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Dehydrogenation of *N*-Heterocycles Using Graphene Oxide as a Versatile Metal-free Catalyst under Air

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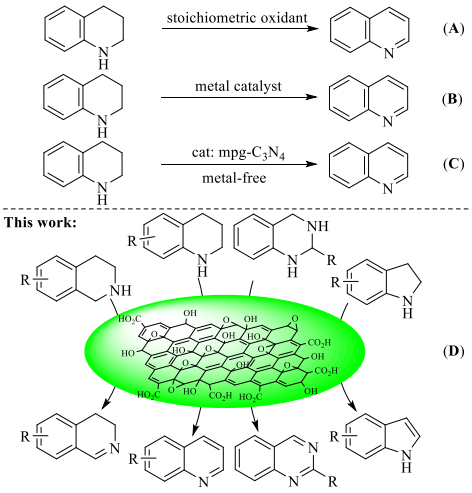
Abstract. Graphene oxide (GO) has been developed as an inexpensive, environmental friendly, metal-free carbocatalyst for the dehydrogenation of *N*-heterocycles. Valuable compounds, such as quinoline, 3,4-dihydroisoquinoline, quinazoline, and indole derivatives, have been successfully used as substrates. The investigation of various oxygen-containing molecules with different conjugated systems indicated that both the oxygen-containing groups and large π-conjugated system in GO sheets are essential for this reaction.

Keywords: Dehydrogenation; Nitrogen heterocycles; Graphene oxide; Heterogeneous catalysis

The dehydrogenation of *N*-heterocycles, which can produce high-value products, such as quinoline, isoquinoline, quinazoline, and indole derivatives, remains an interesting topic in organic synthesis. Most *N*-heterocycles exist as bioactive compounds, pharmaceutical molecules, and functional materials. The traditional dehydrogenation methods of *N*-heterocycles were established using stoichiometric oxidants, such as HgO-I_2, MnO_2, DDQ, peroxide, sulfur, and *o*-iodoxybenzoic acid (Scheme 1, **A**)[1]. However, simple oxygen, particularly air, as the terminal oxidant is the ultimate goal of oxidation reaction. Many catalytic systems for dehydrogenation of *N*-heterocycles have been developed, including metal-catalyzed systems using metals such as ruthenium[2], iridium[3], rhodium[4], palladium[5], gold[6], platinum[7], iron[8], cobalt[9], and zinc[10] (Scheme 1, **B**). Metal-free catalyst systems, such as mesoporous graphite carbon nitride (mpg-C_3N_4), have also been investigated by Blechert et al. (Scheme 1, **C**)[11]. In their work, the initiation of this reaction is considered as the irradiation of mpg-C_3N_4 that produced electron (e^-) and hole (h^+) pairs, and molecular oxygen is reduced to $\cdot O^{2-}$ by the photo-generated electron[11,12]. Similar to this process, graphene oxide (GO) has been found to activate



Scheme 1. Dehydrogenation of *N*-heterocycles.

molecular oxygen to $\cdot O^{2-}$ by heating[13]. Therefore, the GO-catalyzed dehydrogenation of *N*-heterocycles is expected.

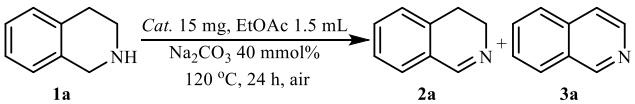
GO, which is known as the popular precursor of graphene, owes its competitiveness as a new-generation catalyst to its availability, low cost, special electronic, thermal, and mechanical properties[14]. GO is a metal-free carbon-based material that is high in oxygen-containing groups and has a large specific surface area[15]. Recently, the catalytic activity of GO has attracted research attention[16]. Various GO-catalyzed reactions, including alkyne hydration[17a], C–H oxidation[17b], C–C formation[17c,d], and carbon–heteroatom binding[17e], have been reported. Several GO-catalyzed dehydrogenation processes were also described[17a,18], such as oxidation of alcohols to carbonyl compounds[17a], oxidation of amines to imines[18a], and oxidation of primary amines to nitriles[18b]. Despite the unusual catalytic activity of GO, the catalytic dehydrogenation of *N*-heterocycles remains limited[16]. In the present study, we report the use of affordable, commercialized GO as an efficient sole metal-free catalyst for the direct

dehydrogenation of a series of nitrogen-containing heterocycles using air as terminal oxidant (Scheme 1, **D**). Both the type of oxygen groups and large π-conjugated system significantly influenced the catalytic activity of GO in this reaction.

Initially, tetrahydroisoquinoline was chosen as the model substrate (Table 1). Only 10% product was detected when the reaction was carried out at 120 °C in the absence of a catalyst (entry 1). However, the dehydrogenation products **2a** and **3a** were obtained in 81% and 11% yields, respectively, when GO (15 mg) was added (entry 2). These findings indicate the involvement of the carbocatalyst GO in dehydrogenation transformation. Other carbocatalysts, such as active carbon, acetylene black, and natural graphite, exhibited almost no catalytic activity in this reaction (entries 3–5). In particular, the reductive-GO (*r*GO) produced from the reduction of GO with hydrazine hydrate showed moderate catalytic activity, which we assumed to be caused by incomplete reduction (elemental analysis of *r*GO: C 64.25%; H 2.45%; N 5.53%; O 27.43%). These results indicate that the oxygen group on carbocatalysts may play a pivotal role in the dehydrogenation reaction. Furthermore, the influence of metal impurities in GO was investigated (Table S2), and the catalytic activity of GO was found to be unrelated to metal impurities.

At least four kinds of oxygen species are present on the surface of graphene sheets, namely, carbonyl (C=O), hydroxyl (-OH), epoxide (C-O-C), and carboxylic acid (-CO_2H) fragments[10]. To investigate the catalytic activity of different oxygen species on GO, a series of oxygen-containing compounds was used as "catalyst" in the reaction. First, four molecules with carbonyl, hydroxyl, epoxide, and carboxylic acid group were tested, and almost no catalytic activity was exhibited (Table 2, entries 1–4). We then assumed that the π-conjugated system exerted some effects on catalytic activity. Subsequently, four similar compounds with a large π-conjugated system were tested. The "catalyst" with carbonyl and epoxide showed certain catalytic activity (entries 5–8). Notably, the epoxide-containing compound exhibited outstanding catalytic activity (entry 7). Thus, we presumed that both the epoxide group and large π-conjugated system were essential for the catalytic activity of GO in the dehydrogenation process. Additionally, even the synergistic effects of neighboring oxygen-containing groups and defects on GO sheets may also have an important contribution[13].

Table 1. Investigation of various carbocatalyses.[a)]

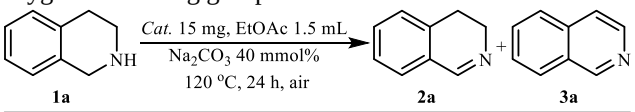


1a 2a 3a

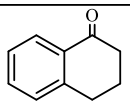
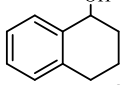
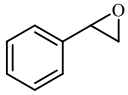
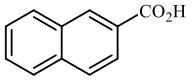
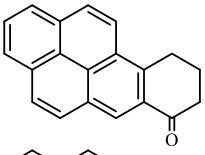
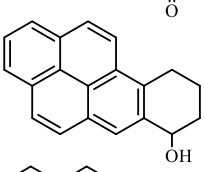
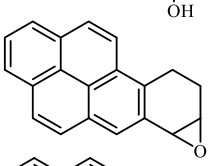
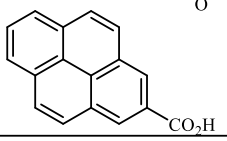
Entry	Carbocatalyst	**1a**(%)	**2a**(%)	**3a**(%)
1	——	80	10	0
2	GO	0	81	11
3	Natural graphite	78	4	trace
4	Active carbon	52	6	trace
5	Acetylene black	80	6	trace
6	*r*GO	5	57	7

[a)] Unless otherwise noted, all reactions were conducted on a 0.1 mmol scale with carbocatalyst (15 mg) in a sealed tube in 1.5 ml EtOAc under an atmosphere of air for 24 h. Yields were determined by ^{1}H NMR using nitromethane as internal standard.

Table 2. Preliminary screening of catalytic activity of oxygen-containing group.[a)]



1a 2a 3a

Entry	Catalyst	**2a**(%)	**3a**(%)
1		4	0
2		3	0
3		3	0
4		3	0
5		13	1
6		5	trace
7		24	2
8		0	0

[a)] All reactions were conducted on a 0.1 mmol scale with catalyst (15 mg) in a sealed tube in 1.5 ml EtOAc under an atmosphere of air for 24 h. Yields were determined by ^{1}H NMR using nitromethane as internal standard.

Systematic research in optimization experiments were conducted (Table S1), and the optimized conditions were obtained (Entry 35). With the reliable direct dehydrogenation protocol of *N*-heterocycles, various *N*-heterocycles, including tetrahydroisoquinolines (**A**), tetrahydroquinolines (**B**), indolines (**C**), tetrahydroquinazolines (**D**), tetrahydroquinoxaline (**E**) and tetrahydro-benzo[*b*]azepin-5-one (**F**), were examined (Table 3). Substrates in classes **A** and **D** are compelling due to these compounds, which could be obtained easily via condensation and Pictet−Spengler reactions[10].

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Table 3. GO-catalyzed dehydrogenation of N-heterocycles and synthetic applications.[a)]

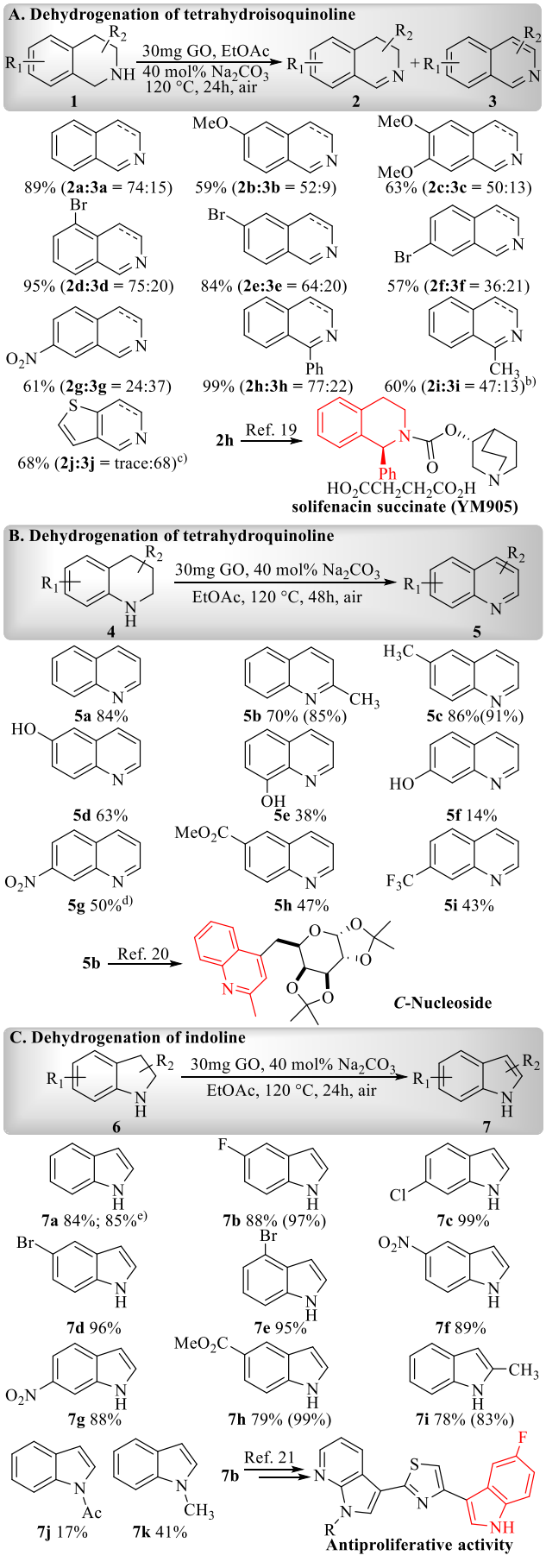
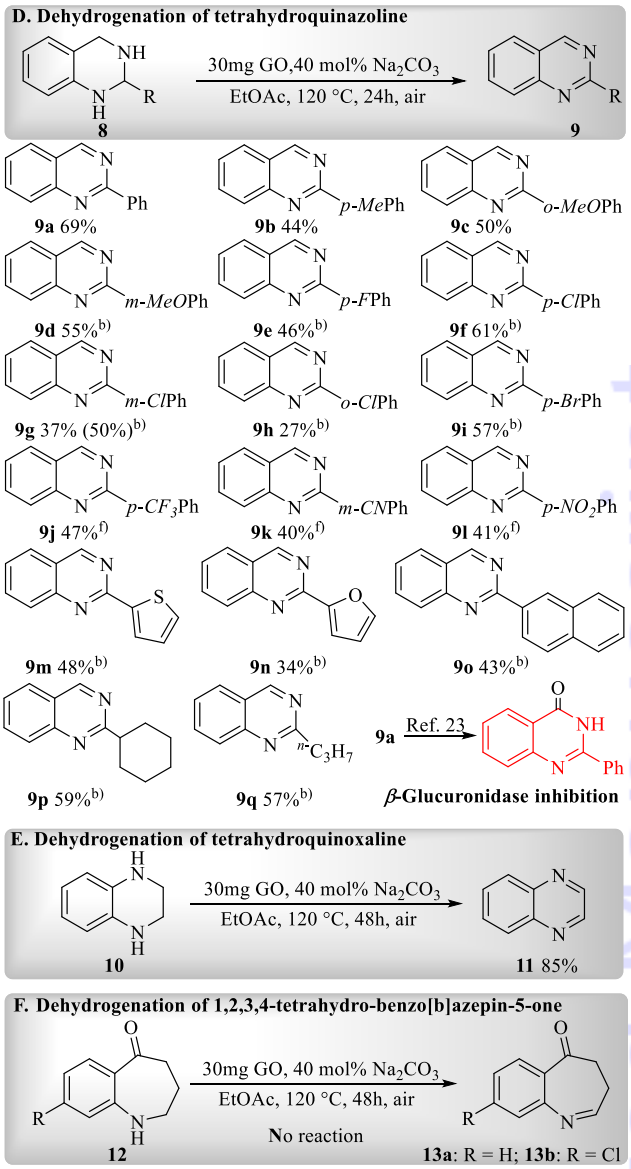


Table 3. (continued)



[a)] Unless otherwise noted, all reactions were conducted on a 0.2 mmol scale with GO (30 mg) in a sealed tube in 1.5 ml EtOAc under an atmosphere of air for 24-96 h. Isolated yield was showed out brackets, ^{1}H NMR yield were showed in brackets; [b)] Reaction time is 48 h; [c)] Reaction time is 36 h; [d)] Reaction time is 96 h; [e)] Gram reaction: 90mg GO was used, O_2 atmosphere, reaction time is 7 days; [f)] Reaction time is 60 h.

The dehydrogenation of substituted tetrahydroisoquinolines was conducted under the optimized conditions, and 3,4-dihydroisoquinoline was the main product in most cases (Table 3, **A**). The strong electron-donating groups and strong electron-withdrawing groups were not beneficial to this conversion, and only moderate yields could be achieved (**2b, c, g**). However, the nonsubstituted substrate or substrates with weak electronic effect group, such as bromo, gave a high yield (**2a, d–f**). In this case, the position of bromo significantly influenced the reaction (95% yield of 5-bromo, 84% yield of 6-bromo, and 57% yield of 7-bromo) (**2d–f**).

When the 1-position was substituted with phenyl, the conjugate system of dehydrogenation product expanded, and conversion proceeded thoroughly (**2h**). Meanwhile, if the 1-position is substituted with methyl, the steric effect of methyl may hinder the closer substrate with catalyst GO, and only moderate yield could be found (**2i**). When 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine was used as substrate, only aromatization product were found (**3j**). Many compounds based on the isoquinoline motif are widely found in bioactive molecules. For example, the desired product **2h** is a prerequisite in the synthesis of solifenacin succinate (YM905), which is a kind of medicine for the treatment of overactive bladder with symptoms of urgency, frequency, and urge incontinence[19].

Subsequently, the substituted tetrahydroquinolines were investigated. Interestingly, the results show a significant difference in selectivity of dehydrogenation using tetrahydroisoquinolines as substrates. In this case, only aromatization products could be found (Table 3, **B**). The effect of substituents to this conversion was similar to that of tetrahydroisoquinolines; the strong electron-donating groups (e.g., -OH) and strong electron-withdrawing groups (e.g., $–NO_2$, $–CO_2Me$ and $–CF_3$) were not beneficial to this conversion (**5d–i**), and the nonsubstituted substrate or substrates with weak electronic effect group, such as methyl, give a high yield (**5a–c**). The desired dihydroisoquinoline product has been widely applied as starting material to product chiral tetrahydroisoquinolines, which are widely present in bioactive molecules. For example, the dehydrogenation product **5b** can be transferred to the chiral *C*-nucleoside through a single step[20].

Indoles were formed in good to excellent yields from indolines, regardless whether the indolines were substituted with electron-donating groups or electron-withdrawing groups on the benzene ring (**7a–h**). However, the electron-withdrawing groups exerted a slightly negative effect on the dehydrogenation reaction (**7f–g**). Even though the 2-position of indolines was substituted with methyl, good yield could still be achieved (**7i**). In the case of *N*-substituted indolines with acetyl (**7j**) and methyl (**7k**), poor yield of 17% and moderate yield of 41% were obtained. This result indicates that the electrophilic and steric effects on nitrogen were harmful to this transformation. Remarkably, the gram-scale reaction of **6a** was conducted using only 90 mg GO (9 wt%) as catalyst. Nearly the same yield (85%) as the model reaction was achieved with prolonged reaction time (**7a**). This useful motif was derivatized to gain other pharmacologically active molecules. For instance, a series of antiproliferative activity molecules could be gained from **7b** after continuous conversions[21].

In most cases, quinazolines were obtained in moderate yields from tetrahydroquinazolines (Table 3, **D**). The substituents of 2-phenyl appeared to have no significant effect on this transformation (**9a–l**). 2-Thienyl and 2-furyl-substituted tetrahydroquinazolines and naphthyl-substituted tetrahydroquinazoline could also be converted to the desired product with moderate yields (**9m–o**). The cycloalkyl- and alkyl-substituted substrates could achieve this reaction at good results (59% and 57% yields, respectively) (**9p-q**). Significantly, quinazolines are pharmaceutical molecules that can be modified to obtain other useful compounds. For example **9a** can be transferred to *β*-glucuronidase inhibitor[22] through a single step[23].

To apply the GO-catalyzed system to a wide scope, the dehydrogenations of 1,2,3,4-tetrahydroquinoxaline (Table 3, **E**) and 1,2,3,4-tetrahydro-benzo[*b*]azepin-5-ones (Table 3, **F**) were also tested. When using 1,2,3,4-tetrahydroquinoxaline as substrate, a good yield of 85% was achieved (Table 3, **E**, **11**), which indicated that the GO-catalyzed system has a potential application in the dehydrogenation of tetrahydroquinoxaline compounds. By contrast, when 1,2,3,4-tetrahydro-benzo[*b*]azepin-5-ones was used as substrate, no desired product could be detected.

In conclusion, GO was developed as a metal-free carbocatalyst for the dehydrogenation of *N*-heterocycles. This transformation has a wide substrate scope, and valuable compounds, such as quinoline, 3,4-dihydroisoquinoline, quinazoline, and indole derivatives, were achieved. Additionally, this strategy possessed the advantages of scalability, simple operation, and being metal-free. Notably, this work provided insights into the roles of various oxygen-containing groups on GO, and the effect of π-conjugation was also preliminarily demonstrated.

Experimental Section

A solution of *N*-Heterocycles compound (0.2 mmol), graphene oxide (GO) (30 mg), Na_2CO_3 (40%, 8.6 mg) in AcOEt (1.5 mL) were stirred in a sealed round bottom microwave reaction tube (35 mL) under an atmosphere of air at 120 °C for 24 h. After being cooled to room temperature, the reaction mixture were filtered, washed with AcOEt (25 mL). Afterward, the solution was evaporated under vacuum. The residue was purified by preparative thin-layer chromatography (TLC) on silica gel with petroleum ether and AcOEt to achieve the pure product.

Acknowledgements

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