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Nano-TiO_2 catalyzed microwave synthesis of α-Hydroxyphosphonates

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Abstract: A simple, novel and green method is reported for the synthesis of α-hydroxyphosphonates by hydro-phosphonylation of various structurally diversified aldehydes (aromatic/ heteroaromatic) using Nano-TiO_2 as catalyst under solvent free microwave condition. Environmentally benign reaction procedures, short reaction times, easy work-up, high product yields, and reusability of catalyst for several cycles with consistent activity makes this protocol a highly attentive one.

Keywords: α-Hydroxyphosphonates; Nano-TiO_2; Hydro-phosphonylation; microwave.

1. Introduction

Phosphorus-containing compounds play a crucial role in various bioinformation exchange pathways in living organisms as carriers of genetic information and are also important signalling, regulatory, energy transfer and structural agents.[1] Hence, they become therapeutic targets in various modern medicinal techniques such as antisense[2] and antigene[3] approaches to modulate the gene expression, or gene silencing technique using short interfering RNA (siRNA).[4] α-Hydroxyphosphonates have acquired an extreme edge both in synthetic chemistry as attractive precursor cum intermediates in development of new synthetic targets[5-7] and in the development of multi-drug agents.[8-11] They are prominent to act as wide-range enzyme inhibitors for farnesyl protein transferase (FPT),[12] human renin,[13] human protein tyrosine phosphatase (PTP),[14] purine nucleoside phosphorylase (PNP),[15] and 5-enolpyruvylshikimate-3-phosphate synthase (EPSP).[16]

The Pudovik reaction involving addition of dialkylphosphite to carbonyl compounds is a direct method for the construction of new C-P bonds and to generate α-hydroxyphosphonates. The efficiency of this reaction has been improved by the action of catalysts such as enzymatics,[17] alkaloids,[18] phosphoric acids,[19] Lewis acids,[20] Al-Li-BINOL complex,[21] alumina/ potassium fluoride,[22] NH_4VO_3,[23] and polymer/ solid supported base.[24] In recent years, some of the disadvantages associated with these procedures have been diminished by adopting the green chemical synthetic procedures involving potassium carbonate,[25] sodium carbonate,[26] triethylamine[27] as catalysts under conventional solventfree conditions and potassium dihydrogenphosphate[28] under ultrasound-assisted solvent-free conditions and iodine in water[29] were reported for the synthesis of *a*-hydroxyphosphonates. But still the disadvantages are not completely eliminated in terms of product yields, catalyst amounts and reusability.

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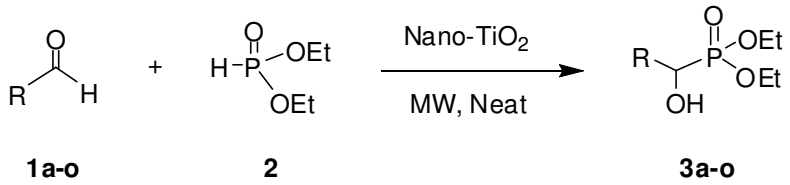
In such search of developing more efficient green synthetic methods, catalyst doped nanoparticle catalysts were identified as best replacements because they are non-toxic, heterogeneous, reusable and they can exist with numerous surface sites with enhanced surface reactivity such as crystal corners, edges or ion vacancies.[30] Located at the crossroad of nanoparticle applications, TiO_2 nanoparticles are coined out as catalyst with high impact of pertinence on synthetic[31-32] and industrial chemistry. They have been successfully used in degradation processes,[33-35] catalyst support for proton exchange membrane fuel cells,[36] co-catalyst for improving wrinkle-resistance of cotton fabric,[37] photodecomposition of methylene-blue by highly dispersed on Ag,[38] and crosslinking of cotton cellulose with succinic acid under UV.[39]

Hence we have selected and used TiO_2 nanoparticles as potential catalyst to overcome most of the unfavourable conditions in the synthesis of *α*-hydroxyphosphonates and achieved fruitful results. In this methodology microwave and solvent free approaches are also investigated to make it a green chemistry approach.

2. Results and discussion

In the present study, microwave induced synthesis of *α*-hydroxy phosphonates (**3a-o**) have been achieved *via* the catalyzed addition reaction of diethylphosphonate (**2**) with various aldehydes (**1a-o**) by Nano-TiO_2 under solvent free conditions (**Scheme 1**).



Scheme 1. Synthesis of *α*-hydroxyphosphonates

In the initial studies of the present investigation, Nano-TiO_2 catalyzed reaction of *m*-nitrobenzaldehyde and diethylphosphite at 70 °C is taken as a model and solvent effect is carefully scrutinized. The variations in product yields and reaction times with respect to change in organic solvents such as EtOH, $CHCl_3$, DCM, CH_3CN, Toluene and THF, water and finally with no solvent. Low product yields (61-76%) even under longer reaction times (120 min) by thermal heating are unsatisfactory. Hence, we opted for microwave irradiation as an alternative potential energizing of the reactants to get enhanced yields and are successful with this method. The reaction yields obtained are proportional with respect to polarity of the solvents and similarly, the use of solvent-free/ microwave condition is found to be the best (Table 1, entry 8). The observations and results are summarized in **Table 1.**

Table 1. Optimization of solvent effect on model reaction

Entry	Solvent	Conventional (70 °C)		Microwave	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1	H_2O	120	75	05	83
2	EtOH	120	69	05	78
3	$CHCl_3$	120	61	05	65
4	DCM	120	68	05	71
5	CH_3CN	120	67	05	75
6	Toluene	120	71	05	76
7	THF	120	62	05	68
8	Solvent free	120	76	05	92

After finalizing solvent effect on the reaction, our attention turned in the direction of catalyst loading. To determine the appropriate concentration of the catalyst, we examined the model reaction with different concentrations of the catalyst (2, 4, 6, 8, 10 and 12 mol%) and without catalyst under microwave irradiation and solvent free conditions. The products were obtained in 54, 68, 81, 85, 89, 92 and 92% yields respectively. From these results, it is evident that, best product yields are obtained with 10 mol% of Nano-TiO_2. On further increments in the concentration of the catalyst loading, yields remained stagnated. These reports are presented in **Figure 1.**

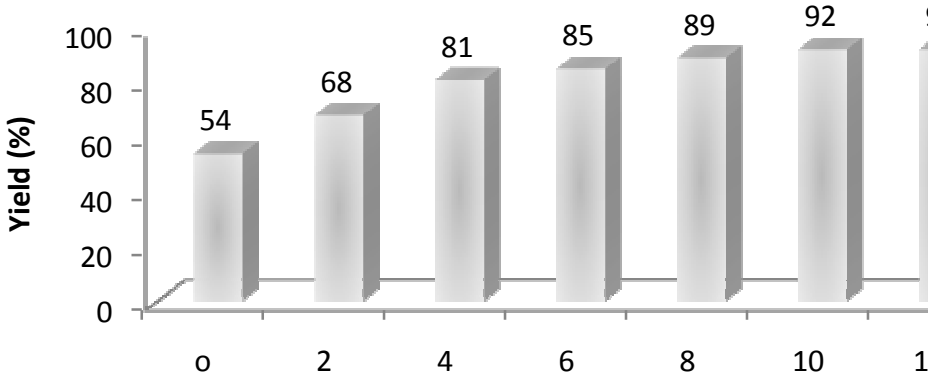


Figure 1. Screening of catalyst concentration on model reaction

To explore the potentiality of the present catalytic approach and to fulfil the requirements of green chemistry, we next concentrated on reusability of the catalyst. After completion of reaction as indicated by TLC with first time use of the catalyst, the mixture is dissolved in DCM and filtered to recover the catalyst. Thus obtained catalyst was washed with DCM twice to eliminate tars on catalyst surface, dried and reused successfully for four cycles and the isolated yields obtained for four successive cycles respectively are 92, 91, 90 and 88 % as summarized in **Table 2**. This data suggests that the catalyst has not lost its activity and could be reused for four times.

Table 2. Reusability of catalyst on model reaction

Cycle	Time (min)	Isolated Yield (%)
1	5	92
2	5	91
3	5	90
4	5	88

The plausible mechanism involved in the catalyst regeneration is illustrated schematically in Figure 2.

With standardized experimental conditions, the reaction is extended to various structurally diversified aldehydes. Structural variations involved on aldehyde functional groups such as aromatic, heteroaromatic, α,β-unsaturation showed effect on their reactivity and the products, yields were observed in the order: α,β-unsaturation < heteroaromatic < aromatic.

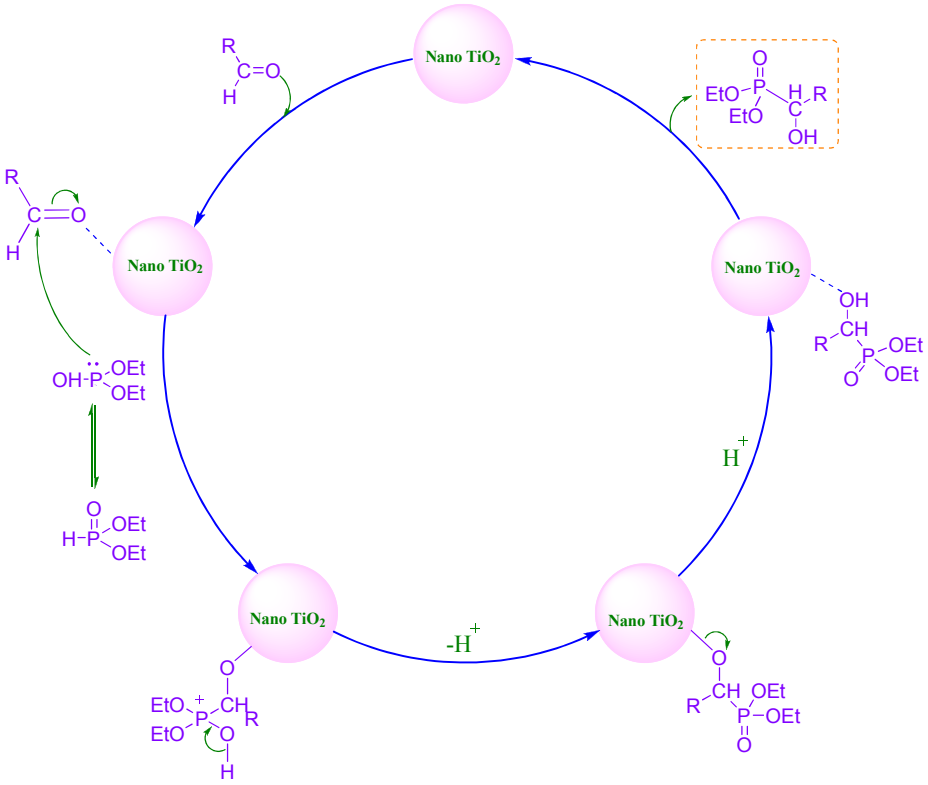


Figure 2. Plausible mechanism involved in the catalyst regeneration

Table 3. Synthesis of α-Hydroxyphosphonates **3a-o**

Product	R	Time (min)	Yield (%)	Melting Point (°C)	
				Found	Literature
3a	C_6H_5-	4	89	76-78	75-77[23,40]
3b	$4(CH_3)C_6H_4$-	5	86	94-96	94-95[23,40]
3c	$4(OCH_3)C_6H_4$-	7	85	119-121	120-121[23,40]
3d	$3(OH)C_6H_4$-	6	91	97-99	97-98.5[23,40]
3e	$4(OH)3(OMe)C_6H_3$-	9	85	Liquid	--
3f	$4(Cl)C_6H_4$-	5	88	68-70	67-68[23,40]
3g	$2(Cl)C_6H_4$-	6	84	75-76	74-75[23,40]
3h	$2,6(Cl)_2C_6H_3$-	8	82	78-80	--
3i	$2(NO_2)C_6H_4$-	4	86	114-116	114-116[40]
3j	$3(NO_2)C_6H_4$-	5	92	80-82	81-82[40]
3k	C_6H_5-CH=CH-	10	80	104-106	105-106[23,40]
3l	$4(CH_3)_2NC_6H_4$-	6	89	80-82	80-81[40]
3m	$4(C_2H_5)_2NC_6H_4$-	5	90	94-96	--
3n	C_6F_5-	4	95	76-78	--
3o	Quinolin-2-yl	8	88	112-114	--

In depth investigation was carried out on aromatic substituents with electron withdrawing and electron releasing groups and their reactivity trend followed in the order phenyl + releasing (Me, OMe, Me_2N, Et_2N, Cl) < phenyl < phenyl + withdrawing (NO_2, F). Along with the substituent effect on phenyl ring, position of the substituent also played a key role in their reactivity. 4-chloro phenyl (88%), 2-chloro phenyl (84%) and 2,6-dichloro phenyl (82%) products gradual decrements in the yields may be attained to both ortho electronic and steric effects. The results of all the observations are represented in **Table 3.**

3. Experimental procedures

3.1. General

Chemicals were procured from Sigma-Aldrich and Merck, were used as such without further purification. All the solvents used for the spectroscopic and other physical studies were reagent grade and were further purified by literature methods. The melting points expressed in degrees centigrade (^oC) were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Infrared (IR) Spectra were obtained on a Nicolet 380 Fourier transform infrared (FT-IR) spectrophotometer at the Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati, India and samples were analyzed as potassium bromide disks and absorptions (ν_{max}) were reported in wave numbers (cm^{-1}). All the compounds were dissolved in $CDCl_3$ and ^1H, ^{13}C, and ^{31}P-NMR spectra were recorded on a Bruker AMX 500 MHz nuclear magnetic resonance spectrometer operating at 500 MHz for ^1H-NMR, 125.71 MHz for ^{13}C-NMR, and 202.37 MHz for ^{31}P-NMR respectively. The chemical shifts were expressed in parts per million and were referenced to TMS in ^1H-NMR and ^{13}C-NMR and 85% H_3PO_4 in ^{31}P NMR. Mass spectra were recorded on a Q-Tof mass spectrometer. Microanalysis was performed on a Thermo Finnigan Flash EA 1112 I instrument at University of Hyderabad, Hyderabad, India.

3.2. General procedure for synthesis of a series of α- hydroxyphosphonates

A mixture of aldehyde (1 mmol), diethylphosphite (1.2 mmol) and Nano-TiO_2 (10 mol %) was stirred under microwave irradiation for 4-10 min. The completion of reaction is determined by TLC monitoring. After completion of reaction, the reaction mixture was dissolved in DCM and filtered to recover the catalyst. The filtrate was concentrated under reduced pressure and resulting crude product was purified by column chromatography using silica gel (60-120 mesh) with ethylacetate: hexane (1:1) as eluent to get the pure product. The catalyst was reused for the next reactions after washing with DCM.

3.3. Spectral data for novel compounds

3.3.1. Diethyl hydroxy(4-hydroxy-3-methoxyphenyl)methylphosphonate (3e): Viscus liquid; IR (KBr): 3226 (OH), 1257 (P=O), 1035 (P-O-C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.08 (s, 1H, Ar-H), 6.84-6.93 (m, 2H, Ar-H), 6.19 (brs, 1H, OH), 4.92 (d, J = 10 Hz, 1H, CHP), 4.13-3.89 (m, 4H, O$\underline{CH_2}CH_3$), 3.85 (s, 3H, Ar-O$\underline{CH_3}$), 1.27 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.21 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$); ^{13}C NMR ($CDCl_3$, 125.71 MHz): δ 146.8, 145.9, 128.4, 120.6, 114.4, 110.1, 71.4, 70.1, 63.4, 56.1, 16.5 (2C); ^{31}P NMR ($CDCl_3$, 202.37 MHz): δ 22.71; ESI-MS: *m/z* 291 $(M+H)^+$; Elemental analysis: Anal. calcd. For $C_{12}H_{19}O_6P$: C, 49.66; H, 6.60; Found C, 49.54; H, 6.51.

3.3.2. Diethyl(2,6-dichlorophenyl)(hydroxy)methylphosphonate (3h): Solid; IR (KBr): 3274 (OH), 1240 (P=O), 1043 (P-O-C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.17 (m, 3H, Ar-H), 5.83 (dd, J = 8 Hz & J = 9 Hz, 1H, CHP), 4.30-4.19 (m, 2H, O$\underline{CH_2}CH_3$), 4.11-4.04 (m, 1H, O$\underline{CH_2}CH_3$), 4.00-3.92 (m, 1H, O$\underline{CH_2}CH_3$), 1.37 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.17 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$); ^{13}C NMR ($CDCl_3$, 125.71 MHz): δ 145.7, 132.3 (2C), 129.6, 128.2, 114.2, 69.9 63.1, 55.9, 16.4 (2C); ^{31}P NMR ($CDCl_3$, 202.37 MHz): δ 22.40; ESI-MS: *m/z* 314 $(M+H)^+$; Elemental analysis: Anal. calcd. For $C_{11}H_{15}Cl_2O_4P$: C, 42.19; H, 4.83; Found C, 42.10; H, 4.79.

3.3.3. Diethyl (4-(diethylamino)phenyl)(hydroxy)methylphosphonate (3m): Solid; IR (KBr): 3273 (OH), 1240 (P=O), 1042 (P-O-C) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36 (d, J = 8 Hz, 2H, Ar-H), 7.18 (d, J = 8 Hz, 2H, Ar-H), 5.19 (brs, 1H, OH), 4.94 (d, J = 10 Hz, 1H, CHP), 4.08-3.92 (m, 3H, O$\underline{CH_2}CH_3$), 3.85-3.79 (m, 1H, O$\underline{CH_2}CH_3$), 3.12-2.98 (m, 4H, N$\underline{CH_2}CH_3$), 1.26-1.17 (m, 6H, OCH$_2\underline{CH_3}$), 1.15-1.08 (m, 6H, NCH$_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 125.71 MHz): δ 148.7, 134.0 (2C), 128.3, 127.1, 126.2, 70.6, 63.2, 63.0, 33.8 (2C), 18.3 (2C), 16.2 (2C). ^{31}P NMR ($CDCl_3$, 202.37 MHz): δ 22.13. ESI-MS: *m/z* 316 $(M+H)^+$; Elemental Analysis: Anal. calcd. For $C_{15}H_{26}NO_4P$: C, 57.13; H, 8.31; N, 4.44; Found C, 56.98; H, 8.25; N, 4.36.

3.3.4. Diethyl hydroxy(perfluorophenyl)methylphosphonate (3n): Solid; IR (KBr): 3273 (OH), 1240 (P=O), 1042 (P-O-C) cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.23 (brs, 1H, OH), 4.89 (d, J = 10 Hz, 1H, CHP), 4.25-4.18 (m, 2H, O$\underline{CH_2}CH_3$), 4.14-4.04 (m, 1H, O$\underline{CH_2}CH_3$), 4.01-3.93 (m, 1H, O$\underline{CH_2}CH_3$), 1.17 (t, J=7 Hz, 3H, OCH$_2\underline{CH_3}$), 1.15 (t, J=7 Hz, 3H, OCH$_2\underline{CH_3}$). ^{13}C NMR ($CDCl_3$, 125.71 MHz): δ 151.3, 149.6, 145.1, 137.2 (2C), 118.7, 71.8, 62.8, 62.4, 16.5, 16.3. ^{31}P NMR ($CDCl_3$, 202.37 MHz): δ 22.28. ESI-MS: *m/z* 335 $(M+H)^+$; Elemental Analysis: Anal. calcd. For $C_{11}H_{12}F_5O_4P$: C, 39.54; H, 3.62; Found C, 39.47; H, 3.54.

3.3.5. Diethyl (hydroxy(quinolin-2-yl)methyl)phosphonate (3o): Solid; IR (KBr): 3248 (OH), 1256 (P=O), 1034 (P-O-C) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.32-7.28 (m, 6H, Ar-H), 4.83 (d, J = 10 Hz, 1H, CHP), 4.28-4.21 (m, 2H, O$\underline{CH_2}CH_3$), 4.13-4.07 (m, 1H, O$\underline{CH_2}CH_3$), 4.03-3.94 (m, 1H, O$\underline{CH_2}CH_3$), 1.27 (t, 3H, J = 7 Hz, OCH$_2\underline{CH_3}$), 1.19 (t, 3H, J = 7 Hz, OCH$_2\underline{CH_3}$); ^{13}C NMR ($CDCl_3$, 125.71 MHz): δ 163.2, 147.1, 134.8, 131.6, 128.5, 126.7, 125.6, 123.4, 120.6, 83.2, 62.8, 61.4, 18.4, 17.3; ^{31}P NMR ($CDCl_3$, 202.37 MHz): δ 23.24; ESI-MS: *m/z* 296 $(M+H)^+$; Elemental analysis: Anal. calcd. For $C_{14}H_{18}NO_4P$: C, 56.95; H, 6.14; N, 4.74; Found C, 56.85; H, 6.09; N, 4.65.

4. Conclusion

We report a novel use of Nano-TiO_2 as a catalyst for the synthesis of α-hydroxyphosphonates under solvent-free microwave irradiation condition within 4-10 min. The advantages of present methodology are green process, easy work up, less catalyst loading, its reusability, appreciably high product yields and less reaction time. Also how TiO_2 nanoparticles with high surface area accelerate the process is explained by plausible mechanism. These advantages makes the process be a valid one when compared to the existing methodologies for the formation of C-P bond and for its industrial use.

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