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A practical and highly efficient protocol for multicomponent synthesis of β-phosphonomalononitriles and 2-amino-4H-chromen-4-yl phosphonates using diethylamine as a novel organocatalyst

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ABSTRACT

Diethylamine has been demonstrated for the first time to be a highly efficient organocatalyst in the solvent-free synthesis of β-phosphonomalononitriles by a three component condensation of aldehyde, malononitrile and dialkyl phosphite at ambient temperature. The applicability of the same catalyst in the synthesis of diethyl (2-amino-3-cyano-chromene-4-yl) phosphonic acid esters has also been described.

1. Introduction

An art to develop operationally simple and environmentally benign routes for organic compounds having high synthetic as well as biological potential is one of the fundamental objectives in synthetic organic chemistry [1]. In this context, the possibility of performing one-pot condensation of three or more components, multicomponent reactions (MCRs), is of relevance both from an economical as well as ecological point of view [2]. Although the main attraction of multicomponent reactions is their ability to construct two or more C-C or C-heteroatom bonds in single step, a typical challenge in performing them is to obtain only the desired product when competitive two component reactions between the selected substrates are equally probable. Two main approaches to address this challenge rely in the selection of an appropriate reaction path as well as catalyst.

Phosphonates are important intermediates in organic synthesis and their utility in Wittig and related reactions is well documented [3]. Currently they have also been the focus of intensive studies due to their usefulness as enzyme inhibitors [4], metabolic probes [5], peptide mimetics [6], antibiotics, pharmacologic agents [7], etc. Many natural products containing C–P bond are also known to exhibit important biological activities [8]. Owing to such a wide range of applications, development of efficient protocols for the synthesis of phosphonates, phosphonic acids and related compounds *via* C–P bond formation is enjoying growing interest. It is worth mentioning that, apart from the Kabaschnik-Field, Michaelis-Beker, and Michaelis-Arbuzov reaction [9], addition of phosphite nucleophile across carbon-carbon double bond (phospha-Michael reaction) is an ever green and widely used method in C–P bond formation [10,11]. The reaction is usually catalyzed by alkaline earth metal oxides [12], transition metal catalysts [13], tetramethylguanidine [14], Lewis/Bronsted acids [15], MWs [16], etc. In the recent

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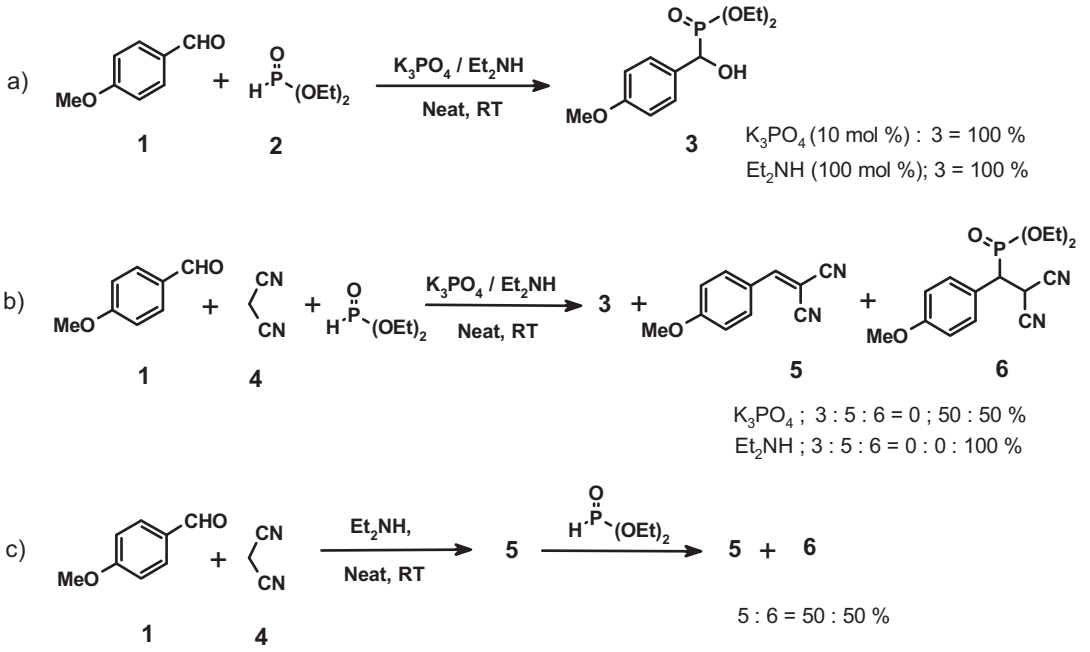

Scheme 1. Screening of reaction path/catalyst for one-pot synthesis of β-phosphonomalononitrile.

past, the phospha-Michael reaction has been explored in the synthesis of β-phosphonomalononitriles using $HClO_4$.-SiO_2 [17a], 3-aminopropylated silica gel [17b], nanoflake-ZnO [17c], sodium stearate [17d], etc. as catalysts. Many of these two component protocols essentially involve addition of phosphite nucleophile to benzylidine malononitrile; however, reports on one-pot synthesis of β-phosphonomalononitriles are scanty [18]. Our interest in this class of compounds stems from the ongoing studies in our laboratory on the development of new synthetic methodologies [19] including a recent report on expeditious synthesis of α-hydroxy phosphonates using potassium phosphate as well as diethylamine as catalyst [20] (Scheme 1a). Based upon these results, we further expand this chemistry towards the synthesis of β-phosphonomalononitriles using diethylamine as a novel organocatalyst.

2. Results and discussion

For one-pot synthesis of β-phosphonomalononitriles, one of the cleaner routes involves a base catalyzed, multicomponent condensation between an aldehyde, malononitrile and di/tri alkyl phosphite. On the other hand, a typical challenge in execution of this route relies in the choice of a base catalyst which would furnish the targeted β-phosphonomalononitrile, **6**, in excellent yields with total avoidance of the formation of α-hydroxy phosphonate, **3**, *via* the competitive Pudovik Reaction [21]. Thus, we planned to develop a base catalyzed one-pot protocol for the synthesis of β-phosphonomalononitriles.

Initial exploratory reaction was carried out between anisaldehyde, malononitrile and diethyl phosphite using potassium phosphate as a catalyst (10 mol %). The crude product which resulted after stirring the reaction mixture over night was identified to be a mixture of Knoevenagel condensation product, **5** and the desired β-phosphonomalononitrile, **6**, in nearly 1:1 proportion (^{1}H-NMR). *Most strikingly*, formation of α-hydroxy phosphonate, **3**, was not noticed (Scheme 1b). In short, although potassium phosphate has been demonstrated by us as a highly efficient catalyst to effect two component condensations between an aldehyde and diethyl phosphite [20b] as well as between an aldehyde and active methylene compounds [19f], during a three component condensation using these substrates, the reaction exclusively followed the tandem Knoevenagel-phospha-Michael pathway. This breakthrough result directed us to test the feasibility in using other base catalysts in one-pot synthesis of β-phosphonomalononitriles. Accordingly, various homogeneous and heterogeneous base catalysts were screened for this three component condensation reaction (Table 1). It was noticed that, under solvent-free condition, compared to inorganic salts (entry 2, 3, 4 & 5, Table 1), organic bases such as pyrrolidine, piperidine and diethylamine (entry 11, 12, 13, Table 1), with very close pKa values, were equally efficient to furnish the desired β-phosphonomalononitrile in excellent yield. On the other hand, with the choice of heterogeneous catalysts like PVP, DBU, DMAP as well as DABCO, the reactions furnished a mixture of α-hydroxy phosphonate and β-phosphonomalononitrile in different proportions. From the view point of operational simplicity, another cleaner route for the synthesis of β-phosphonomalononitriles involves the sequential, one-pot, Knoevenagel-phospha-Michael addition reaction (Scheme 1c). During exploration of this route, Knoevenagel condensation between anisaldehyde and malononitrile was initially effected using diethylamine as catalyst. To the resultant product, **5**, diethyl phosphite (1 eqv) was added and stirring was continued over night. The resultant crude product was identified (^{1}H- NMR) to be a mixture of