SYNLETT Spotlight 292

The $\text{MgCl}_2\text{-Et}_3\text{N}$ Base System: A Useful Reagent in Organic Synthesis

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

The combination of MgCl_2 and Et_3N is a considerably stronger base than Et_3N alone. This base system has been used for a variety of base-induced reactions such as: α -carboxylation of ketones,¹ condensation,² acylation of

malonate derivatives,^{3,4} phosphonoacetates,^{5,6} *anti*-aldol⁷ and imine aldol⁸ reactions, *ortho*-formylation of phenols,⁹ and Mannich reactions.¹⁰ Moreover, this base system was used in Dieckman-type cyclizations¹¹ and also for the preparation of β -ketoamides by the condensation of ketenes and isocyanates.¹²

Abstracts

(A) α -Carboxylation of ketones with carbon dioxide in the presence of $\text{MgCl}_2\text{-Et}_3\text{N}$ followed by reaction with methyl vinyl ketone (MVK) yielded the Michael adducts in 42–75% yields or the Robinson adducts in 56–70% yields. This method reduced the polymerization of MVK usually observed under strong basic conditions.¹

(B) α,β -Unsaturated cyano esters were prepared by the condensation of aryl aldehydes with ethyl cyanoacetate in the presence of $\text{MgCl}_2\text{-Et}_3\text{N}$ as catalyst.²

(C) Acylation of diethyl malonate with an acid chloride using $\text{MgCl}_2\text{-Et}_3\text{N}$ as base gave adducts in excellent yields. This method was also used for the preparation of β -oxo esters from ethyl malonate mono potassium salt and acid chlorides in 92–99% yields.³

(D) Acylation of (acylamino)malonate with $\text{MgCl}_2\text{-Et}_3\text{N}$ as base afforded α -acyl β -keto esters in good to excellent yields with a variety of acid chlorides.⁴

(E) Acylation of triethyl α -fluorophosphonoacetate with 2.2 equivalents of a benzoyl chloride in dry toluene and in the presence of $\text{MgCl}_2\text{-Et}_3\text{N}$ afforded the diacylated adduct, which was deacylated in aqueous ethyl acetate and in the presence of SiO_2 to α -fluoro- β -keto esters. Good to excellent yields (78–94%) were obtained.⁵

(F) Acylation of diethyl phosphonoacetic acid in the presence of $\text{MgCl}_2\text{-Et}_3\text{N}$ as base gave β -keto phosphonates in 40–90% yields.⁶

(G) In 2002 Evans and co-workers used $\text{MgCl}_2\text{-Et}_3\text{N}$ in *anti*-aldol reactions of chiral *N*-acyloxazolidinones in the presence of chlorotrimethylsilane.⁷ The adducts were formed with high diastereoselectivity (dr up to 32:1). The reactions are operationally simple and can be run without rigorous exclusion of water.

(H) Stereoselective imine aldol reactions of *N*-cyclohexylimine with aromatic aldehydes in the presence of $\text{MgCl}_2\text{-Et}_3\text{N}$ were reported recently by Hayashi et al.⁸ High yields of products were obtained consisting essentially of the *erythro* isomer.

(I) A combination of $\text{MgCl}_2\text{-Et}_3\text{N}$ was used as base in the *ortho*-formylation of phenols by Skattebøl and co-workers.⁹ The reaction gave higher yields (70–99%) and fewer byproducts compared to most other methods.

(J) Phenols react with Eschenmoser's salt in the presence of the $\text{MgCl}_2\text{-Et}_3\text{N}$ as base, affording exclusively *ortho*-substituted benzylamines in high yields (66–98%).¹⁰

References

- (1) Olsen, R. S.; Fataftah, Z. A.; Rathke, M. W. *Synth. Commun.* **1986**, *16*, 1133.
- (2) Zhang, M.; Zhang, A.-Q.; Huang, Y.-X. *Youji Huaxue* **2005**, *25*, 1133.
- (3) (a) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622. (b) Rathke, M. W.; Nowak, M. A. *Synth. Commun.* **1985**, *15*, 1039. (c) Kuo, D. L. *Tetrahedron* **1992**, *48*, 9233. (d) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290.
- (4) Krysan, D. J. *Tetrahedron Lett.* **1996**, *37*, 3303.
- (5) Kim, D. Y.; Lee, Y. M.; Choi, Y. J. *Tetrahedron* **1999**, *55*, 12983.
- (6) Corbel, B.; L'Hostis-Kervella, I.; Haelters, J.-P. *Synth. Commun.* **2000**, *30*, 609.
- (7) (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (b) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.
- (8) (a) Hayashi, K.; Kujime, E.; Katayama, H.; Sano, S.; Nagao, Y. *Chem. Pharm. Bull.* **2007**, *55*, 1773. (b) Hayashi, K.; Kogiso, H.; Sano, S.; Nagao, Y. *Synlett* **1996**, 1203.
- (9) (a) Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258. (b) Hansen, T. V.; Skattebøl, L. *Org. Synth.* **2005**, *82*, 64.
- (10) Anwar, H. F.; Skattebøl, L.; Hansen, T. V. *Tetrahedron* **2007**, *63*, 9997.
- (11) Tamai, S.; Ushirogouchi, H.; Sano, S.; Nogao, Y. *Chem. Lett.* **1995**, 295.
- (12) Lasley, C. L.; Wright, B. B. *Synth. Commun.* **1989**, *19*, 59.