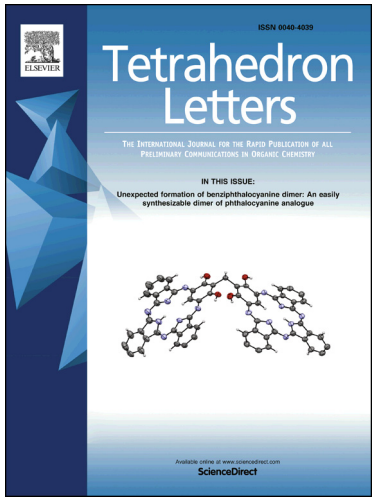


Graphene oxide: A carbocatalyst for the one-pot multicomponent synthesis of highly functionalized tetrahydropyridines

Annah Gupta, Ramneet Kaur, Deepika Singh, Kamal K. Kapoor

PII: S0040-4039(17)30657-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.05.067
Reference: TETL 48960

To appear in: *Tetrahedron Letters*

Received Date: 15 April 2017
Revised Date: 17 May 2017
Accepted Date: 18 May 2017

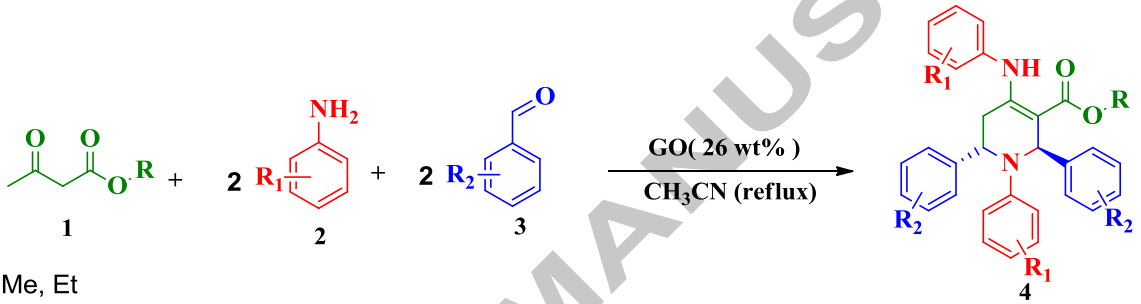
Please cite this article as: Gupta, A., Kaur, R., Singh, D., Kapoor, K.K., Graphene oxide: A carbocatalyst for the one-pot multicomponent synthesis of highly functionalized tetrahydropyridines, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.05.067

Graphical Abstract

Graphene oxide: A carbocatalyst for the one-pot multicomponent synthesis of highly functionalized tetrahydropyridines

Annah Gupta, Ramneet Kaur, Deepika Singh and Kamal K. Kapoor*

Leave this area blank for abstract info.



R=Me, Et

R_1=C_6H_5,4-$OCH_3C_6H_4$,4-ClC_6H_4, 4-BrC_6H_4,3-$OCH_3C_6H_4$,3,4,5-$(OCH_3)_3C_6H_2$, O-CH_2-OC_6H_3, thiophene-2-yl

R_2=C_6H_5 4-$CH_3C_6H_4$,4-ClC_6H_4, 4-FC_6H_4,3-ClC_6H_4,2-ClC_6H_4,

18 examples (86-94% yield)

Tetrahedron Letters
journal homepage: www.elsevier.com

Graphene oxide: A carbocatalyst for the one-pot multicomponent synthesis of highly functionalized tetrahydropyridines

Annah Gupta[a] , Ramneet Kaur[a], Deepika Singh[b] and Kamal K. Kapoor[a*]

[a]*Department of Chemistry, University of Jammu, Jammu-180 006, India*
[b]*Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180001*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Graphene oxide
Carbocatalyst
Multicomponent reaction
Tetrahydropyridine
Heterogeneous catalysis
One-pot reaction

ABSTRACT

A simple, straightforward and efficient methodology is described for the synthesis of polysubstituted tetrahydropyridine *via* one-pot multicomponent reaction of β-ketoester, aldehyde and aniline in presence of catalytic amount of graphene oxide in acetonitrile. Graphene oxide is a versatile carbocatalyst and this is the first report on its application in a five component reaction. Good yield, usage of readily available starting material, operational simplicity, easy work-up and eco-friendly re-usable catalyst are the key features of this protocol.

* Corresponding author Tel.: +91-191-2453969;
fax: +91-191-2450014/2431365; e-mail: kamalkka@gmail.com

Pyridine scaffolds are of interest in organic and medicinal chemistry due to the prevalence of their saturated and partially saturated derivatives in numerous natural products such as NAD nucleotides, pyridoxol (vitamin B_6), pyridine alkaloids[1] and exhibit a plethora of biological properties such as antimalarial, anti-microbial, anesthetic, anti-inflammatory, anticonvulsant, antioxidant and antiparasitic.[2] Despite the importance of pyridine nucleus in pharmaceuticals, it also find its application in agrochemistry[3] (as herbicides, pesticides, fungicides) and in supramolecular chemistry due to π-stacking ability.[4] Tetrahydropyridine, in particular has been recognized as core structure in some natural products and synthetic bioactive molecules.[5] Some of the bioactive tetrahydropyridine derivatives are depicted in **Figure 1.** Arecoline, **I** is known to posses stimulating effect owing to its agonistic influence on muscarinic acetylcholine receptors,[6] **II** is an aroma compound identified in proline-containing foods such as Basmati rice, popcorn, bread crust.[7] Another tetrahydropyridine unit containing natural product is Betanin **III**, a plant pigment, which is used as food additive[8] and 4-[2-(4-Fluorophenyl)-4-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-pyrrol-3-yl]pyridine(**IV)** has been reported to posses proinflammatory protein inhibition activity.[9] Droperidol and Tazomeline are proven to be anti-emetic and antipsychotic agents which are effective for the treatment of cognitive dysfunctional diseases such as Alzheimer's disease and Schizophrenia.[10] The role of tetrahydropyridine as inhibitor of farnesyl transferase[11] and dihydroorotate dehydrogenase[12] is also well documented. Additionally, they can also act as precursor for the synthesis of piperidine derivatives. Due to the broad spectrum of bioactivity (analgesic,[13] hyperglycaemic,[14] anti malarial[15]), tetrahydropyridine derivatives became attractive synthetic target for medicinal and organic chemists. As a result, a variety of methodologies have been developed for their synthesis such as proline mediated cascade Mannich type intramolecular cyclization,[16] reaction of dihydropyran with anilines,[17] amine catalysed annulations of Morita-Baylis-Hillman acetate with 1,3-azadienes.[18] These methodologies suffer from one or other disadvantages such as multistep synthetic sequence, requirement of expensive reagents or catalysts, etc.

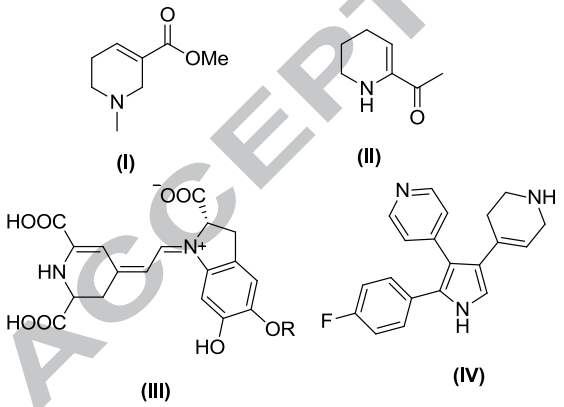


Figure 1: Few bioactive tetrahydropyridine derivatives

In the perspective of green chemistry, the main challenge for organic chemists is to develop synthetic routes which allow selective access to molecular scaffolds with structural diversity under eco-benign conditions. In this context, multicomponent reactions (MCRs) have evoked much attention and proven to be an improved alternative in organic synthesis due to its selectivity, atom and synthetic step economy. In recent years, the synthesis of highly functionalized tetrahydropyridines have been reported *via* five component reaction involving one molecule of β-ketoester, two molecules of aldehyde and two molecules of substituted aniline in presence of various catalysts such as $InCl_3$,[19] $LaCl_3.7H_2O$,[20] bromodimethylsulfonium bromide (BDMS),[21] iodine,[22] BF_3/SiO_2,[23] $ZrOCl_2.7H_2O$,[24] tetrabutylammonium tribromide (TBATB),[25] tartaric acid,[26] cerium ammonium nitrate,[27] α-Fe_2O_3-BIMtribromide,[28] amberlite IRA400-Cl Resin/I_2/KI,[29] $TiCl_2.H_2O$,[30] p-sulfonic acid calix[n]arenes,[31] acetic acid,[32] *p*-TSA,[33] $Y(NO_3)_3$,[34] $La(NO_3)_3.6H_2O$,[35] phenylboronic acid[36] and zinc hydrogen sulphate,[37] $ZrCl_4$.[38]

In our ongoing efforts on the synthesis of various heterocycles [39] and in pursuance of our experience with graphene oxide [40] as eco-benign heterogeneous catalyst in three component reaction for the synthesis of 1-amidoalkyl-2-naphthol and 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin-3-one, we wished to probe its usage in 5-component reactions. Herein, we present our successful findings in one-pot five component reaction between β-ketoester, two molecules of aldehyde and two molecules of substituted aniline using graphene oxide as eco-compatible catalyst to yield highly functionalized tetrahydropyridine in good to excellent yields. To the best of our knowledge, this is the first report on the application of Graphene oxide in a five-component reaction.

Owing to large surface area, ease in synthesis, inertness and bio-compatibility, graphene oxide has proven to be a promising, efficient and economical carbocatalyst[41] in organic synthesis. A number of oxygen containing functionalities such as epoxy, hydroxyl and carboxyl groups are present on the surface of graphene oxide (**Figure 2**) which are responsible for its acidic nature[42] and oxidising properties.[43]

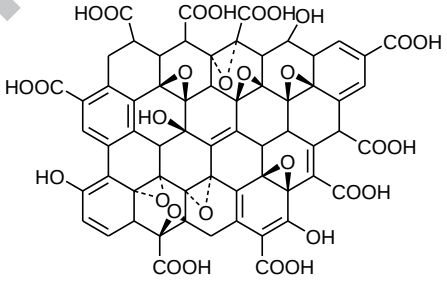
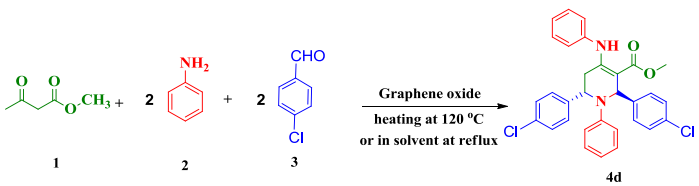


Figure 2: Structural model of graphene oxide

We envisaged our study by choosing methylacetoacetate (1mmol), 4-chlorobenzaldehyde (2mmol) and aniline (2mmol) as model substrates for optimization studies. Methylacetoacetate **1** (1 mmol) and aniline **2** (2 mmol) were heated at 120°C in presence of 50 mg (43 wt% w.r.t β-ketoester) of graphene oxide (prepared by modified Hummers method[44] and characterized by IR spectrum) for 30 min under solvent free condition to form the enamine intermediate followed by the addition of 4-chlorobenzaldehyde **3** (2 mmol). The reaction mixture was further heated till the complete formation of product **4d** (2h, TLC, 65% yield). In order to improve the yield of the reaction various solvents and catalyst loading were screened and the results are depicted in **Table 1**. Among the various tested mediums (CH_3CN, EtOAc, 1,4-Dioxane, THF) and scanned catalyst loading (10, 20, 30, 40 mg), it was found CH_3CN in combination with 30 mg (26 wt% w.r.t β-ketoester) of catalyst gave the best results.

Table 1: Optimization of reaction conditions



S.No.	Solvent	Amount of catalyst in mg[a]	Yield[b] (%)
1	-	50 (43)	65

2	CH_3CN	50 (43)	94
3	EtOAc	50 (43)	33
4	1,4-Dioxane	50 (43)	38
5	THF	50 (43)	42
6	CH_3CN	-	18
7	CH_3CN	10 (9)	60
8	CH_3CN	20 (17)	73
9	**CH_3CN**	**30 (26)**	**94**
10	CH_3CN	40 (35)	94

[a] wt.% w.r.t β-ketoester is given in parenthesis

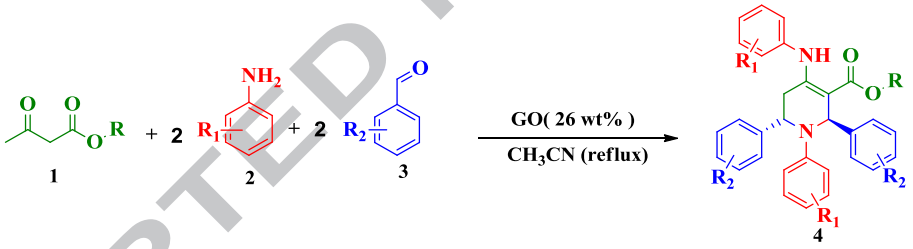
[b] Isolated Yield

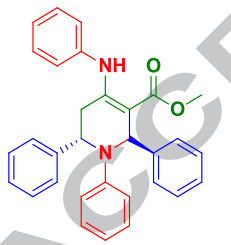
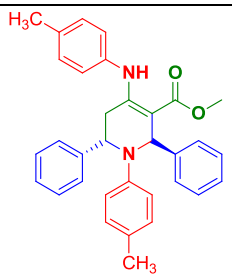
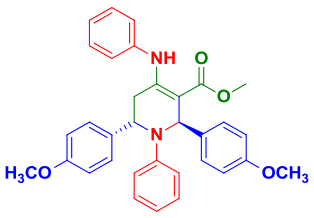
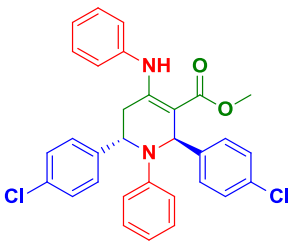
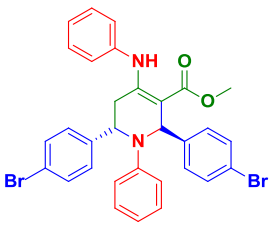
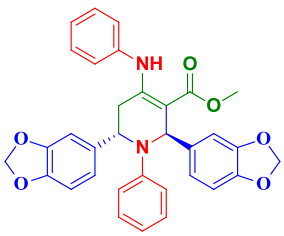
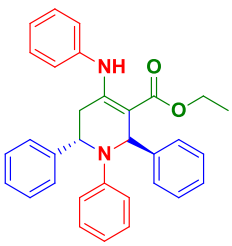
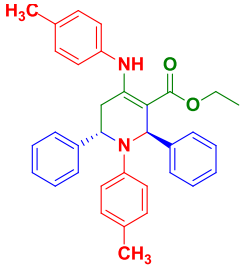
With these optimized conditions in hand, the scope and generality of this five component reaction was investigated. The reaction was successful with various substituted aldehydes, anilines and β-ketoesters (methylacetoacetate and ethylacetoactate) to provide the corresponding tetrahydropyridines **(4a-r)** in good to excellent yields (**Table 2).**

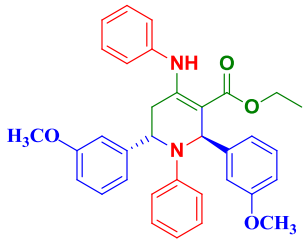
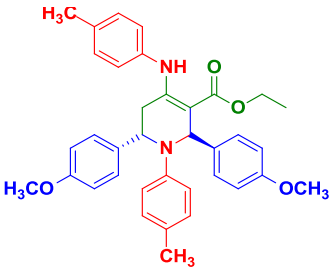
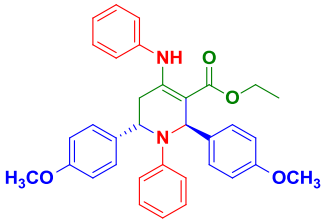
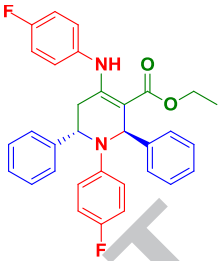
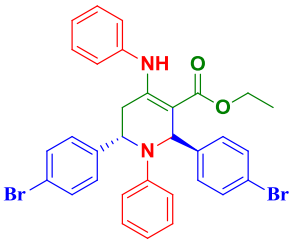
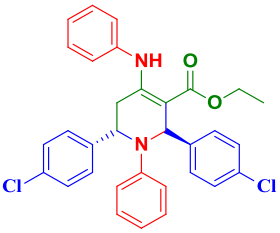
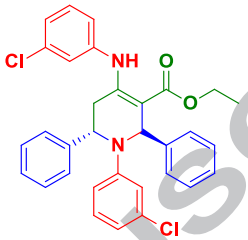
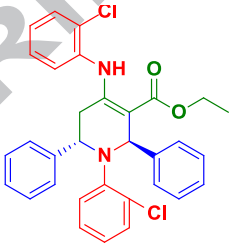
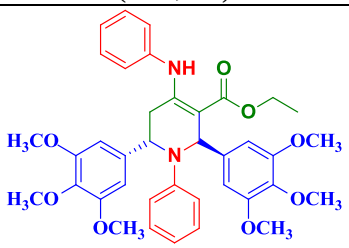
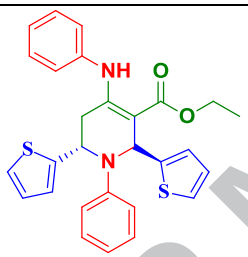
In analogy with reported mechanisms,[31,32,45] the following mechanism is proposed to explain the formation of product (**Scheme 1**). Graphene oxide acts as an acid catalyst and facilitates the respective formation of enamine **(5)** and imine **(6)** from aniline, β-ketoester and aldehyde. Next, intermolecular Mannich type reaction occur between **5** and **6** to yield intermediate **7**, which on further condensation with second molecule of aldehyde generates **8**. Intermediate **8** on tautomerization, followed by intermolecular Mannich type reaction affords the product tetrahydropyridines **(4).**

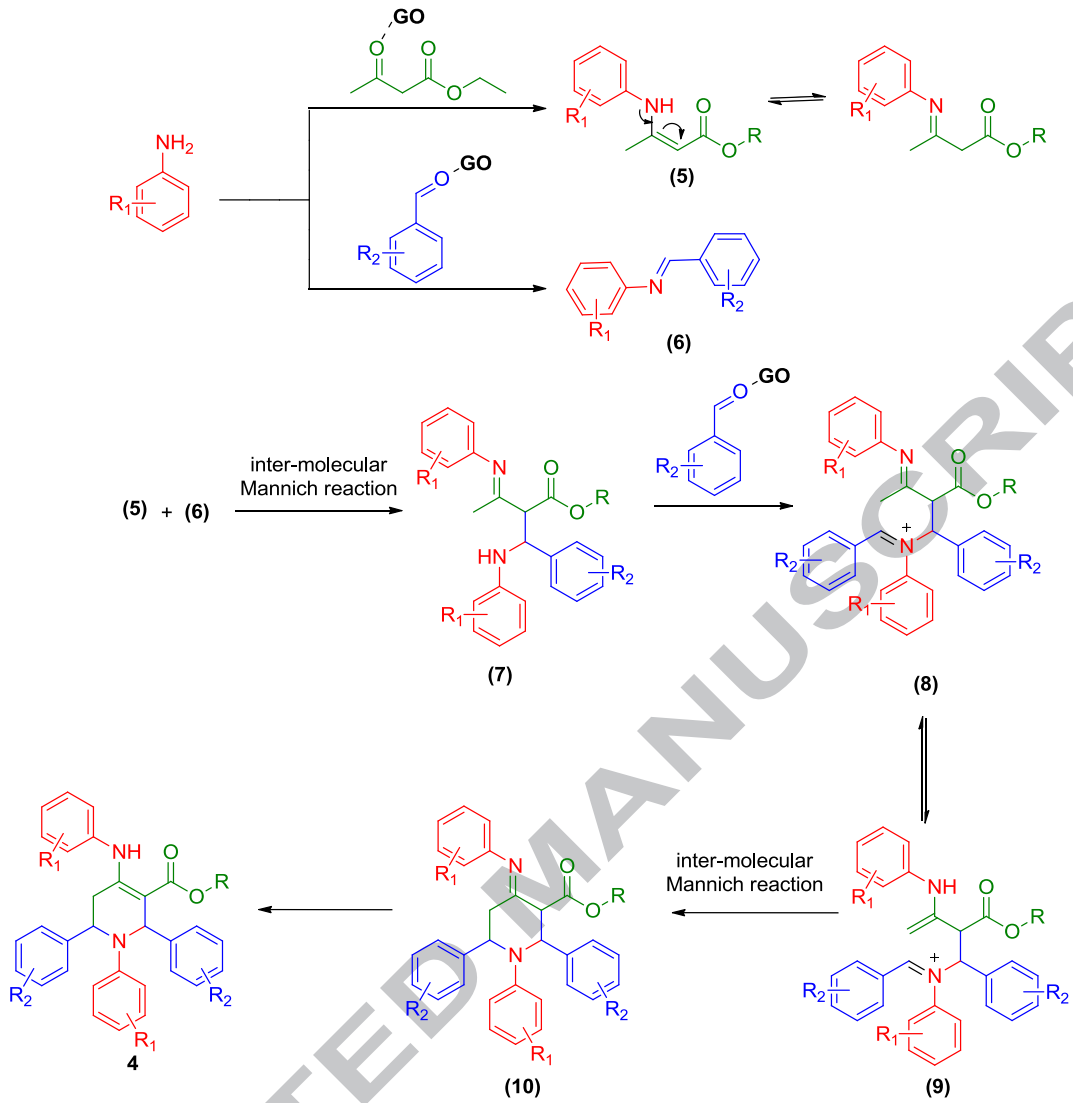
To establish the mechanistic integrity, enamine intermediate (methyl-3-(phenylamino)but-2-enoate) was isolated in one of the experiment and characterized by spectral data and its comparison with the literature reports.[46] The enamine was further reacted with 1 eq. each of aniline and aldehyde to realize the formation of the desirable product.

Table 2: Substituted tetrahydropyridines synthesized by the reaction of β-ketoester substituted aldehyde, and anilines



 **4a** (90%, 3.5 h)	 **4b** (92%, 3 h)	 **4c** (92%, 3.5 h)	 **4d** (94%, 3 h)
 **4e** (89%, 4 h)	 **4f** (86%, 3.5 h)	 **4g** (91%, 3.5 h)	 **4h** (91%, 3 h)

 **4i** (91%, 3h)	 **4j** (90%, 3.5 h)	 **4k** (90%, 3h)	 **4l** (87%, 4 h)
 **4m** (88%, 4 h)	 **4n** (92%, 3.5 h)	 **4o** (90%, 3.5 h)	 **4p** (87%, 4 h)
 **4q** (88%, 3.5 h)	 **4r** (89%, 4 h)		



Scheme 1. Plausible mechanism for one pot synthesis of functionalized tetrahydropyridine

Since graphene oxide can be recovered from the reaction mixture simply by filtration, it was further tested for its reusability. Catalyst obtained from the reaction of methylacetoacetate, aniline and 4-chlorobenzaldehyde was washed with warm acetonitrile and reused in a series of five consecutive runs and results are shown in **Figure 3.** As it is evident from the results that the catalyst is reusable upto five runs without significant loss of activity. The IR spectra of the recovered catalyst after 1st, 3rd and 5th runs were compared with the catalyst before the reaction and no significant changes in the diagnostic bands were noticed.

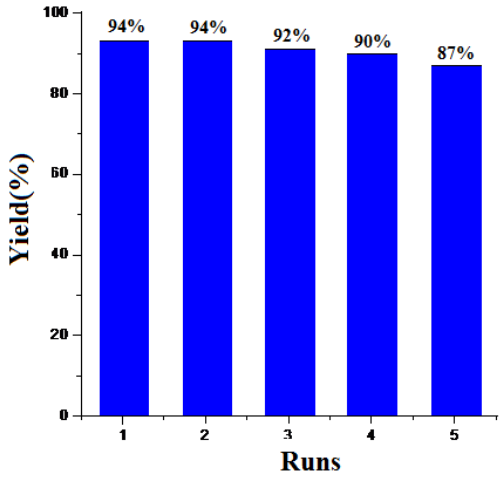


Figure 3: Recyclability of catalyst

In conclusion, an efficient protocol has been developed for the construction of highly functionalized tetrahydropyridines by employing catalytic amount of graphene oxide *via* one-pot multicomponent reaction of β-ketoester, substituted aldehyde, anilines. Graphene oxide is eco-benign and heterogeneous in nature, recoverable and reusable without any significant loss in catalytic activity. The advantages of this protocol are good yield, usage of readily available starting material, operational simplicity, easy work-up and eco-friendly catalyst.

Acknowledgement

The authors are thankful to Department of Chemistry, University of Jammu for providing all necessary facilities and Department of Science and Technology, Government of India, New Delhi for NMR facility under PURSE and INSPIRE fellowship [AG].

References

1. Adib, M.; Tahermansouri, H.; Koloogani, S. A.; Mohammadia, B.; Bijanzadeh, H. R. *Tetrahedron Lett*. **2006**, *47*, 5957-5960.
2. (a) Kim, B. Y.; Ahn, J. B.; Lee, H. W.; Kang, S. K.; Lee, J. H.; Shin, J. S.; Ahn, S. K.; Hong, C. I.; Yoon, S. S. *Eur. J. Med.Chem.* **2004**, *39*, 433-447; (b) Enyedy, I. J.; Sakamuri, S.; Zaman, W. A.; Johnson, K. M.; Wang, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 513-517;(c) Pillai, A. D.; Rathod, P. D.; Franklin, P. X.; Patel, M.; Nivsarkar, M.; Vasu, K. K.; Padh, H.; Sudarsanam, V. *Biochem. Biophys. Res. Commun.* **2003**, *301*, 183-186;(d) Klimesova, V.; Svoboda, M.; Waisser, K.; Pour, M.; Kaustova, J. *II Farmaco* **1999**, *54*, 666-672.

3. Guan, A.-Y.; Liu, C. -L.; Sun, X. –F.; Xie, Y.; Wang, M.-A. *Bioorg. Med. Chem.* **2016**, *24*, 342-353.
4. Watson, Z. C.; Bampos, N.; Sanders, J. K. M. *New J. Chem*. **1998**, *22*, 1135-1138.
5. (a) Kubota, H.; Fujii, M.; Ikeda, K.; Takeuchi, M.; Shibanuma, T.; Isomura, Y. *Chem. Pharm. Bull.* **1998**, *46*, 351-354; (b) Jain, R.; Chen, D.; White, R. J.; Patel, D. V.; Yuan, Z. *Curr.Med. Chem.* **2005**, *12*, 1607-1621.
6. Wen, X.-M.; Zhang, Y.-L.; Liu, X.-M.; Guo, S.-X.; Wang, H. *Cell Biol Int*. **2006**, *30*, 1048-1053.
7. Blank, I.; Devaud, S.; Matthey-Doret, W.; Robert, F. *J. Agric. Food Chem.* **2003**, *51*, 3643-3650.
8. Harmer, R. A. *Food Chem*. **1980**, 5, 81-90.
9. Nakao, A.; Ohkawa, N.; Nagasaki, T.; Kagari, T.; Doi, H.;Shimozato, T.; Ushiyama, S.; Aoki, K. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 4607-4610.
10. (a) Domino, K. B.; Anderson, E. A.; Polissar, N. L.; Posner, K. L. *Anesth. Analg.* **1999**, *88*, 1370-1379;(b) Mashkovskii, M. D.; Glushkov, R. G. *Pharm. Chem. J.* **2001**, *35*, 179-182 .
11. Gwaltney, S. L.; O'Connor, S. J.; Nelson, L. T. J. ; Sullivan, G. M.; Imade, H.; Wang, W.; Hasvold, L.; Li, Q.; Cohen, J.; Gu, W. Z.; Tahir, S. K.; Bauch, J.; Marsh, K.; Ng, S. C.; Frost, D. J.; Zhang, H.; Muchmore, S.; Jakob, C. G.; Stoll, V.; Hutchins, C.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*,1363-1366.
12. Nallan, L.; Bauer, K. D.; Bendale, P.; Rivas, K.; Yokoyama, K.; Horney, C. P.; Pendyala, P. R.; Floyd, D.; Lombardo, L. J.; Williams, D. K.; Hamilton, A.; Sebti, S.; Windsor, W. T.;Weber, P. C.; Buckner, F. S.; Chakrabarti, D.; Gelb, M. H.; Van Voorhis, W. C. *J. Med. Chem*. **2005**,*48*, 3704 -3713.
13. (a) Rao, K. N.; Redda, K. K.; Onayemi, F. Y.; Melles, H.; Choi, J. *J. Heterocycl. Chem*. **1995**, *32*, 307-315;(b) Madhavi, G.; Redda, K. K. *J. Heterocycl. Chem.* **2006**, *43*, 709-718.
14. Yeung, J. M.; Corleto, L. A.; Knaus, E. E. *J. Med. Chem.* **1982**, *25*, 720-723 .
15. Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009,** *17*, 625 – 633.
16. Han, R.-G.; Wang, Y.; Li, Y.-Y.; Xu, P.-F. *Adv. Synth. Catal.* **2008**, *350*, 1474-1478
17. Sun, S.; Cheng ,C.; Yang, J.; Taheri, A.; Jiang, D.; Zhang, B.; Gu, Y. *Org. Lett.* **2014**, *16*, 4520-4523.
18. Chen, R.; Xu, S.; Wang, L.; Tang, Y.; He, Z. *Chem. Commun.* 2013, **49**, 3543-3545.
19. Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C. *Synthesis* **2008**, 3530-3532.
20. Umamahesh, B.; Sathesh, V.; Ramachandran, G.; Sathishkumar, M.; Sathiyanarayanan, K. *Catal. Lett*. 2012, ***142***, 895-900.
21. Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008,** *73*, 8398-8402.
22. Khan, A. T.; Khan, M. M.; Bannuru, K. K. R. *Tetrahedron* **2010**, *66*, 7762-7789.
23. Ramachandran, R.; Jayanthi, S.; Jeong, Y. T. *Tetrahedron* **2012**, *68*, 363-369.
24. Mishra, S.; Ghosh, R. *Tetrahedron Lett*. **2011**, *52*, 2857-2861.
25. Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett.* **2010,** *51*, 4419-4424.
26. Aboonajmi, J.; Maghsoodlou, M. T.; Hazeri, N.; Lashkari, M.; Kangani, M. *Res Chem Intermed.* **2015,** *41*, 8057-8065.
27. Wang, H. J.; Mo, L. P.; Zhang, Z. H. *ACS. Comb. Sci.* **2011,** *13*, 181-185.
28. Paul, B.; Vadivel, P.; Dhar, S. S. *Chin. Chem. Lett*. **2016,** *27*, 1725-1730.
29. Harichandran, G.; Amalraj, S. D.; Shanmugam, P. *J. Hetero. Chem.* **2013,** *50*, 539-543 .
30. Abbasi, M.; Seyedi, S. M.; Sadeghian, H.; Akhbari, M.; Enayaty, M.; Shiri, A. *Heterocycl. Commun.* **2016**, *22*, 117-122.
31. Palermo, V.; Sathicq, A.; Liberto, N.; Fernandes, S.; Langer, P.; Jios, J.; Romanelli, G. *Tetrahedron Lett.* **2016,** *57*, 2049-2054.
32. Balijapalli, U.; Munusamy, S.; Sundaramoorthy, K. N.; Iyer, S. K. *Synth. Commun.* **2014**, *44*, 943-953.
33. Sajadikhah, S. S.; Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Shams-Najafi, S. *J. Monatsh. Chem.* **2012,** *143*, 939-945.
34. Mousavi, M.R.; Aboonajmi, J.; Maghsoodlou, M.T.; Hazeri, N. *J. Chem. Res*. **2014**, *38*, 76-79.
35. Mousavi, M.R.; Aboonajmi, J.; Maghsoodlou, M.T.; Hazeri, N.; Habibi-Khorassani, S.M.; Safarzaei, M. *Lett. Org. Chem.* **2013**, *10*, 171-177.
36. Goswami, S. V.; Thorat, P.B.;.Bhusare, S.R. *Heterocycl Commun*. **2012**, *18*, 245-248.
37. Ghashang, M. *Lett. Org. Chem.* **2012**, *9*, 497-502.
38. Aeluri, R.; Alla, M.; Bommena, V. R.; Murthy, R.; Jain, N. *Asian J. Org. Chem*. **2012**, *1*, 71-79.
39. (a) Gupta, A.; Khajuria, R.; Kapoor, K. K. *Synth. Commun*. **2016**, *46*, 31-38;(b) Saini, Y.; Khajuria, R.; Rana, L. K.; Hundal, M. S.; Gupta, V. K.; Kant, R.; Kapoor, K. K. *Tetrahedron*, **2016,** *72*, 257-263;(c) Kour, D.; Khajuria, R.; Kapoor, K. K. *Tetrahedron Lett.* **2016,** *57*, 4464-4467;**(d)** Khajuria, R.; Kannaboina, P.; Kapoor, K. K.; Gupta, A.; Raina, G.; Jassal, A. K.; Rana, L. V.; Hundal, M. S.; Das, P. *Org. Biomol. Chem.* **2015**, *13*, 5944-5954;(e) Mahajan, S.; Sharma, B.; Kapoor, K. K. *Tetrahedron Lett.* **2015,** *56***,** 1915-1918;(f) Khajuria, R.; Saini, Y.; Kapoor, K. K. *Tetrahedron Lett.* **2013**, *54*, 5699-5702.
40. Gupta, A.; Kour, D.; Gupta, V. K.; Kapoor, K. K. *Tetrahedron Lett.* **2016,** *57*, 4869-4872 (Highlighted in Synfacts, 2017, 13, 108).
41. (a) Bhattacharya, S.; Ghosh, P.; Basu, B. *Tetrahedron Lett.* **2017**, *58*, 926-931; (b)Kundu, S.; Basu. B. *RSC Adv.* **2015**, *5*, 50178-50185;(c) Navalon, S.; Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H. *Chem. Rev*. **2014**, *114*, 6179-6212;(d) Dreyer, D. R.; Todd, A. D.; Bielawski, C. W. *Chem. Soc. Rev*. **2014,** *43*, 5288-5301;(e) Su, C.; Loh, K. P. *Acc. Chem. Res*. **2013**, *46*, 2275-2285;(f) Kumar, A. V.; Rao, K. R. *Tetrahedron Lett*. **2011**, *52*, 5188-5191.
42. Szabo, T.; Tombacz, E.; Illes, E.; Dekany, I. *Carbon* **2006**, *44*, 537-545.
43. (a) Huang, H.; Huang, J.; Liu, Y. -M.; He, H. -Y.; Cao, Y.; Fan, K. -N. *Green Chem*. **2012**, *14*, 930-934; (b) Dreyer, D. R.; Jia, H. -P.; Todd, A. D.; Jeng, G.; Bielawski, C. W. *Org. Biomol. Chem.* **2011**, *9*, 7292-7295; (c) Jia, H. -P.; Dreyer, D. R.; Bielawski, C. W. *Tetrahedron* **2011**, *67*, 4431-4434;(d) Dreyer, D. R.; Park, S.; Bielawski, C. W.; Ruoff, R. S. *Chem. Soc. Rev*. **2010**, *39*, 228-240;(e) Dreyer, D. R.; Jia, H. -P.; Bielawski, C. W. *Angew. Chem. Int. Ed*. **2010,** *49*, 6813-6818.
44. Xavier, P.; Sharma, K.; Elayaraja, K.; Vasu. K. S.; Sood, A. K.; Bose, S. *RSC Adv*. **2014**, *4*, 12376-12387.
45. Brahmachari, G.; Das, S. *Tetrahedron Lett*. **2012**, *53*, 1479-1484.
46. (a) Kataria, M.; Pramanik, S.; Kumar, M.; Bhalla, V. *Chem. Commun.* **2015,** *51*, 1483-1486; (b) Rafiee, E.; Joshaghani, M.; Eavani, S.; Rashidzadeh, S. *Green Chem.* **2008,** *10*, 982- 989; (c) Zhang, M.; Abdukader, A.; Fu, Y. ; Zhu, C. *Molecule* **2012**, *17*, 2812-2822.
47. **General procedure for the synthesis of highly functionalized tetrahydropyridines:** A mixture of β-ketoester (1 mmol) and substituted anilines (2 mmol) in acetonitrile (10 ml) in presence of graphene oxide (30 mg, 26 wt.%) was stirred for 30 min under reflux, followed by addition of aldehyde (2 mmol). The resultant mixture was continued stirring under refluxing solvent till the completion of reaction [TLC; Table 2]. The reaction mixture was filtered while hot to recover the catalyst and precipitation occurred in filtrate upon cooling. The precipitates were filtered and recrystallized with 20% ethanol in chloroform to give pure product.

Highlights

- Works well with various substituted aldehydes, anilines and β-ketoesters.
- Graphene oxide is recoverable and reusable.
- Highly substituted tetrahydropyridines are obtained in high yields.