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Graphical Abstract

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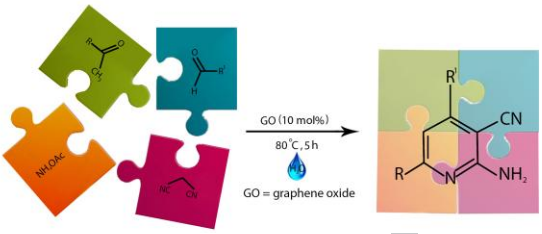

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Graphene oxide: a reusable and Metal-Free Carbocatalyst for the one-pot synthesis of 2-amino-3-cyanopyridines in water

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ABSTRACT

A one-pot synthesis of 2-amino-3-cyanopyridine derivatives has been demonstrated through the multicomponent reaction of aldehydes, ketones, malononitrile, and ammonium acetate using graphene oxide as a heterogeneous catalyst in water as a green medium. The graphene oxide catalyst is very mild, effective, and most of its activity is preserved after being reused for five times.

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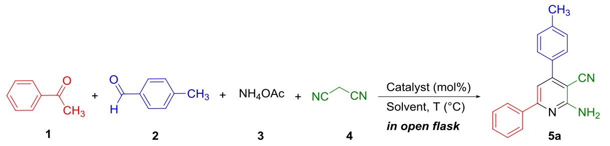
The pyridine nucleus has emerged as a privileged scaffold in view of its prevalence in numerous natural products[1] and its value in biological and medicinal chemistry.[2] Pyridines are also involved in coordination chemistry,[3] materials and surfaces,[4] supramolecular structures,[5] and organocatalysis.[6] Among the pyridine substructures, 2-amino-3-cyanopyridine derivatives have attracted significant attention due to their biological activities.[7] Also, these compounds serve as useful intermediates for the preparation of a variety of heterocyclic compounds.[8] Therefore, development of new methods for their synthesis is still a desirable goal. The most general route to these pyridine derivatives is the multicomponent reaction (MCR) of aldehydes, ketones, malononitrile and ammonium acetate. Recently, MCRs have gained great attention due to their applications in organic, medicinal and combinatorial chemistry,[9] providing rapid and straightforward access to complex molecules without the isolation of intermediates.[10] Due to the prominence of 2-amino-3-cyanopyridine derivatives, a variety of reagents and catalysts have been reported for the synthesis of these compounds.[1,2,7,11,12] However, most of these procedures have limitations such as the use of expensive metal catalysts[1,13] toxic solvents,[14] harsh reaction conditions,[15] complicated reaction procedures, and tedious multistep syntheses and work-up procedures.[7] In addition to environmental and economic concerns, these limitations narrow the reagent choice for the synthesis of these pyridine derivatives. Thus, the development of safe, efficient and metal-free catalytic systems for the synthesis of these compounds is still of importance. Heterogeneous catalysts appear to be a potential solution and carbon based materials[16, 17] can be useful for this purpose. Graphene oxide (GO, graphite oxide sheet), is the product of chemical exfoliation of graphite powder using strong oxidants and has been known for more than a century.[18] The harsh conditions introduce a wide range of polar oxygen-containing functional groups on the sheet surface and allow GO to function as a soft acid and mild oxidant. In fact, the presence of these functional groups enable GO to catalyze various organic transformations.[19-23] Despite this potential activity and advantages such as remarkable electronic and mechanical properties,[24] inexpensive nature, metal-free reactivity and easy recovery from the reaction media, GO has been relatively less explored as a catalyst or oxidant for facilitating organic transformations. Inspired by the potential activity of GO and continuing our ongoing interests in GO catalyzed organic reactions,[25,26] it was of interest to develop a green and safe protocol for the construction of 2-amino-3-cyanopyridines using GO as a heterogeneous catalyst. Herein, an eco-friendly procedure for the synthesis of 2-amino-3-cyanopyridines *via* a GO catalyzed four-component condensation is presented.

GO was synthesized by the oxidation of graphite powder using the modified Hummers method, followed by exfoliation in an aqueous solution. The prepared GO was characterized using XRD, TGA, FT-IR, UV/Vis and Raman spectroscopy and also with an AFM study to establish its characteristics (see ESI). In order to carry out the quantitative characterization of GO, such as the amounts of -COOH and -OH groups, a solid-based titrimetry method was used.[27] Based on the titration curves the amounts of -COOH and -OH were evaluated to be 0.17±0.01% and 2.65±0.02% respectively. The pH value of a dispersion containing GO was 4.6, at approximately 0.1 mg mL^{-1}, which is consistent with that reported in the literature.[19,23]

This study began by investigating the four-component condensation of acetophenone (1 mmol), ammonium acetate (1.5 mmol), 4-methylbenzaldehyde (1 mmol) and malononitrile (1.3 mmol) in the presence of catalytic GO under varying reaction conditions. As GO can be easily dispersed in H_2O, our initial goal was to use this green medium for the condensation reaction.[28] In fact, the use of water as the reaction medium has attracted much interest in the past few years mainly due to the economic and environmental advantages.[29]

Table 1. Optimization of the reaction conditions[a]



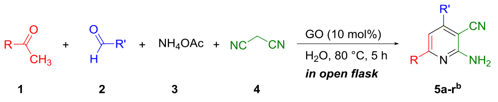
Entry	Catalyst (mol%)	Solvent (condition)	Time (h)	Yield (%)[b]
1[c]	-	H_2O, 80 °C	24	<10
2	GO (5)	H_2O, 80 °C	5	81
3[d]	**GO (10)**	**H_2O, 80 °C**	**5**	**90**
4	GO (15)	H_2O, 80 °C	5	88
5	GO (10)	H_2O, reflux	5	87
6	GO (10)	H_2O, r.t.	24	44
7	GO (10)	$CHCl_3$, reflux	5	70
8	GO (10)	THF, reflux	5	73
9	GO (10)	CH_3CN, reflux	5	84
10	GO (10)	EtOAc, reflux	5	80
11	GO (10)	Toluene, reflux	5	75
12	Graphite	H_2O, 80 °C	24	20
13[e]	r-GO	H_2O, 80 °C	24	36
14	Activated carbon	H_2O, 80 °C	24	57
15	Silica	H_2O, 80 °C	5	49
16	H-beta zeolite	H_2O, 80 °C	5	66
17	TiO_2	H_2O, 80 °C	5	40

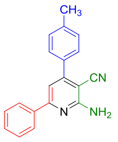
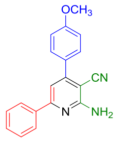
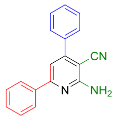
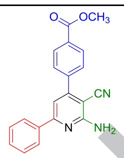
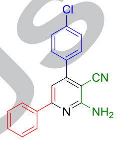
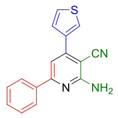
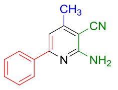
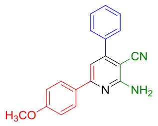
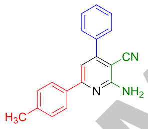
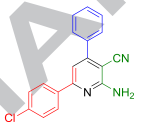
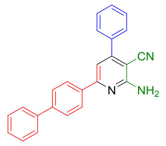
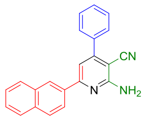
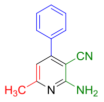
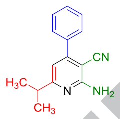
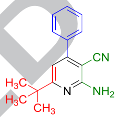
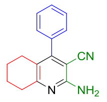
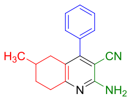
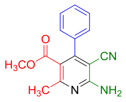
[a]Reaction conditions: acetophenone (1 mmol), 4-methylbenzaldehyde (1 mmol), ammonium acetate (1.5 mmol), malononitrile (1.3 mmol), catalyst (type indicated), open to air, solvent (3 mL). [b]Isolated yields. [c]Blank experiment without GO. [d]Bold value signifies the optimal reaction conditions. [e]r-GO = reduced graphene oxide.

In the absence of GO, only a 8% yield of product **5a** was obtained, even after 24 h (Table 1, entry 1). Product **5a** was obtained in 81% yield at 80 °C using 5 mol% GO loading and 5 h reaction time (entry 2). Further increase of the catalyst loading to 10 mol% resulted in an increased yield of product **5a** after 5 h (90%, entry 3). The yield could not be improved by further increasing the catalyst loading (entry 4). Increasing the reaction temperature did not show any beneficial effect (entry 5) but when the reaction temperature was decreased to room temperature, a low yield of product **5a** was found (44%, entry 6). The effect of different solvents on the reaction outcome was also investigated and the results showed that a significant enhancement of the reaction yield was accomplished when H_2O was used (entry 3). Other solvents afforded the desired compound in moderate yields (entries 7-11). Lower yields were observed when GO was replaced by other carbon based promoters such as natural flake graphite, hydrazine-reduced graphene oxide[17] and activated carbon under the same conditions, even upon prolonging the reaction time (24 h, entries 12-14). Moreover, the catalytic activities of GO were also compared with typical solid acid catalysts such as silica, H-beta zeolite and TiO_2 (entries 15-17) which clearly show that the GO affords better activity than commercially available solid acids.

With the optimized reaction conditions in hand, the scope of this methodology was explored (Table 2). It was observed that the reactions of substituted aldehydes, including aromatic aldehydes bearing electron donating (entries 1, 2) and electron withdrawing substituents (entries 4-6), with acetophenone proceeded smoothly and the rapid synthesis of pyridines **5a-f** occurred in good to excellent yields (89-97%). The substituent on the aromatic aldehyde showed slightly different effects on the yields. Reactions of electron deficient aromatic aldehydes afforded slightly better yields than electron rich ones. In addition to benzaldehyde derivatives, acetaldehyde as an aliphatic aldehyde, was also applied to this protocol, and the desired product **5g** was obtained in good yield (79%, entry 7). The scope of the reaction was further investigated using various ketones instead of acetophenone. The experimental results showed that the reactions proceeded smoothly and showed good to excellent yields. Benzaldehyde underwent a smooth condensation reaction with 4-methoxy-, 4-methyl and 4-chloroacetophenone in the presence of malononitrile, and ammonium acetate to afford the corresponding products **5h**, **5i** and **5j** in 84%, 88% and 92% yields, respectively (entries 8-10). Furthermore, it was found that the reaction of benzaldehyde with 4-acetylbiphenyl and 2-acetylnaphthalene resulted in the formation of products **5k** and **5l** in 84% and 86% yields, respectively. Similarly, the use of alkyl methyl ketones have been found to be pertinent to this methodology (entries 13-15). Sterically demanding ketones such as *iso*-propyl (entry 14) and *t*-butyl methyl ketone (entry 15) did not result in a decrease in the reactivity of the reaction, and afforded the products **5n** and **5o** with satisfying yields. Furthermore, cyclic ketones, including cyclohexanone and 4-methylcyclohexanone, were also found to be adept in efficiently furnishing the desired products **5p** and **5q** in good yields (entries 16, 17). Finally, methyl acetoacetate was used in the reaction, and pyridine derivative **5r** was also obtained in 92% yield.

Table 2: Synthesis of 2-amino-3-cyanopyridine derivatives catalyzed by GO[a]



					
Entry 1: **5a**, 90%	Entry 2: **5b**, 89%	Entry 3: **5c**, 96%	Entry 4: **5d**, 97%	Entry 5: **5e**, 94%	Entry 6: **5f**, 93%
					
Entry 7: **5g**, 79%	Entry 8: **5h**, 84%	Entry 9: **5i**, 88%	Entry 10: **5j**, 92%	Entry 11: **5k**, 84%	Entry 12: **5l**, 86%
					
Entry 13: **5m**, 75%[c]	Entry 14: **5n**, 83%	Entry 15: **5o**, 85%	Entry 16: **5p**, 86%	Entry 17: **5q**, 88%	Entry 18: **5r**, 92%

[a]Reaction conditions: ketone (1 mmol), aldehyde (1 mmol), GO (10 mol%), ammonium acetate (1.5 mmol), malononitrile (1.3 mmol), H_2O (3 mL), 80 °C, open to air. [b]Isolated yields. [c]Performed in a sealed tube.

The role of the carboxylic acid groups of the GO catalyst in the oxidative coupling of amines and the Strecker reaction has been investigated recently by Loh and co-workers.[19, 30] Therefore, to study the role of the active sites, the carboxylic acid groups of GO were transformed into carboxylate groups by treating GO with aqueous sodium hydroxide for 4 h at reflux. The FTIR spectrum of b-GO (base treated GO) showed that the band corresponding to the carboxyl stretching at 1712 cm^{-1} was reduced, whereas the new peak assignable to the carboxylate group increased in intensity (see ESI).

After this, b-GO was employed and it was found that the catalytic activity of b-GO in the model condensation reaction was low and only a trace amount of the desired product **5a** was observed. This finding confirmed that the carboxylic acid groups in GO have a pivotal role in the catalytic action. In order to determine whether residual Mn, which was used in the preparation of GO, was responsible for the observed reactivity, the synthesized GO was analyzed by inductively coupled plasma atomic emission spectroscopy (ICP-AES). The Mn content was measured to be <50 ppb *via* ICP-AES (roughly equivalent to other native metal contaminants found in the material).[31] Furthermore, the recyclability of GO was tested for the model reaction of acetophenone, ammonium acetate, 4-methylbenzaldehyde and malononitrile. The catalytic system maintained its high activity for six consecutive cycles (Table 3).

Table 3. Catalyst reusability study[a]

Run	1	2	3	4	5	6
Yield of **5a**[b]	90%	89%	89%	88%	86%	86%

[a]Reaction conditions: acetophenone (1 mmol), 4-methylbenzaldehyde (1 mmol), ammonium acetate (1.5 mmol), malononitrile (1.3 mmol) GO (10 mol%), H_2O (3 mL), 80 °C, open to air. [b]Isolated yield.

In conclusion, a simple, economical and highly efficient method for the synthesis of 2-amino-3-cyanopyridines by a one-pot, four-component condensation reaction using GO as a heterogeneous catalyst, in an open flask, was described. Various ketones and aldehydes were readily applied to this synthetic protocol, and the desired products were obtained in good to excellent yields. In addition, operational simplicity, high stability, easy separation and reusability of the catalyst with minimal loss of activity and the possibility to perform the transformation in green media are attractive features of this protocol.

Acknowledgments

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References and notes

1. Tang, J.; Wang, L.; Yao, Y.; Zhang L.; Wang, W. *Tetrahedron Lett.*, **2011**, *52*, 509-511.
2. Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.*, **2007**, *72*, 3443-3453.
3. Bora, D.; Deb, B.; Fuller, A. L.; Slawin, A. M. Z.; Woollins, J. D.; Dutta, D. K. *Inorg. Chim. Acta*, **2010**, *363*, 1539-1546.
4. Makiura, R.; Motoyama, S.; Umemura, Y.; Yamanaka, H.; Sakata, O.; Kitagawa, H. *Nat. Mater.*, **2010**, *9*, 565-571.
5. Šmejkal, T.; Breit, B. *Angew. Chem. Int. Ed.*, **2008**, *47*, 311-315.
6. De Rycke, N.; Couty, F.; David, O. R. P. *Chem. – Eur. J.*, **2011**, *17*, 12852-12871.
7. Reddy, T. R.; Reddy, G. R.; Reddy, L. S.; Jammula, S.; Lingappa, Y.; Kapavarapu, R.; Meda, C. L. T.; Parsa, K. V. L.; Pal, M. *Eur. J. Med. Chem.*, **2012**, *48*, 265-274.
8. Shishoo, C. J.; Devani, M. B.; Bhadti, V. S.; Ananthan, S.; Ullas, G. V. *Tetrahedron Lett.*, **1983**, *24*, 4611-4612.
9. Ren, Y.-M.; Jin, S.; Yan, H.-J.; Zhang, Z. *Catalysts*, **2015**, *5*, 1649.
10. Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.*, **2010**, *75*, 1674-1683.
11. Khaksar, S.; Yaghoobi, M. *J. Fluorine Chem.*, **2012**, *142*, 41-44.
12. Fatma, S.; Singh, D.; Ankit, P.; Mishra, P.; Singh, M.; Singh, J. *Tetrahedron Lett.*, **2014**, *55*, 2201-2207.
13. Reddy, L. S.; Reddy, T. R.; Reddy, N. C. G.; Mohan, R. B.; Lingappa, Y. *J. Heterocyclic Chem.*, **2014**, *51*, E104-E113.
14. Girgis, A. S.; Kalmouch, A.; Hosni, H. M. *Amino Acids*, **2004**, *26*, 139-146.
15. Shi, F.; Tu, S.; Fang, F.; Li, T. *Arkivoc*, **2005**, 137-142.
16. Liu, L.; Zhu, Y-P.; Su, M.; Yuan, Z.-Y. *ChemCatChem*, **2015**, *7*, 2765-2787.
17. Compton, O. C.; Nguyen, S. T. *Small*, **2010**, *6*, 711-723.
18. Hummers Jr., W. S.; Offeman, R. E. *J. Am. Chem. Soc.*, **1958**, *80*, 1339-1339.
19. Sengupta, A.; Su, C.; Bao, C.; Nai, C. T.; Loh, K. P. *ChemCatChem*, **2014**, *6*, 2507-2511.
20. Gao, X.; Zhu, S.; Li, Y. *Catal. Commun.* **2015**, *62*, 48-51.
21. Su, C.; Tandiana, R.; Balapanuru, J.; Tang, W.; Pareek, K.; Nai, C. T.; Hayashi, T.; Loh, K. P. *J. Am. Chem. Soc.*, **2015**, *137*, 685-690.
22. Roy, B.; Sengupta, D.; Basu, B. *Tetrahedron Lett.*, **2014**, *55*, 6596-6600.
23. Dreyer, D. R.; Jia, H.-P.; Bielawski, C. W. *Angew. Chem. Int. Ed.*, **2010**, *49*, 6813-6816.
24. Shin, H.-J.; Kim, K. K.; Benayad, A.; Yoon, S.-M.; Park, H. K.; Jung, I.-S.; Jin, M. H.; Jeong, H.-K.; Kim, J. M.; Choi, J.-Y.; Lee, Y. H. *Adv. Funct. Mater.* **2009**, *19*, 1987-1992.
25. Khalili, D. *Phosphorus Sulfur Silicon Relat. Elem.*, **2015**, *190*, 1727-1734.
26. Khalili, D.; Banazadeh, A. *Bull. Chem. Soc. Jpn.*, **2015**, *88*, 1693-1706.
27. Doroodmand, M. M.; Shafie, Z. *Sensor Actuat A*, **2014**, *207*, 32-38.
28. Guo, S.; Zhang, G.; Guo, Y.; Yu, J. C. *Carbon*, **2013**, *60*, 437-444.
29. Lindstroem, U. M. *Organic Reactions in Water*, Blackwell, Oxford, UK, 2007.
30. Su, C.; Acik, M.; Takai, K.; Lu, J.; Hao, S.-j.; Zheng, Y.; Wu, P.; Bao, Q.; Enoki, T.; Chabal, Y. J.; Loh, K. P. *Nat. Commun.* **2012**, *3*, 1298.
31. Jia, H.-P.; Dreyer, D. R.; Bielawski, C. W. *Adv. Synth. Catal.* **2011**, *353*, 528-532.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http: http://dx.doi.org///dx.doi.org/

Research Highlights

- A one-pot synthesis of 2-amino-3-cyanopyridine derivatives is described.
- Graphene oxide was applied as a catalyst for the formation of cyanopyridines.
- The role of the active sites in GO was studied.