



Directed Metalation of Aromatic Aldimines Using Li/Mg-TMP Amides

Cavalcante Silva, S.; Batista, J. H.; Moraes F.; Pereira, N. de A.; Clososki, G.C.

^aResearch Center for Natural and Synthetic Products, Faculty of Pharmaceutical Sciences of Ribeirão Preto

– University of São Paulo

*simonecavalcante@pg.ffclrp.usp.br

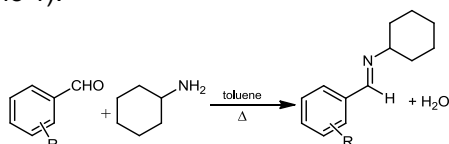
Keywords: Aldimines, Magnesium, Metalation

INTRODUCTION

It has been reported in literature that metal based TMP bases are important reagents for the deprotonation of unsaturated substrates.¹ In this work we describe our results on the directed metalation of N-cyclohexyl aromatic aldimines with Li/Mg TMP bases. Aldimines have attracted great attention by displaying a wide variety of biological activities.² In addition, aldimines can be metalated and trapped with electrophiles and the resulting products can subsequently be converted to the corresponding benzaldehyde derivatives.³

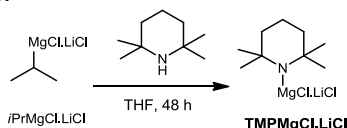
RESULTS AND DISCUSSION

The aldimines were prepared by condensation of aldehydes with cyclohexylamine, providing the products with yields ranging from 90 to 95% (Scheme 1).



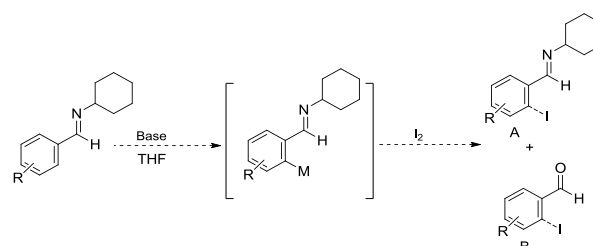
Scheme 1. Preparation of aldimines

Following these studies, we have investigated the metalation of aldimines with TMPLi and TMPMgCl.LiCl bases. The mixed Li/Mg base was obtained through the direct reaction of 2,2,6,6-tetramethylpiperidine (TMPH) with *i*-PrMgCl.LiCl (Scheme 2).



Scheme 2. Preparation of TMPMgCl.LiCl

A number of aromatic aldimines were metalated with the Li/Mg TMP bases (Table 1). Reactions were carried out using 1 mmol of substrates under different reactions conditions and with iodine as electrophile (Scheme 3). As observed in Table 1, according to the nature of the substrate the expected iodo-aldimines (A) were obtained together with the corresponding iodo-aldehydes (B) due to the hydrolysis under the work-up.



Scheme 3. Directed metalation of aldimines

Table 1. Products obtained by metalation of aromatic aldimines with subsequent trapping with iodine.

Entry	R	Base	T[°C], t[h]	Final product (%A:%B)*
1	3-OCH ₃	TMPLi	-20, 1	59%A
2	3-OCH ₃	TMPMgCl.LiCl	t.a., 3	30%A
3	2-Br	TMPLi	0, 2	58%A 11%B
4	2-Br	TMPMgCl.LiCl	t.a., 1,5	20%A 27%B
5	2-Br	TMPMgCl.LiCl	t.a., 2	33%A 10%B
6	3-Br	TMPMgCl.LiCl	t.a., 2	27%A
7	3-Br	TMPMgCl.LiCl	t.a. 3	8%A
8	4-Br	TMPLi	0,2	20%A
9	4-Br	TMPMgCl.LiCl	t.a.,1	29%A 19%B
10	4-Br	TMPMgCl.LiCl	t.a., 2	55%A 33%B
11	4-Br	TMPMgCl.LiCl	t.a. 3	28,4A 41,4B
12	4-Br	TMPMgCl.LiCl	50, 2	45%A 8%B
13	2-F	TMPMgCl.LiCl	t.a. 2	57%B
14	2-F	TMPMgCl.LiCl	t.a., 3	35%B
15	4-F	TMPMgCl.LiCl	t.a. 2	40%B
16	4-F	TMPMgCl.LiCl	50, 2	25%B

*Conversion.

CONCLUSION

Li/Mg-TMP amides appear to be interesting reagents for the metalation of aromatic aldimines. In addition, it may be an interesting method for the preparation of functionalized aldehydes. Our ongoing work aims to improve reaction yields and apply the methodology to the synthesis of bioactive molecules.

ACKNOWLEDGEMENTS

CAPES, CNPQ and FAPESP

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