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Selectivity matters: Graphene oxide-mediated oxidative coupling of benzylamine to *N*-benzylidine-1-phenylmethanamine under microwave irradiation

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ABSTRACT

A selective, efficient and benign oxidative coupling of benzylamine under microwave irradiation was achieved at mild reaction conditions in the absence of oxidant using graphene oxide as catalyst. Reaction conditions seem to point to the favoured formation of an imine intermediate which subsequently reacts with benzylamine to provide high selectivities at almost quantitative conversion of starting material to the oxidative coupling product *N*-benzylidine-1-phenylmethanamine. A plausible reaction mechanism is proposed.

1. Introduction

Graphene and chemically modified graphenes (CMGs) have attracted much attention in recent years due to their interesting physico-chemical properties [1–3]. These materials are expected to have a significant impact in different fields including chemistry, physics, biotechnology, engineering and materials science [4–7]. Although the synthesis of these materials was complex in the early stages of research, advances on the development of CMGs have granted access to high quality materials with a wide range of properties.

In particular, the use of these materials in catalytic applications has been only explored very recently following the seminal reports by Dreyer et al.,[8] but is currently gaining much interest, particularly related to the development of functionalised graphene systems for various catalytic applications [9].

In this regard, most applications of graphene and CMGs in catalysis have been mainly focused on their functionalisation via deposition of metal nanoparticles and/or doping graphene through dopant elements (i.e. N, P, S, halogens) and covalent functionalisation (i.e. $-$COR, $-SO_3H$, $-$SH, $-$CN, $-$NHR) [10,11].

Comparatively, the use of metal-free carbonaceous materials in synthetic chemistry offers a more promising alternative to highly valuable products derived from different chemistries [12].

Graphene oxide (GO), a material that can be easily obtained from the oxidative exfoliation of graphene, can in principle be a good candidate for catalytic applications [13,14].

This material is a readily available and inexpensive material that has been proven as catalytically active in oxidation of various alcohols, alkenes, epoxides, thiols, sulfides and alkynes to produce alcohols, sulfones and ketones [12–17].

More recently, graphene oxide has been proved to be catalytically active in the conversion of carbohydrates into 5-ethoxymethylfurfural via etherification [18].

The main advantages of the use of GO as catalyst are the use of a simple and inexpensive catalyst, metal-free reactivity and easy recovery of the GO by filtration from the reaction media. However, catalytic results reported to date for GO have been obtained under relatively extreme conditions, especially in terms of catalyst load (200% wt.) and times of reaction (24 h+) [8,19]. These conditions have to be improve for future applications of GO as catalyst in the chemical industry. For this reason, current research efforts of the group have been focused on the improvement of the catalytic prop-

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erties of GO in terms of versatile transformations to be performed as well as to switch to milder and benign conditions including the use of microwave irradiation and continuous flow processes combined with benign reagents (e.g. hydrogen peroxide as oxidant, water and ethanol as solvents).

Imines are important and versatile intermediates for the synthesis of a broad variety of nitrogen-containing compounds with significant application in biological and pharmaceutical fields [20–26]. For this reason, their synthesis is attracting high interest in recent years [25,27–29]. Traditionally, imines have been prepared by condensation of carbonyl compounds with amines in the presence acid catalysts, but these procedures present disadvantages including high reaction temperature, prolonged reaction times and require costly dehydrating reagents [22]. The direct coupling of amines to imines represents an alternative strategy of increasing interest [20,22,25,27,28,30].

Main advances in this field have been focused in the catalytic oxidation of secondary amines into imines [31], but much lower attention has been paid to the synthesis of imines from primary amines because it generally leads to other nitrogen containing compounds, normally nitriles [21,26]. However, increasing efforts are being made with the aim of developing the catalytic oxidation of the primary amines to the corresponding imines [21,26–28,32]. Most of these efforts have been focused in the development of metal-based catalytic processes. Nevertheless, the high prices and low availability of most of these metals (V, Ru) make it necessary to find alternative catalysts. Carbon materials, and more precisely graphene-based materials could constitute an attractive alternative [33].

In recent years, organic chemistry has been virtually rewritten using microwaves as non-conventional heating source. A significant body of work has shown considerable reduction in reaction times and improved yields and selectivity of obtained products by means of microwaves [34–36]. However, there is a lack of studies of the microwave-assisted oxidative coupling of benzylamine beyond the mechanistic study of Atanassova et al., where very high catalyst loadings were used [37].

In this work, we report a simple approach to microwave-assisted selective oxidative coupling of benzylamine catalysed by GO in which we show significant improvements compared to both uncatalysed and metal-catalysed protocols. A plausible reaction mechanism is also proposed to provide molecular insights into the oxidative coupling.

2. Experimental

2.1. Preparation of graphene oxide (GO) and reduced GO (rGO)

GO was kindly donated by the company NanoInnova (Madrid, Spain) and its synthesis can be briefly described as follows: graphene oxide was synthesized by using a modified Hummers' method [38]. Briefly graphite powder (<150 μm Sigma–Aldrich) was chemically oxidized in a solution containing $NaNO_3$, H_2SO_4 and $KMnO_4$. Reduced GO was also kindly provided by NanoInnova, with a surface area of around 100 $m^2\,g^{-1}$ and different structural features as compared to GO [39]. Full details, including characterization of the materials, can be seen at the website of the company http://www.nanoinnova.com/Product

2.2. Catalytic tests

A series of experiments under different conditions was performed in order to study the catalytic properties of the GO provided by NanoInnova. The tests were performed under microwave heating in a pressure-controlled CEM-discover microwave reaction. Reactions were performed controlling temperature (150–200 °C). Different times of reaction were also studied (30 and 60 min). The reaction mixture was composed by acetonitrile (2 mL), benzylamine (0.2 mL), H_2O_2 (0.3 mL, 50% v/v aqueous solution) and a weighted amount of GO as catalyst. The influence of the presence of the oxidant species (H_2O_2) was determined by carrying out some test without H_2O_2. The influence of a previous sonication pre-treatment to improve the exfoliation of the GO layers was also studied by including a test with 15 min of pre-treatment of the reaction mixtures. An additional test with a reduced GO was carried out to as blank run. Table 1 summarises the conditions of the experiments.

After the experiments, the reacting mixtures were filtered off and the filtrate was analysed by means of a GC and GC/MS Agilent 6890N fitted with a capillary column HP-5 (30 m × 0.32 mm × 0.25 μm) and a flame ionisation detector (FID).

3. Results and discussion

The oxidative coupling of benzylamine was selected as key process to investigate the influence of graphene oxide in the selectivity to products, particularly related to the main products of oxidative coupling: *N*-benzylidine-1-phenylmethanamine and *N*-benzylacetamide. Blank runs, in the absence of catalyst and oxidant (labelled as a and b), gave no conversion in the systems even at high temperatures (>200 °C). However, the simple addition of an oxidant (hydrogen peroxide) to reaction mixture in the absence of catalyst provided quantitative conversion of benzylamine (Fig. 1, run c).

An interesting 40–45% selectivity to *N*-benzylacetamide was observed, together with a very low selectivity to the oxidative coupling product (*N*-benzylidine-1-phenylmethanamine). Benzaldehyde, benzonitrile, the corresponding oxime (Y) and benzamide were also detected in moderate quantities in the catalyst-free reaction under the investigated conditions. Following previous literature reports on mechanistic insights on the reaction, we envisaged graphene oxide (GO) as a potentially interesting candidate to achieve a selective conversion to the oxidative coupling product as opposed to the formation of *N*-benzylacetamide. These reports speculated about the formation of an *N*-oxide intermediate on oxidative active sites followed by conversion to benzaldehyde that reacts with benzylamine (Fig. 2) [37].

Results under optimised conditions are shown in Figs. 1 and 3 (runs d–h) as compared to the blank runs. All experiments provided high conversions (in the range of 85–99%), with the exception of the GO experiment in the absence of oxidant (run e) for which conversion remained under 50%. These findings pointed out that oxidant species are required to achieve high conversions if low loadings of catalyst are used. At increasing GO loadings (experiments f and g), the conversion remains high even in the absence of oxidant (run f).

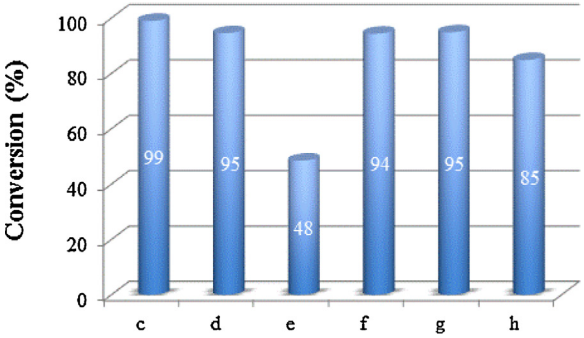

Fig. 1. Conversions achieved in the oxidative coupling of benzylamine (runs c–h).

Table 1
Experimental conditions of the tests performed.

Run	Conditions	GO (mg)	H_2O_2	Temperature (°C)	Time (min)	Sonication
a	Blank (absence of oxidant)	0	No	150	60	No
b	Blank (absence of oxidant and high temperature)	0	No	200	60	No
c	Blank (presence of oxidant)	0	Yes	150	60	No
d	GO experiment	50	Yes	150	60	No
e	GO experiment in the absence of oxidant	50	No	150	60	No
f	Experiment doubling catalyst loading in the absence of oxidant	100	No	150	30	No
g	Experiment doubling catalyst loading in the presence of oxidant	100	Yes	150	30	No
h	Experiment with reduced graphene oxide	50	Yes	150	60	No

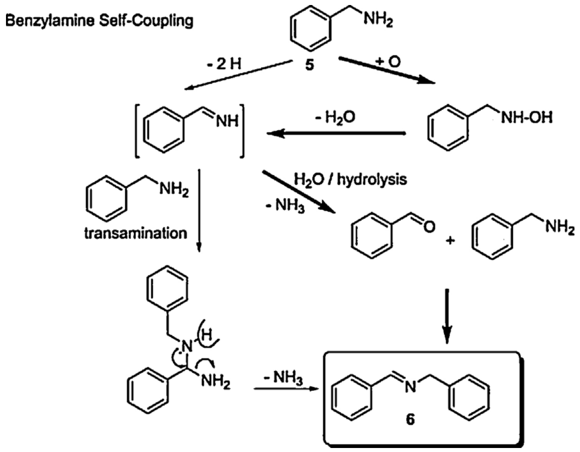

Fig. 2. Mechanism for the self-coupling of benzylamine over K-10 montmorillonites (from Atanassova et al.) [37].

The effect of the addition of GO in the conversion of the systems can be also inferred from results observed when reduced GO was used as catalyst (run h). In this run, the conversion was slightly reduced (85% instead of 95%) as compared to reactions with GO.

In any case, the relevant findings of this work relate to the remarkable changes in selectivity observed for the different reactions as depicted in Fig. 3. The addition of GO favoured the formation of the oxidative coupling product (*N*-benzylidine-1-phenylmethanamine) at the expense of *N*-benzylacetamide (reaction c-blank with oxidant vs reactions d–f). Interestingly, a complete selectivity to the target oxidative coupling product could be obtained at 94% conversion for the GO catalysed process in the absence of oxidant after a few minutes of microwave irradiation (see entry f, Figs. 1 and 3). Reducing the time of reaction (from 30 to 15 min) did have a detrimental effect on the conversion of the systems, decreasing to ca. 60% under the investigated conditions. These findings demonstrate the unique potential of GO as oxidising catalyst *per-se*, especially for the oxidative coupling mechanism, which was found to be strongly favoured by the presence of GO. The presence of oxidant has a negative effect in terms of selectivity over the process even when GO is present, since the selectivity to the oxidative coupling product slightly decreased upon oxidant addition while the selectivities to other products (mainly benzaldehyde) increased, as clearly observed from results of runs d (presence of H_2O_2) and e (absence of H_2O_2) and between runs g (presence of H_2O_2) and f (absence of H_2O_2).

This can be explained due to the reaction mechanisms proposed by Atanassova et al. (Fig. 2). When the process is carried out using clays as catalysts (such as K-10 montmorillonites), the reaction took place through two different mechanisms, favouring the formation of benzaldehyde as intermediate product. The addition of H_2O_2 in these experiments seems to promote the same chemistries. However, the use of GO as catalyst in absence of H_2O_2 may promote the alternative pathway.

Based on this observation, a mechanism for imine formation via graphene oxide (GO) catalysed oxidative coupling is proposed in Fig. 4. In this mechanism, the carboxyl groups in the surface if the GO give rise to a reaction intermediate. This intermediate, in combination with the surface ether groups, gives rise to the hydroxylamine intermediate. This intermediate subsequently dehydrates to produce an unstable imine which undergoes transamination with another unreacted benzylamine molecule to form *N*-benzylidine-1-phenylmethanamine. Depending on the reaction conditions, the process can switch to both previously

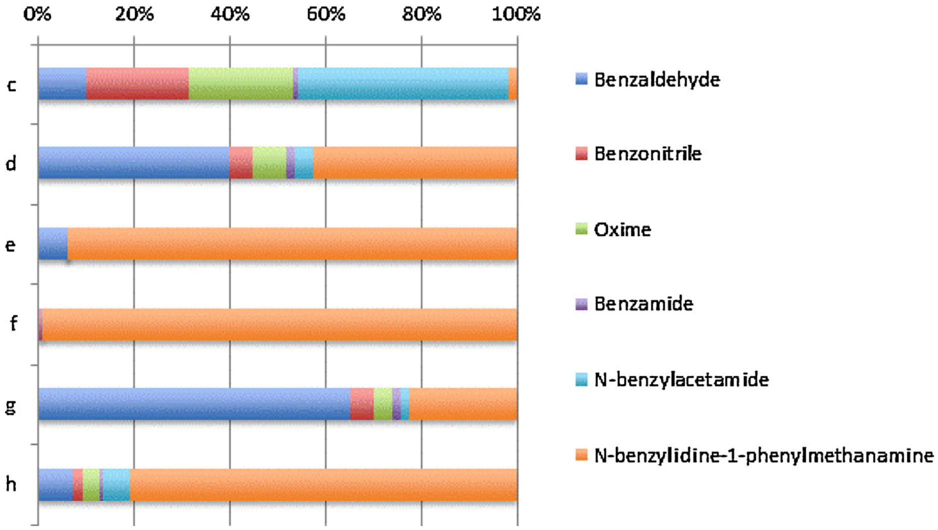

Fig. 3. Selectivity distribution in the oxidative coupling of benzylamine (runs c–h).

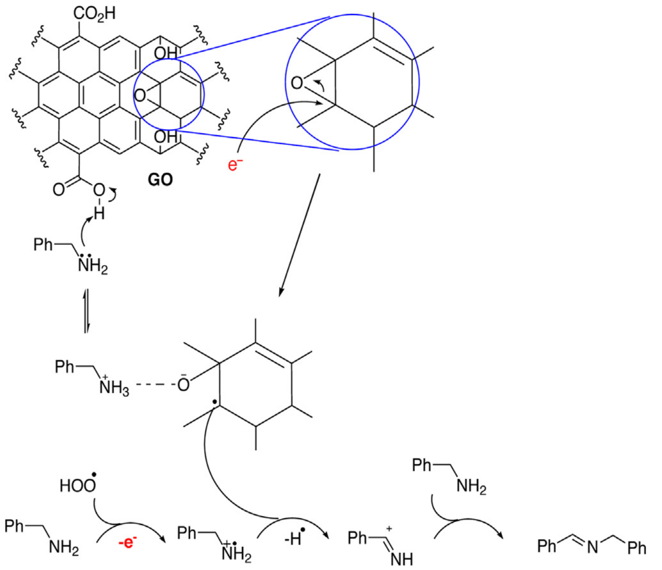

Fig. 4. Proposed mechanism for the imine formation by oxidative self-coupling of benzylamine using graphene oxide (GO) as catalyst.

proposed mechanisms. When GO is used in the presence of an oxidant, the reaction seems to take place through the formation of an *N*-oxide intermediate on oxidative active sites followed by conversion to benzaldehyde. This intermediate quickly reacts with benzylamine to generate *N*-benzylacetamide as major product. Comparatively, the use of GO in the absence of oxidant seems to promote the conversion of the formed *N*-oxide intermediate to the unstable imine that reacts with benzylamine to generate the oxidative coupling product *N*-benzylidine-1-phenylmethanamine.

The use of reduced GO as catalyst (entry h) provided a range of products, with the target *N*-benzylidine-1-phenylmethanamine also obtained as major compound. These were relatively similar as compared to the analogous process with GO but with reduced selectivity to the oxidative coupling product, which may indicate the presence of different catalytic sites on reduced GO leads to the kinetically favoured product (*N*-benzylacetamide), in good agreement with previous reports [40]. The experiment with GO provided an improved selectivity for the formation of the imine when no oxidant was used as well as using double catalyst loading (almost quantitative yields to *N*-benzylidine-1-phenylmethanamine).

4. Conclusions

The synergy between GO and microwave irradiation has been demonstrated for the selective production of *N*-benzylidine-1-phenylmethanamine from the oxidative coupling of benzylamine. Relatively low catalyst loadings (typically 0.1 g) were able to provide almost quantitative yields of imine in the absence of any oxidant as compared to significantly reduced selectivities observed in the presence of oxidant even using similar catalyst loadings, favouring the benzaldehyde formation. The reported results illustrate the potential of GO to selectively promote oxidative processes under mild conditions, with additional possibilities in the selective oxidations of alcohols, alkenes and alkynes currently under investigation in our laboratories that will be reported in due course.

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