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Nano TiO_2/SiO_2: An Efficient and Reusable Catalyst for the Synthesis of α-aminophosphonates

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Abstract: *Nano TiO_2/SiO_2 acts as a Lewis acid, which is Nano TiO_2 supported on SiO_2 was found to be an effective and reusable catalyst for the Kabachnik–Fields reaction of benzhydrylamine, substituted benzaldehyde and dialkyl phosphites using ethyl alcohol as solvent, when stirred for 1hr at room temperature. Convesion of 88-94% were obtained.*

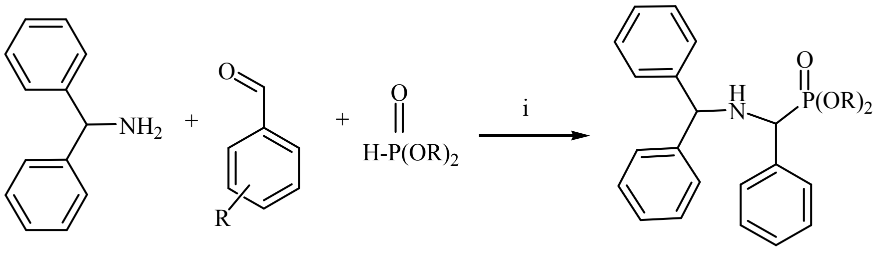
Keywords: TiO_2/ SiO_2 Nonocatalyst, Kabachnik–Fields reaction, α-aminophosphonates

I. INTRODUCTION

P-analogues of α-aryl-α-amino acids are α-aminophosphonates. They have various pharmacological and Medicinal applications such as enzyme inhibitors, antibiotics, antiviral or anticancer agents [1–4]. The N–C–P moiety, which is present in the α-aminophosphonic and α -aminophosphinic derivatives have been in a focus due to their potential biological activity. The natural counterparts of α-aminophosphonates consist of the acid derivatives of species under discussion. They are recognized by receptors and enzymes as false substrates/inhibitors, because of their different properties such as tetrahedral P vs. planar C, different acidity, and steric bulk [5-9]. Due to the bioactivity realized in this manner, these derivatives may be manifested in applications as agrochemicals and medicines.

Kabachnik–Fields reaction described by different publications. Usually phospha-Mannich protocol describes the use of various catalysts, such as Lewis and Brönsted acids, metal perchlorates, Amberlysts, succinic-, sulfonic-, and oxalic- acids, zinc, iron, and niobium salt, lanthanide triflates, boron trifluoride etherate, and titanium dioxide etc. [10]. However, it has been found that catalyst-free methods may also be appropriate, especially under solvent-free and/or microwave-assisted conditions. [11-17]. Herein, we have developed an efficient method for the synthesis of α-aminophosphonate compounds in the presence of TiO_2/ SiO_2 nanocatalyst as a recyclable catalysts in mild reaction conditions and excellent yields.

II. EXPERIMENTAL



Scheme 1: *Reagent and Conditions*: i) Benzhydrylamine (1mmol), Benzaldehyde (1mmol),dialkyl phosphite (1.2eqiv.), ethyl alcohol(5ml), Nano TiO_2/SiO_2 (5mg), stir, 1hr at RT, yield 88-94%.

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2.1 General Details

All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 $F_{254,}$ Merck grade was used for thin layer chromatography to determine progress of reaction. Melting points were determined in open capillary tube and are uncorrected. IR, ^{1}H and ^{13}C-NMR spectra were recorded on a Brucker AV-300 MHz and 75MHZ spectrometer in $CDCl_{3,}$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific MS.

General Procedure for the Synthesis of α-aminophosphonates:

Benzhydrylamine (1mmol), substituted benzaldehyde(1mmol) and dimethyl/diethylphosphite (1.2 equiv.) was added into ethyl alcohol (5mL) solvent containing TiO_2/SiO_2 (5mg) catalyst. The mixture was stirred at room temperature for one hour. TLC monitored the progress of the reaction. After completion of reaction, ethylacetate (20 mL) was added and filtered. The solid residue was washed with ethylacetate (2·5mL). The solvent was evaporated and the residue purified by chromatography on silica gel using n-hexane/ethyl acetate (1:1) to afford the pure products. All the products were characterized by ^{1}H NMR, ^{31}P-NMR, ^{13}C-NMR and Mass spectra and compared their spectroscopic data with literature.

***Dimethyl (benzhydrylamino)(phenyl)methylphosphonate (4a)*:** White solid; M.P. 106-107°C; **^{1}H NMR ($CDCl_3$, 300MHz):** δppm 2.82 (s, 1H, NH), 3.55 (d, 3H), 3.95 (d, 3H), 4.2 (d,1H), 4.75 (s, 1H), 7.5–8.22 (m, 15H)); **^{31}P NMR ($CDCl_3$)**: δ 26.5 **^{13}C NMR (75 MHz, $CDCl_3$)**:δppm 54.5, 56.0, 59.8, 66.7, 127.30, 128.22 , 128.8 , 129.2, 129.5, 129.7, 129.8, 130.6, 131.35, 132.5, 140.8, 142.3; **m/z**: 382(M^+); **Anal. calcd. for**: $C_{22}H_{24}NO_3P$ (%):C, 69.28; H, 6.34; N, 3.67; O, 12.58; P, 8.12. Found (%): C, 69.30; H, 6.36; N, 3.69,O, 12.61;P, 8.14.

Diethyl(benzhydrylamino)(phenyl)methylphosphonate (4h): Yellow solid; M.P.:102–103 °C; **^{1}H NMR ($CDCl_3$, 300MHz):** δppm 1.24(t, 3H), 1.26(t, 3H), 3.9(s, 1H), 4.07(q, 2H), 4.09(q, 2H), 2.32(s, 1H, NH), 5.23 (s,1H), 7.08–7.92 (m, 15H)); **^{31}P NMR ($CDCl_3$)**:δppm 23.7; **m/z**: 410.34(M^+); **Anal. calcd. for**: $C_{24}H_{28}NO_3P$ (%):C, 70.40; H, 6.89; N, 3.42; O, 11.72; P, 7.56. Found (%): C, 72.42; H, 6.91; N, 3.45; O, 11.74; P, 7.58.

III. RESULT AND DISCUSSION

We initiated our investigation by choosing the reaction of benzhydril amine, benzaldehyde and dimethylphosphite for the synthesis of dimethyl (benzhydrylamino)(phenyl)methylphosphonate **4a** as a model reaction (Table 1). Initially, commercially available iodine, $PdCl_2$, $Zn(OTf)_2$ and ruthenium catalysts (each, 5mol%) were tested for model reaction at room temperature in different solvent systems. At first, to get the desired product we applied iodine catalyst in ethanol but it gives only 65% of product yield with approximately one-hour reaction time. Latter on for the screening of reaction conditions, $PdCl_2$ and $Zn(OTf)_2$ were also tested in water and ethanol but desired product obtained with poor yield and requires longer reaction time. Unexpectedly, NiO_2/SiO_2 nano catalyst exhibited the good catalytic activity in 1, 2-DCE and chloroform providing 85-90% yield of the desired product **4a** with short reaction time (Table1; entry 6 and 7). In order to make proposed protocol more greener and catalytic media reusable, the reaction was attempted in ethanol. Gratifyingly, highest desired product was obtained giving 92% yield with short reaction time than earlier (Table 1, entry 8).

Table 1: Screening of the reaction conditions for the synthesis of dimethyl (benzhydrylamino) (phenyl) methylphosphonate.

Entry	Catalyst	Solvent	Catalytic loading (mol %)	Reaction Time (min)	Yield (%)
1	Iodine	Ethanol	5	65	65
2	$PdCl_2$	Ethanol	5	70	56
3	$PdCl_2$	Water	5	130	40
4	$Zn(OTf)_2$	Water	5	90	70
5	$Zn(OTf)_2$	Ethanol	5	100	75
6	NiO_2/ SiO_2	1, 2-DCE	5	60	80

7	NiO_2/ SiO_2	Chloroform	5	62	82
8	NiO_2/ SiO_2	Ethanol	5	60	92*

* Reaction proceeds under same condition.

Next, the effect of catalytic loading was determined, by lowering and increasing catalyst concentration leads to a decrease in yield and increased time for the completion of reaction **(Table 2)**.

Table 2: Effect of catalytic concentration and temperature

Entry	Catalyst	Solvent	Catalytic loading (mg)	Temperature (°C)	Time (Min)	Yield (%)
1	NiO_2/ SiO_2	Ethanol	3	25	120	80
2	NiO_2/ SiO_2	Ethanol	7	25	75	85
3	NiO_2/ SiO_2	Ethanol	**5**	**25**	**60**	**92**
4	NiO_2/ SiO_2	Ethanol	5	60	50	82
5	NiO_2/ SiO_2	Ethanol	5	80	30	78

In order to show the reusability, the model condensation of benzhydrine **1**, benzaldehyde **2** and dimethylphosphine **3** has been performed within 5 runs. In each step after completion of the reaction, the catalyst was filtered and washed with ethyl acetate. Overnight drying at room temperature under atmosphere made the recovered solid nano TiO_2/SiO_2 ready for another run.

With the identified optimized reaction conditions in hand, the synthetic versatility of the proposed protocol is highlighted by screening the compatibility of a diverse set of benzhydrine, dimethyl/diethyl phosphite and substituted benzaldehyde bearing both electron donating as well as electron withdrawing substituent **(Table 3**). The reaction takes place smoothly with a high degree of translation without the formation of any by-product. Electron withdrawn and donating groups on the benzaldehyde gives smooth reactions with the good yield.

Synthesized products were characterized by ^{1}H-NMR, ^{31}P-NMR, ^{13}C-NMR, Mass spectroscopy, and elemental analysis and by comparison with authentic samples. This method affords the products in excellent yields than the earlier methodologies.

Table 3: Exploration of substrate scope for the Synthesis of α-aminophosphonate derivatives [a]

Entry	Benzhydrylamine **1**	Substituted Benzaldehyde **2(R)**	Dialkyl phosphate **3**	Product **4(a-n)**	Time in (Min)	M.P. °C	Yield %
1	Benzhydrylamine	H	Dimethyl phosphite	4a	60	106-107	92
2	Benzhydrylamine	p-Cl	Dimethyl phosphite	4b	62	88-90	94
3	Benzhydrylamine	o-Cl	Dimethyl phosphite	4c	60	95-96	90
4	Benzhydrylamine	p-NO_2	Dimethyl phosphite	4d	65	110-111	88
5	Benzhydrylamine	p-OCH_3	Dimethyl phosphite	4e	61	116-117	90
6	Benzhydrylamine	p-Br	Dimethyl phosphite	4f	60	92-93	91
7	Benzhydrylamine	o-Br	Dimethyl phosphite	4g	61	98-99	90
8	Benzhydrylamine	H	Diethyl Phosphite	4h	65	102-103	89
9	Benzhydrylamine	p-Cl	Diethyl Phosphite	4i	62	113-114	91

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10	Benzhydrylamine	o-Cl	Diethyl Phosphite	4j	60	78-79	90
11	Benzhydrylamine	p-NO_2	Diethyl Phosphite	4k	66	122-123	88
12	Benzhydrylamine	p-OCH_3	Diethyl Phosphite	4l	61	119-120	90
13	Benzhydrylamine	p-Br	Diethyl Phosphite	4m	60	84-85	91
14	Benzhydrylamine	o-Br	Diethyl Phosphite	4n	58	126-127	88

[a] Benzhydrylamine (1mmol), Benzaldehyde (1mmol), dialkyl phosphite (1.2eqiv.), ethyl alcohol (5ml), Nano TiO_2/SiO_2 (5mg), stir, 1hr at RT, yield 88-94%.

IV. CONCLUSION

In conclusion, we have developed an efficient method for the synthesis of symmetrical α-aminophosphonate derivatives using TiO_2/SiO_2 nanocatalyst, readily available, reusable and eco-friendly solid acid catalyst at ambient temperature. Simple experimental procedure associated with high yield and short reaction times makes this protocol interesting for organic chemists. The reusability of the catalyst is a emphasize point in this method.

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