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Graphene Oxide Promotes Site-Selective Allylic Alkylation Of Thiophenes With Alcohols.

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Supporting *Information* *Placeholder*

ABSTRACT: The graphene oxide (GO)-assisted allylic alkylation of thiophenes with alcohols is presented. Mild reaction conditions and low GO loading enabled the isolation of a range of densely functionalized thienyl and bithienyl compounds in moderate to high yields (up to 90%). The cooperative action of the BrØnsted acidity, epoxide moieties and π-surface of the 2D-promoter is highlighted as crucial in the reaction course of the present Friedel-Crafts-type protocol.

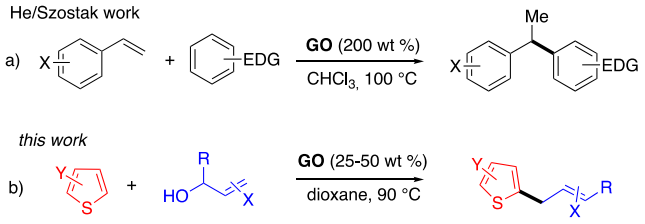
The site-selective functionalization of thienyl nucleous is still of undoubted importance due to their ubiquitous use in the realization of functionalized molecular materials for organic electronics and photonics.[1] Catalysis represents an ultimate synthetic tool for the chemical "decoration" of this class of heteroarenes, enabling critical aspects such as selectivity, simplicity and sustainability to be satisfied simultaneously. In this context, the Friedel-Crafts (FC) allylic alkylation reaction is still facing growing attention since it makes feasible further chemical manipulations of the aromatic core due to the installation of carbon-carbon double bonds.[2] The synthetic interest for this approach can be further amplified by adopting cheap, readily available and user-friendly π–alcohols (*i.e.* allylic, propargylic and allenylic alcohols) as alkylating agents.[3] However, important synthetic challenges such as regioselectivity and single- *vs* poly-alkylation, with specific reference to electron-rich aromatic rings, are still not fully addressed.

Bearing all that in mind, we envisioned the emerging "carbocatalytic" approach[4] as a promising tool to overcome these difficulties. In particular, we identified graphene oxide (GO),[5] as a mediating agent to carry site-selective allylation of functionalized thiophenes with readily accessible alcohols. As a matter of fact, due to its moderate BrØnsted acidity, diversified surface functionalization and possible implementation into composite materials, GO already found elegant applications in several synthetic organic transformations such as: oxidation of alcohols/amines,[6a-e] hydrogenation of alkenes,[6f] click chemistry[6g] and aminolysis.[6h] Contrarily and unexpectedly the use of GO in carbon-carbon bond forming reactions is still limited.[7]

In this context, He and Szostak have recently reported an elegant GO-assisted alkylation of arenes that caught our attention. In detail, the benzylation of electron-activated aromatic compounds with styrenes was discussed by using GO (200 wt%) as the promoting agent (Figure 1a).[8]

In combination with our on-going interest in catalytic methodologies for the direct functionalization of arenes with alcohols,[9] we envisioned the possibility of implementing a metal-free GO-assisted allylating protocol on thiophenes (Figure 1b). In this communication, preliminary findings and mechanistic investigations on the topic are documented.

Figure 1. Previous study on GO-based Friedel-Crafts-type alkylation of alkenes (a) and the present work (b).

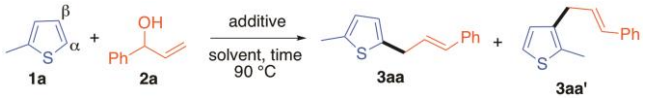


At the outset of our investigation, we considered the commercially available 2-methyl-thiophene **1a** and 1-phenylprop-2-en-1-ol **2a** as model substrates with the specific intent to assess the reliability of the protocol towards (a) poly-alkylation, (b) α *vs* β-regioselectivity, (c) S_N *vs* S_N' mechanism (*i.e.* regiochemistry towards the allylic framework) and (d) stereochemistry of the newly formed C=C. A range of carbocatalysts and reaction conditions were screened (Table 1).

Interestingly, a promising isolated yield of the **3aa**/**3aa'** mixture was recorded by using only 50 wt% of catalyst in $CHCl_3$ at 90 °C (entry 1) that was subsequently reduced to 25 wt% (entry 2) with a decrease of the overall performance (23% yield). Contrarily, the use of

an aqueous solution of GO failed in producing the final product. DCE and 1,4-dioxane were elected as best solvents providing comparable outcomes (yields 89-90% and up to 86:14 **3aa**/**3aa'** ratio). However, the shorter reaction time (4 hs *vs* 8 hs) led us to choose 1,4-dioxane for the reaction scope investigation.[10] It is worth mentioning that while the blank reaction clearly emphasized the pivotal role of the GO[11] (entry 10), graphene and reduced graphene oxide (rGO) proved completely inefficiency in the present protocol. Last but not least, only the thermodynamically more stable linear compounds **3aa** and **3aa'** were isolated ($S_{N'}$ *vs* S_N) along with the exclusive formation of the (*E*)-isomer. As a matter of fact, only in sporadic cases, traces of branched **3aa** (*i.e. b*-**3aa**) were also observed in the reaction crude.[12]

Table 1. Optimization of the reaction conditions[a]

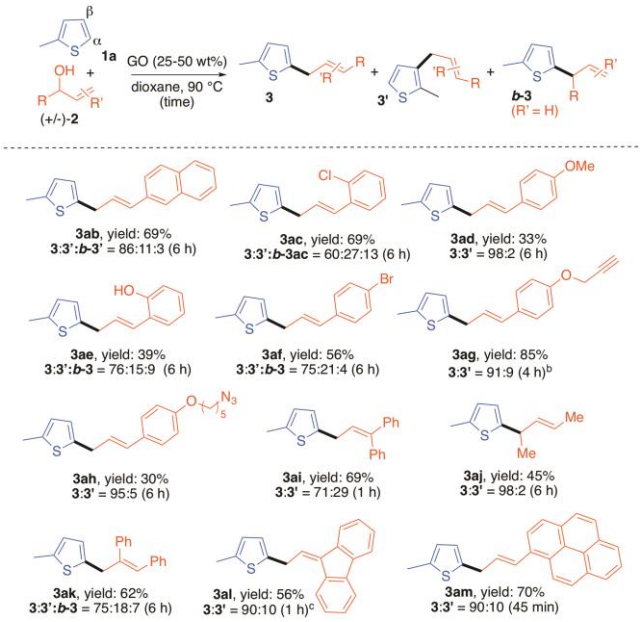


Run	additive (wt%)	Solvent / t (h)	Yield (%)[b]	**3aa**:**3aa'**[c]
1	GO (50)	$CHCl_3$ / 16	36	86:14
2	GO (25)	$CHCl_3$ / 16	23	85:15
3	GO_{aq}[d] (25)	$CHCl_3$ / 16	traces	--
4	GO (25)	THF / 4	34	72:28
5	GO (25)	ACN / 4	51	75:25
6	GO (25)	DMF / 4	NR	--
7	GO (25)	$(CH_2Cl)_2$ / 4	77	78:22
8	GO (25)	DCE / 8	89	78:22
9	GO (25)	Dioxane / 4	90	86:14
10	Graphene (25)	Dioxane / 4	NR	--
11	rGO (25)	Dioxane / 4	NR	--

[a] All the reactions were carried out in reagent-grade solvents without any moisture exclusion (**1a**:**2a** = 3:1). [b] Isolated yield after flash chromatography. [c] Both **3aa** and **3aa'** were isolated as *E*-stereoisomers and resulted inseparable via flash chromatography. [d] Aqueous solution (5 mg/mL) of GO was employed. NR: no reaction. ACN: acetonitrile.

The optimized reaction conditions were applied to a range of diversely substituted allylic alcohols (**2b-m**, see SI) in the Friedel-Crafts alkylation of **1a** (Scheme 1). In all cases, S_N2'-type allylation compounds **3** were obtained exclusively with (*E*)-C=C configuration in moderate to very good yield (30-85%). 1-Aryl-propen-1-ols carrying both electron-donating (*e.g.* OH, OR) and electron-withdrawing (*e.g.* Cl, Br) groups are proved efficient under optimal conditions. Additionally, synthetically useful alkyne (**3ag**) and azide (**3ah**) groups were effectively tolerated. It is worthy to note that the unprotected phenolic group was also tolerated in the process, underlying that the FC-based C-C bond forming product **3ae** was favoured with respect to the C-O bond formation under GO-assistance. The synthetic approach was also applied to the site-selective functionalization of **1a** with the concomitant formation of tri-substituted styryl units (**3ai** and **3ak**). The reactivity of aliphatic allylic alcohols was also demonstrated by condensing **2j** with **1a** under optimal conditions. Interestingly, the corresponding C(2)-alkylated thienyl compound **3aj** was isolated in 45% yield as a single regio- and stereoisomer. Last but not the least, the protocol enabled also the incorporation of chromophoric units (*e.g.* fluorenyl and 1-pyrenyl) into the model aromatic compound in moderate to good yield (56-70%) with very short reaction time (45 min - 1 h)

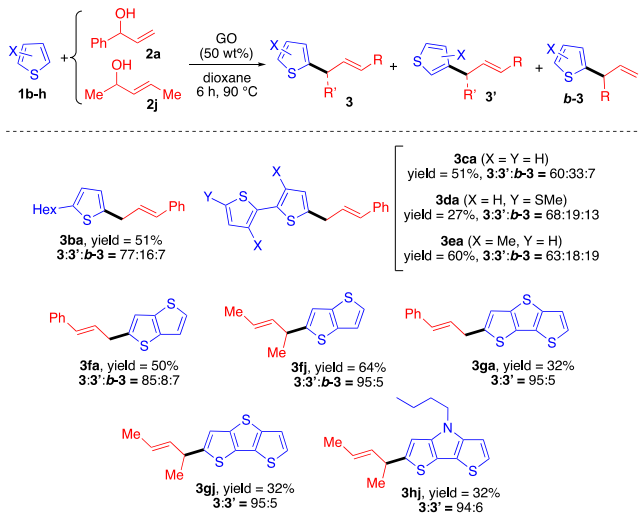
Scheme 1. Scope of the reaction: alcohols.[a]



[a] 0.2 mmol of **2** (**1a**:**2** = 3:1) unless otherwise specified. [b] With **1a**:**2g** = 6:1 and GO loading of 50 wt%. [c] T = 80 °C. In some specific cases, minor amounts of branched **3** were also detected by NMR (see SI).

Therefore, we turned our attention towards the generality of the method related to thiophene derivatives. 2-*n*Hex-thiophene **1b** displayed feasibility for present methodology furnishing the corresponding alkylated compound **3ba** in 51% yield. Analogously, differently substituted bithienyl compounds **1c-h** underwent the FC-allylative process in satisfying manner (yields up to 64%) by means of 50 wt% of GO. In all cases, monosubstituted linear α-allylated compounds **3** were obtained as the predominant arene (Scheme 2). β–Functionalized linear allyl-thiophenes were also observed in non-negligible amount in the case of **3ca**-**3ea.** Differently, α–branched isomers ***b*-3** were formed only in traces with the exception of substituted-bithiophenes **1d** and **1e**.[13] Additionally, also widely employed rigid "cores" in organic electronics such as dithienothiophene **1g**[14a] and dithienopyrrole **1h**[14b] underwent allylic alkylation with alcohols **2a** and **2f** in moderated yield (32%) and very high regioselectivity (up to 95:5).

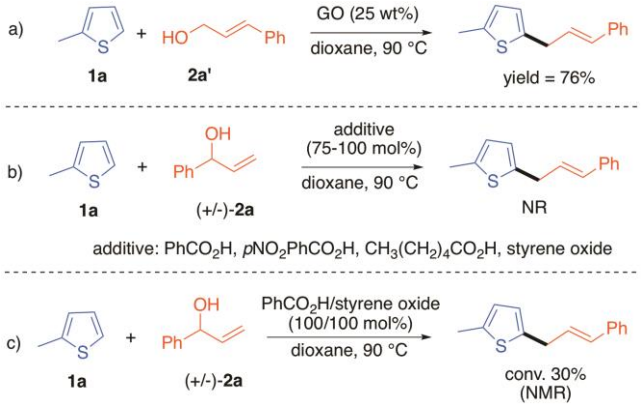
Scheme 2. Scope of the reaction: thiophenes.[a]



[a] Isolated yields after flash chromatography. Regioselectivity was determined by GC-MS and/or ^{1}H-NMR on the reaction crudes.

In order to obtain mechanistic insight, some control experiments were performed. Firstly, when branched or linear allylic alcohols **2a** and **2a'** were utilized, comparable chemical and stereochemical outcomes in (*E*)-**3aa** were recorded (yields 90% and 76%, respectively, Scheme 3a). Additionally, the impact of the sole BrØnsted acidity conferred by the GO solution in dioxane (~ 5 mg/mL → pH = 3.70) was assessed by running the model process in the presence of several organic BrØnsted acids (loading = 75-100 wt%) namely: benzoic acid (pH = 5.10, 5 mg/mL), *p*NO_2-benzoic acid (pH = 3.82, 1 mg/mL) and *n*-hexenoic acid (pH = 4.22, 5 mg/mL) but no formation of **3aa** was observed. Analogously, when (+/-)-styryl epoxide (100 wt%) was employed the reaction did not proceeded at all (Scheme 3b).[15] Such evidences unambiguously highlight the concerted action of the GO skeleton and the functional groups present in the 2D-material in making effective the C-C bond formation process. Differently, when **1a** and **2a** were reacted with the simultaneous presence of benzoic acid and styryl oxide (both at 100 wt%), **3aa** was formed in 30% conversion (^{1}H-NMR), providing preliminary evidences of the synergistic action of the BrØnsted acidity and the oxirane units in promoting the condensation of the thiophene ring and the allylic alcohol.

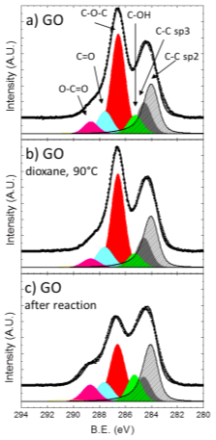
Scheme 3. Control experiments for the present GO-assisted Friedel-Crafts condensation.[a]



[a] 0.2 mmol of **2a**/**2a'** (**1a**:**2** = 3:1).

To further prove the direct involvement of epoxide units in the reaction mechanism, X-Ray Photoelectron Spectroscopy (XPS) analysis was carried out in samples of GO before and after the catalytic protocol (Figure 2).

Figure 2. C 1s XPS spectra of (a) pristine GO, (b) GO after 4 hours at 90 °C in dioxane and (c) GO after the allylic alkylation of thiophenes with alcohols.



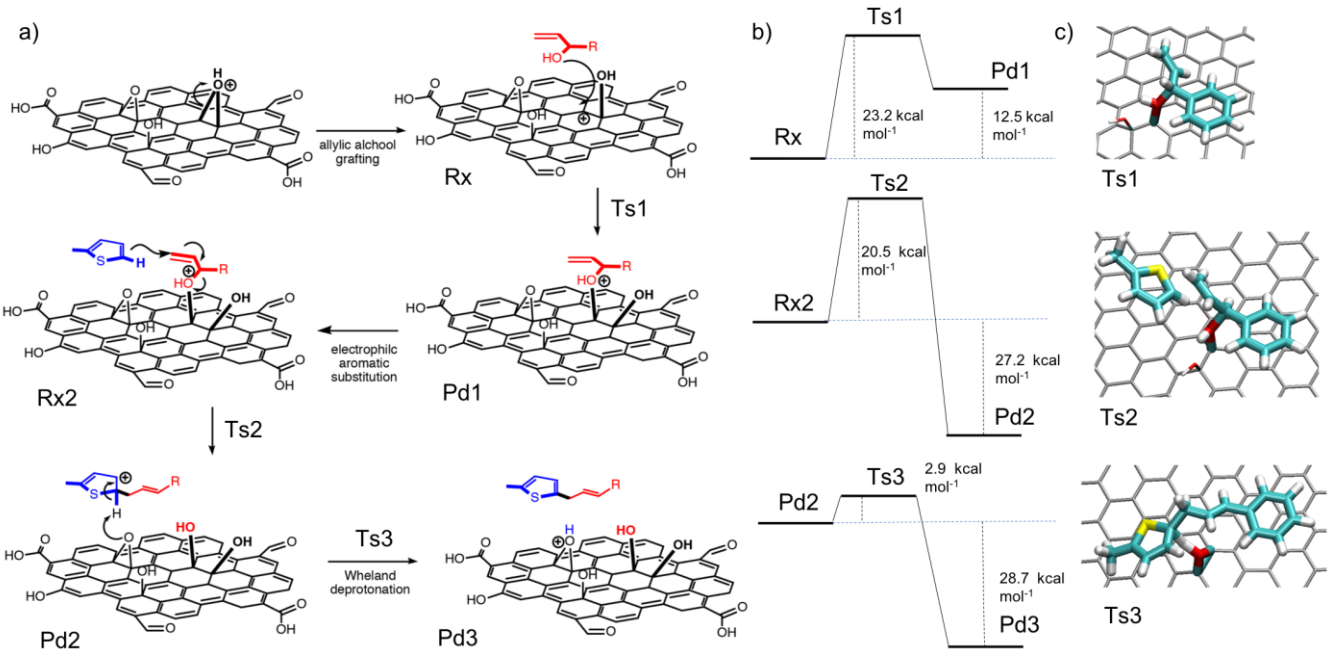


Figure 3. a) Schematic representation of the reaction mechanism; b) Energy profiles for the 3 steps; c) 3D representation of the identified transition states.

The fitting of the high-resolution C 1s peak quantified the relative amounts of aromatic carbon (C-C sp2, 284.4 eV), aliphatic carbon (C-C sp3, 285.0 eV), hydroxyl (C-OH, 285.7 eV), epoxy (C-O-C, 286.7 eV), carbonyl (C=O, 288.0 eV) and carboxyl (O-C=O, 290.1 eV).[16]

Figure 2 shows the C 1s spectra of (a) pristine GO, (b) GO after 4 hours at 90 °C in dioxane and (c) GO after the site-selected allylic alkylation of thiophenes with alcohols (c). Firstly, it is possible to exclude any reaction between GO and dioxane at 90 °C since GO (a) and GO after 4 hours at 90 °C in dioxane (b) have no remarkable differences. Differently, after reaction (Figure 2c) the relative abundance of the epoxy groups decreased substantially from 40.3 ± 0.8% to 27.4 ± 0.6%, while the hydroxyl groups increased from 7.6 ± 0.3% to 11.9 ± 0.3% suggesting that a partial ring-opening of the epoxide units of the promoting agent took place concomitantly to the reaction course. As expected, aromatic carbons are not affected by the reaction (see SI for details).

We combined all spectroscopic and experimental information with QM/MM study to elucidate in detail the reaction mechanism.[17] We used **1a** and **2a** as model substrates. In details, the reaction mechanism resulted to be a three-step process as depicted in Figure 3. In step 1 the allylic alcohol grafts to the GO surface. The reaction follows a S_N1 mechanism where the protonation (proton source could rely on the intrinsic BrØnsted acidity of GO) of the epoxide ring on the GO surface leads to an unstable oxonium unit that opens without overcoming any barrier (**Rx**). This gives a reactive α carbocation that undergoes a nucleophilic attack by the allylic alcohol (**Ts1**). From this picture emerges the crucial role of the GO π-system in the stabilizating the carbocation generated by the epoxide ring opening event. The concerted action of the GO π-system and the functional groups present in the 2D-material is highlighted in agreement with experimental observations. The obtained protonated allyl ether may undergo a Friedel-Crafts-type allylic alkylation providing the observed allyl-thiophene (**Pd1**). Step 2 follows a concerted mechanism where the α carbon of the 2-methyl-thiophene attacks the allylic position (**Ts2**), inducing a reorganization of the π system (Figure 3c). The leaving O-H group remains grafted on the GO surface (**Pd2**). Such mechanism justifies the overall increase of alcoholic moieties versus the oxirane ones spectroscopically observed by XPS.

The GO catalyst played also a role in the regioselectivity of the attack carried out by the α carbon of the thiophene derivatives (**3aa** *vs* **3aa'**). In fact, if the attack is carried out by the α carbon (major regioisomer, Figure SI1) the sulphur atom of the thiophene points toward the graphene sheet, while if the attack is carried out by the β–carbon there is no interaction between the S atom and GO. It is well known that sulfur–π interactions are strongly stabilizing,[18] favouring the attack in α by 6.5 kcal mol^{-1} (Figure SI1). The final step namely the deprotonation of the Wheland-like intermediate (**Ts3**), is a fast process (a barrier of only 2.9 kcal mol^{-1} was computed) carried out by other epoxide groups present on the GO surface. The recorded drop in catalytic performance (isolated yields in **3aa**) by the recovered GO (I run: 88%, II run: 66%, III run: 45%, IV run: 29%) supports the current mechanistic hypothesis. In particular, the lower is

the content of epoxide units on the GO surface the less effective is the carbocatalysis.[19]

In conclusion, the regioselective allylic alkylation of thiophenes with alcohols is documented under the assistance of readily available and chemically unmodified graphene oxide. The protocol features unique key aspects such as high functional group tolerance, mild reaction conditions and low to moderate GO loading. The extension of the present GO-based protocol to other C-C bond forming functionalizations of π-systems is currently under investigation in our laboratories.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information for synthetic procedures, XPS analysis and NMR spectra of unknown compounds and computational details is available free of charge on the ACS Publications website.

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10. The flakes of GO tended to dissolve completely during the heating and reaction time.

11. GO was used in flakes and it exfoliated during the reaction. In a comparative experiment GO was exfoliated for 10 hours in the reaction solvent and the suspension used as it for the catalysis. No differences in reaction performances were recorded.

12. Additionally, other "conventional" Lewis acids were tested in the model reaction providing unsatisfying results in terms of yields or **3aa:3aa'** regioselectivity: *p*TSA (10 mol%) → 18% yield; $FeCl_3$ (10 mol%) → NR; $In(OTf)_3$ → 84% yield (2:1).

13. Attempts to extend the protocol to longer thiophene oligomers such as quaterthiophene failed in performing the FC-type process.

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15. The control experiment carried out with stoichiometric amounts of styrene oxides intents to verify the potential role of the oxiranes moieties present on the GO surface on the reaction mechanism.

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