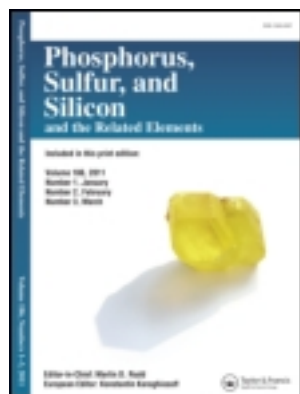


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Nano-TiO₂: An Eco-Friendly and Clean Reusable Heterogeneous Catalyst for Preparation of α -Aminophosphonates Under Ambient and Solvent-Free Conditions

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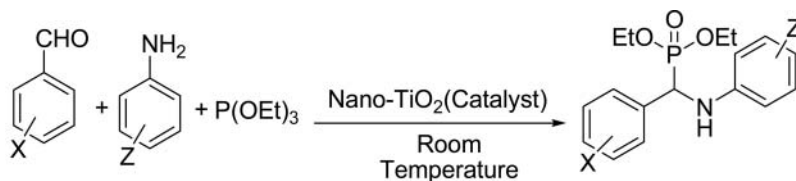
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NANO-TiO₂: AN ECO-FRIENDLY AND CLEAN REUSABLE HETEROGENEOUS CATALYST FOR PREPARATION OF α -AMINOPHOSPHONATES UNDER AMBIENT AND SOLVENT-FREE CONDITIONS

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GRAPHICAL ABSTRACT



X=H, OCH₃, Cl, NO₂
 Z=H, CH₃, OCH₃, NO₂

Abstract A one-pot catalytic three-component synthesis of α -aminophosphonates from arylaldehydes, anilines, and triethylphosphite by employing TiO₂ nanoparticles as a catalyst is described. Nano-TiO₂ has been found to be an excellent catalyst for the green synthesis of α -aminophosphonates under ambient and solvent-free conditions. This green and mild nano catalytic procedure showed good recyclability and provides cleaner conversion in a short reaction time. These advantages make the protocol feasible and economically attractive for researchers.

Keywords Nano-TiO₂; three-component reaction; α -aminophosphonates; catalyst; solvent-free; ambient conditions

INTRODUCTION

Phosphonic acids and their phosphonate derivatives are of immense interest in synthetic organic chemistry due to their biological activities.¹ The synthesis of α -aminophosphonates has attracted much interest because of their biological activity and structural analogy to α -amino acids as well as heterocyclic phosphonates.² Their diverse applications include inhibition of synthase,³ HIV protease,⁴ renin,⁵ and PTPases,^{6,7}

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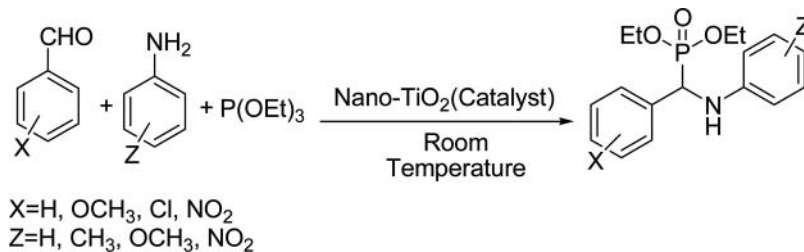
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some of these derivatives are potential antibiotics⁸ or herbicides.⁹ Furthermore, α -aminophosphonates are chief substrates in the synthesis of phosphonopeptides.¹⁰

Nanoparticles are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. A bulk material should have constant physical properties regardless of its size, but at the nanoscale, size-dependent properties are often observed. Thus, the properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant.^{11,12}

Original research on synthetic approach to α -aminophosphonates is the Kabachnik–Fields reaction.^{13,14} A number of synthetic methods for the preparation of α -aminophosphonates have been developed using various Brønsted acids, Lewis acids, heteropoly acids, heterogeneous catalysts, ionic liquids, and nano catalysts such as silica-supported boron trifluoride (BF₃–SiO₂),¹⁵ *N,N,N*-trimethyl-*N*-propanesulfonic acid ammonium hydrogensulfate [TMPSA][HSO₄],¹⁶ choline chloride·2ZnCl₂ ionic liquid,¹⁷ cadmium perchlorate hydrate,¹⁸ cerium(III) chloride heptahydrate CeCl₃·7H₂O,¹⁹ ethyl ammonium nitrate [EtNH₃][NO₃],²⁰ 1-hexanesulphonic acid sodium salt,²¹ tetramethyl-tetra-3,4-pyridinoporphyrazinato copper (II) methyl sulfate [Cu(3,4-tmtppa)](MeSO₄)₄,²² thiamine hydrochloride (VB1),²³ nano-Fe₃O₄,²⁴ nano-CeO₂,²⁵ and commercial bulk TiO₂.²⁶ However, many of these catalysts involve tedious separation procedures^{21,23} with prolonged reaction times.^{22,24} Therefore, the development of a simple, convenient, and an efficient protocol would extend the scope of the synthesis of α -aminophosphonates.

In this article, we report that nano-TiO₂ (10 mol%) is a highly efficient catalyst for the one-pot three-component coupling synthesis of α -aminophosphonates from arylaldehydes, anilines, and triethylphosphite under ambient and solvent-free conditions (see Scheme 1).



Scheme 1 Nano-TiO₂ catalyzed three-component synthesis of α -aminophosphonates.

RESULTS AND DISCUSSION

In order to optimize the reaction conditions, the reaction between benzaldehyde (1 mmol), aniline (1 mmol), and triethylphosphite (1 mmol) was chosen as a model. Initially, we tried to optimize the amount of nano-TiO₂ in the reaction model. Thus 0.008 g (10 mol%), 0.020 g (25 mol%), and 0.035 g (43 mol%) of nano-TiO₂ (size < 3 nm) were used (see Table 1). We found that the amount of nano-TiO₂ 0.008 g (10 mol%) was the most effective in catalyzing preparation of α -aminophosphonates under ambient conditions.

Then, to establish the generality, the reaction of several substituted arylaldehydes, anilines, and triethylphosphite using nano-TiO₂ as a catalyst under solvent-free and ambient conditions were examined. The results are shown in Table 2. We have carried out the

Table 1 Optimization of the amount of nano-TiO₂ as a catalyst in the synthesis of α -aminophosphonates under ambient conditions

Entry	Catalyst (mol%)	Time (min)	Yield (%) ^a
1	10	9	90
2	25	5	93
3	43	2	92

^aYields refer to isolated pure product.

similar reaction with various aromatic aldehydes containing electron donating or electron withdrawing functional groups at *ortho*, *meta*, and *para* positions, but it did not showed any remarkable differences in the yields of product and reaction time.

We also investigated the recycling of the nano-TiO₂ as the catalyst under solvent-free conditions using the model reaction of benzaldehyde, aniline, and triethylphosphite (10 mol%) (see Table 2, Entry 1). After completion of the reaction, the reaction mixture was diluted with dichloromethane and the catalyst was separated by centrifugation and was reused for subsequent experiments under similar reaction conditions. The results showed us that the nano-TiO₂ is a stable catalyst and reused several times without significant loss of its catalytic activity.

In order to show the accessibility of the present work in comparison with several reported results in the literature, we summarized some of the results for the preparation of diethyl phenyl(phenylamino)methylphosphonate from the reaction of benzaldehyde, aniline, and triethylphosphite (see Table 3). The results show that nano-TiO₂ relative to cerium(III) chloride heptahydrate (CeCl₃·7H₂O),¹⁹ tetramethyl-tetra-3,4-pyridinoporphyrazinato copper (II) methyl sulfate ([Cu(3,4-tmtppa)](MeSO₄)₄),²² nano-Fe₃O₄,²⁴ and bulk TiO₂²⁶ are the most efficient catalysts with respect to the reaction time and in terms of yields. In addition, nanosize of TiO₂ with high surface area as a catalyst shows high catalytic activity

Table 2 Synthesis of α -aminophosphonate from the reaction of substituted arylaldehydes, anilines, and triethylphosphite using nano-TiO₂ (10 mol%) as a catalyst under solvent-free and ambient conditions

Entry	Arylaldehydes	Anilines	Time (min)	Yield (%) ^a	Found mp (°C)	Literature mp (°C) ^{Ref}
1	C ₆ H ₅ CHO	C ₆ H ₅ NH ₂	9	90	89–90	87 ¹⁹
2	C ₆ H ₅ CHO	4-NO ₂ C ₆ H ₅ NH ₂	35	85	145–147	145–146 ¹⁹
3	C ₆ H ₅ CHO	4-BrC ₆ H ₄ NH ₂	12	90	123–124	122 ¹⁹
4	C ₆ H ₅ CHO	4-MeC ₆ H ₄ NH ₂	12	93	116–118	117–118 ¹⁹
5	C ₆ H ₅ CHO	4-MeOC ₆ H ₄ NH ₂	11	87	116	115 ¹⁹
6	4-NO ₂ C ₆ H ₄ CHO	C ₆ H ₅ NH ₂	23	90	122–123	120 ¹⁹
7	4-MeC ₆ H ₄ CHO	C ₆ H ₅ NH ₂	15	85	65–67	66–67 ¹⁹
8	4-MeOC ₆ H ₄ CHO	C ₆ H ₅ NH ₂	18	90	110–111	108 ¹⁹
9	4-HOC ₆ H ₄ CHO	4-Cl-2-NO ₂ C ₆ H ₅ NH ₂	20	92	143–144	141–143 ²⁰
10	3-NO ₂ C ₆ H ₄ CHO	4-Cl-2-NO ₂ C ₆ H ₅ NH ₂	22	92	109–111	107–110 ²⁰
11	4-ClC ₆ H ₄ CHO	4-Cl-2-NO ₂ C ₆ H ₅ NH ₂	19	92	75–76	75–76 ²⁰
12	2-HOC ₆ H ₄ CHO	4-Cl-2-NO ₂ C ₆ H ₅ NH ₂	20	92	127–128	125–128 ²⁰
13	3,4-diMeOC ₆ H ₃ CHO	C ₆ H ₅ NH ₂	18	94	76–78	77 ¹⁹
14	3,4-diMeOC ₆ H ₃ CHO	4-Cl-2-NO ₂ C ₆ H ₅ NH ₂	19	93	108	105–107 ²⁰

^aYields refer to isolated pure product. The desired known pure products were characterized by comparison of their physical data (mp, melting points; IR, ¹H NMR, and ¹³C NMR) with those of known compounds.^{19,20}

Table 3 Comparing the results of nano-TiO₂ with other metallic catalysts such as cerium (III) chloride heptahydrate (CeCl₃·7H₂O),¹⁹ tetramethyl-tetra-3,4-pyridinoporphyrazinato copper (II) methyl sulfate ([Cu(3,4-tmtppa)](MeSO₄)₄),²² nano-Fe₃O₄,²⁴ and bulk TiO₂²⁶ in the synthesis diethyl phenyl(phenylamino)methylphosphonate

Entry	Catalyst	Conditions	Time	Yield (%) [Ref]
1	CeCl ₃ ·7H ₂ O (5 mol%)	Solvent-free, room temperature	5 h	95 ¹⁹
2	[Cu(3,4-tmtppa)](MeSO ₄) ₄ (160 mol%)	H ₂ O, 80°C	30 min	96 ²²
3	Nano-Fe ₃ O ₄ (5 mol%)	50°C	48 min	94 ²⁴
4	Bulk TiO ₂ (20 mol%)	50°C	3.5 h	98 ²⁶
5	Nano-TiO ₂ (10 mol%)	Solvent-free, room temperature	9 min	90 (present work)

^aYields refer to isolated pure products and based on the reaction of benzaldehyde, aniline, and triethylphosphite.

relative to commercial bulk TiO₂.²⁶ Nano-TiO₂ acts with a low catalytic amount under ambient and solvent-free conditions, whereas micron-size bulk TiO₂ acts with 20 mol% under thermal conditions.²⁶

CONCLUSIONS

In summary, we have developed a novel efficient solvent-free protocol for the synthesis of α -aminophosphonates using catalytic TiO₂ nanoparticle. The method is effective and provides excellent yields of the products in short reaction time, which makes this protocol a novel, environmentally friendly, and economically valuable process for the synthesis of this class of compounds. The nano-TiO₂ as a catalyst exhibits a straightforward approach to be used in green organic synthesis. Nano-TiO₂ shows high activity (like a homogeneous and a heterogeneous system) in spite of micron-size bulk TiO₂ (like a heterogeneous system).

EXPERIMENTAL

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. Nanopowder TiO₂ with a size of ellipsoid <3 nm was purchased from Merck chemical company (95% anatase, 5% brokite); CAS no: 1317-70-0. All yields refer to isolated products after purification. Products were characterized by the comparison of physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a Bruker Avance DPX 500 MHz instrument. The spectra were measured in CDCl₃ relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. Thin layer chromatography (TLC) was performed on silica-gel polygram SILG/UV 254 plates.

General Procedure for the Preparation of α -aminophosphonates

Arylaldehydes (1 mmol), anilines (1 mmol), triethylphosphite (1 mmol), and nano-TiO₂ (10 mol%, 0.008 g) were mixed under solvent-free and ambient conditions. The reaction mixture was stirred at room temperature for appropriate time (see Table 2). The

completion of the reaction was monitored by TLC. After the completion of the reaction, dichloromethane was added to the reaction mixture and the catalyst was removed from the reaction mixture by centrifugation, washed with dichloromethane, and dried. The reusable nano catalyst clearly reveals that the nano-TiO₂ can be used for four cycles without any significant loss in its activity. The organic solvent was removed under reduced pressure. After purification by column chromatography on silica gel (ethyl acetate/n-hexane 20:80 as eluent), the α -aminophosphonates were obtained. All products were characterized by NMR and FTIR spectral data and compared with the known compounds in the literature.^{19,20}

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