CHEMISTRY LETTERS, pp. 689-692, 1978. Published by the Chemical Society of Japan

A REGIOSELECTIVE COUPLING REACTION OF ALLYL PYRIDYL ETHERS WITH GRIGNARD REAGENTS

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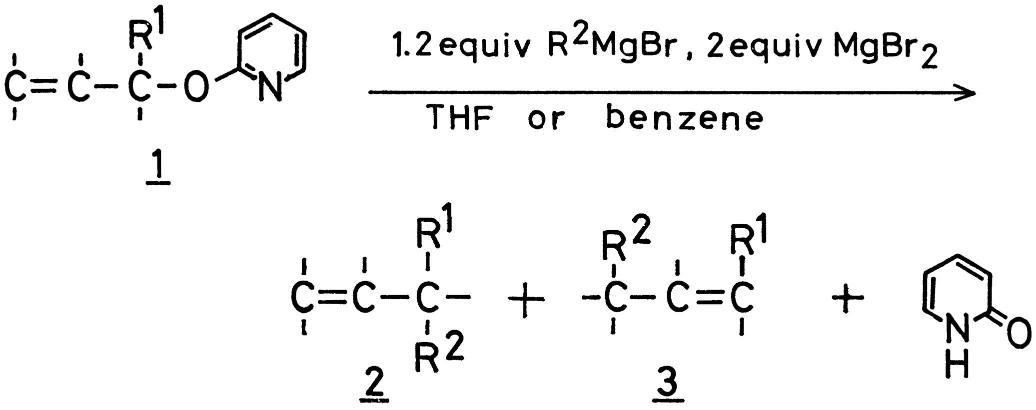
A regioselective coupling reaction of Grignard reagents with allyl pyridyl ethers in the presence of $MgBr_2$ is reported. Grignard reagents reacted easily with primary allyl ethers to afford C-1 alkylated products (S_N2 reaction), and also reacted with secondary and tertiary allyl ethers to afford C-3 alkylated products (S_N2' reaction).

The regio- and stereoselective coupling reaction of various derivatives of allyl alcohols with Grignard reagents is one of the most important and useful synthetic methods for the preparations of a variety of alkenes. Several methods have been proposed,1) but allyl transposition takes place in the reactions of allyl chloride,2) acetate1b) or mesitoate1c) with Grignard reagents. Higher regioselectivity was achieved by the reaction of allyl methyl or ethyl ethers with Grignard reagents in the presence of cuprous chloride or bromide.3) In this method, however, some limitations were noted especially in the variations of Grignard reagents.

In the present communication, we wish to report a highly regioselective coupling reaction of several Grignard reagents with allyl 2-pyridyl ethers by the promotion of $MgBr_2$.

A variety of allyl pyridyl ethers (1) were alkylated with 1.2 equiv Grignard reagent in the presence of 2 equiv $MgBr_2$ to afford the corresponding alkenes, (2). and/or (3), in good yields according to the following equation.

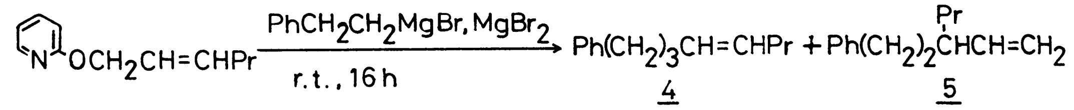


A typical procedure is described for the reaction of 1-(2-pyridyloxy)-2-hexene4) with 2-phenylethyl magnesium bromide: to anhydrous $MgBr_2$5) (2 mmol), prepared in situ under an argon atmosphere, was added a THF (4 ml) solution of 1-(2-pyridyloxy)-

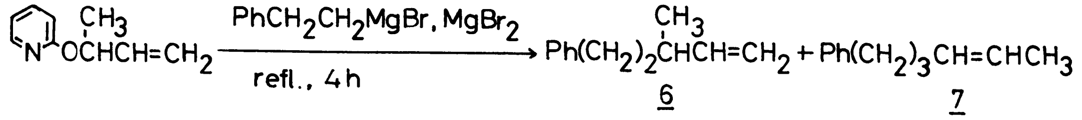
2-hexene (182 mg, 1.03 mmol), and was successively added dropwise a THF solution (2.7 ml, 1.2 mmol) of 2-phenylethyl magnesium bromide. The mixture was further stirred for 16 h at room temperature. It was quenched with several drops of 2N hydrochloric acid, and organic materials were extracted with ether. The ether extracts were dried over magnesium sulfate. 1-Phenyl-4-octene (181 mg, 96%) was isolated by thin layer chromatography on silica gel.

In the absence of $MgBr_2$, the reaction was very slow and it required several days for the completion of the reaction. Solvent played an important role in the regioselectivity of the present reaction and it was shown in the Table 1 that THF was the best solvent for the alkylation of primary ethers. On the other hands, for secondary ethers, the better results were obtained when the reaction was carried out in benzene.

Table 1 The Effect of the Solvents



solvent	4/5	total yield(%)
THF	4	94
C_6H_6	80/20	91
Et_2O	90/10	86



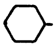
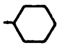
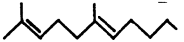
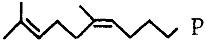
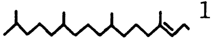
solvent	6/7	total yield(%)
THF	20/80	62
C_6H_6	7	84

As shown in the Table 2, most of the simple primary allyl pyridyl ethers were alkylated selectively at C-1 carbon (S_N2 reaction). For example, the alkylation reaction of crotyl pyridyl ether proceeded predominantly at C-1 carbon, contrary to the result that the alkylation at C-3 carbon predominated in the reaction of crotyl chloride with 2-phenylethyl magnesium bromide.[2)]

Allyl pyridyl ethers derived from geraniol, nerol and phytol were alkylated regioselectively, and with retention of the double bond configuration. On the other hands, secondary and tertiary allyl ethers reacted regioselectively at C-3 carbon (S_N2' reaction).

It is considered that the nitrogen atom of the pyridine ring in allyl pyridyl ether (1) coordinates with $MgBr_2$ to form an active intermediate complex (8). In case of primary allyl 2-pyridyl ethers, Grignard reagent, interacting with $MgBr_2$, comes close to C-1 carbon, and an S_N2 reaction takes place readily (path A). This consideration is supported by the fact that the regioselectivity is lower in the reaction of allyl 4-pyridyl ether with Grignard reagent.[17)] But, in case of secondary and

Table 2 Alkylation Reaction of Allyl Ethers with Grignard Reagents

	R^2	Conditions[a]	Products (ratio)	E/Z	Yield(%)
$CH_3CH=CHCH_2$-[h]	$PhCH_2CH_2$-	r,t., 18 h	$Ph(CH_2)_3CH=CHCH_3$(90)	7/3[f]	77
			$Ph(CH_2)_2CH(CH_3)CH=CH_2$[b] (10)	-	
Ph  6)	Ph-	r,t., 18 h	$PhCH=CHCH_2Ph$[b]	E[g]	83
		r,t., 21 h	$PhCH=CHCH_2$-  [b], [12]	-	65
$PrCH=CHCH_2$-[7]	$PhCH_2CH_2$-	r,t., 16 h	$PrCH=CH(CH_2)_3Ph$[b]	-	96
	Ph-	r,t., 8 h	$PrCH=CHCH_2Ph$[b], [13]	-	80
 8)	$PhCH_2CH_2$-[c]	refl., 3.5 h	 [b], [14]	E	95
 9)	$PhCH_2CH_2$-[c]	refl., 9 h	 [b], [15]	Z	58
 10)	$PhCH_2CH_2$-[d]	refl., 9 h	 [b], [16]	E[g]	94
$CH_2=CH-CH(CH_3)$-	$PhCH_2CH_2$-	refl., 4 h[e]	$Ph(CH_2)_3CH=CHCH_3$	4/6[f]	84
$CH_2=CH-C(CH_3)_2$-[11]	$PhCH_2CH_2$-	refl., 5 h	$Ph(CH_2)_3CH=C(CH_3)_2$[b]	-	87

a) Tetrahydrofuran was used as solvent.

b) These products were pure by glc(>97%) and $AgNO_3$-tlc.

c) Two equiv of RMgBr were required to obtain the products in good yield.

d) Three equiv of RMgBr were required to obtain the products in good yield.

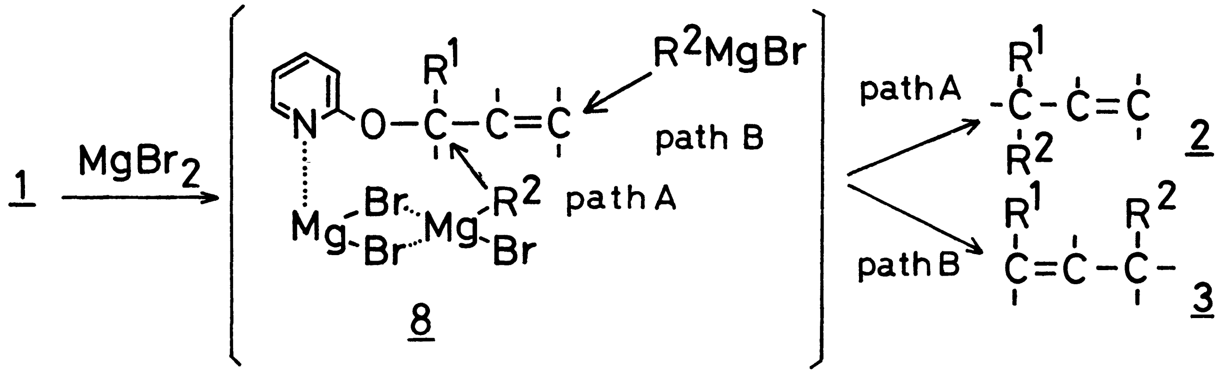
e) Benzene was used as solvent.

f) Each isomer was separated by $AgNO_3$-tlc.

g) Determined by spectral data.

h) E/Z=8/2[f].

tertiary allyl pyridyl ethers, an intermolecular reaction may predominate because of the steric hindrance, and the alkylation reaction proceeds selectively at C-3 carbon (path B).



It is noted that allyl 2-pyridyl ether in the presence of $MgBr_2$ is a good allyl substrate for the regioselective alkylation with Grignard reagents.

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4) Allyl 2-pyridyl ethers were prepared by the method of G. H. Schmid and A. W. Wolkoff Can. J. Chem., 50, 1181(1972). In the cases of primary and secondary alcohols, the yields were more than 70%, but, in the cases of tertiary alcohols they were less than 50%.

5) $MgBr_2$ was prepared by reacting excess 1,2-dibromoethane with magnesium (2 mmol) in ether. After solvent evaporated, it was dried in vacuo at 150°C for 1 h.

6) NMR (CCl_4) δ 4.90 (2H, d, J=4Hz, CH_2); bp 128-129°C/0.6 mmHg.

7) NMR (CCl_4) δ 0.89(3H, t, J=7Hz, CH_3), 4.6-4.8(2H, m, CH_2O), 5.6-5.8(2H, m, vinyl), 6.5-6.8(2H, m, 3,5-H of pyridine ring), 7.3-7.6(1H, m, 4-H of pyridine ring), 7.9-8.1(1H, m, 6-H of pyridine ring); bp 70-71°C/0.6 mmHg; Found: C,74.72;H,8.72; N 7.82%. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90%.

8) NMR(CCl_4) δ 1.57(3H, s, 3-CH_3), 1.64(3H, s, H-C=C-C$\underline{H}_3$), 1.73(3H, s, H-C=C-C$\underline{H}_3$), 4.71(2H,d,J=6Hz,CH_2O), 4.9-5.5(2H, m, vinyl); bp 150°C/1 mmHg.[18]

9) NMR(CCl_4) δ 1.57(3H, s, 3-CH_3), 1.62(3H, s, H-C=C-C$\underline{H}_3$), 1.72(3H, s, H-C=C-C$\underline{H}_3$), 4.76(2H, d, J=6Hz, CH_2O), 4.8-5.3(2H, m, vinyl); bp 150°C/1 mmHg.[18]

10) NMR(CCl_4) δ 1.70(3H, s, 3-CH_3), 4.67(2H, d, J=6Hz, CH_2O), 5.2-5.5(1H, m, vinyl):oil.

11) NMR(CCl_4) δ 1.62(6H, s, CH_3), 4.8-5.2(2H, m, =CH_2), 5.9-6.4(1H, m, -CH=); bp82-84°C/14 mmHg.

12) NMR(CCl_4) δ 5.7-6.4(2H, m, vinyl); bp 130°C/2 mmHg[18]; Found: C, 90.12;H, 9.99%. Calcd for $C_{15}H_{20}$: C, 89.94;H, 10.06%.

13) NMR(CCl_4) δ 0.85(3H, t, J=6Hz, CH_3), 2.52(2H, t, J=7Hz, Ph-C$\underline{H}_2$), 5.2-5.4(2H, m, vinyl); bp 100°C/1.5 mmHg[18];Found: C, 89.21; H, 10.62%. Calcd for $C_{14}H_{20}$: C, 89.29;H, 10.71%.

14) NMR(CCl_4) δ 1.54(6H, s, H-C=C-C$\underline{H}_3$), 1.63(3H, s, H-C=C-C$\underline{H}_3$), 2.53(2H, t, J=7Hz,Ph-C$\underline{H}_2$), 4.8-5.2(2H, m, vinyl); bp 130°C/0.1 mmHg[18], Found: C, 89.13;H, 10.90%. Calcd for $C_{18}H_{26}$: C,89.19;H, 10.81%.

15) NMR(CCl_4) δ 1.55(3H, s, H-C=C-C$\underline{H}_3$), 1.64(6H, s, H-C=C-C$\underline{H}_3$), 2.52(2H, t, J=7Hz, Ph-C$\underline{H}_2$), 4.8-5.2(2H, m, vinyl); bp 130°C/0.1 mmHg[18]; Found: C, 89.46; H, 10.55%. Calcd for $C_{18}H_{26}$: C, 89.19; H, 10.81%.

16) NMR(CCl_4) δ 1.54(3H, s, =C-CH_3), 2.54(2H, t, J=7Hz, Ph-C$\underline{H}_2$), 4.9-5.2(1H, m, vinyl); oil.

17) Unpublished result.

18) By short path distillation.

(Received April 17, 1978)