



Direct oxidative synthesis of nitrones from aldehydes and primary anilines using graphite oxide and Oxone



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ABSTRACT

One-pot condensation/oxidation of aldehydes and primary anilines into nitrones using graphite oxide (GO) and Oxone as the oxidant under very mild reaction conditions is described. The proposed method provides a direct oxidative synthesis of various nitrones in good to excellent yields under metal-free conditions in short reaction times.

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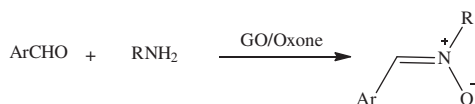
Nitrones are useful and valuable intermediates for the synthesis of heterocyclic compounds.¹ They have shown utility as spin-trap reagents² and therapeutic agents,³ and are used in 1,3-dipolar cycloadditions.⁴ A number of methods have been developed for the synthesis of nitron compounds including oxidation of secondary amines,⁵ *N,N*-disubstituted hydroxylamines⁶ or imines,⁷ and alkylation of aldoximes.⁸ Various types of oxidants such as hydrogen peroxide (H₂O₂), urea-hydrogen peroxide (UHP), and alkyl hydroperoxides in the presence of a catalyst such as Mo(VI),^{5a} Pt(II),^{5b} Ti(IV),^{5c} or W(VI)^{5d} have been investigated for the oxidation of secondary amines into nitrones. Recently, Cardona et al. reported a one-pot condensation/oxidation of primary amines and aldehydes into nitrones using UHP as the oxidant in the presence of methyltrioxorhenium (MTO) as the catalyst.^{9a} In another report, Singh et al. investigated Nafion-immobilized MoOCl₄ and silica-immobilized oxo-rhenium as recyclable catalysts for the direct synthesis of nitrones through one-pot condensation/oxidation of primary amines and aldehydes using solid UHP as the oxidant.^{9b,c} The immobilized catalysts displayed higher activity than their analogous homogeneous catalysts with the benefit of recyclability and recovery without loss of activity.^{9b} Independently, Colacino et al. described a solvent-free synthesis of nitrones via condensation of an equimolar amount of aldehydes and *N*-substituted hydroxylam-

ines in a ball-mill apparatus.^{9d} Similarly, the condensation of aldehydes and *N*-substituted hydroxylamines over MgO under solvent-free conditions has been successfully applied for the synthesis of various nitrones in excellent yields.^{9e} However, in some cases these methods present major drawbacks such as low selectivity, poor recovery of the catalyst, and procedures that require harsh conditions. Thus, it is desirable to use a cheap and environmentally benign oxidant in combination with suitable catalysts in order to overcome these problems.

In recent years, carbon-based materials have been extensively studied in the revitalized field of carbocatalysis.¹⁰ For example, graphite oxide (GO), a readily available and inexpensive material, has been used as a heterogeneous catalyst for several organic transformations.^{11–14} We have reported on the use of GO as a highly efficient reagent for the preparation of aldehydes or ketones via the oxidation of various alcohols under ultrasonic irradiation.¹⁵ We have also applied Oxone/iron(II)sulfate/GO as a highly efficient system for the oxidation of alcohols into the corresponding carboxylic acids or ketones under ultrasonic irradiation in water.¹⁶ More recently, we demonstrated a sonochemical procedure for the direct oxidative formation of esters from a mixture of an aldehyde and an alcohol using GO and Oxone in an alcoholic solvent.¹⁷ In continuation of our investigations on the use of GO as an oxidant,^{14–17} we report herein a new and simple method for the direct condensation/oxidation of various aldehydes and primary amines using GO/Oxone as the oxidant under metal-free and very mild reaction conditions (Scheme 1).

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Scheme 1. Direct condensation/oxidation of aldehydes and primary anilines using GO/Oxone.

Initially, we tested the efficacy of hydrogen peroxide (H_2O_2), a commonly used oxidant for this chemical transformation, by screening the reaction of benzaldehyde (1 mmol) with aniline (1.2 mmol) in the presence of GO (0.1 g)/ H_2O_2 (3 mmol) in acetonitrile. The resulting mixture was stirred at 5 °C for 30 min and 3 h at room temperature. The results indicated recovery of the starting materials even after 24 h at room temperature or at reflux (entries 1 and 2, Table 1). Under similar conditions, the reaction of benzaldehyde (1 mmol) with aniline (1.2 mmol) in the presence of GO (0.1 g)/Oxone (3 mmol) in acetonitrile afforded several products including benzoic acid and the corresponding nitronium ion (entry 3, Table 1). Thus we optimized the conditions to eliminate byproduct formation. The reaction of benzaldehyde (1 mmol) with aniline (1.2 mmol) in the presence of GO (0.1 g) afforded only the corresponding imine *N*-benzylideneaniline after 2 h at room temperature (entry 4, Table 1). In contrast, the reaction of benzaldehyde (1 mmol) with aniline (1.2 mmol) in the presence of Oxone (1 mmol) and in the absence of GO led to oxidation of the starting materials (entry 5, Table 1). Phenazine in the form of yellow needles and benzoic acid were isolated after work-up of this mixture. By decreasing the Oxone concentration to 1 mmol, the reaction of benzaldehyde (1 mmol) with aniline (1.5 mmol) in the presence of GO (0.1 g) afforded *N*-benzylideneaniline oxide in 94% yield after 4 h in acetonitrile (entry 6, Table 1). Having found suitable amounts of GO and Oxone, the influence of different solvents such as acetone, THF, and acetonitrile/THF (1:1) on the reaction yield was investigated (entries 6–9, Table 1). By applying the optimized amounts of GO (0.1 g) and Oxone (1 mmol), the reaction of benzaldehyde (1 mmol) with aniline (1.5 mmol) gave *N*-benzylideneaniline oxide in 10%, 25%, and 20% yields after 24 h using acetone, THF, and acetonitrile/THF as solvents, respectively. The results indicate that the yield of the corresponding nitronium ion was better in acetonitrile as the solvent.

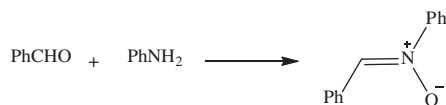
Under the optimized reaction conditions, various aromatic aldehydes (1 mmol) reacted smoothly with aromatic and aliphatic amines (1.5 mmol) in the presence of GO (0.1 g) and Oxone (1 mmol) in CH_3CN at 5 °C for 30 min and then at room tempera-

ture for the time indicated in Table 2 to give the corresponding nitronium ions in good to excellent yields. The results of condensation/oxidation of a variety of aldehydes and primary amines are summarized in Table 2. Under these conditions, the reaction of benzaldehyde, 4-chlorobenzaldehyde, 4-, 3-, 2-nitrobenzaldehyde, 4-*N,N*-dimethylaminobenzaldehyde, and 4-hydroxybenzaldehyde with aniline gave the corresponding nitronium ions in 52–97% yields (entries 1–7, Table 2). The reaction of benzaldehyde with 4-chloro- and 4-methoxyaniline gave *N*-benzylidene-4-chloroaniline oxide and *N*-benzylidene-4-methoxyaniline oxide in 50% and 83% after 8 h and 6 h, respectively (entries 8 and 9, Table 2). We also investigated the direct condensation/oxidation of aniline with heterocyclic aldehydes such as pyridine-4-carbaldehyde and thiophene-2-carbaldehyde. *N*-(Pyridin-4-ylmethylene)aniline oxide and *N*-(thien-2-ylmethylene)aniline oxide were obtained in 86% and 83% yields after 5 h and 2 h, respectively (entries 10 and 11, Table 2). Finally, we extended the direct condensation/oxidation to aliphatic amines. The reaction of benzaldehyde with propylamine gave *N*-benzylidenepropan-1-amine oxide in 90% yield after four hours (entry 12, Table 2). However, the condensation/oxidation reaction of the aliphatic aldehyde octanal with aniline was not successful. Octanal was recovered even after a prolonged reaction time of 24 h.

Various conditions were tested to clarify the role of GO and Oxone for this transformation, and a reasonable mechanism is suggested for this reaction (Scheme 2). When the reaction of benzaldehyde (1 mmol) with aniline (1.2 mmol) was performed in the presence of GO (0.1 g) and in the absence of Oxone, we observed only the formation of the corresponding imine (entry 4, Table 1). On the other hand, the reaction of benzaldehyde (1 mmol) with aniline (1.2 mmol) in the presence of Oxone (1 mmol) and in the absence of GO led to oxidation of the starting materials (entry 5, Table 1). According to these results, we concluded that GO was responsible for the condensation of the aldehyde and aniline to give the corresponding imine. It should be noted that GO surface comprises different oxygen-containing groups such as hydroxyl, epoxy, and carboxylic acid groups, which confer an acidic character to the material.²⁶ The obtained results indicate that GO reacted as both a dehydration agent and an efficient solid acid¹³ for the one-pot condensation of anilines with aldehydes for the generation of the corresponding imines (Scheme 2). The oxidation of the imine into the nitronium ion compound can proceed through intermediate **I** (formed by the reaction of Oxone with the imine), and subsequent elimination of potassium hydrogen sulfate from intermediate **I** to generate the corresponding oxaziridine intermediate **II**. Finally

Table 1

Optimization of the reaction conditions for the synthesis of *N*-benzylideneaniline via condensation/oxidation of benzaldehyde and aniline



Entry	Conditions ^a	Solvent	Time (h)	Product (yield %)
1	GO (0.1 g)/ H_2O_2 (3 mmol)	CH_3CN ^b	3	Starting material
2	GO (0.1 g)/ H_2O_2 (3 mmol)	CH_3CN ^b	24	Starting material
3	GO (0.1 g)/Oxone (3 mmol)	CH_3CN	90	Several products
4	GO (0.1 g)	CH_3CN	2	Imine (98)
5	Oxone (3 mmol)	CH_3CN	3	Oxidation of the starting materials
6	GO (0.1 g)/Oxone (1 mmol)	CH_3CN	4	Nitronium (94)
7	GO (0.1 g)/Oxone (1 mmol)	Acetone	24	Nitronium (10)
8	GO (0.1 g)/Oxone (1 mmol)	THF	24	Nitronium (25)
9	GO (0.1 g)/Oxone (1 mmol)	$\text{CH}_3\text{CN}/\text{THF}$	24	Nitronium (20)

^a Conditions: benzaldehyde (1 mmol), aniline (1.2 mmol for entries 1–5 and 1.5 mmol for entries 6–9), with the oxidant stirred for 30 min at 5 °C and then at room temperature for the time indicated in Table 1.

^b The reaction was performed at room temperature or at reflux.

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