GRAPHENE OXIDE AS RECYCLABLE CATALYST FOR ONE-POT SYNTHESIS OF \( \alpha \)-AMINOPHOSPHONATES

Kiran B. Dhopte, Dnyaneshwar S. Raut, Anand V. Patwardhan, and Parag R. Nemade

1Department of Chemical Engineering, Institute of Chemical Technology, N. Parekh Marg, Mumbai, Maharashtra, India
2Department of Chemistry, Dynopasak College, Parbhani, Maharashtra, India
3Department of Chemical Engineering and Department of Oils, Oleochemicals, and Surfactant Technology, Institute of Chemical Technology, N. Parekh Marg, Mumbai, Maharashtra, India

GRAPHICAL ABSTRACT

Abstract We report the synthesis of \( \alpha \)-aminophosphonates from aromatic aldehydes, aromatic and aliphatic amines, and trimethylphosphite (Kabachnik–Fields reaction) using a “carbocatalyst,” graphene oxide, at room temperature with excellent yield and recyclability. Enhanced catalytic activity of graphene oxide as compared to other catalysts studied is possibly due to the presence of carboxylic acid and hydroxyl groups.

Keywords Aldehyde; amine; \( \alpha \)-aminophosphonates; carbocatalyst; graphene oxide

INTRODUCTION

\( \alpha \)-Aminophosphonates are structurally and biologically analogous to amino acids, and hence their synthesis has attracted much interest. Their applications span from antitubercular, antioxidant, antimicrobial, antibacterial, and anticancer agents to fungicides, etc.[1–6] Lewis acids such as SnCl\(_4\),[7] tin(II) salts,[8] Bi(OTf)\(_3\),[9]
nanoceria, BF₃SiO₂, Yb(OTf)₃, zirconocenebis (perfluorobutanesulfonate), and AlCl₃ have been reported to catalyze the synthesis of α-aminophosphonates but with reported disadvantages such as high cost, large amounts required, difficult separation, limited reuse potential, and moisture instability.

Recent trends in chemical research have focused on developing metal-free synthetic routes to minimize wastes, coupled with reuse of catalysts to decrease the environmental footprint. Metal-free, environmentally friendly, synthetic protocols for replacement of Lewis acid catalysts using ultrasound, organocatalysts (tartaric acid, oxalic acid, (S)-1-acetyl-N-tosylpyrrolidine-2-carboxamide etc.), baker’s yeast, sodium dihydrogenphosphate, and amberlyst-15 have been reported. However, these catalysts suffer from various drawbacks such as long reaction times, limited recyclability, or difficulty in isolating the catalyst for reuse because of its homogeneous nature, expense, or requirement for large amount of catalyst.

Recently, much attention has been focused on the use of carbonaceous materials such as natural graphite, activated carbon, reduced graphene oxide, and functionalized carbon material as heterogeneous catalysts as well as catalyst supports. Graphene oxide has been widely reported as an efficient catalyst for various organic transformations, replacing metal-based traditional pathways and is commonly known as “carbocatalyst.” Graphene oxide exhibits localized charge distribution on the account of conjugated aromatic skeleton and functional groups such as -COOH, -OH, epoxide, etc., which makes it a suitable material for catalyst support. Graphene oxide is an excellent acidic catalyst with significant number of acid functional groups, inherently insoluble nature, low toxicity, and ease of synthesis, separation, and reuse. The reaction is benefitted by the presence of additional acids, wherein large number of acidic sites on graphene oxide are mechanistically advantageous. As the reaction proceeds via charge stabilization on imine intermediate followed by phosphite attack, polar solvents are expected to enhance the reaction. Graphene oxide disperses easily in polar solvents, and hence graphene oxide dispersed in polar solvents is expected be an efficient “green” catalyst to replace environmentally hazardous Lewis acid catalysts. Herein, we report the use of graphene oxide as heterogeneous catalyst for the one-pot synthesis of α-aminophosphonates from aliphatic and aromatic amines, aromatic aldehydes, and trimethylphosphite at room temperature with excellent yield, low catalyst loading, and recyclability of catalyst.

RESULTS AND DISCUSSION

Catalyst Characterization

The presence of various functional groups on both edges of graphene oxide sheets after successful exfoliation of natural graphite powder under strong oxidizing conditions were characterized by Fourier transform infrared (FTIR) spectroscopy, x-ray diffraction (XRD), zeta potential, and high resolution transmission electron microscope (HR-TEM) analysis. FTIR spectrum (Fig. 1a) shows a broad stretching band at 3457 cm⁻¹, which can be attributed to hydroxyl groups (υ O-H), whereas a sharp band at 1745 cm⁻¹ confirms the presence of carbonyl groups (υ C=O) in carboxylic acid. Additional bands at 1325 cm⁻¹ and 1048 cm⁻¹ can be attributed to the
presence of ($\nu$ C-O) stretching and epoxy groups respectively, thereby confirming the presence of hydroxyl, carboxylic, and epoxy groups.

Figure 2 shows the XRD pattern of both natural graphite powder and graphene oxide (GO). XRD spectra of natural graphite powder (Fig. 2a) display a sharp peak at $2\theta = 26.8$, corresponding to a d-spacing of 0.33 nm, while the corresponding peak in the GO spectra (Fig. 2b) is present at $2\theta = 11.6$, corresponding
to (001) reflection and indicating an interlayer spacing of $d = 0.76$ nm. This significant increment in the interlayer spacing can be ascribed to the insertion of functional groups on both planes as well as edges of GO sheets. Figure 3 shows an HR-TEM image of GO nanosheets, confirming that GO is made up of only a few layers of GO as opposed to the flakes of graphite. This observation is significant as it indicates that the GO nanosheets will exhibit much larger surface area than graphite flakes and hence are expected to show greater catalytic activity.

Figure 4 gives $\zeta$ potential ($-34.8$ mV) of dispersed GO, which shows the localized surface charge distribution due to the presence of various functional groups. Uniformly dispersed GO plays a key role for increased catalytic performance due to high mobility of surface charges, thereby stabilizing GO anions. Zeta potential

| Zeta Potential (mV) | Mean (mV) | Area (%) | Width (mV) |
|---------------------|-----------|----------|-------------|
| -34.8               | -34.8     | 100.0    | 9.72        |
| Zeta Deviation (mV) | 9.72      | 0.00     | 0.00        |
| Conductivity (mS/cm)| 0.0250    | 0.00     | 0.00        |

**Result quality: Good**

Figure 4. Zeta potential result of graphene oxide.
value (i.e., \(-34.8 \text{ mV}\)) gives clear evidence of the presence of negatively charged carboxylate groups, which selectively catalyze Kabachnik–Fields reaction for synthesis of \(\alpha\)-aminophosphonates.

**Catalyst Screening**

The activity of the catalyst was studied by measuring the yield of \(\alpha\)-aminophosphonate in which 3 mg of GO catalyst was dispersed in solvents containing aromatic aldehyde, amine (1 mmol), and trimethylphosphite in a stoichiometric ratio at room temperature under constant stirring. Table 1 presents a comparative study of yields of reaction among benzaldehyde, aniline, and trimethylphosphite as depicted in Scheme 1 using different catalysts. Graphene oxide gives better yield as well as shorter reaction times than both Indion-130, a strongly acidic resin with sulfonic acid groups, and Indion-652, a weakly acidic resin with carboxylic acid groups. It must be noted that stannic chloride, a Lewis acid, shows slightly better yield for the same reaction time without recyclability. Reduced GO, which is structurally similar but does not have as many acidic groups as are present in GO, failed to catalyze the reaction, elucidating the beneficial effect of acidic groups present on GO and confirming the carboxylate-mediated pathway for the reaction.

The effects of solvents such as water, methanol, ethanol, dichloromethane, and toluene on the reaction were studied and are presented in Table 2. Because the reaction is aided by polar solvents and GO disperses effectively in polar solvents, the reaction performance is expected to be better in polar solvents than in a nonpolar solvent. Among the solvents studied, methanol was found to be the most effective solvent, whereas toluene was found to be a poor solvent for this reaction. In toluene, only trace yields were observed, due to lack of dispersion of GO in toluene. Water was also found to be a poor solvent with a reaction yield of only 25\% even though it is polar and GO disperses excellently in water. The poor reaction yield may perhaps be attributed to sensitivity of phosphite to water.

The effects of the presence of electron-donating and electron-withdrawing groups on aromatic aldehydes and aromatic/aliphatic amines on the catalytic activity of GO were studied and are presented in Table 3. The presence of electron-withdrawing groups at the meta position on aldehyde (entry 2b, Table 3)

| Entry | Catalyst | Catalyst loading | Time | Yield (\%)$^b$ |
|-------|----------|------------------|------|--------------|
| 1     | —        | —                | 10   | Trace        |
| 2     | Graphene oxide | 3 mg           | 3    | 88           |
| 3     | Reduced graphene oxide | 3 mg       | —    | —            |
| 4     | Indion-130 | 30 mg          | 4    | 88           |
| 5     | Indion-652 | 30 mg          | 7    | 85           |
| 6     | SnCl$_2$·H$_2$O | 10 (mol %) | 3    | 91           |

*Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), trimethylphosphite (1 mmol), graphene oxide (3 mg), methanol (3 mL), room temperature, and time (3 h).

*Isolated yield.
gives better yield as compared to presence of electron-donating groups on aldehyde (entries 3c–5e, Table 3). Both o-iodoaniline and ethylenediamine required longer reaction times as compared to other substrates studied (entries 10j and 11k, Table 3). Various aromatic amines substituted with electron-withdrawing groups react cleanly with expected yields (entries 7g–9i, Table 3).

One of the shortcomings of Lewis acid catalysts is their poor recyclability, which adds to the environmental load of the process. Graphene oxide catalyst employed for the reaction was, therefore, recycled to ascertain its reuse potential. The recycling efficiency of GO was confirmed by carrying out four consecutive runs after isolation from the reaction mixture. For isolation of catalyst, the reaction mixture was transferred to a separating funnel, where the dispersed GO particles settled at the bottom and were separated with ease. The separated catalyst was washed three times with methanol to remove traces of any organic material adsorbed on catalyst surface. This recycled catalyst exhibited sufficient catalytic activity and yield for reaction of benzaldehyde, aniline, and trimethylphosphite as per Scheme 1. No aggregation of GO occurred during catalyst recycling procedures; therefore, the catalyst maintains its dispersability on recycling. After recycling the catalyst four times, the catalyst was analyzed using FTIR spectroscopy to identify if the catalyst has undergone any functional modification during the reaction. A narrowing of the –OH peak and reduction in the intensity of carbonyl peak was observed (Fig. 1b); therefore there may be a reduction in the number of functional groups as the catalyst is recycled. However, the yield and catalytic efficiency of GO was found to be high, which confirms excellent recyclability (Fig. 5).

| Entry | Catalyst     | Yield (%) |
|-------|--------------|-----------|
| 1     | Water        | 25        |
| 2     | Methanol     | 88        |
| 3     | Dichloromethane | 81   |
| 4     | Ethanol      | 85        |
| 5     | Toluene      | Trace     |

*Reaction conditions: benzaldehyde (1 mmol), aniline (1 mmol), trimethylphosphite (1 mmol), graphene oxide (3 mg), methanol (3 mL), room temperature, time (3 h).

*Isolated yield.
Table 3. Graphene oxide-catalyzed synthesis of α-aminophosphonates<sup>a</sup>

| Entry | Aldehyde | Amine | Product | Time (h) | Yield<sup>b</sup> (%) |
|-------|----------|-------|---------|---------|-----------------------|
| 1a    | \(\text{C}_6\text{H}_5\text{CHO}\) | \(\text{C}_6\text{H}_5\text{NH}_2\) | \[\text{C}_6\text{H}_5\text{NH}\text{P}(-\text{O})\text{OCH}_2\text{OCH}_3\] | 3          | 88                    |
| 2b    | \(\text{C}_6\text{H}_5\text{CHO} \text{Cl}\) | \(\text{C}_6\text{H}_5\text{NH}_2\) | \[\text{C}_6\text{H}_5\text{NH}\text{P}(-\text{O})\text{OCH}_3\] | 3          | 85                    |
| 3c    | \(\text{C}_6\text{H}_4\text{NH}_2\text{CHO}\) | \(\text{C}_6\text{H}_5\text{NH}_2\) | \[\text{C}_6\text{H}_4\text{NH}\text{P}(-\text{O})\text{OCH}_3\] | 4          | 82                    |
| 4d    | \(\text{C}_6\text{H}_5\text{CHO} \text{OH}\) | \(\text{C}_6\text{H}_5\text{NH}_2\) | \[\text{C}_6\text{H}_5\text{NH}\text{P}(-\text{O})\text{OCH}_3\] | 5          | 81                    |
| 5e    | \(\text{C}_6\text{H}_5\text{CHO} \text{MeO}\) | \(\text{C}_6\text{H}_5\text{NH}_2\) | \[\text{C}_6\text{H}_5\text{NH}\text{P}(-\text{O})\text{OCH}_3\] | 6          | 86                    |

<sup>a</sup> Conditions: catalyst (Graphene oxide), solvent (water), temperature (room temperature), reaction time (2-6 h), yield determined by NMR spectroscopy.

<sup>b</sup> Yield values are given in %.
| Entry | Aldehyde | Amine | Product | Time (h) | Yield\(^b\) (%) |
|-------|----------|-------|---------|----------|-----------------|
| 6f    |          |       | ![Product 6f](image) | 7        | 78              |
| 7g    | ![Aldehyde 7g](image) | ![Amine 7g](image) | ![Product 7g](image) | 4        | 86              |
| 8h    | ![Aldehyde 8h](image) | ![Amine 8h](image) | ![Product 8h](image) | 4        | 86              |
| 9i    | ![Aldehyde 9i](image) | ![Amine 9i](image) | ![Product 9i](image) | 4        | 78              |
| 10j   | ![Aldehyde 10j](image) | ![Amine 10j](image) | ![Product 10j](image) | 5        | 75              |

(Continued)
EXPERIMENTAL

All reagents were purchased from commercial sources and used as received. Natural graphite flakes (325 mesh, Alfa Aesar), potassium carbonate (S D Fine Chem. Ltd., Mumbai), sulfuric acid (99%, Merck), nitric acid (99%, Merck), hydrogen peroxide (30%, S D Fine Chem. Ltd., Mumbai), amines (99% Sigma Aldrich), trimethylphosphite (99%, Lobachem), and aldehydes (Sigma Aldrich) were used without any further purification.

General Procedure for Synthesis of α-Aminophosphonates

Aromatic aldehyde (1 mmol), amine (1 mmol), and trimethyl phosphite (1 mmol) were mixed with well-dispersed GO (3 mg) in methanol and stirred at room temperature except for diamine (entry 11k, Table 3), where the molar amount of
carbonyl compound and phosphite was twice as much as the amine. The progress of the reaction was monitored by thin-layer chromatography (TLC) using a solvent system consisting of a mixture of hexane and ethyl acetate (7:3). After completion, the catalyst was separated from the reaction mass by decantation. The reaction mass was then quenched with 5% NaHCO₃ solution (3 mL). Crude product was extracted with dichloromethane (5 mL × 3). The organic layer was again washed with 5% brine (3 mL) solution and dried over sodium sulfate for an appropriate time. The crude product was analyzed without further purification using various analytical techniques such as mass spectrometry (MS), ¹H NMR, ¹³C NMR, IR, and elemental analysis techniques.

CONCLUSIONS

In conclusion, we have demonstrated a simple and environmentally friendly methodology for the one-pot synthesis of ω-aminophosphonates from aromatic aldehydes, both aliphatic and aromatic amines, and trimethylphosphite using a metal-free pathway catalyzed by GO catalyst. Further, the catalyst offers simple workup, good yield, and excellent recyclability. We believe that this methodology can replace Lewis acid–catalyzed pathways for ω-aminophosphonate synthesis without loss in yield using similar reaction times and conditions.

FUNDING

The authors are thankful to the University Grants Commission of India for providing a Special Assistance Programme fellowship and to the Department of Science and Technology Funding for Infrastructure in Science and Technology program, government of India, for support.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

REFERENCES

1. Mulla, S. A. R.; Pathan, M. Y.; Chavan, S. S.; G ampl e, S. P.; Sarkar, D. RSC. Adv. 2014, 4, 7666–7672.
2. Varalakshmi, M.; Srinivasulu, D.; Rajasekhar, D.; Naga, R. C.; Sreevani, S. Phosphorus. Sulfur Silicon Relat. Elem. 2014, 89, 106–112.
3. Narayana, R. M. V.; Siva, K. B.; Balakrishna, A.; Reddy, C. S.; Nayak, S. K.; Reddy, C. D. Arkivoc 2007, 246–254.
4. Dake, S. A.; Raut, D. S.; Kharat, K. R.; Mhaske, R. S.; Deshmukh, S. U.; Pawar, R. P. Bioorg. Med. Chem. Lett. 2011, 21, 2527–2532.
5. Bhattacharya, A. K.; Raut, D. S.; Rana, K. C.; Polanki, I. K.; Khan, M. S.; Iramb, S. Eur. J. Med. Chem. 2013, 66, 146–152.
6. Smith, W. W.; Bartlett, P. A. 1998. J. Am. Chem. Soc. 1998, 120, 4622–4628.
7. Laschat, S.; Kunz, H. Synthesis 1992, 112, 90–95.
8. Gallardo-Macias, R.; Nakayama, K. Synthesis 2010, 1, 57–62.
9. Banik, A.; Batta, S.; Bandyopadhyay, D.; Banik, B. K. *Molecules* **2010**, *15*, 8205–8213.
10. Agawane, S. M.; Nagarkar, J. M. *Tetrahedron Lett.* **2011**, *52*, 3499–3504.
11. Reddy, M. V.; Dindulkar, S. D.; Jeong, Y. T. *Tetrahedron Lett.* **2011**, *52*, 4764–4767.
12. Shen, M.; Shang, S.; Song, Z.; Wang, D.; Rao, X.; Gao, H.; Wang, J. *Synth. Commun.* **2014**, *44*, 361–367.
13. Li, N.; Wang, X.; Qiu, R.; Xu, X.; Chen, J.; Zhang, X.; Chen, S.; Yin, S. *Catal. Commun.* **2014**, *43*, 184–187.
14. Manjula, A.; Rao, V.; Neelakantan, P. *Synth. Commun.* **2003**, *33*, 2963–2969.
15. Xia, M.; Lu, Y. D. *Ultrason. Sonochem.* **2007**, *14*, 235–240.
16. Dar, B.; Singh, A.; Sahu, A.; Patidar, P.; Chakraborty, A.; Sharma, M.; Singh, B. *Tetrahedron Lett.* **2012**, *53*, 5497–5502.
17. Gangwar, N.; Kasana, V. K. *Synth. Commun.* **2011**, *41*, 2800–2804.
18. Vahdat, S. M.; Baharfar, R.; Tajbakhsh, M.; Heydari, A.; Baghbanian, S. M.; Khaksar, S. *Tetrahedron Lett.* **2008**, *49*, 6501–6504.
19. Thorat, P. B.; Goswami, S. V.; Magar, R. L.; Patil, B. R.; Bhusare, S. R. *Eur. J. Org. Chem.* **2013**, *43*, 5509–5516.
20. Bhattacharya, A. K.; Mujahid, M. *Synth. Commun.* **2013**, *43*, 2583–2589.
21. Karimi-Jaberi, Z.; Amiri, M.; Sadeghi, N. *Synth. Commun.* **2010**, *40*, 2948–2953.
22. Sudhakar, D.; Siddaiah, V.; Rao, C. V. *Synth. Commun.* **2011**, *41*, 976–980.
23. Auer, E.; Freund, A.; Pietsch, J.; Tacke, T. *Appl. Catal. A.* **1998**, *173*, 259–271.
24. Fuente, A. M.; Pulgar, G.; González, F.; Pesquera, C.; Blanco. C. *Appl. Catal. A* **2001**, *208*, 35–46.
25. Gao, Y.; Ma, D.; Wang, C.; Guan, J.; Bao, X. *Chem. Commun.* **2011**, *47*, 2432–2434.
26. Planeix, J. M.; Coustel, N.; Coq, B.; Bretons, V.; Kumbhar, P. S.; Dutartre, R.; Geneste, P.; Bernier, P.; Ajayan, P. M. *J. Am. Chem. Soc.* **1994**, *116*, 7935–7936.
27. Su, C.; Loh, K. P. *Acc. Chem. Res.* **2013**, *46*, 2275–2285.
28. Wang, H.; Deng, T.; Wang, Y.; Cui, X.; Qi, Y.; Mu, X.; Hou, X.; Zhu, Y. *Green Chem.* **2013**, *15*, 2379–2383.
29. Dhakshinamoorthy, A.; Alvaro, M.; Concepción, P.; Fornés, V.; Garcia, H. *Chem. Commun.* **2012**, *48*, 5443–5445.
30. Verma, S.; Mungse, H. P.; Kumar, N.; Choudhary, S.; Jain, S. L.; Sain, B.; Khatri, O. P. *Chem. Commun.* **2011**, *47*, 12673–12675.
31. Mirza-Aghayan, M.; Boukherroub, R.; Nemati, M.; Rahimifard, M. *Tetrahedron Lett.* **2012**, *53*, 2473–2475.