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ON THE REGIOSELECTIVITY OF THE REACTION OF N-METHOXYCARBONYLPYRIDINIUM CHLORIDE WITH GRIGNARD REAGENTS: HIGHLY REGIOSELECTIVE SYNTHESIS OF 2-SUBSTITUTED N-METHOXYCARBONYL-1,2-DIHYDROPYRIDINES.1)

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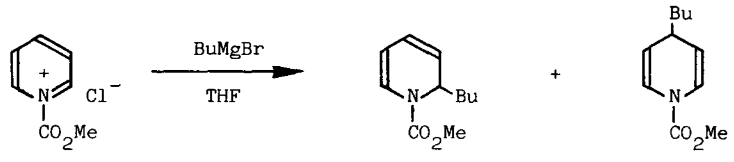
Abstract: Whereas alkyl Grignard reagents undergo 1,2- and 1,4-additions to N-methoxycarbonylpyridinium chloride in a variable ratio, alkenyl and alkynyl Grignard reagents do the exclusive 1,2-addition to afford 2-substituted N-methoxycarbonyl-1,2-dihydropyridines in fair to excellent yields.

Nucleophilic addition of organometallic reagents to pyridinium salts has been utilized to prepare 2- and 4-substituted pyridines via the corresponding 1,2- and 1,4-dihydropyridine derivatives.2) Regioselectivity of these reactions has shown to be dependent on the kind of organometallic reagents. Whereas 4-substituted 1,4-dihydropyridine derivatives are exclusively produced when organocopper reagents are used,3,4) Grignard5-9) and organocadomium reagents9) have been reported to predominantly attack the 2-position of the pyridinium salts. The regioselectivity claimed in the latter reactions, however, is apparently biased, because in most of the cases 4- and/or 3-substituted pyridines have been used as the starting materials.

In order to obtain 2-substituted N-acyl-1,2-dihydropyridine which may be a potential intermediate for alkaloid synthesis,2) we have examined reaction of N-methoxycarbonylpyridinium chloride with several organometallic reagents. We wish to report here that the regioselectivity is highly dependent on the nature of Grignard reagent: (1) With alkyl Grignard reagents a mixture of 2-substituted 1,2- and 4-substituted 1,4-dihydropyridines is obtained in a variable ratio.10) (2) With alkenyl and alkynyl Grignard reagents the reaction proceeds in a highly regioselective manner to afford exclusively 2-substituted 1,2-dihydropyridines.

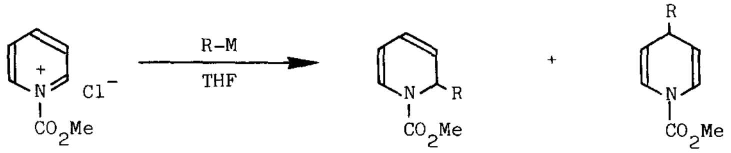
At first we have found that a reaction of N-methoxycarbonylpyridinium chloride (**1**) with



1 **2a** **3a**

butylmagnesium bromide in THF at 0°C gave 2-butyl-N-methoxycarbonyl-1,2-dihydropyridine (**2a**) 13) and 4-butyl-N-methoxycarbonyl-1,4-dihydropyridine (**3a**) 13) in a ratio of 78:22, along with a small amount of 5-butyl-5-nonanol. The reaction conducted at -78°C afforded again a mixture of **2a** and **3a** in a ratio of 67:33. Since these results are apparently contradictory to those of Fraenkel et al., 5) who described only the formation of 2-butyl-1,2-dihydropyridine derivative, we have examined in more detail the reaction with several alkyl Grignard reagents as well as other organometallic reagents. The results are summarized in Table 1.

Table 1. Reactions of N-Methoxycarbonylpyridinium Chloride with Alkyl Grignard as well as Other Organometallic Reagents.



1 **2** **3**

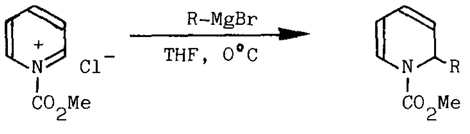
entry	R	M	Temp(°C)	Method a)	Yield(%) b)	Ratio(2/3) c)
1	Bu	MgBr	0	A	41	78/22 d)
2	Bu	MgBr	-78	A	99	67/33
3	Bu	MgBr	-78	B	79	60/40
4	Bu	MgCl	-78	A	86	67/33
5	Bu	ZnCl e)	0	A	99	19/81
6	Bu	Li	-78	B	f)	
7	Me	MgI	0	A	54	92/8
8	Et	MgBr	-78	A	51	57/43
9	i-Pr	MgBr	-78	A	99	37/63

a) Method A: Methyl chloroformate was added to a mixture of pyridine and organometallic reagent. 5) Method B: N-Methoxycarbonylpyridinium chloride was preformed before adding organometallic reagent. b) Combined, isolated yield. c) Determined by glc and/or ^{1}H NMR. d) A small amount of 5-butyl-5-nonanol was obtained. e) Prepared by adding $ZnCl_2$ to BuMgBr. f) Pentanoic anhydride was obtained in 99% yield.

Table 1 evidently demonstrated that the regioselectivity is dependent on the character of metals as well as alkyl moiety. Very recently, Akiba et al. have suggested 4) that the softer the anion, the more preferably the 4-position is attacked, as is exemplified by the reaction with organocopper reagents. 3,4,14) Our results may be explained by the same context. For example, methylmagnesium iodide, which is harder than butylmagnesium bromide, attacks more predominantly the 2-position (entry 7). Unfortunately, with much harder organolithium reagent (entry 6), pentanoic anhydride was produced exclusively, probably through the attack on the carbonyl moiety of the pyridinium salt.

Succeedingly, we have examined the reaction with alkenyl as well as alkynyl Grignard reagents, which are considered to be harder than the alkyl derivatives. The results are summarized in Table 2. As is shown in Table 2, the regioselectivity is far better than the expected and 2-substituted 1,2-dihydropyridines 16) are exclusively obtained in fair to excellent yields with a variety of alkenyl and alkynyl Grignard reagents. 17)

Table 2. Reactions of N-Methoxycarbonylpyridinium Chloride with Alkenyl and Alkynyl Grignard Reagents to give the 2-Substituted 1,2-Dihydropyridines. a)

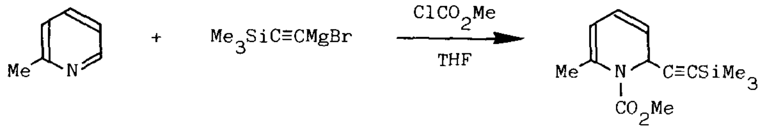

1 **2**

entry	R	Yield(%) b,c)
1	$CH_2=CH-$	81
2	(E)-HexCH=CH-	71 d)
3	BuC≡C-	85
4	PentC≡C-	88
5	HexC≡C-	85
6	PhC≡C-	85
7	$Me_3SiC≡C-$	99
8	$Me_3SiOCH_2C≡C-$	62

a) All reactions were carried out by Method A described in Table 1. b) Isolated Yield. c) The regioselectivity was shown to be $>$99% by glc analysis in all of the cases. d) The reaction was conducted at -40°C.

A typical procedure is as follows: To a solution of trimethylsilylethynylmagnesium bromide, prepared from ethynyltrimethylsilane (242 mg; 2.46 mmol) and ethylmagnesium bromide, in THF (5 ml) was added a solution of pyridine (117 mg; 1.48 mmol) in THF (3 ml) at 0°C under Ar. Then, a solution of methyl chloroformate (116 mg; 1.23 mmol) in THF (3 ml) was added to the above solution over 20 min and the mixture was stirred at 0°C for additional 15 min. Usual work-up and short-column chromatographic purification gave 2-trimethylsilylethynyl-N-methoxycarbonyl-1,2-dihydropyridine (287 mg, 99%): MS m/e(rel. int): 235(M$^+$, 67), 234(66), 73(100). IR (neat): 2160, 1735 cm^{-1}. ^{1}H NMR δ($CDCl_3$): 6.65(1H, br. d), 5.17-6.00(4H, m), 3.77(3H, s), 0.15(9H, s). ^{13}C NMR δ($CDCl_3$): 153.9(s), 125.2(d), 122.3(d), 118.9(d), 105.5(d), 102.9(s), 87.8(s), 53.4(q), 44.5(d), 0.0(q). Anal. Found:C, 61.19; H, 7.26%. Calcd for $C_{12}H_{17}NO_2Si$: C, 61.24; H, 7.28%.

Furthermore, this method can be applicable also to the regioselective synthesis of 2,6-disubstituted-1,2-dihydropyridine derivative. For example, 2-methylpyridine was treated with methyl chloroformate in the presence of trimethylsilylethynylmagnesium bromide to give exclusively 2-trimethylsilylethynyl-6-methyl-N-methoxycarbonyl-1,2-dihydropyridine (**4**) in 79% yield, which may be a useful synthetic intermediate for 2,6-disubstituted piperidine alkaloids. Further work along this line is in progress.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10) During the preparation of this manuscript, Comins and Abdullah reported the reaction of N-acylpyridinium salts with alkyl Grignard reagents.[11] According to them, a mixture of 2- and 4-substituted regioisomers was obtained when alkyl Grignard reagent alone was used, while nearly exclusive formation of the 4-substituted product was observed in the presence of catalytic amount of cuprous iodide. Although the former results are in accordance with ours, we believe that actual reactive species are organocopper reagents in the case of the latter.[12]

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13) Spectral data of **2a** and **3a** are as follows: **2a**, ^{1}H NMR δ(CDCl$_3$): 6.50-6.83(1H, m), 4.50-6.00 (4H, m), 3.75(3H, s), 1.12-1.60(6H, m), 0.88(3H, m). ^{13}C NMR δ(CDCl$_3$): 154.3(s), 125.3(d), 122.9(d), 121.4(d), 105.9(d), 52.9(q), 52.4(d), 33.8(t), 26.6(t), 22.8(t), 14.0(q). **3a**, ^{1}H NMR δ(CDCl$_3$): 6.69 (2H, br. d), 4.47(2H, br. d), 3.74 (3H, s), 2.73-3.06(1H, m), 1.12-1.60(6H, m), 0.88(3H,m). ^{13}C NMR δ(CDCl$_3$): 151.9(s), 122.8(d), 110.3(d), 53.1(q), 38.3(t), 32.7(d), 28.1(t), 22.9(t), 14.1(q). Authentic **3a** was prepared by the reported method[4] and identical with our sample in all respects.

14) It should be also mentioned that the bulky substituent (e.g., triphenylmethyl or t-butyldimethylsilyl) at N-position induces the preferencial 1,4-addition.[6,11,15]

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16) All new compounds gave satisfactory spectral data and elemental analyses.

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