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An Efficient Synthesis of α-Aminophosphonates through Kabachnik-Fields Reaction Protocol by using Cobalt Chloride Doped Polyaniline as the Nano Catalyst

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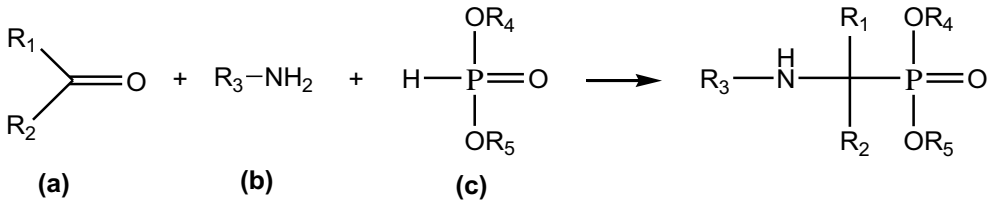
Abstract: Cobalt Chloride Doped Polyaniline (PANI-Co) was found to be a convenient catalyst for the synthesis of α-Aminophosphonates through Kabachnik-Fields Reaction Protocol through one-pot three-component reaction of using carbonyl compound (a), amine (b) and dialkylphosphite(c) at 80°C under solvent-free conditions. This new method provides advantages such as excellent yields (up to 93%), as well as the short duration of the reaction. PANI-Co composite was found to be efficient and easily recyclable catalytic heterogeneous system.



1. Introduction

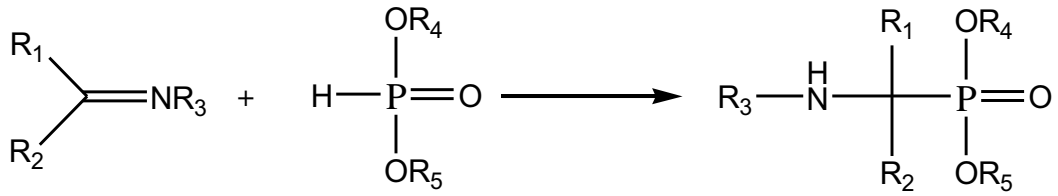
The Multicomponent reactions (MCR) are defined as the reaction in which three or more different reactant molecules react to form a product, where most, if not all of the atoms are incorporated in the final product. This reaction tool allows compounds to be synthesized in a few steps and usually in one-pot operation. The Multicomponent Reactions (MCRs) define the new horizons towards the development of organic synthesis. Obviously, due to this reason MCRs are underlined as important routes and protocols in organic synthesis and medicinal chemistry1.

In medicinal chemistry, bioisosteres are substituents or groups with similar physical or chemical properties which produce broadly similar biological behaviour. In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure. The main use of this term and techniques is related to pharmaceutical sciences.2Bioisosterism is used to reduce toxicity or modify the activity of the lead compound (LC), and may alter the metabolism of the lead.3

The coining of the term bioisosterism goes back to the pioneer work of Friedman and Thornber during the early 50s. Friedman4, recognizing the usefulness of the concept isosterism to design bioactive molecules, defined bioisosters as compounds which fit the definitions of isosteres and which exercise their biological activity of bioreceptor, whether through agonist or antagonist actions. Among the most recent numerous examples used in the strategy of bioisosterism for designing new pharmaco-therapeutically attractive substances, 5-7 there is a significant predominance on non-classic bioisosterism, distributed in distinct therapeutic categories.

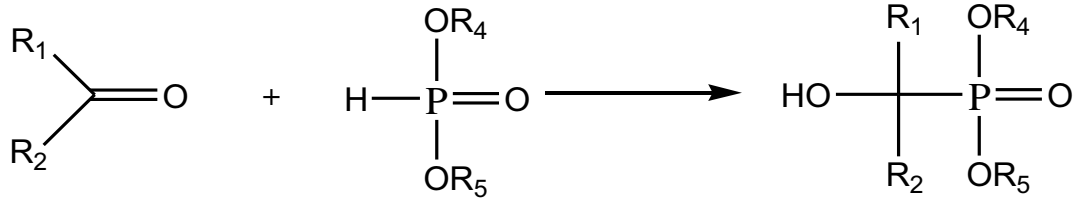
α-Aminophosphonic acids may be considered as phosphorus analogues of α-amino acids ("bioisosterism") and have received considerable attention owing to their pronounced biological activities. A large number of α-aminophosphonic acids and their phosphonate esters and a few short peptides of natural and synthetic origin bearing similar structural features exhibit enzyme inhibitory,8 antibiotic, antibacterial,9 antiviral,antifungal, herbicidal activities, antitumorand antihypertensive ones.10 As the biological activity of α-aminophosphonates is markedly influenced by the absolute configuration of the α-carbon atom directly linked to the phosphorous center,11 the synthesis of α-aminophosphonates and their derivatives with desired property constitutes an important task in organic synthesis.12

Various synthetic methods for α-aminophosphonic acids and α-aminophosphonates have been reported13 and the straightforward one is the addition of the compounds, containing P-H bond to the C=N- bond of imines (Pudovik reaction,14 Scheme 5.1).



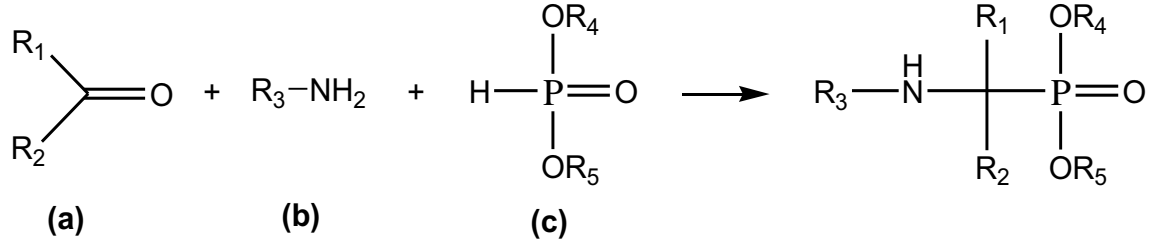
Scheme 5.1: Pudovik reaction

In fact, dialkylphosphites are able to undergo many addition reactions, including addition to the C=O bond to give α- hydroxyphosphonates (Abramov reaction,15 Scheme 5.2).



Scheme 5.2: Abramov reaction

However, the most remarkable pathway to the synthesis of α-aminophosphonates is the Kabachnik-Fields reaction,16 which is a one-pot, three-component procedure using carbonyl compound(a), amine (b) and dialkylphosphite(c) (Scheme 5.3).



Scheme 5.3: Kabachnik-Fields reaction

This process was discovered at a time, when multicomponent processes were rather "exotic birds"; from a modern point of view this protocol is obviously very attractive for combinatorial chemistry and has been rarely used for parallel synthesis.
This approach is especially satisfactory for reactions with aldehydes (R1=H); in contrast, only few examples of the Kabachnik-Fields reaction of rather simple ketones (mainly, acetone, acetophenone and cyclohexanone)17 have been documented. Thus, the synthetic potential of the Kabachnik-Fields reaction had not been developed in full scale in 20th century.
Keeping the green approach in the mind with the awareness of environmental issues and the synthetic importance of this reactions and our interest to develop the new synthetic route for the synthesis of α-aminophosphonates, we report a heterogeneous Cobalt Chloride Doped Polyaniline as Catalyst (PANI-Co) as an alternative, cheap, and efficient catalyst for the Kabachnik-Fields reaction. PANI-Co composite was found to be efficient. The said protocol provide an improved procedure for the synthesis of α-aminophosphonates under solvent free conditions. The heterogeneous Cobalt Chloride Doped Polyaniline (PANI-Co) as Catalyst has been proved recyclable and environmental friendly.

2. Experimental:

2.1 General:
All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. The UV-Visible spectra were recorded on Schimadzu make UV 1800 spectrophotometer at Department of Chemistry, JijamataMahavidyalaya, Buldana.

The IR spectra of the synthesized compounds were recorded on Nicolet Instruments Corporation, USA make MAGNA 550 spectrometer. The PMR spectra were recorded on Varian, USA make Mercury plus-300 MHz NMR spectrometer. The GC-MS analysis of synthesized compounds was performed on Hewlett Packard make GCD-1800A EI source analyzer at Sophisticated Analytical Instrument Facility (SAIF), IIT Bombay, Powai, Mumbai.

2.2 Preparation of PANI-Co composite as a catalyst:
The Cobalt Chloride Doped Polyaniline (PANI-Co) composite as Catalyst was prepared by the chemical doping method. The polyaniline was synthesized by the chemical oxidization method at low temperature (0 to 3^{0}**C**). Ammonium Persulphate and Hydrochloric Acid used as an oxidizing agent as received without further purification. 10 ml Aniline was first dissolve in 2M 100 ml Hydrochloric Acid (HCl) (Merk). Then this solution is kept in the ice bath below 5 ^{0}**C**temperature. Ammonium Persulphate solution (Usually 10%) was added to the above solution with constant stirring. This polymerization process were completed within the three to four hours and finally the green colored polyaniline was formed. It was washed with the hot dilute HCl and dried it in the oven for 24 Hours.

An appropriate amount of the Cobalt Chloride 0.1 M was dissolve in polyaniline (PANI) solution. Doping of cobalt was done by the chemical doping method. For uniform distribution of cobalt to form the Cobalt Chloride Doped Polyaniline (PANI-Co) composite stirring was continued for 2 hours. PANI-Co composite was formed and confirmed by the instrumental technique and used as the effective catalyst.

2.3 Preparation of α-aminophosphonates:
A mixture of aldehyde (10 mmol), amine (10 mmol), diethyl phosphite (10mmol), and 20 Wt. % of Cobalt Chloride Doped Polyaniline (PANI-Co) composite as a catalyst under solvent-free conditions were stirred at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate. Evaporation of the solvent followed by purification on silica gel afforded pure a-amino phosphonate.

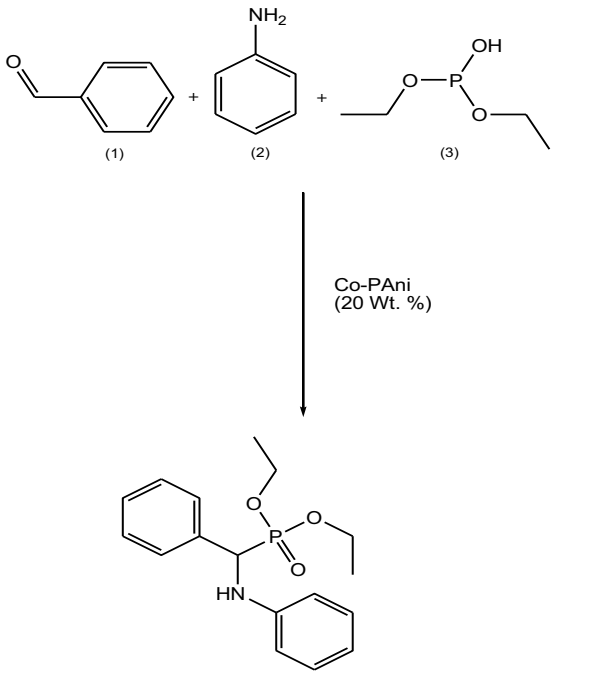
3. Results and Discussion:

Following α-Amino Phosphonates were prepared:

a) Diethyl-phenyl (phenylamino)-methylphosphonate
MF- $C_{17}H_{22}O_3NP$ MW- 319 Yield- 87%
b) Diethyl (4-methoxyphenyl)(phenylamino) methylphosphonate
MF- $C_{17}H_{24}O_4NP$ MW- 336 Yield- 80%
c) Diethyl (2-methoxyphenyl)(phenylamino) methylphosphonate
MF- $C_{17}H_{24}O_4NP$ MW- 336 Yield- 78%
d) Diethyl (2-chlorophenyl)(phenylamino) methylphosphonate
MF- $C_{17}H_{21}O_3ClP$ MW- 339 Yield- 76%
e) Diethyl (4-chlorophenyl)(phenylamino)methylphosphonate
MF- $C_{17}H_{21}O_3ClP$ MW- 339 Yield- 83%
f) Diethyl (3-nitrophenyl)(phenylamino) methylphosphonate
MF- $C_{17}H_{21}O_5N_2P$ MW-364 Yield- 93%
g) Diethyl (4-nitrophenyl)(phenylamino) methylphosphonate
MF- $C_{17}H_{21}O_5N_2P$ MW- 364 Yield- 91%
h) Diethyl (4-hydroxyphenyl)(phenylamino) methylphosphonate
MF- $C_{17}H_{22}O_4N$ MW- 304 Yield- 80%
i) Diethyl (3-methylphenyl)(phenylamino) methylphosphonate
MF- $C_{18}H_{24}O_3NP$ MW-333 Yield- 76%
j) Diethyl (4-methylphenyl)(phenylamino) methylphosphonate
MF- $C_{18}H_{24}O_3NP$ MW-333 Yield- 78%
k) Diethyl (4-bromophenylamino)(phenyl) methylphosphonate
MF- $C_{17}H_{21}O_3NBrP$ MW-398 Yield- 85%

Representative Data of Diethyl-phenyl (phenylamino)-methylphosphonate:

Reaction:



Diethyl- phenyl (Phenylamino)-methylphosphonate

Properties of Diethyl-phenyl (phenylamino)-methylphosphonate :

1. From analytical data, the molecular formula was found to be $C_{17}H_{22}O_3NP$.
   The molecular weight is 319.
2. **UV-VIS :Wavelength range :** 190nm to 1100nm
   λmax values are 274 nm and 224 nm.
3. **IR : Freq. Range-** 4000-6000 cm^{-1}.

Literature Value (cm^{-1})	**Absorption observed (cm^{-1})**	**Assignment**
845-725	738	P-O stretch (medium band)
900-690	854	=C-H out of plane bending
1350-1000	1190	C-N stretch (3^0 amine)
1300-1240	1253	P-O stretch (very strong band) one band
1440-1400	1437	P-C stretch

1465	1482	-CH_2 Bend
1600-1475	1535	Aromatic C=C ring stretch
2000-1667	1892	Weak overtone combination bands (mono substituted aromatic ring)
3000 (3000-2840)	2932	sp^3 CH stretch
3050-3010	3043	=C-H stretch sp^2 C-H

4. **PMR- Internal reference-**TMS

Solvent- CDCl3

The chemical shift can be corelated as follows

Peak observed in δ ppm	**Multiplicity**	**Inference**
1.30	t	-CH_3, 6H
4.25	s	-CH,1H
4.47	s	NH, 1H
4.51	dd	-CH_2, 4H
6.92-7.58	m	Ar-H, 10H

Mass range -10 - 2000 amu

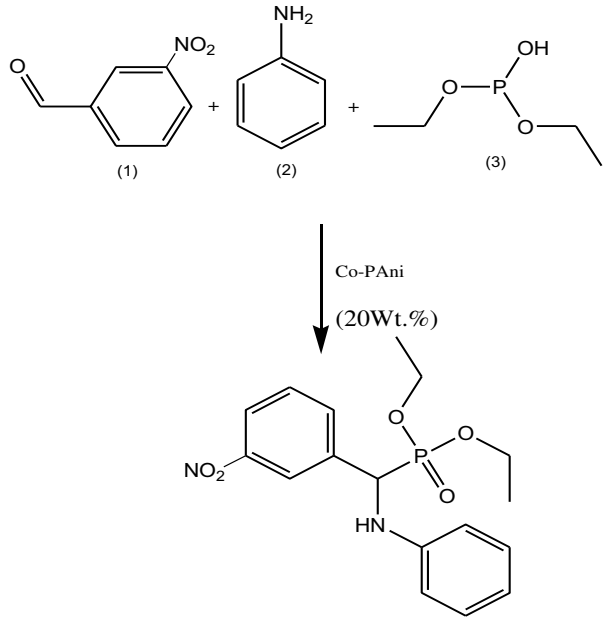
Mass resolution - 6000

Molecular Ion peak: 319

Base Peak: 237

Representative Data of Diethyl (3-nitrophenyl)(phenylamino) methylphosphonate:

Reaction:



Diethyl-phenyl (phenylamino)-methylphsphonate

Properties of Diethyl-phenyl (phenylamino)-methylphosphonate :

1. From analytical data, the molecular formula was found to be $C_{17}H_{21}O_5N_2P$.
   The molecular weight is 364.
2. **UV-VIS :Wavelength range :** 190nm to 1100nm

λmax values are 289.17 nm and 234.57 nm

3. **IR : Freq. Range-** 4000-6000 cm^{-1}.

Literature Value (cm^{-1})	**Absorption observed (cm^{-1})**	**Assignment**
690 and 780	684 and 772	Meta disubstituted ring (out of plane)
900-690	693	=CH out of plane bending
845-725	826	P=O stretch (medium band)
1350-1000	1209	C-N stretch (amine)
1300-1240	1274	P=O stretch (very strong one band)
1375	1337	$-CH_3$ Bend
1440-1400	1427	P-C stretch
1465	1451	$-CH_2$ Bend
1550-1490	1512	$C-NO_2$ Asym stretch (strong)

1600-1475	1554	Aromatic C=C ring stretch
3000 (3000-2840)	2852	SP^3 CH stretch

4. **PMR- Internal reference-**TMS

   Solvent- CDCl3

   The chemical shift can be corelated as follows

Peak observed in δ ppm	**Multiplicity**	**Inference**
1.43	t	$-CH_3$, 6H
4.40	s	-CH,1H
4.57	s	-NH, 1H
4.72	dd	$-CH_2$, 4H
6.74-7.42	m	Ar-H, 10H

5. **Mass range** -10 - 2000 amu

   Mass resolution - 6000

   Molecular Ion peak: 364

   Base Peak: 282

4. Conclusion:

In above reported work, the green methodology for the synthesis of the α-aminophosphonates has been developed. The said protocol provides reaction route for new catalytic reagent viz. Cobalt Chloride Doped Polyaniline (PANI-Co) composite with greater efficiency, simpler operational procedure, and simple reaction condition. Also, it provides a higher yield of latent bioactive α-aminophosphonates up to 93 %.

5. Acknowledgement:

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