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Recyclable graphite oxide catalyzed Friedel–Crafts addition of indoles to α,β-unsaturated ketones

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ABSTRACT

The Friedel–Crafts addition of indoles to α,β-unsaturated ketones, and nitro styrenes was studied with graphite oxide as catalyst. Various indole derivatives were synthesized in good to excellent yields. The preparation of graphite oxide catalyst from simple and readily available starting materials makes this method more affordable. The heterogeneous graphite oxide can be easily recovered and recycled up to five cycles without loss of activity.

Indole moiety is the constituent of various natural products, biologically active compounds and drugs. Indole based molecules are very important in drug discovery. Many indole ligands with high-affinity for G-protein coupled receptors have been identified.[1] Of these, the 3-substituted indoles show significant biological activity and are precursors for the synthesis of various natural and unnatural drug based structures.[2] They are accessed by Friedel–Crafts Michael type addition of indole to α,β-unsaturated ketones. Existing methods of synthesis require metal catalysts and stoichiometric amounts of the reagents with cumbersome isolation procedures and longer reaction times.[3] The extra expenses and efforts to process this inevitably generated toxic metal waste hinders them from being adopted for large scale synthesis. In view of these drawbacks, the synthetic protocols utilizing carbon and modified carbon based catalysts devoid of metals are becoming more important due to the growing concern for sustainable chemistry. Graphene, modified graphite has received much attention owing to its interesting properties in material science with wide range of applications.[4] Graphene oxide, a delaminated layer of graphite oxide is shown in Figure 1.

The modified graphite especially graphite oxide (GO), prepared by the exhaustive oxidation of graphite is being explored as a catalyst for various organic transformations.[5] In this context, we present herein the Friedel–Crafts addition of indoles to α,β-unsaturated ketones catalyzed by graphite oxide (GO). The graphite oxide turns out to be an economical catalyst as it can be prepared simply from the readily available graphite flakes by oxidation with $KMnO_4/H_2SO_4$.[6] We adopted a modified Hummers procedure for the preparation of graphite oxide.[6,7] The prepared GO was dialyzed in a dialysis bag for 24 h to ensure the complete removal of residual metallic impurities. After the final purification procedure, we found that Mn was present in less than 30 ppb by ICP–MS analysis. The other metals like Fe, Co, Cu, Pb, etc. were below the detection limit. Thus ensuring that GO was free of metal impurities, the prepared GO was characterized completely with Raman, IR, XRD and TGA techniques to establish its authenticity. The powder XRD has shown the complete disappearance of the diffraction peak at 26.6° (3.34 Å) which is characteristic of graphite. The FTIR spectrum (KBr) has shown peaks at v = 3380 cm $^{-1}$ assigned to the hydroxyl group vibration of the C–OH, 1577 and 1381 cm^{-1} assigned to the O–H deformation of the C–OH group and 1048 cm^{-1} strong band attributed to C–O stretching vibration.[8] On the other hand pristine graphite was IR inactive and did not show any of these characteristic peaks. Raman spectroscopy is another

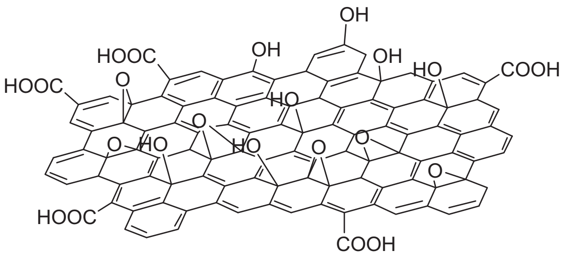

Figure 1. Schematic representation of graphene oxide.

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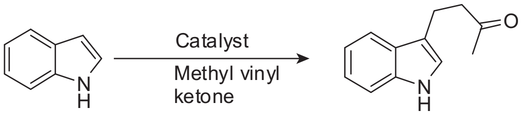
widely used noninvasive tool for the characterization of carbon. The Raman spectra of GO showed two strong bands, one at 1359 and 1595 cm^{-1} which can be attributed to D and G bands, respectively. Graphite shows a weak D band at 1353 cm^{-1}, strong G band at 1580 cm^{-1} and a broad D′ band at 2580 cm^{-1}. The increase in intensity of the band at 1359 cm^{-1} and disappearance of the D′ band at 2580 cm^{-1} in GO confirms the creation of sp^3 domains due to extreme oxidation of graphite.[9] The IR and Raman analysis significantly gratified the formation of GO from graphite. After having established the authenticity of GO, we tested it for the catalysis of Freidel–Crafts addition of indole to methyl vinyl ketone. Various solvents and catalysts were screened for the optimum conditions to obtain the maximum yield of the product. When only water was employed as solvent, 69% of the product conversion was observed, whereas reaction with H_2O/THF (7:3 ratios) with 20 wt % of GO gave maximum yield of the product in 92% within 3 h at ambient conditions. However, when 50 wt % of GO was used, the reaction time has drastically reduced to 1 h with nearly the same yield. The reaction proceeded smoothly at the β-position of indole to MVK without any NH protection thus exemplifying the efficiency of the catalyst. Other catalytic systems like PTSA, cyclodextrins, nano catalysts, acidic Al_2O_3 were inferior in performance when compared with GO. The reaction with mineral acids like HCl, H_2SO_4 also gave only moderate yields of the product. However, graphite itself was not able to catalyze the reaction, whereas 20% conversion was observed in the case of activated charcoal (results summarized in Table 1). With the reaction conditions being optimized, various substituted indoles were checked for their conversion with methyl vinyl ketone and nitro styrenes. Indoles with fluoro, bromo, iodo, cyano, nitro, methyl, and methoxy substituents underwent reactions smoothly in the addition to methyl vinyl ketone.

The methoxy substituted indole gave the highest yield followed by bromo, methyl, cyano, *N*-methyl, nitro, chloro, iodo, and fluoro within 2.5–8 h for complete conversion with no polymerized or dimerized side products, whereas the reaction of in-

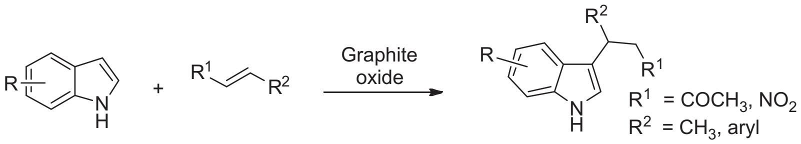
Table 1
Screening of solvents for graphite oxide catalyzed indole addition to α,β-unsaturated ketones[a]

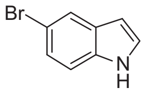
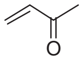
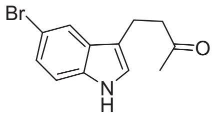
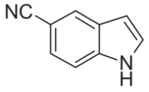
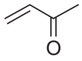
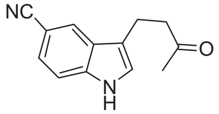
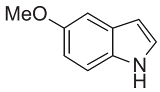
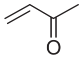
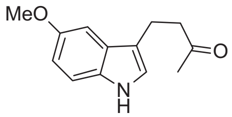
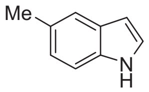
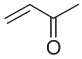
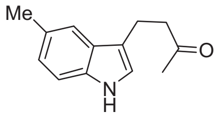


Entry	Catalyst	% of catalyst	Solvent	*t* (h)	Yield[b] (%)
1	Graphite oxide	50 wt %	H_2O	2.5	69
2	Graphite oxide	10 wt %	H_2O/THF	5.5	81
3	Graphite oxide	20 wt %	H_2O/THF	3	92
4	Graphite oxide	30 wt %	H_2O/THF	2	90
5	Graphite oxide	50 wt %	H_2O/THF	1	94
6	Graphite oxide	50 wt %	Toulene	3	71
7	Graphite oxide	50 wt %	1,4-Dioxane	3.5	56
8	Graphite oxide	50 wt %	CH_3CN	4	64
9	Graphite oxide	50 wt %	CH_2Cl_2	6	66
10	Graphite oxide	50 wt %	MeOH	5	52
11	Activated charcoal	50 wt %	H_2O/THF	12	20
12	Graphite	50 wt %	H_2O/THF	24	5
13	Fe_2O_3 nano	10 mol %	H_2O/THF	24	13
15	Fe_3O_4 nano	10 mol %	H_2O/THF	24	11
16	—	—	H_2O	—	—
17	PTSA[c]	10 mol %	H_2O/THF	8	31
18	HCl	10 mol %	H_2O/THF	2	55
19	H_2SO_4	10 mol %	H_2O/THF	2	67
20	β-CD[d]	10 mol %	H_2O	24	12
21	Sulfo-β-CD[e]	10 mol %	H_2O	24	10
22	CuO nano	10 mol %	H_2O/THF	24	25
23	Al_2O_3 acidic	50 wt %	H_2O/THF	10	14
24	MgO nano	10 mol %	H_2O/THF	24	9

[a] Reaction conditions: indole (1 mmol), methyl vinyl ketone (1.1 mmol), H_2O/THF 7:3 ratio, rt.
[b] Isolated yield.
[c] *para*-Toluene sulfonic acid.
[d] β-Cyclodextrin.
[e] Carboxymethyl-β-cyclodextrin sodium salt.

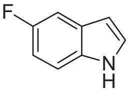
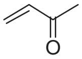
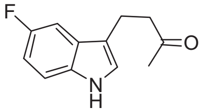
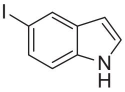
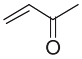
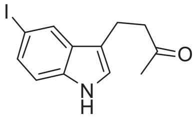
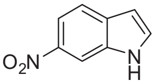
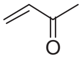
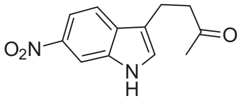
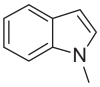
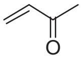
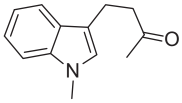
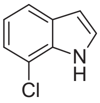
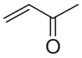
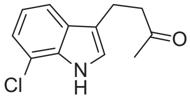
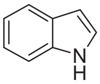
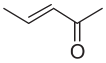
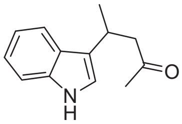
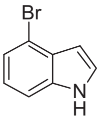
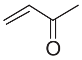
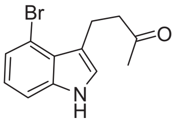
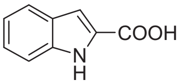
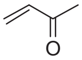
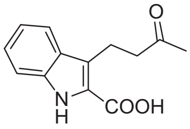
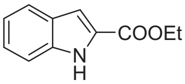
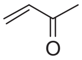
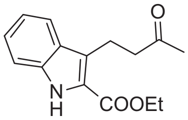
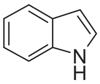
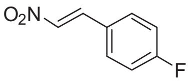
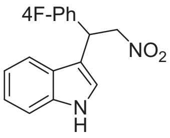
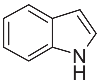
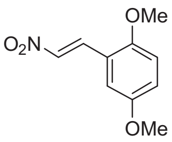
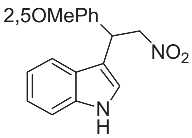
Table 2
Graphite oxide catalyzed various indoles addition to α,β-unsaturated ketones[a]



Entry	Indole	Acceptor	Product	*t* (h)	Yield[b] (%)
1				2.5	89
2				4	81
3				3.5	92
4				4	83

(*continued on next page*)

Table 2 (*continued*)

Entry	Indole	Acceptor	Product	*t* (h)	Yield[b] (%)
5				4	79
6				3.0	73
7				6.5	77
8				5.5	80
9				6	76
10				6.5	72
11				8	61
12				24	0
13				24	0
14				36	58
15				36	40

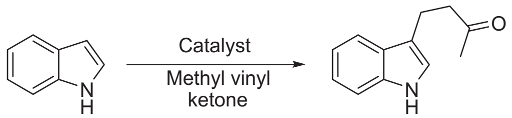
[a] Reaction conditions: indole (1 mmol), acceptor (1.1 mmol), GO (20 wt %), H_2O/THF 7:3 ratio, rt.

[b] Isolated yield.

dole with the less reactive electron deficient nitro styrenes took longer time to give moderate yields of the product. Though 4 and 7 substituted indoles do undergo the reaction, the more hindered 4-substituted indole took much longer time than the 7-substituted indole to afford the Michael adduct. However, there was no reaction in the case of 4-bromoindole versus 3-pentene-2-one, which might be due to steric crowding. No reaction was observed in the case of indole with carboxylic acid and carboxylic ester substituents at the α-position of indole even after 24 h. In the case of β-methyl vinyl ketone, the reaction did take place with indole, whereas, no reaction was observed with β-phenyl vinyl ketone as well as simple styrene (results summarized in Table 2).

To evaluate the reusability of GO, the catalyst after completion of the reaction was filtered and washed with water, dried in a dessicator and employed for the next reaction. Likewise the catalyst was found to be recyclable up to five cycles with no loss of activity. The performance of GO in effectively catalyzing the reaction was consistent without any activation and thus validates its recyclability (Table 3).[10]

Table 3
Recyclability of graphite oxide[a]



Entry	GO recovered	*t* (h)	Product yield[b] (%)
Native	–	3	92
Cycle 1	96%	3.2	89
Cycle 2	94%	3.5	88
Cycle 3	92%	3.5	86
Cycle 4	92%	4	86
Cycle 5	89%	4	82

[a] Reaction conditions: indole (1 mmol), methyl vinyl ketone (1.1 mmol), H_2O/THF 7:3 ratio, rt.

[b] Isolated yield.

In conclusion we have studied the Friedel–Crafts addition of indoles to α,β-unsaturated ketones and nitro styrenes with graphite oxide as catalyst. The graphite oxide was synthesized from the inexpensive graphite with readily available reagents. The synthesized GO was completely characterized. Graphite oxide was found to be efficiently catalyzing the Friedel–Crafts reaction of indoles with various electron rich and deficient α,β-unsaturated ketones affording good yields of products with simple adoptable procedures at ambient conditions in H_2O/THF solvent mixture with short reaction times and no side product formation. In addition GO was easily recoverable from the reaction mixture and was recyclable up to five times with no loss of activity. Overall, graphite oxide turned out to be an environmentally benign catalyst for the Friedel–Crafts addition of indoles to α, β-unsaturated ketones and nitro styrenes.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.002.

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10. Though the powder XRD, Raman spectra of the catalyst after five cycles have shown Graphitic peaks, the catalyst did not show any loss of activity. Refer Supplementary data for spectra.