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# THE ROLE OF CHELATION IN THE FORMYLATION OF GRIGNARD REAGENTS WITH N-FORMYL AMINES.

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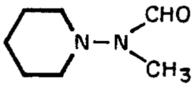
**Abstract:** The formylation of Grignard reagents with N-alkyl-N-formyl amines is best carried out with reagents such as N-(N-formyl-N-methyl)aminopiperidine which contain an additional ligand.

The preparation of aldehydes from Grignard reagents using 2-(N-formyl-N-methyl) aminopyridine has been described recently by Comins and Meyers[1] who attributed the success of their reaction in part to the presence of an additional ligand (pyridyl nitrogen) which could stabilize the incipient aldehyde through the formation of a six-membered ring chelate and prevent its further reaction with the Grignard reagent. Our interest in the development of a versatile, fully recyclable polymeric formylation reagent prompted us to consider a number of N-alkyl-N-formyl amines (I-X) for possible grafting to a polymer backbone. While this work was in progress, a report from Olah and Arvanaghi[2] appeared which suggested that no additional ligands were in fact necessary for this reaction to be successful as N-formyl piperidine (VI) also gave excellent results in the formylation of Grignard and organolithium reagents.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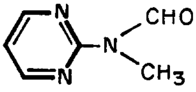
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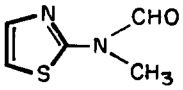
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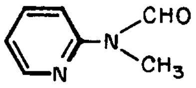
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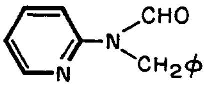
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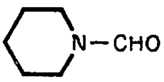
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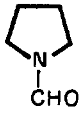
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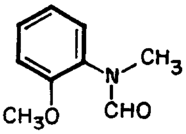
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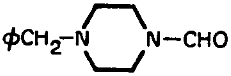
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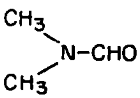

X

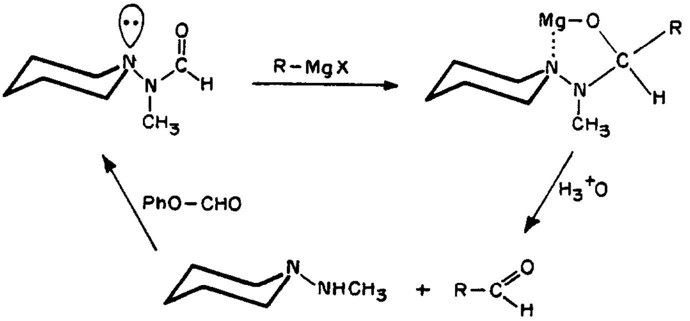
Our results with reagents I-X are shown in Table 1. Since the formylation gives consistent results with a variety of Grignard reagents (Table 2), most of the results of this comparative study were obtained in reactions with phenyl magnesium bromide under strictly similar reaction conditions[3]. All yields reported in Table 1 were calculated on isolated benzaldehyde and efforts were made to isolate any benzhydrol which might have been produced by reaction of benzaldehyde with a second mole of the Grignard reagent.

**TABLE 1.** Reaction of PhMgBr with N-formate reagents I-X

| Reagent | % Ph–CHO* | % Ph–CHOH–Ph* | Reagent | % Ph–CHO* | % Ph–CHOH–Ph* |
|---|---|---|---|---|---|
| I | 85 | 0 | VI | 61 (64) | 14 (15) |
| II | 84 | 0 | VII | (63) | (9) |
| III | 66 (78) | 11 (19) | VIII | 60 | 11 |
| IV | 79 | 0 | IX | 65 | 9 |
| V | 77 | 0 | X | 69 (66) | 9 (9) |

* Yields for reactions carried out under the conditions of Ref. 1, or of Ref. 2 for values in parentheses.

As can be seen in Table 1, best results were obtained with N-(N-formyl-N-methyl)aminopiperidine (I)[4] which affords an excellent yield of benzaldehyde without any trace of benzhydrol. As shown in the scheme below, this reagent can form a five-membered chelate which is resistant to further reaction with the Grignard reagent.



Excellent results were also obtained with 2-(N-formyl-N-methyl)aminopyrimidine (II), while both N-formylpiperidine (VI) and N-formylpyrrolidine (VII) gave less satisfactory results with the formation of a significant amount of benzhydrol, indicating that some attack of the liberated benzaldehyde had occurred. It should be noted however, that while we had no difficulties in obtaining yields which were comparable to those reported by Comins and Meyers[1], our results in the use of (VI) were vastly inferior to those of Olah et al.[2]. With 2-(N-formyl-N-methylamino)thiazole (III) and 2-methoxy-N-formyl-N-methyl-aniline (VIII), little chelating effect was expected due to the weak nature of the additional ligands present in the reagents, and, in fact, both gave significant amounts of benzhydrol in their reaction with phenylmagnesium bromide. With N-formyl-N′-benzyl piperazine (IX) the extra ligand is located too far from the reaction center to have a strong chelating influence and benzhydrol formation is also observed.

**Table 2.** Isolated yields of aldehydes (alcohols) in the reaction[5] of selected N-formates with RMgX or RLi at 0 or -10°C.

| **FORMATE** | **I** | | **II** | **VI** | | **X** |
|---|---|---|---|---|---|---|
| | 0°C | -10°C | 0°C | 0°C | -10°C | 0°C |
| Ph-$CH_2CH_2$MgBr | 86 (0) | | 81 (0) | 71 (9) | | 67 (14) |
| Ph-C≡C-MgBr | 73 (1) | 80 (0) | | 60 (12) | 68 (10) | 64 (10) |
| Ph-C≡C-Li | 92 (0) | | | | 71 (6) | |
| Ph-Li | 79 (5) | 81 (0) | 81 (0) | | 68 (18) | 69 (9) |
| Ph-MgBr | 85 (0) | | 84 (0) | 61 (14) | | 69 (9) |

Similar results were obtained in reactions with other Grignard and organolithium reagents as shown in Table 2. The influence of the reaction temperature is clearly apparent as a very small amount of secondary alcohol is obtained even with (I) in the reaction with the Grignard of phenylacetylene or with phenyl lithium at 0°C, while no formation of secondary alcohol is observed at -10°C. This is in agreement with the observation of Comins and Dernell[6] who were able to prepare unsymmetrical secondary alcohols in excellent yields by successive reaction of (VIII) with two different Grignard reagents at 0° and 65° respectively.

The formylation of a ring-lithiated 1% crosslinked polystyrene resin[7] is a reaction we have used extensively to prepare reactive resins containing vinylbenzaldehyde units. The reagent of choice for this reaction is usually DMF which is used in large excess to quench the lithiated resin[4]. Further study of this reaction reveals that while excellent results can be obtained when a large excess of DMF is used, the reaction is unsatisfactory when DMF is used in equimolar amount as interaction between the reactive sites of the polymer[8] results in the formation of a significant amount of the polymer-bound secondary alcohol. In contrast, very little alcohol formation is observed with (I) used in equimolar amount.

This study indicates clearly that although the presence of an additional ligand group in N-formyl amines is not necessary for satisfactory yields to be obtained, it does offer a significant advantage as the final product which is obtained with reagents such as (I), (II) or (IV) is free of secondary alcohol by-product. It is likely that the formation of a five or six-membered ring chelated intermediate occurs as claimed by Comins and Meyers[1] or by Nahm and Weinreb for their N-methoxy-N-methylamide acylating agents[9]. While (I) is probably the reagent of choice for the clean formylation of Grignards, it should be noted that very adequate results[10] can be obtained with the more readily available dimethylformamide (X).

**Acknowledgement:** Financial assistance by the Natural Sciences and Engineering Council of Canada is gratefully acknowledged.

## References and Notes

1) D. Comins and A.I. Meyers, Synthesis, 403 (1978).

2) G.A. Olah and M. Arvanaghi, Angew. Chem. Int. Ed., 20, 878 (1981).

3) All the reactions given in Table 1 were carried out in THF at 0° using a 10% excess of the Grignard reagent with work-up as in ref. 1. Some experiments were carried out using the conditions of ref. 2 with a 1:1 ratio of reagents at 0-25°; the yields for these experiments are shown in parentheses in Table 1. The secondary amines recovered after reaction could be recycled after regeneration with phenyl formate.

4) Compound (I) was prepared by reaction of N-aminopiperidine with a 10% excess of phenyl formate, followed by distillation and methylation as described for (IV) in ref. 1. All the other reagents were prepared by similar procedures except (VI) and (X) which were commercially available, and (IX) which was prepared from piperazine and phenyl formate in 2:1 ratio.

5) These reactions were carried out in dry THF at the temperature shown in Table 2, with processing of the reaction mixture using the conditions of ref. 1. Phenylacetylene magnesium bromide was prepared from phenyl acetylene and methyl magnesium bromide immediately before use.

6) D.L. Comins and W. Dernell, Tetrahedron Lett., 22, 1085 (1981)

7) M.J. Farrall and J.M.J. Fréchet, J. Org. Chem., 41, 3877 (1976).

8) J.M.J. Fréchet, Tetrahedron, 37, 663 (1981)

9) S. Nahm and S.M. Weinreb, Tetrahedron Lett., 22, 3815 (1981).

10) E.A. Evans, J. Chem. Soc., 4691 (1956); E.R.H. Jones, L. Skattelbol and M.C. Whiting, J. Chem. Soc., 1054 (1958).

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