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A ONE POT SYNTHESIS OF UNSYMMETRICAL SECONDARY ALCOHOLS FROM TWO GRIGNARD REAGENTS

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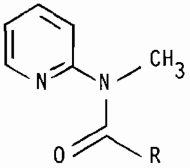
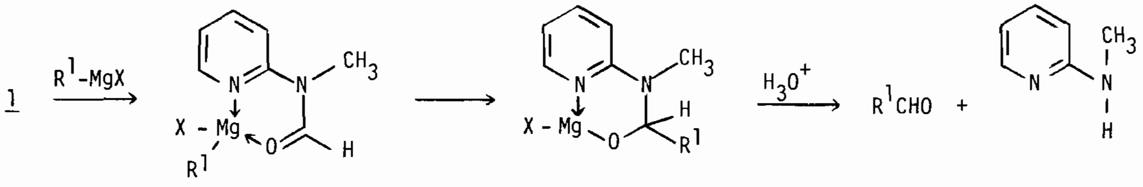
Summary: The sequential addition of two Grignard reagents to 2-(N-methyl-N-formyl)-aminopyridine in tetrahydrofuran provides a high yield one pot synthesis of unsymmetrical secondary alcohols.

The classical preparation of unsymmetrical secondary alcohols from two Grignard reagents requires two synthetic steps. A Grignard reagent is subjected to a formylation reaction. The crude aldehyde is isolated, purified, and treated with the second Grignard reagent in a subsequent reaction to provide the desired secondary alcohol. In many instances the overall yield of the two step process is low due to the instability of the intermediate aldehyde or because of losses during isolation and purification. It would be beneficial and convenient if an aldehyde, or aldehyde equivalent, could be formed in situ from the first Grignard reagent, and then treated with the second Grignard reagent to provide the desired alcohol in one synthetic operation. We report here the development of such a process utilizing 2-(N-methyl-N-formyl)-aminopyridine[1] (MFAP) (1) as the formylating agent.

The synthetic utility of N-methyl-N-(2-pyridyl)-carboxamides (1-3) for the preparation of aldehydes, ketones, alcohols, amides, and esters has been recently described.[1,2] 2-(N-Methyl-N-formyl)-aminopyridine (MFAP)(1) was shown to efficiently formylate a wide variety of Grignard reagents in a facile one-step reaction.[1] The success of this reaction was assumed to be due to the presence of the pyridyl nitrogen atom which provides a strong bidentate (4) for magnesium and facilitates carbanion transfer to the formamide carbonyl. This results in the formation of a six-membered chelate 5 which is resistant to further reaction with Grignard reagent under the reaction conditions (0°THF).

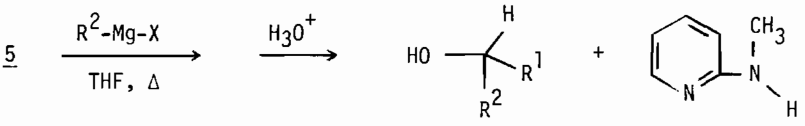


1, R=H
2, R=C_6H_5
3, R=C_2H_5



4 5

We now report that chelate 5 will react with Grignard reagents at 65° (THF, reflux). This allows for a one pot synthesis of unsymmetrical *sec*-alcohols 6 via the sequential addition of two Grignard reagents to 2-(N-methyl-N-formyl)-aminopyridine (MFAP)(1).



6

The reaction is easily carried out by adding the first Grignard reagent (1.0 equiv./THF) to a solution of MFAP (1) in tetrahydrofuran at 0°. After a few minutes the second Grignard reagent (1.3 equiv.) is added and the reaction mixture is heated at reflux for 3 hours and then quenched (aqueous 10% HCl). After isolation and purification, good to high yields of *sec*-alcohols (6) are obtained as indicated in the table.

Of particular interest are those examples where the *sec*-alcohols were prepared from benzylmagnesium chloride. Studies of the reaction between benzylmagnesium chloride and a variety of aldehydes have shown that the "expected" addition product (benzylalkylcarbinol) is formed in low yield along with substantial amounts of *ortho*-substituted products.[3,4] In contrast, our method provides good to high yields of benzylalkylcarbinols and may be the method of choice for the preparation of *sec*-alcohols from benzyl Grignard reagents. In addition, the lack of formation of *ortho*-substituted products[5] (entries 6j, k) provides evidence that aldehydes are not intermediates in this reaction and that substitution is occuring directly on chelate 5.[6]

A limitation of this method occurs when the second Grignard reagent is bulky and contains β-hydrogens. In these cases (entries 6c, f, i) the yield of the desired product is low due to side reactions such as reduction.[6] This limitation is only a problem if both Grignard reagents are bulky and contain β-hydrogens. In cases where only one of the two Grignard reagents has reducing capability, high yields of alcohols can be obtained simply by choosing the proper order of addition of the Grignard reagents. The Grignard reagent containing β-hydrogens should be added first followed by the second "non-reducing" Grignard reagent.

This method is amenable to large scale reactions as demonstrated in the preparation of 1-phenyl-4-penten-2-ol (entry 6m) on a 0.2 mol scale in 88% yield. The by-product, 2-(methylamino)pyridine, was isolated (86%) from the aqueous layer (by neutralization with sodium hydroxide and extraction with methylene chloride) and economically recycled to MFAP (1) via formylation with formic acid-acetic anhydride mixture (F.A.M.)[7] in 90% yield.

Application of this methodology to asymmetric syntheses of secondary alcohols via chiral α-amino alcoholates is presently in progress.

ACKNOWLEDGEMENT Financial support of this work was provided by the Research Corporation.

Table. Conversion of Grignard Reagents to Alcohols (6)

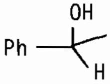
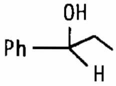
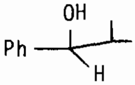
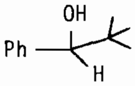
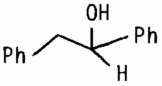
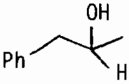
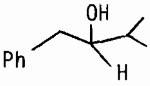
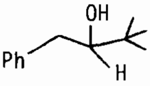
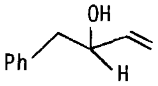
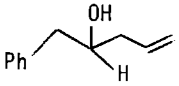
Entry	First Grignard Reagent	Second Grignard Reagent	Product[d]	% Yield[a,b]
6a	PhMgBr	MeMgCl		82
6b	PhMgBr	EtMgCl		84
6c	PhMgBr	i-PrMgCl		58
6d	i-PrMgCl	PhMgBr	c	87
6e	t-BuMgCl	PhMgBr		85
6f	PhMgBr	t-BuMgCl	c	27
6g	$PhCH_2MgCl$	PhMgBr		96
6h	$PhCH_2MgCl$	MeMgCl		73
6i	$PhCH_2MgCl$	i-PrMgCl		41
6j	i-PrMgCl	$PhCH_2MgCl$	c	73
6k	t-BuMgCl	$PhCH_2MgCl$		87

Table. (continued)

Entry	First Grignard Reagent	Second Grignard Reagent	Product[d]	% Yield[a,b]
6ℓ	$PhCH_2MgCl$	$H_2C{=}CHMgBr$		67
6m	$PhCH_2MgCl$	$H_2C{=}CHCH_2MgCl$		88[e]

[a] Unless indicated, reactions were performed on a 3 mmol scale.

[b] All yields are for isolated, pure, material obtained from preparative layer chromatography (silica gel, 20% acetone-hexane) or by distillation (entry 6m).

[c] This product was identical to the one above.

[d] All known products had identical spectral and physical properties with authentic samples. Products from entries 6k and 6m were new compounds and their structures are consistent with all spectral and elemental analyses.

[e] This reaction was performed on a 0.2 mol scale and the product was purified by distillation (bp 63-65° at 0.2 torr).

REFERENCES AND NOTES

1. D. L. Comins and A. I. Meyers, Synthesis, 403 (1978).
2. A. I. Meyers and D. L. Comins, Tetrahedron Lett., 5179 (1978).
3. S. Siegel, S. K. Coburn and D. R. Levering, J. Am. Chem. Soc., 73, 3163 (1951); S. Siegel, W. M. Boyer, R. R. Jay, J. Am. Chem. Soc., 73, 3237 (1951).
4. R. A. Benkeser and T. E. Johnston, J. Am. Chem. Soc., 88, 2220 (1966).
5. No ortho-substituted products were isolated or detected; however, minor impurities in the crude product were not identified and the presence of trace amounts of ortho-substituted products cannot be ruled out at this time.
6. The mechanism of this reaction is presently under study.
7. W. Stevens and A. Van Es, Rec. Trav. Chim., 83, 863 (1964); W. Stevens and A. Van Es, Rec. Trav. Chim., 84, 1247 (1965).

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