The MgCl₂–Et₃N Base System: A Useful Reagent in Organic Synthesis

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Synthesis of heterocyclic compounds and natural products.

Introduction

The combination of MgCl₂ and Et₃N is a considerably stronger base than Et₃N 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 MgCl₂–Et₃N 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 MgCl₂–Et₃N as catalyst.²

(C) Acylation of diethyl malonate with an acid chloride using MgCl₂–Et₃N 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 MgCl₂–Et₃N 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 MgCl₂–Et₃N afforded the diacylated adduct, which was decylated in aqueous ethyl acetate and in the presence of SiO₂ 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 MgCl₂–Et₃N as base gave β-keto phosphonates in 40–90% yields.⁶

(G) In 2002 Evans and co-workers used MgCl₂–Et₃N 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 MgCl₂–Et₃N were reported recently by Hayashi et al.⁸ High yields of products were obtained consisting essentially of the erythro isomer.

(I) A combination of MgCl₂–Et₃N 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 MgCl₂–Et₃N as base, affording exclusively ortho-substituted benzylamines in high yields (66–98%).¹⁰

References