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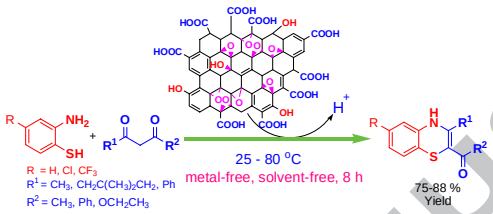

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Graphene Oxide (GO): An Efficient Carbocatalyst for the Benign Synthesis of Functionalized 1,4–Benzothiazines

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ABSTRACT

Graphene oxide (GO) has been found to be highly efficient and recyclable carbocatalyst for the benign construction of heterocyclic molecule 1,4–benzothiazine from 2–aminothiophenol and 1,3–dicarbonyl compound. A vast range of highly functionalized 1,4–benzothiazine derivatives has been synthesized constituting a general and sustainable protocol. It is proposed that the large surface area of GO nanosheet along with the presence of acidic and oxidative groups present on the edges, basal plane and intercalated layers catalyze the oxidative cyclization effectively.

Introduction

Heterocyclic compounds are ubiquitous in nature,[1] and synthesis of functionalized heterocyclic molecules has remained always attractive target because of their vast applications in pharmaceutical industries.[2,3] Functionalized 1,4–benzothiazines, containing benzene fused with a six–membered thiazine ring, represent an important class of heterocyclic compounds, which exhibit vast array of biological properties such as antimicrobial,[4,5] antifungal,[4] 15–lypoxygenase inhibitor,[4] anti–HIV,[4] neuroleptics,[4] anti–rheumatic,[4] calcium antagonist,[4] antioxidant,[4] cardiovascular,[4] antimalarial,[4] anthelmintic[4] etc. A few important drug molecules,[4,8] bearing 1,4–benzothiazine scaffold are shown in Figure 1. Apart from versatile pharmaceutical applications, the 1,4–benzothiazine is a subunit of many natural pigments, dyestuffs and also present in one type of melanin, pheomelanin.[6,7]

Because of versatile applications of this heterocyclic scaffold, a vast array of synthetic methods has been developed. The most straightforward approach for its synthesis is the direct condensation–cyclization between 2–aminobenzenethiol and 1,3–dicarbonyl compound in the presence of various reagents / catalysts. Among the myriads, some notable examples are: the use of DMSO,[9-11] H_2O_2,[12] Baker's yeast,[13] hydrazine hydrate,[14] etc. Most conditions however suffer from one or more constraints such as use of strongly basic media, strong oxidizing agent, high temperature as well as formation of disulfide as by–product,[14,15] or decomposition of the intermediate to benzothiazole.[16] In another synthetic approach, microwave–assisted synthesis of 1,4–benzothiazine has been reported.[17] The author observed that the reactants mixed in a mortar at room temperature can produce the same product in lower yield. The scheme 1 is presented with some protocols showing various drawbacks and limitations. As a result, there is demand for greener and selective new method for its synthesis applicable to broader range substrates.

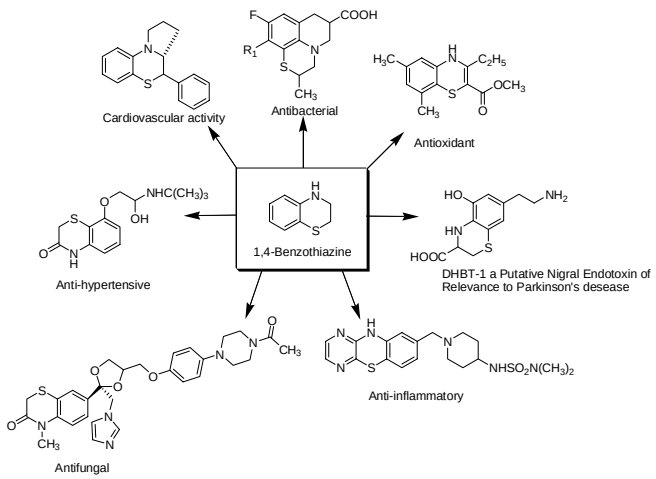

Figure 1. Representative examples of biologically active molecules containing 1,4–benzothiazine scaffold

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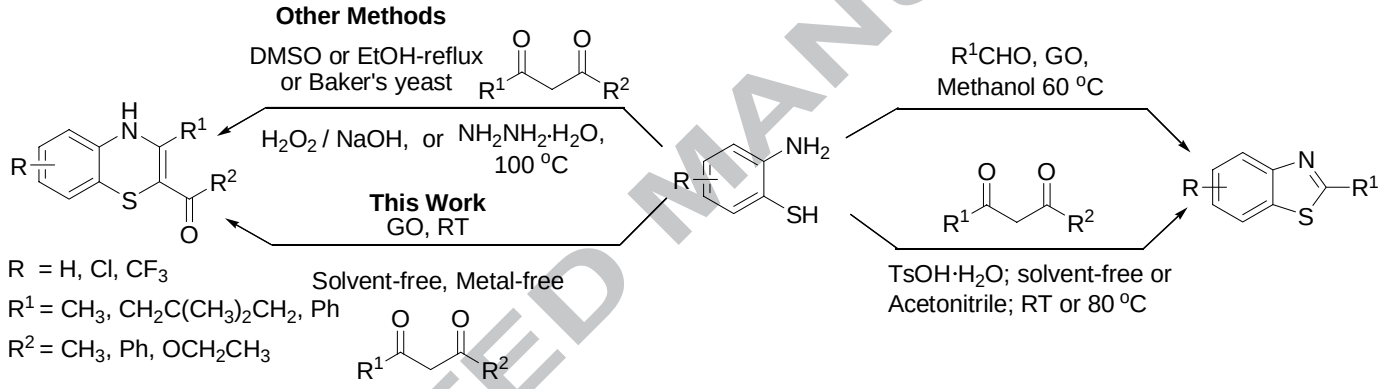
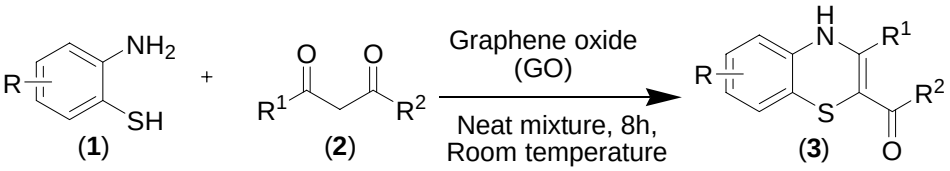
Carbonaceous nanomaterials are important in various fields like nanotechnology, tailoring new composites, electrochemistry, sensor, catalysis etc. Graphene oxide (GO) has been considered as a promising carbocatalyst since the seminal paper published by Bielawaski in 2010.[18] Since then, a considerable variety of organic reactions have been reported to be catalyzed efficiently by GO. Single or few layers of GO with large surface area and oxygenated functional groups like carboxyl groups on the edges, hydroxyl or epoxy on the basal plane did show acidic and oxidative properties in the catalytic process. We explored first time the catalytic function of GO towards the synthesis of small heterocyclic molecules, 3–sulphenyl imdazo[1,2–*a*]pyridine, an important class of biologically active pharmacophore, using a combination of GO–NaI under multi–component manner.[19] Recently, GO–catalyzed synthesis of benzothiazoles has been reported starting from 2–aminobenzenethiol and aryl aldehyde.[20] On the other hand, the same product benzothiazole was obtained from the reaction of 2–aminobenzenethiol with 1,3–diketone in the presence of catalytic *p*–TsOH,[21] (Scheme 1). Under this situation, it would be interesting to explore the reaction between 2–aminobenzenethiol and 1,3–diketone in the presence of GO as the catalyst. We report herein our studies, which constitute a robust protocol for the GO–catalyzed selective synthesis of 1,4–benzothiazines with diverse functional groups of pharmaceutical interests (Scheme 1). Our studies also establish clearly that there is profound effect of the catalyst GO in governing the course of the reaction and the product. In consonance with the demand for developing new reactions using metal–free sustainable catalysts like graphene oxide (GO), the present protocol expands its diverse catalytic functions leading to the formation of a different class of heterocycles 1,4–benzothiazine and not the benzothiazole. Further recyclability and post–reaction characterization of the catalyst have also been made in this study.



Scheme 1. Different processes of 1,4–benzothiazine synthesis

Result and Discussion

We began our investigations using a mixture of 2–aminothiophenol and acetylacetone, as the model reaction. Firstly, we tried the reaction in different solvents like acetonitrile, DMF, toluene, ethanol and water. Loading of the catalyst GO was started at 50 mg per mmol of 2–aminothiophenol. The results are presented in Table 1. It was observed that except DMF (entry 2), other solvents afforded the desired product **3a** in varying yields (entries 1–5). Poor yield of **3a** in the reaction carried out in water could be due to the low solubility of acetylacetone (entry 5). In general, different solvents except DMF produced the desired product in the range of 56–71% yield. However, while performing the reaction under complete solvent–free condition and stirring the neat mixture at room temperature, excellent yield of **3a** was achieved. (entry 6). Encouraged by this finding, we examined the loading of the catalyst GO that is required for the conversion. Thus, reducing the quantity of GO by 50% i.e. loading of 25 mg also afforded excellent conversion (entry 7). However, further decrease of GO loading resulted in lower yield (entry 8) and without the catalyst GO, the reaction did not proceed at all (entry 9). Formation of no product in the absence of GO at our hand in contrast to previous observation by Dandia et al.,[17] which gave 1,4–benzothiazine in poor yield, may be due to the use of a mortar–pastel that gave intimate mixing in addition to generation of some heat. Scaling up the reaction using 10 mmol each of the starting components using much lower loading of the catalyst GO also afforded significant conversion to the desired product (entry 10).



Scheme 2. GO–catalyzed synthesis of functionalized 1,4–benzothiazines at room temperature and solvent–free conditions

Table 1. Optimization of reaction conditions for GO–catalyzed synthesis of 1,4–benzothiazine from 2–aminothiophenol and acetylacetone[a]

Entry	GO (mg)	Solvent	Temp (^oC) / time (h)	(**3a**) Yield (%)[b]
1	50	CH_3CN	RT / 8	71
2	50	DMF	RT / 8	No product
3	50	Toluene	RT / 8	63
4	50	Ethanol	RT / 8	68
5	50	Water	RT / 24	56
6	50	Neat	RT / 8	90
7	**25**	**Neat**	**RT / 8**	**88**
8	10	Neat	RT / 20	39
9[c]	None	Neat	RT / 24	NR
10[d]	100	Neat	RT / 12	82

[a] Reactants (1mmol each)

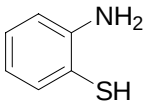
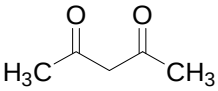
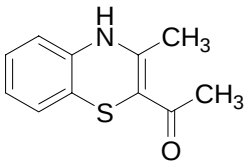
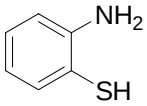
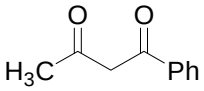
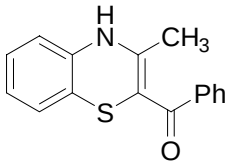
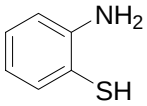
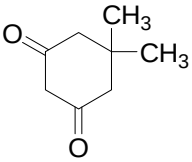
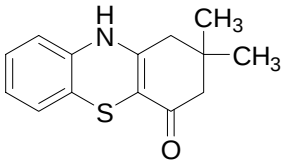
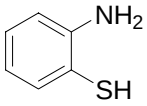
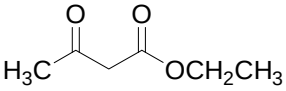
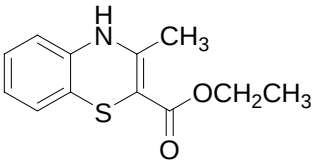
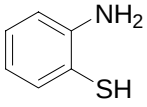
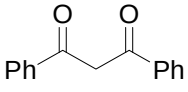
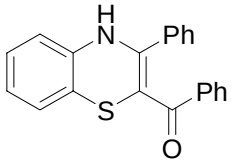
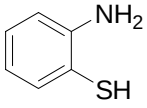
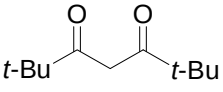
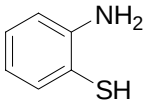
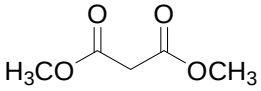
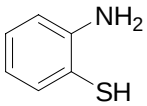
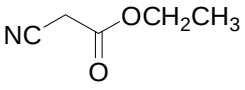
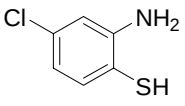
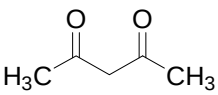
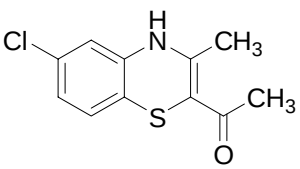
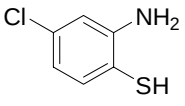
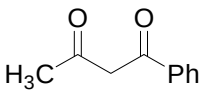
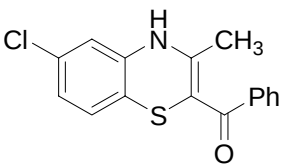
[b] Isolated yield after purification by column chromatography on silica gel.

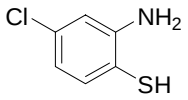
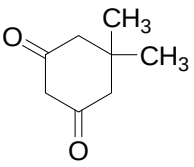
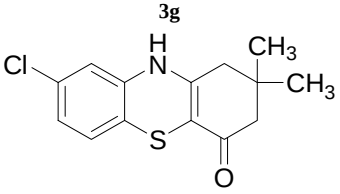
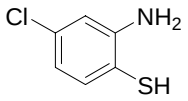
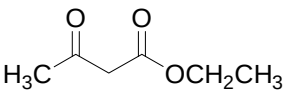
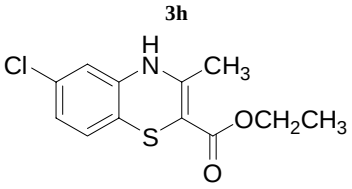
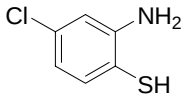
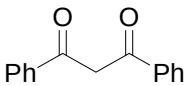
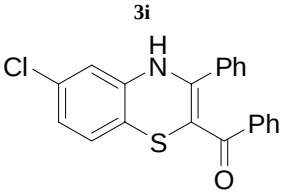
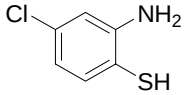
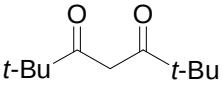
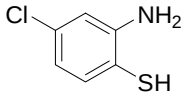
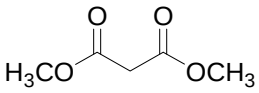
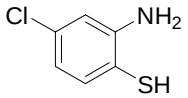
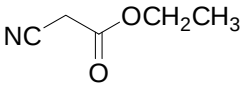
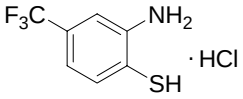
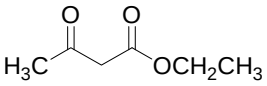
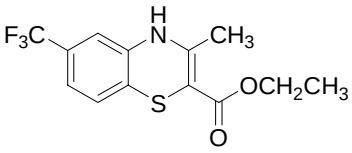
[c] No GO was added.

[d] Reactants are used (10 mmol each)

With this optimized condition, as in entry 7, i.e., carrying out the reaction simply by mixing 2–aminothiophenol (1 mmol) and acetylacetone (1 mmol) with the catalyst GO (25 mg) and stirring for 8 h at room temperature, we then explored the generality of the reaction with regard to varying both reacting partners. First, we varied the dicarbonyl compounds such as acyclic 1,3–diketone (Table 2, entries 1, 2, 5) , cyclic diketone (entry 3), *β*–ketoester (entry 4), dimethyl malonate (entry 7), and ethyl cyanoacetate (entry 8). Again, we changed the 2–arylaminothiol with substituents like –Cl, $–CF_3$ groups (entries 9–17). It can be seen from Table 2 that 1,3–diketo compounds worked well giving high yields of the desired products except for 1,3–di *t*–butyl ketone (entry 6). There was no reaction in this case, presumably due to the steric hindrance rendered by two bulky substituents (*t*–butyl) and preventing the approach at the other reacting partner. On the other hand, cyclic diketone like dimedone reacted efficiently yielding the desired product in 80% isolated yield (entry 3). On some occasions, the reaction worked at higher temperatures (60–80 ^oC). In the case of using dibenzoyl methane (entry 5), the presence of two phenyl rings considerably reduce the electrophilicity of the carbonyl groups and hence the reactivity is lowered thereby affording relatively poor yield of the product (entry 5). While the reaction was found to be smooth with ethyl acetoacetate (*β*–keto ester) (table 2, entry 4), similar reaction with dimethyl malonate (diester) was not successful even after 24 h at 80 ^oC (table 2, entry 7). This reactivity difference can be attributed to the more active keto–carbonyl group in ethyl acetoacetate as compared to both ester–carbonyl functions in dimethyl malonate. Further extension of the protocol was performed with substituted 2–aminothiophenols derivatives. Both 1,3–diketones or *β*–ketoester reacted with substituted 2–aminothiophenols in the similar manner producing corresponding functionalized derivatives of 1,4–benzothiazines in good yields (entries 9–17). It is therefore clear that the presence of strong electron withdrawing group like $–CF_3$ does not have significant effect towards the reaction.

TABLE 2. Synthesis of diversely functionalized 1,4–benzothiazine[a]

Entry	2–Aminothiophenol	1,3–diketo compound	Temp (°C)	Time (h)	Product (**3**)	Yield[b] (%)
1			RT	8	 **3a**	88
2			RT	8	 **3b**	84
3[c]			60	8	 **3c**	80
4			RT	8	 **3d**	81
5[d]			80	24	 **3e**	75
6[d]			80	24	No reaction	–
7[d]			80	24	No reaction	–
8[d]			80	24	No reaction	–
9			RT	8	 **3f**	82
10			RT	8		83

11[c]			60	8	**3g** 	76
12			RT	8	**3h** 	81
13[d]			80	24	**3i** 	79
14[d]			80	24	**3j** No reaction	–
15[d]			80	24	No reaction	–
16[d]			80	24	No reaction	–
17[c]			60	8	**3k** 	84

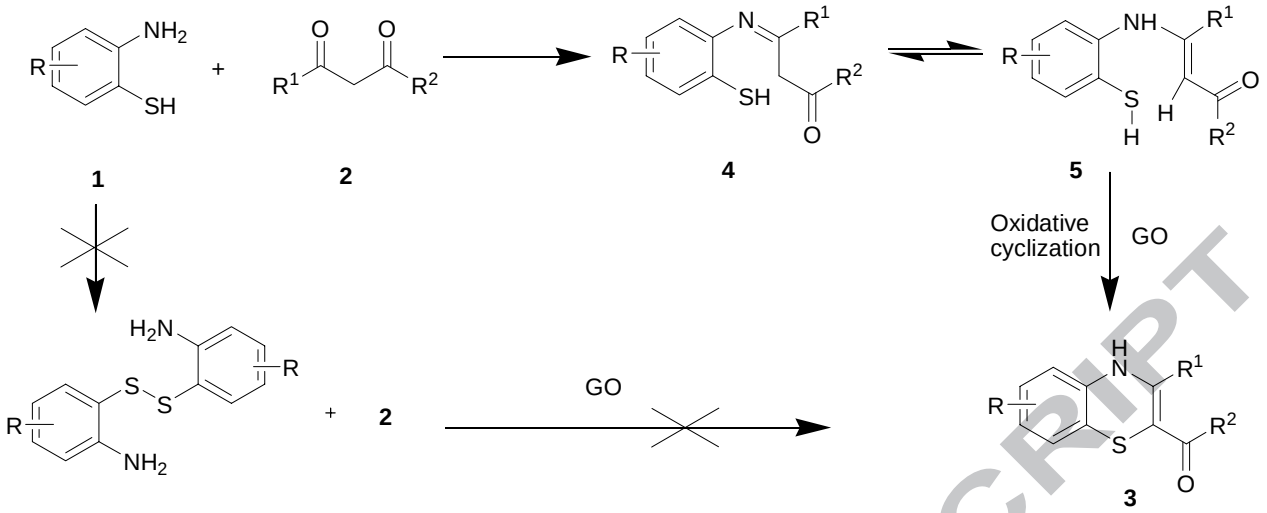
[a]2–Aminothiophenol (1 mmol), 1,3–diketo compound (1 mmol), GO (25 mg) were mixed and stirred at room temperature

[b]Isolated yield after purification through column chromatography on silica gel.

[c]Reaction was carried out at 60 °C

[d]Reaction was carried out at 80 °C for 24 h

Towards the plausible mechanism of the reaction, most literature reports using other catalysts or reagents suggest the formation disulfide from 2–aminothiophenol, which actually acts as the electrophile. Although GO is known to catalyze thiols to disulfide via oxidative dimerization,[22] we did not notice the formation of any disulfide in our reaction conditions (checked tlc at different intervals). The preparation of GO following Hummers method is most common,[23] though it may contain some S–containing oxygenated groups depending on the washing procedure.[24] Recent method for the preparation of GO by Tour *et al.*,[25] using H_3PO_4 however rule out such possibility and we preferred to prepare pristine GO following this method (see SI). Now, we propose that the condensation between amino ($–NH_2$) and keto (C=O) groups occurred to form an imine **4** (Scheme 3), and then the tautomer **5** undergoes oxidative cyclization in the presence of GO to produce 1,4–benzothiazine **3**. The proposition is in good agreement with the lower reactivity of some diketo components (entries 5, 6, 13, 14) towards the corresponding imine formation. The initial attack of $–NH_2$ at the carbonyl center to form the imine is difficult in diphenylketone due to lower electrophilicity, while steric hindrance by bulky *t*–butyl groups did stop initial formation **3**. Similarly, in the case of dimethyl malonate, a diester, there is no chance for the formation of imine **4** and thus no reaction was realized (entries 7 and 15). Since there is no disulfide formed during the reaction, possibility of other routes as proposed in some reports may be ruled out.



Scheme 3. Plausible mechanism for the formation of **3** via GO–catalyzed oxidative cyclization of **5**

Furthermore, we tested the recycling of the catalyst GO in the model reaction between 2–aminothiophenol (2 mmol) and acetylacetone (2 mmol) in the presence of GO (50 mg). After performing the first run, the reaction mixture was taken in ethyl acetate (5 mL) and centrifuged at 5000 rpm. The supernatent liquid containing the product was transferred and this process was repeated for two times. The catalyst was then washed with ethyl acetate and acetone followed by drying to afford the free–flowing dark GO for further use. Recovery of the catalyst was slightly lower than the quantity used in the first run, which may be due to the loss of some oxygenated functional groups present on GO as well as for manual process. However, the recovered catalyst used for subsequent five runs with almost equal efficiency and no significant drop in the conversion (Figure 2) and exhibited similar FT–IR data (Figure 3). It confirms that the recovered GO, though might lose some oxygenated groups, is equally effective for the reaction with residual functional groups.

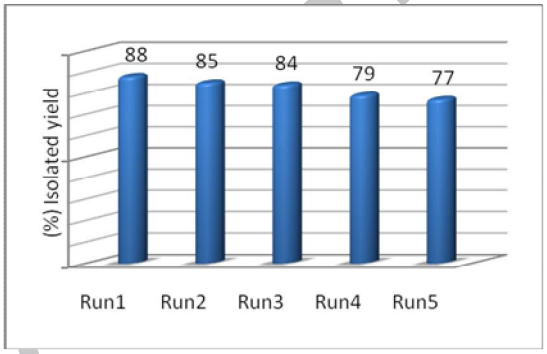


Figure 2. Recyclability of GO in the oxidative cyclization between 2–aminothiophenol and acetyleacetone

Acknowledgments

Financial support under the SERB project (No. EMR/2015/000549) is gratefully acknowledged. SB is thankful to CSIR, India for awarding JRF–NET fellowship.

Supplementary Material

Supplementary data associated with this article can be found in the online version, at

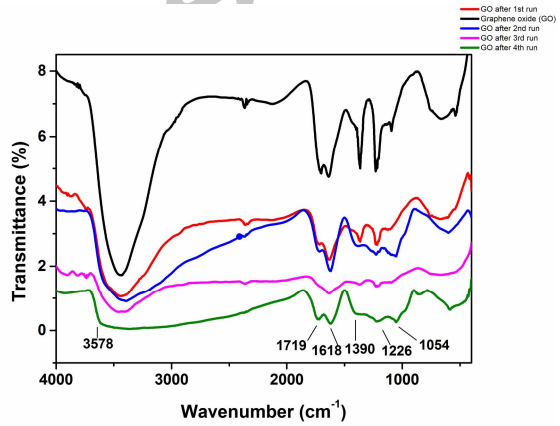


Figure 3. Comparative FT–IR of GO, after 1st, 2nd, 3rd. 4th run

In summary, graphene oxide (GO) has been found to act as a good carbocatalyst in the reaction between 2–aminothiophenol and 1,3–dicarbonyl compounds at 25–80 °C under solvent–free conditions leading to the formation of 1,4–benzothiazines in good to excellent yields. Functionally substituted substrates also work efficiently and no byproducts like disulfide or benzothiazole are formed. The catalyst is recyclable for five runs tested. Towards the effort to harness catalytic activity of sustainable carbon material like GO in diverse organic reactions, the present protocol is not only an addition but also an example for catalytic applications in the synthesis of small heterocyclic molecules of biological importance and until now, this exploration is very limited.[26]

References

1. Arora, P.; Arora, V.; Lamba, H. S.; Wadhwa, D. *Int. J. Pharm. Res. Sci.* **2012**, *3*, 2947–2955.
2. Fan, W.–Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W., Seriven, E. F. V., Eds.; Elsevier Science Oxford, U. K, 1996; Vol. 4, pp 1–126.
3. Wamhoff, H. H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 669–732.
4. Maheshwari, M.; Goyal, A. *Asian J. Pharm. Clin. Res.* **2015**, *8*, 41–46.
5. Sonawane, E. A.; Pawar, A. Y.; Nagle, S. P.; Mahulikar, P. P.; Dhananjay H. *Chin. J. Chem.* **2009**, *27*, 2049–2054.

6. Napolitano, A.; Memoli, S.; Prota, G. *J. Org. Chem*. **1999**, *64*, 3009–3011.
7. Simon, N.; Peles, D.; Wakamatsu, K.; Ito, S. *Pigment Cell Melanoma Res*. **2009**, *22*, 563–579.
8. Li, H.; Dryhurst, G. *J. Neurochem.* **1997**, *69*, 1530–1541.
9. Gupta, R.R.; Kumar, P. *J. Fluorine Chem.***1986**, *31*, 19–24.
10. Gupta, R. R.; Kumar, R.; Gautam, R. K.; *J. Heterocyclic Chem*. **1984**, *21*, 1713–1714.
11. Srivastav, V.; Gupta, R.; Gupta, R. R. *Indian J. Chem*. **2000**, *39B*, 223–224.
12. Sheibani, H.; Islami, R. M.; Hassanpour, A.; Saidi, K. *Phosphorus, Sulfur, and Silicon*, **2008**, *183*,13–20.
13. Pratap, U. R.; Jawale, D. V.; Londhe, B. S.; Mane, R. A. *J. Mol. Catal. B: Enzym.* **2011**, *68*, 94–97.
14. Munde, S. B.; Bondge, S. P.; Bhingolikar, V. E.; Mane, R. A. *Green Chem*. **2003**, *5*, 278–279.
15. Aloui, S.; Forsal, I,; Sfaira, M.; Touhami, M. E.; Taleb, M.; Baba, M. F.; Daoudi, M. *Portugaliae Electrochimica Acta* **2009**, *27*, 599–613.
16. Alyea, E. C.; Malek, A. *J. Heterocycl. Chem.* **1985**, *22*, 1325–1326.
17. Dandia, A.; Sarawgi, P.; Hursthouse, M. B.; Bingham, A. L.; Light, M. E.; Drake, J. E.; Ratnani, R. *J. Chem. Res*. **2006**, 445-448.
18. Dreyer, D. R.; Jia, H.–P.; Bielawski, C. W. *Angew. Chem. Int. Ed*., **2010**, *49*, 6813–6816.
19. Kundu, S.; Basu, B. *RSC Adv*. **2015**, *5*, 50178–50185.
20. Dhopte, K. B.; Zambare, R. S.; Patwardhana, A. V.; Nemade, P. R. *RSC Adv*. **2016**, *6*, 8164–8172.
21. Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M. *Org. Lett*. **2014**, *16*, 764−767.
22. Dreyer, D. R.; Jia, H.–P.; Todd, A. D.; Geng, J.; Bielawski, C. W. *Org. Biomol. Chem*. **2011**, *9*, 7292–7295.
23. Hummers, W. S.; Offemann, R. E. *J. Am. Chem. Soc*. **1958**, *80*, 1339.
24. Dimiev, A. M. In *Graphene Oxide: Fundamentals and Applications*; Dimiev, A. M.; Eigler, S. Eds.; Wiley, 2016; Chapter 2; pp 36–84.
25. Marcano, D. C.; Kosynkin, D. V.; Berlin, J. M.; Sinitskii, A.; Sun, Z.; Slesarev, A,; Alemany, L. B.; Lu, W.; Tour, J. M. *ACS Nano*, **2010**, *4*, 4806–4814.
26. Khalili, D. *Tetrahedron Lett*. **2016**, *57*, 1721–1723.

Highlights

Graphene Oxide (GO): An Efficient Carbocatalyst for the Benign Synthesis of Functionalized 1,4–Benzothiazines

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- Synthesis of functionalized 1,4-benzothiazines using GO as recyclable catalyst
- Solvent–free and metal–catalyst free reaction is generalized with diverse examples
- No byproducts like disulfide or benzothiazole are formed in this protocol
- Expands the scope of GO as carbocatalyst in heterocyclic synthesis

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