_2)_4-$		C_6H_5	$C_6H_5CH_2CH_2$	65	69—70/0.5	(**15**)
				76		(**15**)
				38		(**15**)
14				98		(**15**)
			C_6H_5	80	96—100/22	(**16**)
			n-C_8H_{17}	75	95—96/3	(**17**)
CH_3	C_2H_5	C_6H_5	$C_6H_5CH_2$	51	75—78/10	(**20**)
18			$C_6H_5CH_2CH_2$	87	106—110/12	(**19**)
			C_6H_5	82	65—68/22	(**21**)
			n-C_8H_{17}	71	76—78/15	(**22**)
			$C_6H_5CH_2$	77		(**20**)

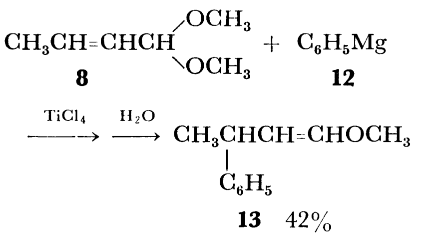
a) Isolated by silica gel chromatography. b) All boiling points were uncorrected. c) 1 mmHg = 133.322 Pa.

Table 2. Reaction of alkyl 2,4-dichlorophenyl acetals with Grignard reagents in benzene

Acetal R¹	Acetal R²	Grignard reagent R³	Ether yield[a]/%	Bp (°C/mmHg)	
$-(CH_2)_4-$		$C_6H_5CH_2CH_2$	88[c]		(**15**)
(**14**)		C_6H_5	84		(**16**)
		n-C_3H_7	67[b]	78—79/30	(**23**)
		n-C_8H_{17}	85		(**17**)
			60	104—109/21	(**24**)
			79	82—84/2	(**25**)
		 $CH{=}C(CH_3)_2$	86[b,d]	86—88/2	(**27**)
(**26**)		 $CH_2CH(CH_3)_2$	79[b,d]	63—64/10	(**28**)
CH_3	C_2H_5	n-C_8H_{17}	87		(**22**)
(**18**)			49[b]	61—62/18	(**29**)
		C_6H_5	83		(**21**)
			76	104—106/20	(**30**)
		$C_6H_5CH_2CH_2$	88		(**19**)
C_6H_5	CH_3	$C_6H_5CH_2CH_2$	83	131—133/2	(**32**)
(**31**)		C_6H_5	76	145—148/20	(**33**)
		n-C_6H_{13}	81	143—146/31	(**34**)

a) Isolated by silica gel chromatography. b) Isolated by distillation. c) The unsymmetrical ether was obtained in 82% yield when the reaction was carried out in toluene. d) The composition of the product as determined by GLPC analysis, comparing with the authentic sample, was 32% *cis* and 68% *trans* isomer. e) The composition of the product was 19% *cis* and 81% *trans* isomer.

of $TiCl_4$, and 1-methoxy-1-phenyl-2-butene could not be detected.



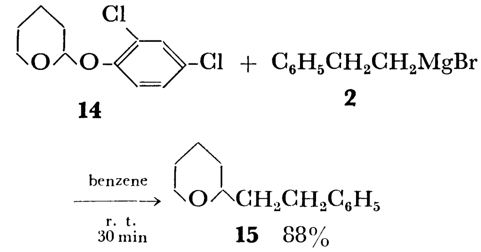
$$CH_3CH{=}CHCH(OCH_3)_2 + C_6H_5Mg \xrightarrow{TiCl_4} \xrightarrow{H_2O} CH_3CH(C_6H_5)CH{=}CHOCH_3$$

8 **12** **13** 42%

Contrary to such results, dialkyl acetals derived from aromatic and aliphatic aldehydes, such as benzaldehyde dimethyl acetal and β-phenylpropionaldehyde dimethyl acetal, were not alkylated by the coupled use of $TiCl_4$ and Grignard reagents, considerable amounts of the starting materials were recovered. But it was established that the $TiCl_4$-promoted reaction of some mixed acetals, alkyl aryl acetals synthesized from 3,4-dihydro-2*H*-pyran or ethyl vinyl ether, and phenol with Grignard reagents gave various unsymmetrical ethers by the replacing the aryloxyl group with an alkyl group (Table 1).

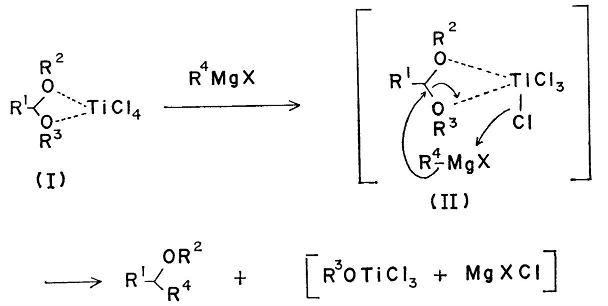
As shown in Table 1, when various mixed acetals synthesized from 3,4-dihydro-2*H*-pyran and phenol were treated with Grignard reagent in the presence of $TiCl_4$ in THF at −78 °C, it was found that the reaction of 2-(2,4-dichlorophenoxy)tetrahydropyran with Grignard reagent afforded the cross coupling product in higher yield than that obtained for mixed acetals. The generality of $TiCl_4$-promoted reaction was examined by the use of various alkyl 2,4-dichlorophenyl acetals, and in all cases the corresponding ethers were obtained in good yields (see Table 1).

Further, the reaction of 2-(2,4-dichlorophenoxy)-tetrahydropyran with a Grignard reagent such as phenethylmagnesium bromide in the absence of $TiCl_4$ took place in benzene or toluene at room temperature and the corresponding unsymmetrical ether was isolated in 88% yield. Even when the same reaction was carried out in tetrahydrofuran under refluxing, the yield of the unsymmetrical ether was below 60%. In a similar manner, various unsymmetrical ethers were obtained in good yields, as shown in Table 2.

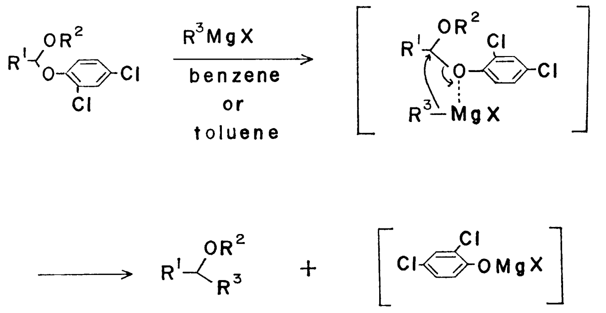


14 **2** **15** 88%

The mechanism of the $TiCl_4$-promoted reaction of α,β-unsaturated acetals and alkyl aryl acetals with Grignard reagents may be explained as follows; the acetal forms a coordinated compound (I) with $TiCl_4$, which subsequently reacts smoothly with the Grignard reagent, probably through a six-membered cyclic intermediate (II), to afford the corresponding ethers, as sketched below:



The 2,4-dichlorophenoxyl group of alkyl 2,4-dichlorophenyl acetals can leave easily; thus the mechanism of the reaction of alkyl 2,4-dichlorophenyl acetals with Grignar dreagents in bezene or toluene may be a magnesium-promoted replacement reaction of 2,4-dichlorophenoxyl group with alkyl group, as shown below.



In conclusion, it has been shown that the reaction of dialkyl acetals derived from α,β-unsaturated aldehydes and mixed acetals synthesized from 3,4-dihydro-2*H*-pyran or ethyl vinyl ether and phenols with Grignard reagents, using $TiCl_4$ in THF at low temperature, afforded the cross-couling products, various ethers, in high yields. Further, when the mixed acetals synthesized from aromatic aldehydes or vinyl ethers and 2,4-dichlorophenol were treated with Grignard reagents in an aromatic hydrocarbon such as benzene or toluene at room temperature, various ethers are obtained in good yields.

Experimental

Spectra. The proton NMR spectra were recorded using a Hitachi R-24 spectrometer and a Varian EM 360 spectrometer. Chemical shifts are reported on δ scale relative to tetramethylsilane as an internal standard. Infrared spectra were taken using a Hitachi 215 grating infrared spectrophotometer. Products were identified by NMR and IR spectra and elemental analyses.

Material. Commercially available $TiCl_4$ was distilled under argon atmosphere before use. All solvents used here were distilled according to the usual methods and were stored over sodium metal as a drying agent. Various α,β-unsaturated acetals were readily prepared from α,β-unsaturated aldehyde and orthoformic esters in alcoholic solution in the presence of a catalyst such as anhydrous hydrogen chloride. Alkyl 2,4-dichlorophenyl acetals were easily prepared by the addition of 2,4-dichlorophenol to vinyl ether derivatives and by the replacement reaction of sodium 2,4-dichlorophenoxide to α-methoxybenzyl chloride.[10]

Descriptions in this experimental section are typical examples; other products are shown in the table.

Reaction of Cinnamaldehyde Dimethyl Acetal (1) with Phenethyl-

Table 3. Physical properties and analytical data of the products

Products	IR (cm^{-1})[a]	NMR (δ)[b]	Found (%) (Calcd)	
			C	H
3[d]	2900 1105 740 695	1.6—2.1(m, 2H), 2.71(t, 2H, J=7 Hz), 3.25(s, 3H), 3.4—3.8(m, 1H), 5.94(dd, 1H, J=16, 7 Hz), 6.45(d, 1H, J=16 Hz), 7.0—7.4(m, 10H)	85.54 (85.67)	7.91 (7.99)
5[e]	2910 1100 970 700	0.92(t, 3H, J=7 Hz), 1.2—1.9(m, 2H), 3.24(s, 3H), 3.3—3.6(m, 1H), 5.93(dd, 1H, J=16, 7 Hz), 6.45(d, 1H, J=16 Hz), 7.20(br s, 5H)	81.90 (81.77)	9.21 (9.15)
7[f]	2940 1110 995	2.35(t, 2H, J=6 Hz), 3.26(s, 3H), 3.4—3.8(m, 1H), 4.8—5.2(m, 2H), 5.4—6.0(m, 1H), 5.94(dd, 1H, J=16, 7 Hz), 6.48(d, 1H, J=16 Hz), 7.26(br s, 5H)	82.76 (82.93)	8.45 (8.57)
9[g]	2900 1100 700	1.73(d, 3H, J=6 Hz), 1.5—2.0(m, 2H), 2.70(t, 2H, J=7 Hz), 3.27(s, 3H), 3.3—3.6(m, 1H), 5.0—5.8(m, 2H), 7.29(s, 5H)	81.85 (82.06)	9.38 (9.54)
11[h]	2900 1115 745 695	1.17(t, 3H, J=7 Hz), 1.5—2.0(m, 2H), 2.68(t, 2H, J=7 Hz), 3.0—3.7(m, 3H), 4.9—5.3(m, 2H), 5.4—6.0(m, 1H), 7.17(s, 5H)	81.83 (82.06)	9.36 (9.54)
13[i]	2960 1115 750 695	1.26(d, 3H, J=6 Hz), 3.24(s, 3H), 3.6—4.0(m, 1H), 5.96(dd, 1H, J=16, 7 Hz), 6.51(d, 1H, J=16 Hz), 7.27(s, 5H)	81.32 (81.44)	8.81 (8.70)
15	2930 1090 700	1.1—1.9(m, 8H), 2.5—2.9(m, 2H), 2.9—3.5(m, 2H), 3.7—4.0(m, 1H), 7.12(s, 5H)	81.88 (82.06)	9.39 (9.54)
16	2930 1090 695	1.2—2.1(m, 6H), 3.2—3.7(m, 1H), 3.9—4.4(m, 2H), 7.22(s, 5H)	81.61 (81.44)	8.84 (8.70)
17	2930 1090	0.7—1.1(m, 3H), 1.2—2.0(m, 20H), 2.9—3.5(m, 2H), 3.7—4.0(m, 1H)	78.48 (78.72)	13.09 (13.21)
19	2950 1110 700	1.08(t, 3H, J=7 Hz), 1.20(d, 3H, J=7 Hz), 2.7—2.9(m, 2H), 3.2—3.9(m, 4H), 4.5—4.8(m, 1H), 7.19(s, 5H)	80.66 (80.85)	10.01 (10.18)
20	2920 1110 700	1.05(d, 3H, J=7 Hz), 1.10(t, 3H, J=7 Hz), 2.3—3.0(m, 2H), 3.1—3.7(m, 3H), 7.15(s, 5H)	80.12 (80.44)	9.95 (9.83)
21	2970 1110 700	1.13(t, 3H, J=7 Hz), 1.35(d, 3H, J=7 Hz), 3.28(q, 2H, J=7 Hz), 4.28(q, 1H, J=7 Hz), 7.23(s, 5H)	79.78 (79.95)	9.31 (9.39)
22	2930 1110	0.8—1.5(m, 23H), 3.1—3.6(m, 3H)	77.50 (77.35)	14.22 (14.07)
23	2930 1095	0.88(t, 3H, J=7 Hz), 1.1—1.9(m, 10H), 2.9—3.6(m, 2H), 3.7—4.0(m, 1H)	74.78 (79.94)	12.40 (12.58)
24	2930 1095	0.8—2.1(m, 17H), 2.7—3.4(m, 2H), 3.7—4.3(m, 1H)	78.32 (78.51)	11.89 (11.98)
25	2940 1090 770	1.2—2.1(m, 6H), 2.36(s, 6H) 3.2—3.6(m, 1H), 3.5—4.2(m, 1H), 4.4—4.7(m, 1H), 6.83(s, 3H)	81.85 (82.06)	9.30 (9.54)
27	2930 1090	c) 1.02(dd, 3H, J=6 Hz), 1.2—2.2(m, 5H), 1.67(s, 3H), 1.70(s, 3H), 3.3—4.5(m, 3H), 5.1—5.4(m, 1H)	77.98 (77.86)	11.84 (11.76)

Table 3. Continued

Products	IR (cm^{-1})a)	NMR(δ)b)	Found (%) (Calcd)	
			C	H
28	2930 1100	c) 0.8—2.0(m, 17H), 3.1—4.1(m, 3H)	76.70 (76.86)	12.78 (12.90)
29	2390	1.01(d, 3H, J=7 Hz), 1.13(t, 3H, J=7 Hz), 1.0—2.0(m, 11 Hz), 2.8—3.2(m, 1H), 3.43(q, 2H, J=7 Hz)	76.90 (76.86)	12.98 (12.90)
30	2930 1100 770	1.15(t, 3H, J=7 Hz), 1.43(d, 3H, J=7 Hz), 2.36(s, 6H), 3.22(q, 2H, J=7 Hz), 4.76(q, 1H, J=7 Hz), 6.83(s, 3H)	80.65 (80.85)	10.11 (10.18)
32	2950 1100 700	1.9—2.3(m, 2H), 2.5—2.8(m, 2H), 3.13(s, 3H), 3.94(t, 1H, J=7 Hz), 7.00(s, 5H), 7.11(s, 5H)	85.05 (84.91)	7.88 (8.02)
33	2940 1098 740 695	3.30(s, 3H), 5.05(s, 1H), 7.28(s, 10H)	84.60 (84.81)	7.07 (7.12)
34	2930 1100 755 700	0.7—1.8(m, 13H), 3.12(s, 3H), 3.93(t, 1H, J=7 Hz), 7.11(s, 5H)	81.35 (81.50)	10.67 (10.75)

a) Neat. b) In CCl_4. c) In $CDCl_3$. d) Bd 123—126 °C/0.5 mmHg. e) Bp 120—123 °C/20 mmHg. f) Bp 102—104 °C/3 mmHg. g) Bp 127—129 °C/16 mmHg. h) Bp 120—123 °C/16 mmHg. i) Bp 110—113 °C/18 mmHg.

magnesium Bromide (2) in the Presence of $TiCl_4$. To a mixture of cinnamaldehyde dimethyl acetal (0.89 g, 5 mmol) and $TiCl_4$ (0.95 g, 5 mmol) in 20 ml of dry THF was added a THF solution of 7.5 mmol of phenethylmagnesium bromide, prepared from phenethyl bromide (1.29 g, 7.5 mmol) and magnesium metal (0.19 g, 7.5 mmol), at −78 °C under an argon atmosphere. The reaction mixture was stirred for 6 h at −78 °C. The reaction was quenched by the addition of 20 ml of 10% aqueous potassium carbonate. The white precipitate which appeared was filtered off. The filtrate was extracted with diethyl ether. The ether extract was washed with saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent under reduced pressure, 3-methoxy-1,5-diphenyl-1-pentene (**3**) was isolated by column chromatography (silica gel), using benzene–dichloromethane (1:2) as an eluent, in 81% (1.02 g) yield.

Reaction of Crotonaldehyde Dimethyl Acetal (8) with Phenylmagnesium Bromide (12) in the presence of $TiCl_4$. To a mixture of crotonaldehyde dimethyl acetal (0.58 g, 5 mmol) and $TiCl_4$ (0.95 g, 5 mmol) in 20 ml of dry THF was added a THF solution of 7.5 mmol of phenylmagnesium bromide at −78 °C under an argon atmosphere. The reaction mixture was stirred for 6 h at −78 °C. The reaction mixture was worked up as mentioned in the previous case. After removal of the solvent and purification by column chromatography (silica gel), 1-methoxy-3-phenyl-1-butene (**13**) was isolated in 42% (0.34 g) yield.

Reaction of 2-(2,4-Dichlorophenoxy)tetrahydropyran (14) with Phenethylmagnesium Bromide (2). To a benzene solution[11] (4 ml) of phenethylmagnesium bromide (4 mmol) was added a benzene solution (2 ml) of 2-(2,4-dichlorophenoxy)tetrahydropyran (0.50 g, 2 mmol) under an argon atmosphere at room temperature. The reaction mixture was stirred for 30 min. After quenching with water, the product was extracted with ether. The ether extract was washed with 10% aqueous sodium hydroxide and dried over sodium sulfate. After removal of the solvent under reduced pressure, 2-phenethyltetrahydropyran (**15**) was isolated by column chromatography (silica gel) using hexane–dichlorometane (1:1) as an eluent in 88% (0.35 g) yield. The NMR and IR spectra of the product (**15**) are shown in Table 3.

Reaction of α-Methoxy-α-(2,4-dichlorophenoxy)toluene (31) with Phenethylmagnesium Bromide (2). To a benzene solution (5 ml) of phenethylmagnesium bromide (10 mmol) was added a benzene solution (5 ml) of α-methoxy-α-(2,4-dichlorophenoxy)toluene (1.42 g, 5 mmol) under an argon atmosphere at room temperature. The reaction mixture was stirred for 30 min and then worked up as mentioned in the previous case. After removal of the solvent, purification by column chromatography (silica gel) using hexane-dichloromethane (1:1) gave 1.06 g (94%) of 1,3-diphenyl-1-methoxypropane (**32**).

References

1) H. Ishikawa and T. Mukaiyama, *Chem. Lett.*, **1974**, 1077.

2) H. Ishikawa, S. Ikeda, and T. Mukaiyama, *Chem. Lett.*, **1975**, 1051.

3) R. A. Mallory, S. Rovinsky, and I. Scheer, *Proc. Chem. Soc.*, **1964**, 416.

4) A. Feugeas, *Bull. Soc. Chim. Fr.*, **1963**, 2568.

5) R. Zepter, *J. Prakt. Chem.*, **1964**, 74.

6) R. H. Bible, Jr., U. S. Patent 3081315 (1963); Chem. Abstr., **59**, 10180b (1963).

7) C. Blomberg, A. O. Vreugdenhil, and T. Homsma, *Recl. Trav. Chim., Pays-Bas*, **72**, 335 (1963).

8) H. Ishikawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **51**, 2059 (1978).

9) H. Ishikawa and T. Mukaiyama, *Chem. Lett.*, **1976**, 737.

10) F. Straus and H. Heinze, *Ann.*, **493**, 191 (1932).

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