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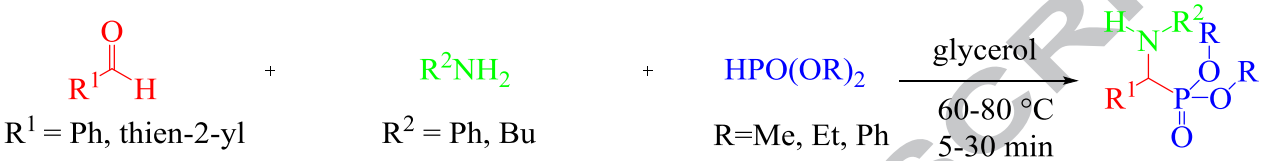

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A catalyst-free synthesis of α-aminophosphonates in glycerol

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ABSTRACT

A simple and efficient method is described using glycerol as a solvent in the catalyst-free synthesis of α-aminophosphonates in high purity. The products are prepared by the Kabachnik–Fields reaction from amines, phosphites, and carbonyl compounds. The method is does not require a toxic catalyst.

α-Aminophosphonic acids and their derivatives exhibit a wide range of biological properties,[1] and are able to function as α-aminocarboxylic acid surrogates.[2] α-Aminophosphonate esters have attracted attention because not only are they biologically attractive peptide mimics of α-amino acids, but they also exhibit intriguing biological activities.[3] α-Aminophosphonates play a significant role in hapten design for antibody generation.[4] α-Aminophosphonic acids act as herbicides,[5] and antibacterial,[1,6] antiviral and antitumor agents.[7] Owing to their widespread applications, different strategies for the synthesis of these compounds have been designed. One known approach in this field is Kabachnik–Fields reaction.[8] In this reaction, a carbonyl compound (aldehyde or ketone), an amine and a di- or trialkyl phosphite react in a one-pot fashion in the presence of either a Lewis acid or a Brønsted acid. A variety of acid catalysts such as CAN,[9] $Mg(ClO_4)_2$,[10] $TaCl_5$–SiO_2,[11] an ethereal solution of $LiClO_4$ [12] and other catalysts such as quinine,[13] and a bis(8-quinolinolato) (TBOx) aluminum(III) complex[14] have been used in methylene chloride or other organic solvents to promote this addition. Since the amines and the water that form during imine formation can decompose or deactivate some of the catalysts, these reactions cannot be carried out in a 'one-pot' operation.

However, organic solvents, particularly chlorinated hydrocarbons, are high on the list of damaging chemicals because of their volatile nature, considerable toxicity, and their use in large quantities. Additionally, the metal halides utilized as catalysts in these procedures are not all ecofriendly, and often entail severe environmental pollution during the waste disposal process. These problems encourage researchers to design new green and catalyst-free strategies, such as solvent-free methods or the use of media with dual solvent/catalyst roles, e.g. trifluoroethanol (TFE)[15] and deep eutectic solvents (DES)[16] for chemical synthesis.

Glycerol is produced as a co-product during the production of long-chain carboxylate salts used as soaps, and because of the presence of three hydroxyl groups that are responsible for its solubility in water and its hygroscopic nature, it can act as a hydrogen bond donor and water attracting agent. Glycerol is a simple polyol, and a colorless, odorless, viscous liquid that is widely used in pharmaceutical formulations, and is one of the most important biomass-derived materials. It is the simplest trihydric alcohol and its chemical nature is similar to that of other alcohols. Glycerol is widely used as a solvent because it can accelerate considerably the rate of an organic reaction. The primary hydroxyls are usually more reactive than the secondary group, and the first OH to react does so more readily than the second.[17] Glycerol can be considered as "organic water" since, like water, it is abundant, biodegradable, inexpensive, non-toxic, highly polar, immiscible with hydrocarbons, is able to form strong hydrogen-bond networks and can dissolve a wide range of organic and inorganic compounds, including transition metal catalysts.[18]

In addition, compared to water, it has the advantage of a higher boiling point, lower vapor pressure, and is able to dissolve organic compounds usually immiscible with water.[19]

One of the possible uses of glycerol and its derivatives is as a solvent. Just like the majority of organic substances, organic solvents are petroleum-derived, and many are volatile, toxic, and harmful compounds. Glycerol has previously been used as a solvent for the aza-Michael addition of aromatic amines to electron-deficient α,β-unsaturated ketones.

Based on these reports,[8, 20] we decided to explore the possibility

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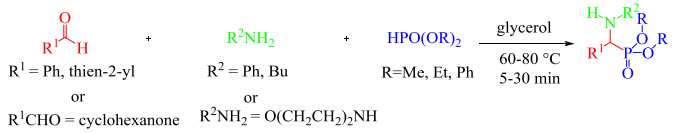
of executing a three-component Kabachnik–Fields reaction for the preparation of α-aminophosphonates from amines, phosphites, and carbonyl compounds in glycerol (Scheme 1). Glycerol has been described as an effective promoting medium for these kinds of reactions which are conventionally carried out using acid catalysts.[21]



Scheme 1: Non-catalyzed Kabachnik–Fields reaction in glycerol

In order to establish the optimum conditions for the reaction, the results of the model reaction between aniline, benzaldehyde and dimethyl phosphite in conventional solvents were compared with glycerol (Table 1). The use of glycerol led to a much better result than with conventional organic solvents including toluene, THF, CH_2Cl_2, $CHCl_3$, CH_3CN, methanol, ethanol and water at room temperature for 10 hours. Glycerol has been used as a green solvent in the synthesis of phosphonates in examples where it facilitated the solubility of the organic reagent.

Table 1: Comparison of the results of the synthesis of α-aminophosphonates in different solvents [a]

Entry	Solvent	Yield (%)[b]
1	toluene	0
2	$CHCl_3$	0
3	THF	0
4	CH_2Cl_2	0
5	CH_3CN	trace
6	MeOH	trace
7	EtOH	25
8	H_2O	40
9	glycerol	70

[a] Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), dimethyl phosphite (1.1 mmol), solvent, room temperature, 10 h.
[b] Yield of isolated pure product

Subsequently we determined the optimum temperature for this model reaction. Temperature optimization revealed that 60-80 °C was suitable to provide the best yield of the α-aminophosphonate (Figure 1).

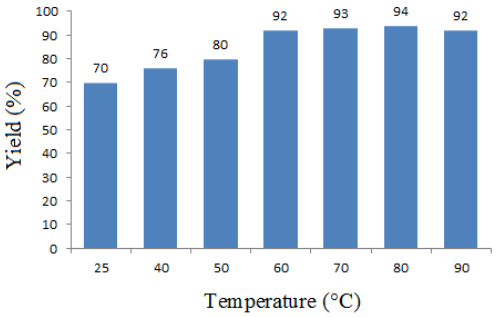


Figure 1: Effect of the reaction temperature on aminophosphonate yield

Several α-aminophosphonates were prepared using the optimized reaction conditions (Figure 2). Aromatic aldehydes generated phosphonate derivatives in good to excellent yields and the products were characterized by comparison of their physical data with those of known compounds.[22,23] Acid-sensitive aldehydes such as thiophene-2-carbaldehyde and cinnamaldehyde underwent the reaction with aniline and dimethyl phosphite to produce the corresponding α-aminophosphonates. Several other aniline derivatives were coupled with aldehydes and phosphite derivatives to give good yields of the desired products. Both aromatic and aliphatic amines provided excellent yields of products (70–95%) in short reaction times. Also, cyclohexanone gave the corresponding phosphonate in good yield (80%). Furthermore, diethyl phosphite and diphenyl phosphite demonstrated good activity.

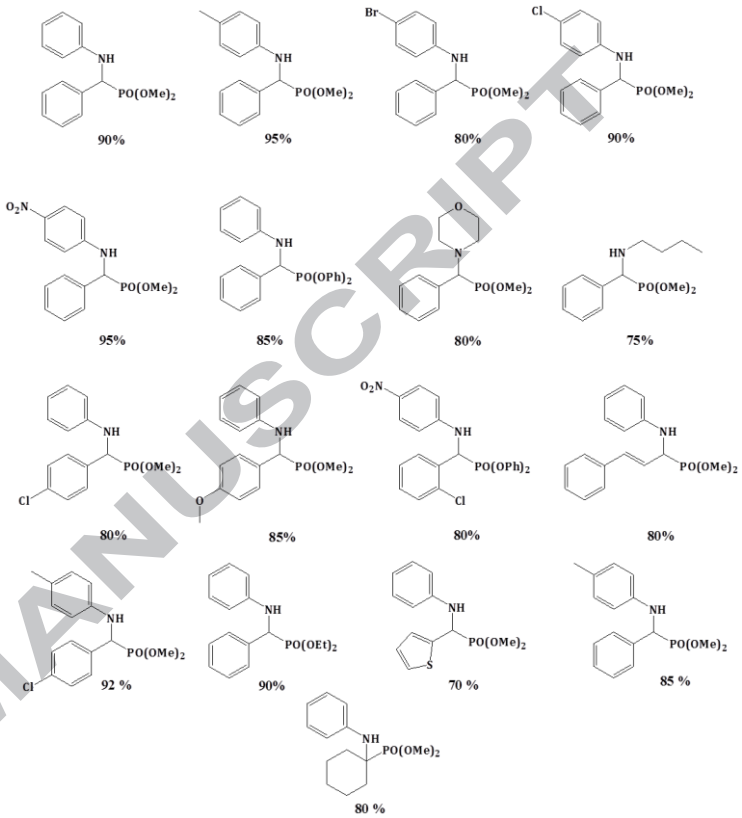
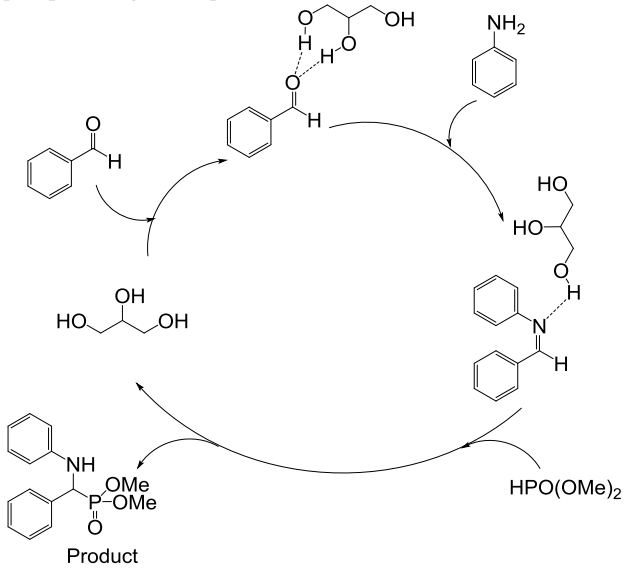


Figure 2: Products of the Kabachnik–Fields reactions of various carbonyl compounds, amines and phosphites in glycerol

In this case, the hydrogen-bonding activation of glycerol resulted in catalysis of the Kabachnik–Fields reaction (Scheme 2). According to this mechanism, glycerol catalyzed the in situ formation of the imine intermediate through generation of hydrogen bonds between the hydroxyl groups and the oxygen atom of the carbonyl group. In the presence of glycerol, the imine carbon is attacked by dimethyl phosphite to give the product.[24]



Scheme 2: A plausible mechanism for the one-pot synthesis of α-aminophosphonates in glycerol

The recyclability of glycerol was investigated in the case of the reaction of aniline, benzaldehyde and dimethyl phosphite. Upon completion of the reaction, the mixture was extracted with hexane–ethyl acetate. The glycerol phase (glycerol is insoluble in hydrocarbons) was dried and reused up to four more times without any significant reduction in the product yield (from 90% on the first use to 80% on the fourth) (Table 2).

Table 2: Reusability of glycerol in the Kabachnik–Fields reaction[a]

Run	Isolated Yield (%)[b]
1	90
2	87
3	82
4	80

[a] Reaction conditions: benzaldehyde (1 mmol), aniline (1.1 mmol), dimethyl phosphite (1 mmol), 20 min. [b] Yield of isolated pure product

Finally, a comparative study of this system with our recent report on the one-pot synthesis of α-aminophosphonates in the presence of dehydroascorbic acid (DHAA) capped magnetite nanoparticles[24] revealed that this system is comparable in terms of the reaction time and catalyst-free conditions.

Glycerol is one of the renewable resources produced as a waste chemical during the production of fatty acids, biofuels and biolubricants in quantities greater than the current demand. The abundant availability of glycerol as a waste at low cost has drawn much attention aimed toward its use in academia and industry.

In conclusion, we have shown that glycerol combines the advantages of water (low toxicity, low cost, ready availability, renewability) and ionic liquids (high boiling point, low vapor pressure). The advantages of glycerol for this synthesis of α-aminophosphonates include: (i) the non-assistance of acid catalysts, which not only simplifies the work-up procedure and minimizes the generation of waste, but also allows the use of acid-sensitive substrates; (ii) easy separation of the reaction products; and (iii) no volatile organic solvent was required for the reaction to occur.

Acknowledgments

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22. *General procedure for the synthesis of α-aminophosphonates in glycerol:* A mixture of carbonyl compound (1 mmol), amine (1 mmol) and phosphite (1.1 mmol) was stirred at 60-80 °C in glycerol (4 mmol) for 5-30 min. After completion of the reaction as indicated by TLC, the mixture was extracted with EtOAc. The combined organics were dried and evaporated under reduced pressure. The residue was purified by recrystallization from CH_2Cl_2/*n*-hexane. The identity of the products was confirmed by comparison of their spectroscopic data with literature data.
23. Dimethyl 1-(phenylamino)cyclohexylphosphonate: yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.51 (m, 6H), 1.55–2.12 (4H, m), 3.63 (d, *J* = 10.4 Hz, 3H), 3.65 (d, *J* = 10.4 Hz, 3H), 4.50 (br s, 1 H), 7.01 (t, *J* = 7.1 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.17 (t, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8, 26.6, 26.1, 53.2 (d, *J* = 7.4 Hz), 54.1 (d, *J* = 7.4 Hz), 66.8 (d, *J* = 155.1 Hz), 118.4, 118.5, 130.1, 146.7.
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