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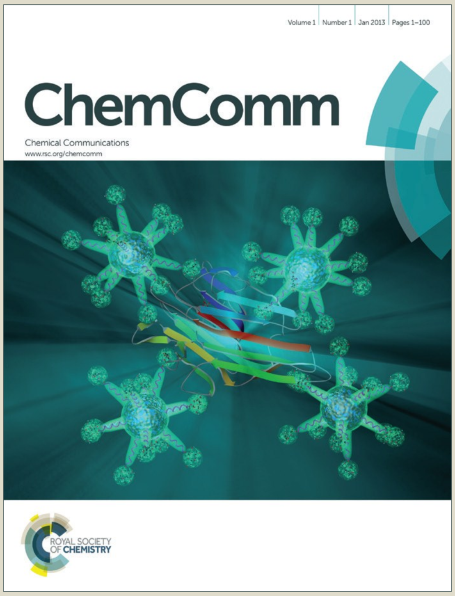

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Graphene oxide as metal-free catalyst for hypochlorite oxidation of primary amines to nitriles

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Graphene oxide catalyzes NaClO oxidation of primary benzyl and aliphatic amines to a product distribution comprising nitriles and imines. Nitriles are the sole product for long chain aliphatic amines. Spectroscopic characterization suggests that percarboxylic and perlactone groups could be the active sites of the process.

The use of graphene (G) and related 2D materials as metal-free catalysts has emerged as a hot topic in catalysis. [1-4] The long term goal is to determine the potential of Gs as alternative catalysts to conventional metal and metal oxides for certain reaction types. In this context, one process that has attracted considerable attention recently as benchmark reaction is the oxidation of primary benzylamines. [5-7] In the most common process, benzylamines undergo oxidative condensation to N-benzylidene benzylamines promoted by a large variety of metal oxides of various compositions as well as Au NPs supported on a variety of metal oxides.[5, 7, 8] More closely related to the present study, Loh and co-workers have found that graphene oxide (GO) conveniently purified from amorphous acidic carbon debris by basic washings and subsequent neutralization by acids, is an efficient catalyst for the aerobic oxidation of benzyl amines into the corresponding N-benzylidene benzyl amines without the presumed assistance of any metal.[9] It has been proposed that base washings and removal of acid amorphous carbon residues generated in the Hummers oxidation of graphite results on the release of free holes on the GO sheet that are the active sites of the process.[9] From the synthetic point of view, oxidation of amines into nitriles is an important functional group transformation.

Continuing with the oxidation of benzylamines by carbocatalysts, in the present manuscript it will be reported that deeper oxidation by NaClO using G as metal-free catalyst can result in the conversion of primary amines into the corresponding imines or nitriles. Particularly useful from the synthetic point of view is the conversion of long chain aliphatic amines into the corresponding aliphatic nitriles. Nitriles have large interest in their own as solvents and also as synthetic intermediates in the preparation of carboxylic acids, ketones and N-containing heterocycles, including phthalocyanines. [10 2

The catalyst is a GO sample (1 to 5 μm lateral size, 51, 8 and 44 % of C, H and O content, respectively) obtained by Hummers oxidation of graphite and subsequent exfoliation, as reported.{Stankovich, 2006 #60} Using GO as catalyst, preliminary tests were carried out to determine the most adequate reaction conditions to oxidize benzyl amine (**1a**) by NaClO as oxidizing reagent. Table 1 summarizes conversion and selectivity data for this reaction. Controls using NaClO as oxidant in the absence of any catalyst shows that **1a** is converted around 40 % into two products, namely N-benzylidene benzylamine (**2a**) and benzylidene imine (**3a**) (Table 1, entries 1 and 2). Benzylidene imine **3a** is highly reactive against nucleophiles, including H_2O and amines, leading to benzaldehyde or benzylidene benzyl amine **2a**. For this reason, imine **3a** is not a common reaction product in benzyl amine oxidations. In the present case, formation of **3a** was safely identified by the absence in ^{13}C NMR spectra of peaks at about 190 ppm corresponding to benzaldehyde and the presence of a peak at 150 ppm (see supplementary information). Also in GC-MS, the M^+ and its main fragment appeared at 105 and 104 Dalton, respectively. No benzonitrile was detected in the solution. An increase in the excess of NaClO in the absence of catalyst did not result in a significant increase in the conversion of benzylamine **1a**.

In contrast, under the same conditions but using 10 wt % of GO as catalyst, a substantial percentage of nitrile **4a** with selectivity above 50 % was observed at similar conversions of **1a** (Table 1, entry 3). It is interesting to note that formation of benzonitrile **4a** is accompanied by a concomitant decrease in the selectivity of benzylidene imine (**3a**) from 55 to 6 %, while the selectivity of benzylidene benzylamine (**2a**) was mostly

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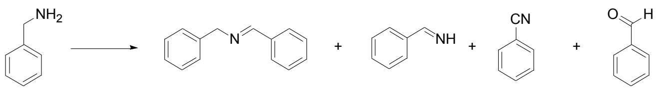
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x unaffected (compare entries 1 and 3 in Table 1). This change in product selectivity suggests that benzyl imine **3a** is the precursor of nitrile **4a** and that the presence of GO does not promote the conversion of **1** into **3a,** since conversion of the starting material **1a** was similar in the absence and presence of GO catalyst. Thus, under the present experimental conditions, GO is promoting oxidation of imine **3a** to nitrile **4a** without promoting the oxidation of the starting material **1a** that is spontaneously oxidized in a certain extent by NaClO (Table 1, entries 1 and 2). This would explain the similar conversion of **1a** and selectivity to **2a** in the presence and absence of GO and the exclusive change in the selectivity between **3a** and **4a** comparing the results with and without GO. A plausible reaction mechanism compatible with the results obtained is shown in Scheme 1.

Table 1. Results of the oxidation of benzyl amine (**1a**) catalyzed by GO. Reaction conditions: 0.27 mmol of **1a**, 5 mL CH_3CN as solvent, 0.59 mmol NaClO, 5 h reaction time, 75 °C reaction temperature, catalyst: 10 wt % GO respect to **1a**.



1a 2a 3a 4a 5a

Entry	Conversion (%)	Selectivity (%)			
	1a	**2a**	**3a**	**4a**	**5a**
1[a]	43	45	55	0	-
2[a,b]	42	29	71	0	-
3	48	40	6	54	-
4[b]	47	26	33	41	-
5[b,c]	54	60	24	16	-
6[d]	42	88	-	10	1

a) no catalyst; b) no oxygen; c) double amount NaClO; d) 1 mL water; e) dried NaClO; f) reaction time :1 h; g) reaction time: 3 h**.**

The presence of water was found to be an important factor controlling conversion of **1a**, selectivity and product distribution (Table 1, entry 6). If water is purposely added, the conversion of **1a** decreases somewhat from 48 to 42 % with the complete absence of imine **3a**, a high selectivity towards benzylidene benzylamine (**2a**) and only a marginal formation of nitrile (**4a)** about 10 %. Importantly, in the presence of water, instead of imine (**3a**), benzaldehyde (**5a**) was detected in a very small percentage (Table 1, entry 6), in agreement with the expected reactivity of imine **3a**.

A reasonable explanation for the influence of H_2O in the process is also included in Scheme 1. According to this, H_2O will promote hydrolysis of imine **3a** to benzaldehyde **5a** that would react quickly with starting benzylamine **1a** affording additional amounts of **2a.** The presence of H_2O should also affect to all the pathways indicated in Scheme 1.

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Another point to be addressed is the influence of oxygen on the benzylamine oxidation by NaClO. It is very common in oxidation reactions that the presence of oxygen influences conversion and selectivity, commonly by favoring radical chain mechanisms involving the intermediacy of peroxyl radicals. In the reaction under study, it has also been reported that GO can be catalyst for the oxidation of benzylamine **1a** under certain conditions. For this reason the influence of oxygen using NaClO as oxidizing reagent was also checked. It was observed that the presence of oxygen has not influence on benzylamine (**1a**) conversion (Table 1, compare entries 1, 2, 3 and 4). In contrast, the presence of oxygen has a remarkable influence on product selectivity when using GO as catalyst, decreasing the percentage of imine (**2a**)**,** in favor of the formation of benzonitrile (**4a**) and benzyl imine (**3a)** (Table 1, compare selectivity of **2a** and **3a** in entries 1, 2, 3 and 4). This catalytic data suggests that in Scheme 1, while the initial steps starting from benzyl amine (**1a**) as substrate are not promoted by oxygen, subsequent secondary processes can be boosted by the presence of oxygen. Accordingly, using NaClO as oxidizing reagent and GO as catalyst, the best conditions in terms of benzonitrile (**4a**) selectivity were achieved in the presence of oxygen (Table 1, entry 3).

In order to determine the scope of the reaction, primary benzylamines (Table 2) having substituents on the aromatic ring as well as aliphatic amines (Table 3) were also tested as substrates. Overall, Table 2 shows that for substituted benzylamines the major product of the NaClO oxidation promoted by GO are the corresponding benzyl imines **3b-d** or related compounds (**6e**) and aryl nitriles **4b-e** are obtained in very minor percentages (see supporting information for MS, ^{1}H and ^{13}C NMR spectroscopic data of the reaction products). Thus, the presence of methyl substituent at the para position (Table 2) disfavors the selectivity towards nitrile (**4b**) and the major product was the corresponding benzylidene imine (**3b)** accompanied by some 4-methylbenzaldehyde (**5b**). **3b** exhibits in ^{13}C NMR spectroscopy no peak at 190 ppm corresponding to aldehyde and a peak at 150 ppm attributable to the imine carbon (see supporting information). Similarly, 2- and 4-methoxybenzyl amine (Table 2) undergo oxidation in the presence of NaClO resulting in the predominant formation of the corresponding benzylidene imines (**3c** and **3d**) with very high selectivity particularly for the 2-methoxy derivative. In the case of the 4-methoxy derivative, the percentage of 4-methoxybenzaldehyde (**5d**), probably derived from the hydrolysis of the imine (**3d**), was significantly higher in the final reaction mixture. The case of 4-chlorobenzylamine is remarkable, since for this compound, particularly under dry conditions, the major final product observed was the corresponding *N,N*-bis(4-chlorobenzyl)hydroxylamine (**6e**) accompanied by small percentages of 4-chlorobenzaldehyde (**5e**) and 4-chlorobenzonitrile (**4e**). Compound **6e** was identified by the presence in ^{1}H NMR spectroscopy of the methylene groups as singlets at 3.85 ppm and their corresponding aliphatic C in ^{13}C NMR spectrum appearing at 52

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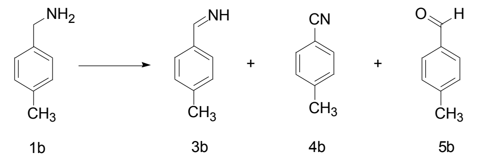
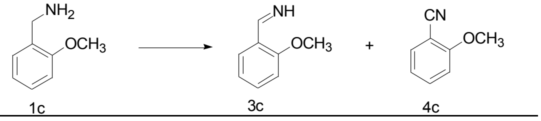
ppm (see supporting information). It seems that the presence of moderate electron withdrawing Cl substituent changes the reactivity pattern from the formation of benzyl imines **3a** to the hydroxylamine **6e**. In the case of the chloro derivative, the presence of water in the reaction mixture does not alter substantially product distribution, although a slight increase in the percentage of 4-chlorobenzonitrile (**4e**) was measured, the most remarkable catalytic data being the conversion decrease of the starting material (**1e**) in the presence of water (Table 2 compare entries 7 and 8 with 9 and 10). It is, however, evident that bis(4-chlorobenzyl)hydroxylamine **6e** is structurally related to benzylidine benzylamine **2e** by water addition.

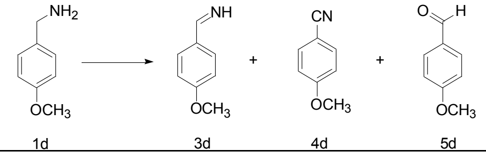
Table 2. Conversion and selectivity for the NaClO oxidation of different amines catalyzed by GO. Reaction conditions: 0.27 mmol of substrate, 5 mL CH_3CN, 0.59 mmol NaClO, 5 h, 75 ^oC, catalyst: 10 % w/w GO respect to substrate, 5 atm O_2



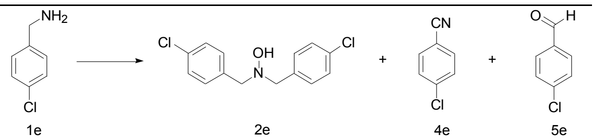
Entry	Conversion (%)	Selectivity (%)		
	1b	**3b**	**4b**	**5b**
1	98	93	3	4
2^{a}	94	91	5	4



Entry	Conversion (%)	Selectivity (%)	
	1c	**3c**	**4c**
3	79	96	4
4^{a}	91	99	1



Entry	Conversion (%)	Selectivity (%)		
	1d	**3d**	**4d**	**5d**
5	100	83	2	15
6^{a}	99	63	3	34



Entry	Conversion (%)	Selectivity (%)		
	1e	**4e**	**5e**	**2e**
7	64	4	1	94
8^{a}	76	5	6	89
9^{b}	100	1	1	98
10^{a,b}	100	1	4	95

[a] No oxygen; [b] dry conditions;

Aliphatic amines can also be oxidized by NaClO using GO as metal-free catalyst. The results shown in Table 3 are remarkable since generally aliphatic amines undergo oxidation giving rise to a wide range of products that make this process extremely unselective and lacking of synthetic interest.[11] [12] . In contrast, using NaClO as oxidant and GO as catalyst either the oxidative coupling product or the nitrile were selectively obtained, depending on the chain length. The change in the reactivity pattern was observed for heptamine. A salient observation was that for the long alkyl chain, the corresponding nitriles **4** were formed as the only products observed at any substrate conversion (Table 3, entries 5-8). Data of Table 3 contrasts with the current state of the art and opens the possibility to develop a general process for aliphatic nitrile formation from amines.

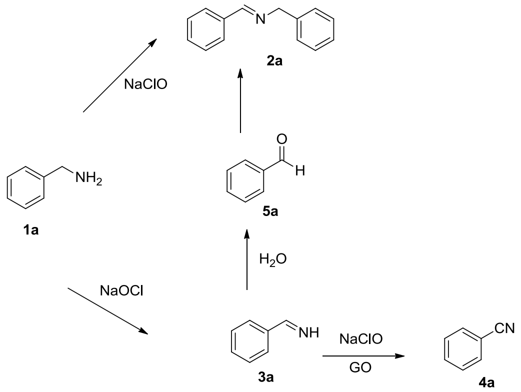
Table 3. Results of the oxidation of aliphatic amines by NaClO catalyzed by GO. Reaction conditions: 0.27 mmol aliphatic amine, 5h, 75 ^oC, 10% w/w GO respect substrate, 5 ml CH_3CN, 5 atm O_2.

Entry	Amines	Amine conversion (%)	Selectivity (%)		
			Coupling **2**	Nitrile **4**	Aldehyde **5**
1	pentylamine	73	100	0	0
2	pentylamine^{b}	100	100	0	0
3	Heptylamine	68	84	11	5
4	Heptylamine^{b}	68	94	<1	6
5	Dodecylamine	37	0	100	0
6	Dodecylamine^{b}	25	0	100	0
7	Hexadecylamine^{a}	43	0	100	0
8	Hexadecylamine^{a,b}	27	0	100	0
9	Stearylamine	58	0	100	0
10	Stearylamine^{b}	57	0	100	0

[a] solvent is hexane; [b] no oxygen;

Comparison of the product distribution of Tables 1, 2 and 3 shows that the reaction mechanism should be complex and that the outcome of the oxidation is influenced by the structure of the starting material and the reaction conditions. Focusing on the oxidation of benzylamine **1a**, additional support to the mechanistic proposal shown in Scheme 1 was sought. Temporal evolution of the products showed that upon full conversion of **1a,** no change in the selectivity of benzylidene benzylamine **2a** occurs upon prolonged reaction time. In contrast, some decrease in the selectivity of **3a** in favor of **4a** is observed. This indicates that compound **2a** is not involved in the formation of benzonitrile **4a** that derives from imine **3a**. In this route the role of water seems to be the promotion hydrolytic conversion of benzyl imine **3a** into aldehyde **5a**.

To gain at deeper insight into the role of benzaldehyde in the process, an additional experiment in which an equimolar mixture of benzaldehyde and ammonium chloride in acetonitrile was submitted to NaClO oxidation under the conditions employed in the oxidation of **1** was performed. The formation of benzonitrile (**4a**) was observed, although the yield (1 %) was very low with respect to the amount of benzaldehyde (**5a**). Further attempts to increase the formation of benzonitrile (**4a**), by adding an excess of ammonium to the acetonitrile solution of benzaldehyde (**5a**), only increased the yield of benzonitrile (**4**) marginally to 3 %. Therefore, these experiments indicate that if benzaldehyde (**5a**) is formed by hydrolysis of imine **3a**, the main product to be expected in the presence of benzylamine **1a** is the benzylidene benzylamine **2a**, as reported in other cases.[9]



Scheme 1. Mechanistic proposal for benzonitrile formation by NaClO oxidation of benzylamine catalysed by GO.

To understand the role of GO as catalyst, a suspension of GO in acetonitrile was treated with NaClO for 3 h at 75 °C and the resulting treated GO was characterized by Raman spectroscopy (see Figure 1). It was observed that under these oxidizing conditions, new vibration bands appear in the spectrum at 1750 and 1875 cm^{-1}. These new peaks are attributable to the formation of C=O groups on the G sheet, probably in strained cycles or as esters and anhydrides. Also, variations on the relative intensity and position of the G and D bands upon NaClO treatment were noticed (see Figure 1). Accordingly, we propose that percarboxylic acids, perlactones and related oxygenated substructures generated on GO under oxidative conditions could act as the active sites in this oxidation. The oxidizing activity of hydroperoxy acids, perlactones and related hydroperoxy functional groups is well known in general organic chemistry and due to the presence of abundant carboxylic acid groups on GO, it could be expected that similar substructures could be generated upon treatment with ClO$^-$ as oxidant.

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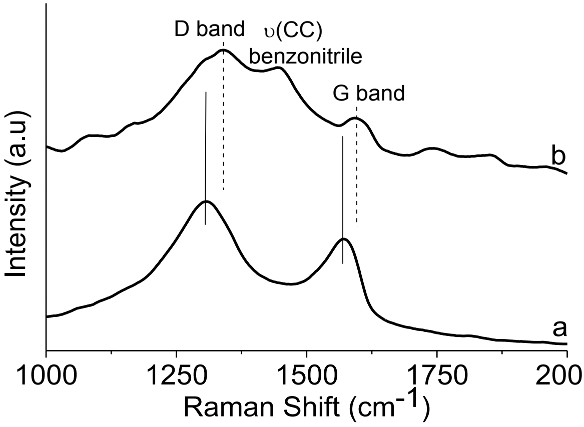

Figure 1. Raman spectra of GO before (a) and after treatment with NaClO under reaction conditions (b).

In summary, in the present study, it has been shown that GO is a suitable carbocatalyst to promote NaClO oxidation of aromatic and aliphatic benzyl amines, leading to the formation of benzonitriles and benzyl imines in variable proportion depending on the reaction conditions. Kinetic data show that benzyl imines are the initial oxidation product that are converted into nitriles due to the catalytic activity of GO. The reaction is of synthetic interest for the preparation of the corresponding nitriles from long alkyl chain aliphatic amines, for which complete selectivity are attained. Overall, our report constitutes another remarkable example on the use of GO as metal-free oxidation catalyst and complements prior studies on benzylamine oxidation by Gs.

Notes and references

See supporting information for experimental procedures and product characterization data.

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