Tetrahedron Letters, Vol.31, No.33, pp 4723-4726, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ELECTROPHILIC FORMAMIDINES. ORGANOMETALLIC ADDITION TO 2-METHOXY PYRROLIDINE OR PIPERIDINE N-t-BUTYL FORMAMIDINES. FORMATION OF 2-SUBSTITUTED PYRROLIDINES AND PIPERIDINES.

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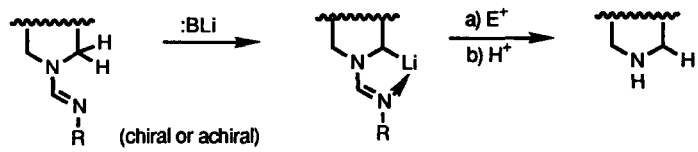
Summary: The title compounds were prepared by addition of Grignard reagents to methoxyformamidines **6** and **8** in ether at room temperature. Hydrolysis gives the free secondary amines, or in cases of volatile products, their thiourea derivatives.

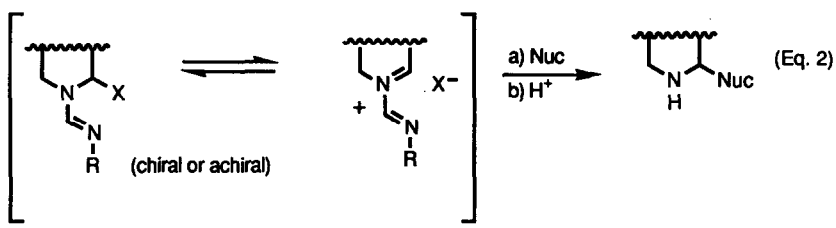
Previous studies from these laboratories have resulted in the use of chiral and achiral formamidines as precursors to α-amino carbanions which were smoothly alkylated to give elaborated amines[1] (eq. 1). In this fashion both racemic and enantiomerically pure amines of a diverse nature have been prepared.[2] In related systems Gawley[3] has also shown that affixing



(Eq. 1)

an oxazoline moiety to secondary amines also leads to efficient C-alkylation both in racemic and enantiomeric form. Recently Beak[4] has shown that carbamates may also serve as useful stabilizing groups for α-anion formation.

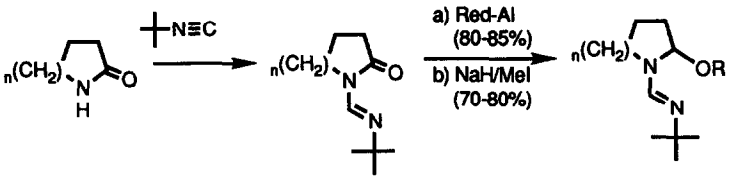
In our search for wider and more general utility of the formamidine methodology we questioned the possibility of using *nucleophilic* addition to form C-C bonds adjacent to the formamidine (eq. 2). If this process could be implemented, it would open the possibility of using a



(Eq. 2)

broader range of alkylating agents as well as possessing the potential for asymmetric alkylation to 2-substituted amines. There is now a considerable body of knowledge on nucleophilic addition to acyl iminium ions[5] and the current proposal would add N-formamidinyl iminium ions to the list.

We report herein some preliminary results on the achiral systems **6** and **8** which support the original contention that nucleophilic addition to alkoxy formamidines is indeed feasible. Both pyrrolidine and piperidine formamidines (**6** and **8** respectively) were prepared from the pyrrolidone



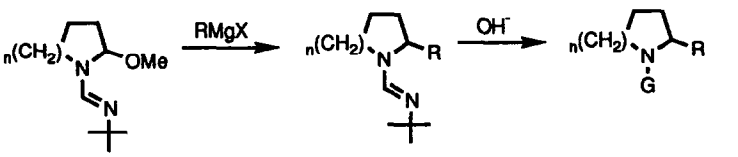
1, n = 1
2, n = 2

3, n = 1 (85%)
4, n = 2 (95%)

5, n = 1, R = H
6, n = 1, R = Me
7, n = 2, R = H
8, n = 2, R = Me

1 or piperidone **2** *via* copper-catalyzed addition of t-butyl isocyanide (Cu_2O, toluene, reflux, 24 h). Reduction of the lactam carbonyl (Red-Al, THF, 0 - 25°C) gave the carbinol amines **5** and **7** in 80-85% yield. All attempts to exchange the latter to methoxylamines **6** and **8** resulted only in elimination to the α,β-unsaturated amine. Direct anodic oxidation of the piperidine formamidine, as used extensively by Shono,[6] gave moderate yields of **8** along with formamidine hydrolysis products. It was ultimately found that treatment of the carbinol amines **5** and **7** with sodium hydride-methyl iodide (0°C, THF) gave the desired methoxy derivatives **6** and **8** in 48 and 64% overall yields from **1** and **2** respectively.

Nucleophilic additions to **6** and **8** were carried out under various conditions using Grignard, lithium, zinc, and cuprate reagents. Furthermore, Lewis acids (i.e. $BF_3 \cdot Et_2O$) were also employed in conjunction with the various organometallic reagents. Although all reagents employed led to



6 or **8**

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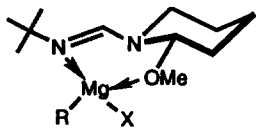
10, G = H
11, G = C(=S)NHPh

alkylated products **9**, many reactions were accompanied by various amounts of α,β-unsaturated amines, *via* elimination of methanol from **6** or **8**, along with significant amounts of starting materials. It was found, however, that the optimum conditions for these additions lie in the use of 2.0 equiv of Grignard reagents in diethyl ether at room temperature for 12 h. It is presumed that the first equiv of Grignard forms a complex **12** which weakens the C-O bond and allows nucleophilic substitution to occur. Interestingly, the carbamate **13** requires a Lewis acid[6] for Grignard addition, whereas the better leaving group in **14** is displaced by an organozinc reagent.[7]



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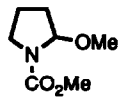

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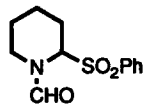

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A series of Grignard reagents were added to the formamidines **6** and **8** and the results are given in Table 1. After addition, the formamidine moiety was removed by hydrolysis in aqueous methanolic KOH.[8] In those cases where the amine was of relatively high molecular weight, it was isolated and purified. As seen from the table, the overall yields from **6** or **8** were quite satisfactory. In cases where volatility of the amine was a problem, they were transformed, using phenylisothiocyanate, into their thiourea derivatives. These, too, gave overall yields of 41-64%.

Table 1. Addition of Grignard Reagents to Formamidines **6** and **8**.

Formamidine	RMgX[a]	Amine **10** (%)[b,c]	Thiourea **11** (%)[b,d]
6 (n = 1)	$PhCH_2MgCl$	76	
6 (n = 1)	PhMgCl	75	
8 (n = 2)	$PhCH_2MgCl$	72	
8 (n = 2)	PhMgCl	75	64
8 (n = 2)	$PhC{\equiv}CMgCl$	45	
8 (n = 2)	$CH_2{=}CHMgBr$		63
8 (n = 2)	i-BuMgCl		52
8 (n = 2)	$CH_2{=}CH\text{-}CH_2MgBr$		48
8 (n = 2)	i-PrMgCl		47
8 (n = 2)	n-PrMgCl		41
8 (n = 2)	t-BuMgCl	0[e]	-0-

a) 4.0 equiv of RMgX in ether was added to **6** or **8**. b) Overall yields of isolated, purified material. c) See reference 2b and procedure in reference 8. d) The crude amines were treated with phenylisothiocyanate, heated and recrystallized or purified by flash chromatography. See reference 8. e) Elimination to α,β-unsaturated amine and replacement of methoxy by hydrogen (reduction) were the only products.

In summary, we have demonstrated that formamidines are useful auxiliaries for mediating nucleophilic additions adjacent to nitrogen, and our efforts are now being focused on the use of chiral formamidines to effect asymmetric additions.

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8. In the case of volatile amines, those isolated only as thioureas, the hydrolysis was performed as follows: The ethereal extract after Grignard addition was partially concentrated at atmospheric pressure (35-40°C) and the residual ethereal solution was treated with MeOH-H_2O (5:1), containing ~ 1 gr KOH and trace of 18-Crown-6. The mixture was heated to reflux overnight and the amine extracted with CH_2Cl_2, which after drying and filtering was treated with PhNCS (1 eq), and heated at reflux for 1-2 h. The solvent was evaporated and the residue purified by chromatography and/or recrystallization.

Acknowledgement

Financial support from the National Science Foundation is gratefully acknowledged.

(Received in USA 17 May 1990)