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A Novel Efficient Deoxygenation Process for *N*-Heteroarene *N*-Oxides

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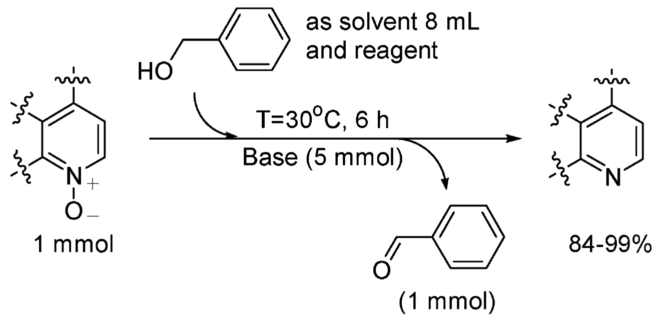

A novel deoxygenation process for *N*-heteroarene *N*-oxides is described. The deoxygenation process has been carried out by utilizing some short C-chain alcohols, benzyl alcohol, or 1-phenylethanol as the solvent in the presence of a base, such as sodium alkoxide or sodium hydroxide. A series of *N*-heteroarene *N*-oxides was submitted to the developed conditions to provide the corresponding *N*-heteroarenes with high yield and excellent selectivity. When the deoxygenation is carried out with benzyl alcohol or 1-phenylethanol as the reaction medium, the process can be performed under very mild conditions, at only 30 °C. The deoxygenation process is in contrast to several other methods performed without the presence of any transition metal as a catalyst or stoichiometric reagent. DFT calculations suggest that the alkoxide performs a nucleophilic attack on the *N*-heteroarene in the ortho or para position. This bond is cleaved homolytically with the overall result being that a single electron-transfer step has occurred. The products of this process are an *N*-heteroarene *N*-oxide radical anion and an alkoxyl or benzyloxy radical, depending on the solvent that has been used. Successive steps of the mechanism result in an oxygen transfer from the *N*-oxide to give the deoxygenated *N*-heteroarene and 1 equiv of the aldehyde, which is the oxidation product of the solvent alcohol.

Introduction

Selective deoxygenation of *N*-heteroarene *N*-oxides is a matter of substantial importance in organic synthesis, and this is reflected by numerous disclosed reports. Several of the methods comprise the utilization of different metals in various oxidation states as catalysts or as stoichiometric reagents. Several of the previously disclosed methods require somewhat harsh conditions such as high temperatures, large quantities of the reducing reagent, and cumbersome preparations of the reagent or catalyst.

An early report by Brown and Rao[1] demonstrated the deoxygenation of pyridine *N*-oxide at room temperature by means of sodium borohydride in the presence of aluminum chloride with diglyme as the solvent. Some modifications of the sodium borohydride method have been disclosed; for example, the protocol by Ram and coworkers[2] used LiCl and $NaBH_4$ as the reducing system. Howard and Olszewski[3] described the use of triphenylphosphine with triethylene glycol as the solvent at elevated temperature (230−280 °C) for several hours to provide yields in the range of 50−92%. Sandhu and co-

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[1] Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 2582−2587.

[2] Ram, S. R.; Chary, K. P.; Iyengar, D. S. *Synth. Commun.* **2000**, *30*, 3511−3515.

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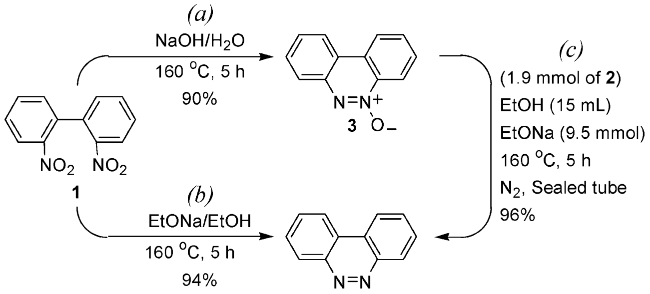
workers[4] used aluminum iodide as the reagent in refluxing acetonitrile as the reaction medium for the deoxygenation of *N*-arylnitrones, azoxybenzenes, and *N*-heteroarene *N*-oxides. A modification of this system was demonstrated by Boruah and Konwar,[5] who used $AlCl_3 \cdot 6H_2O$ and KI (1:2) with acetonitrile and water (2:1) as the reaction medium for the deoxygenation of pyridine *N*-oxide to pyridine (76%). Lu, Sun, and Tao[6] used the tetravalent molybdenum complex, $[(C_2H_5)_2NCS_2]_2Mo(IV)O$, as the catalyst with triphenylphosphine as the terminal reductant for the deoxygenation of *N*-heteroarene *N*-oxides. A very fast method was disclosed by Malinowski,[7] namely, by treating the *N*-oxide for 15 min with a slurry of titanium(0) in tetrahydrofuran at ambient temperature, which provided a yield in the range of 75−98%. The solid-phase methodology for the purpose of deoxygenation of pyridine *N*-oxide was demonstrated by Sim and Yoon,[8] in which borohydride exchange resin in the presence of 10 mol % copper sulfate was used in refluxing methanol to achieve a yield of 99% pyridine. During recent years, some protocols utilizing indium as the reducing agent have been disclosed. Yadav and coworkers[9] refluxed (3−5 h) some *N*-oxides in aqueous methanolic (ethanolic) ammonium chloride with indium metal present as the reducing agent to achieve a yield in the range of 87−96%. A variation of the utilization of indium was disclosed by Sandhu and co-workers.[10] Yields of 75−80% deoxygenated products were achieved when some pyridine *N*-oxide derivatives were treated with indium(III) chloride in refluxing acetonitrile for 1 h.

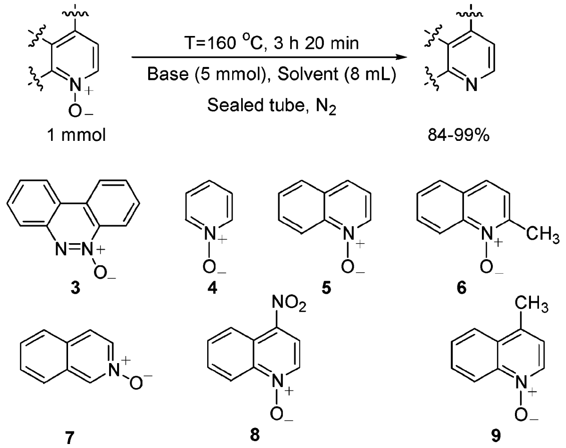
Typically, protocols for the deoxygenation of *N*-heteroarene *N*-oxides are saddled with drawbacks such as the applicable temperature range, the reaction time, side reactions, the requirements for large quantities of reduction reagents, and workup problems. The focus on green chemical methodology (see, for example, ref 11) in recent years has led to the continuous demand for more benign and sustainable synthetic methods and processes and thus encouraged us to further investigate a novel protocol we recently disclosed for the synthesis of benzo[*c*]cinnoline *N*-oxide (**3**) and benzo[*c*]cinnoline (**2**) from 2,2′-dinitrobiphenyl (**1**) and for the conversion of **3** → **2**[12] (Scheme 1). This protocol is very simple: the *N*-oxide is dissolved in ethanol, treated with a base, and heated at an elevated temperature (160 °C) for 5 h in a sealed-tube reactor. This method provides a yield of 96% (Scheme 1).

To the best of our knowledge, such a deoxygenation process of *N*-heteroarene *N*-oxides has not been reported earlier, which spurred us to explore the capacity of this reaction as a general synthetic method for the deoxygenation of *N*-heteroarene *N*-oxides and to investigate the reaction in order to propose a reaction mechanism.

SCHEME 1



SCHEME 2



Methods and Results

The main goals of this investigation were thus (1) to verify whether the process outlined in pathway *c* of Scheme 1 can be used as a general method for the deoxygenation of *N*-heteroarene *N*-oxides, (2) to discover the efficacy of the deoxygenation process under milder conditions and thus its value as a synthetic method, and (3) to investigate the process from a mechanistic point of view and thus arrive at a proposal for the reaction mechanism.

The initial screening of the process comprised the investigation of a series of *N*-heteroarene *N*-oxides, namely, benzo[*c*]cinnoline *N*-oxide (**3**), pyridine *N*-oxide (**4**), quinoline *N*-oxide (**5**), 2-methylquinoline *N*-oxide (**6**), *iso*-quinoline *N*-oxide (**7**), 4-nitroquinoline *N*-oxide (**8**), and 4-methylquinoline *N*-oxide (**9**). For this initial screening, the previously disclosed deoxygenation conditions were utilized (reproduced in Scheme 2). Benzo[*c*]cinnoline *N*-oxide (**3**) was prepared according to our recently disclosed process in which *N*-oxides **4**−**9** were prepared according to a slightly modified protocol disclosed by Hirota and co-workers.[13]

In addition to the various *N*-oxides, a small series of solvent (methanol, ethanol, *n*-propanol, 2-propanol, and *n*-butanol) and base (sodium methoxide, sodium ethoxide, sodium propoxide, sodium *iso*-propoxide, and sodium hydroxide) pairs were investigated. All of the combinations that were explored, except for methanol and sodium

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TABLE 1. Deoxygenation of *N*-Hetroarene *N*-Oxides

	experimental conditions[a]					responses[b]		
no.	*N*-oxide	solvent	base	*T* (°C)	*t* (min)	C%	S%	Y%
1	**3**	EtOH	NaOH	160	200	~100	~100	~100
2	**5**	MeOH	MeONa	160	200	10	~100	~10
3	**4**	EtOH	NaOH	160	200	~100	>99	>99
4	**5**	EtOH	EtONa	160	200	>99	99	99
5[c]	**5**	*n*-PrOH	*n*-PrONa	160	200	>99	85	~85
6[d]	**5**	*i*-PrOH	*i*-PrONa	160	200	>99	95	~95
7	**5**	EtOH	NaOH	160	200	>99	98	~98
8[e]	**5**	*n*-BuOH	EtONa	reflux	180	35	93	32
					270	53	91	48
					360	55	91	50
9	**5**	EtOH	NaOH	reflux	200	13	~100	~13
10	**5**	EtOH		160	200	10	~100	~10
11	**5**	EtOH	NaOH[f]	160	200	16	~100	~16
12[g]	**7**	EtOH	EtONa	160	200	>98	93	91
13[h]	**6**	EtOH	NaOH	160	200	>99	91	90
14	**5**	BzOH	EtONa	160	200	>99	>99	98
15[i]	**7**	BzOH	NaOH	160	200	~100	~100	~100
16[j]	**7**	BzOH	NaOH	120	200	92	100	92
17[k]	**7**	BzOH	NaOH	80	200	~100	~100	~100
18[k]	**7**	BzOH	NaOH	30	360	~100	~100	~100
19	**8**	BzOH	NaOH	30	270	~100	~100	~100
20[l]	**8**	BzOH	NaOH	30	360	95	95	90
22	**7**	1-PhEtOH	NaOH	30	360	~100	~100	~100
23	**9**	BzOH	NaOH	30	360	80	100	80

[a] The deoxygenation of the *N*-heteroarene *N*-oxide (1 mmol) was carried out in a sealed-tube reactor under nitrogen when a high temperature was utilized (160 °C). In the other cases, a round-bottom flask with a reflux condenser was utilized. The reaction mixture with the *N*-heteroarene *N*-oxide was heated with a base (5 mmol) in an alcohol (8 mL). The specific reaction temperatures and times are given for each experiment. [b] C% = conversion, S% = selectivity, and Y% = yield of the corresponding *N*-heteroarene measured by GC with an internal standard or by application of correction factors. [c] GC−MS analysis shows side products $M^{\bullet+}$ 157 (dimethyl-quinoline or ethyl-quinoline) and $M^{\bullet+}$ 185/186 (diethyl-quinoline). [d] GC−MS analysis shows side product $M^{\bullet+}$ 143 (methyl-quinoline). [e] GC−MS analysis shows side product $M^{\bullet+}$ 185/187 (methyl-propyl-quinoline). [f] The reaction was performed using 10 mol % NaOH (0.1 mmol). [g] GC−MS analysis shows side product $M^{\bullet+}$ 157 (dimehyl-isoquinoline). [h] GC−MS analysis shows side products $M^{\bullet+}$ 169/168 and $M^{\bullet+}$ 187 (ethoxy-quinaldine). [i] In addition to the *N*-heteroarene, the reaction mixture also contained ~0.5 mmol of benzoic acid. [j] In addition to the *N*-heteroarene, the reaction mixture also contained ~0.8 mmol of benzaldehyde and 0.06 mmol of benzoic acid, which corresponds to a Cannizzaro disproportination of a small fraction (0.12 mmol) of the benzaldehyde formed during the reaction. [k] In addition to the *N*-heteroarene, the reaction mixture also contained ~1 mmol of benzaldehyde. At the actual temperature, the Cannizzaro disproportionate did not proceed. [l] The molar fraction of *N*-heteroarene/NaOH is 1:1. In addition to the major product 4-benzyloxy-quinoline, a small quantity (~5%) of 4-nitro quinoline was formed.

methoxide, provided excellent yield and selectivity when the deoxygenation was conducted at a reaction temperature of 160 °C.

An attempt to perform the deoxygenation at milder conditions, that is, by decreasing the reaction temperature, resulted merely in reduced conversion and yield but still with excellent selectivity (see entries 8 and 9 of Table 1). Attempts to perform the deoxygenation without any base present, or with only catalytic quantities (10 mol %) present, afforded very low yields and conversion but still with high selectivity (entries 10 and 11). These two experiments demonstrated the necessity for a high concentration of the alkoxide anion to operate the process satisfactorily. The variation of the *N*-oxide and the reaction medium appeared to be of minor importance, except for the case when methanol was utilized.

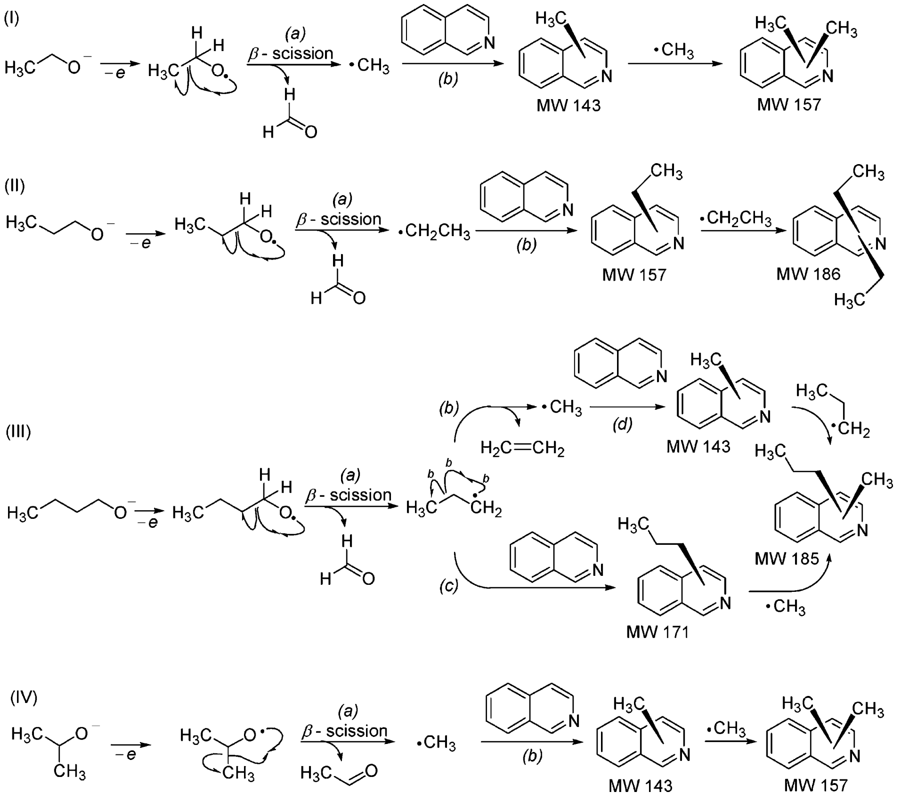
Small quantities (2−6%) of alkylated side products were observed in the experiments performed with ethanol, 2-propanol, *n*-propanol, and *n*-butanol (entries 5, 6, 8, and 12, Table 1), products that most probably are formed via radical processes. The experiment reported in entry 12 of Table 1 was repeated at a decreased reaction temperature (120 °C) to explore the effect of the reaction temperature on byproduct formation. The experiment revealed a decreased yield (81%) but with a superior selectivity, namely, >99% because of only trace quantities of the alkylated byproduct.

In the experiments conducted with *iso*-quinoline *N*-oxide, with *n*-butanol as the reaction medium, a methyl-propyl-*iso*-quinoline derivative was observed. This product can be formed via radical processes involving the alkoxide anion in a process leading to the *n*-butoxyl radical, which upon β-scission (path *a*, Scheme 3) forms the *n*-propyl radical that can again undergo a C−C homolytic bond breaking, forming ethene and a methyl radical. Both of the radical species possess a C-centered radical, which can react with the *N*-heteroarene to produce the corresponding propylated and methylated products, respectively. Similar processes can take place in which ethanol, 2-propanol, and *n*-propanol are utilized. In fact, the expected side products from reaction pathways I and II of Scheme 3 were determined (GC−MS) in a quantity of ~5% when the reactions were conducted in these solvents. When the reaction was conducted in 2-propanol, the dimethylated-*N*-heteroarene was determined to be the major byproduct. This can be explained by reaction pathway IV of Scheme 3.

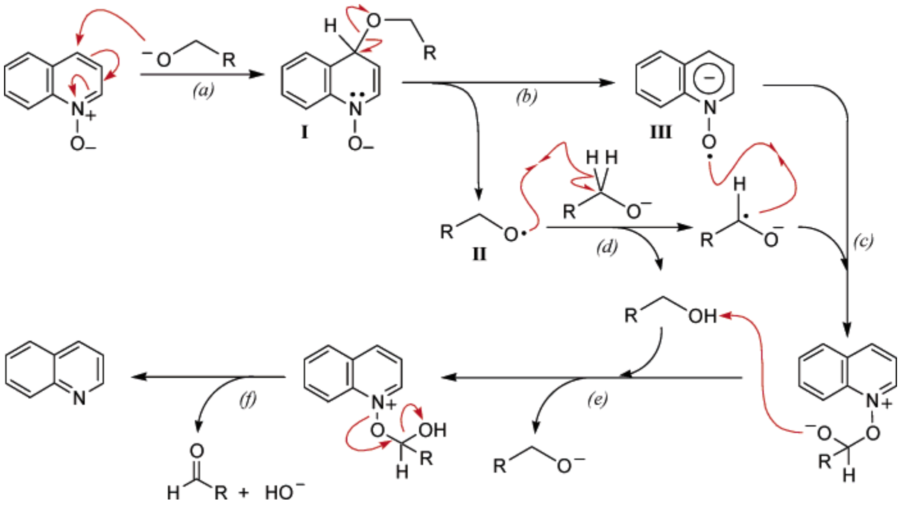
The alkylated *N*-heteroarene demonstrates that the process most likely involves free-radical processes, and this piece of information was utilized in our endeavor to establish a mechanistic rationalization of the observed process.

Furthermore, in our effort to establish mechanistic information, we performed quantum chemical calculations on the quinoline *N*-oxide and ethoxide reactant pair

SCHEME 3



SCHEME 4



(Figure 1). Our proposal for a reaction mechanism is provided in Scheme 4. This proposal is founded on an assumed high electron affinity of the aromatic *N*-oxide and comparably low ionization potential of the alkoxide. These factors could spur a nucleophilic addition of the alkoxide to the *N*-oxide (pathway *a*) to produce anion **I** and a subsequent single electron transfer from the alkoxide to the *N*-oxide. The electron affinity of quinoline *N*-oxide is calculated (DFT) to be significant, −16.0 kcal/mol (given as ΔH_{298}), and the corresponding ionization potential for ethoxide is calculated to be 37.0 kcal/mol. Assuming that the product of complete electron transfer represents the highest point on the reaction profile, this indicates that the activation enthalpy for the formation of *O*-centered radical **II** and radical anion **III** could be reasonably low (21.0 kcal/mol), as shown in Scheme 4.

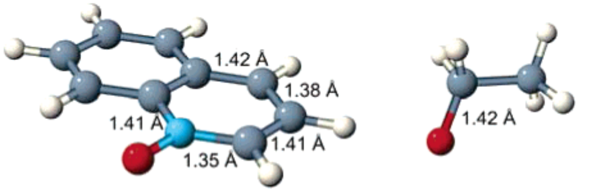


FIGURE 1. Quinoline *N*-oxide (left) and ethoxide (right) as optimized using DFT. Color coding: C - dark gray, H - light gray, N - blue, O - red.

The electrostatic potential on the molecular surface of quinoline *N*-oxide (Figure 2) is negative only in the

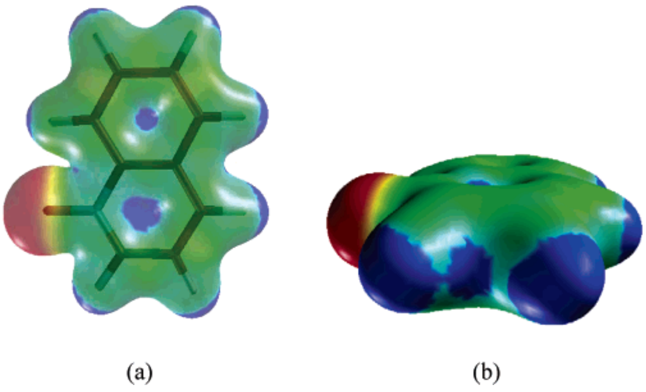


FIGURE 2. Transparent top view (a) and side view (b) showing the electrostatic potential mapped on the 0.02 au density isosurface of quinoline *N*-oxide. The electrostatic potential is color coded as follows: red, <-0.05 au; yellow, $-0.05-0.00$ au; green, $0.00-0.05$ au; light blue, $0.05-0.10$ au; and dark blue, ≥ 0.10 au.

vicinity of oxygen and thus confirms the electron-deficient nature of the molecule. The highest potentials (blue, ≥ 0.10 au, Figure 2) are found at the hydrogen atoms in the molecular plane and at the center of the aromatic rings, in deep and narrow wells. On the basis of these two areas of high electrostatic potential, nucleophilic attacks might be expected to take place at the side of the molecule or along the normal of the molecular plane, in the latter case possibly forming an intermediate prior to the formation of alkoxide addition product **I**. However, the wells of high electrostatic potential in the middle of the aromatic rings are small and shielded by the surrounding cloud of π electrons and are thus not accessible. The hydrogen atoms and the sides of the molecule, however, are easily reached, and the areas of high potential (blue, ≥ 0.10 au and light blue, $0.05-0.10$ au, Figure 2) are large. This is commensurate with the experimental observation of nucleophilic attacks at C_4 in the aromatic ring.

The geometry optimization for quinoline *N*-oxide and ethoxide together using a series of different starting structures confirms our analysis of the electrostatic potential of the *N*-oxide reactant: ethoxide binds to the carbon atoms of the ring and forms products of nucleophilic addition (see Figure 3) with the ortho and para products being essentially equally preferred (enthalpy of addition, $\Delta H_{298} \approx -20$ kcal/mol). The structures of the products confirm the favorable addition and formation of a reasonably strong C−O bond in the process. The latter C−O bonds are calculated to be 1.47−1.52 Å long, only a few angstroms longer than standard C−O single bonds. The acceptor carbon atom (denoted C_a in the following, where $a = 2$ or 4) rehybridizes from sp^2 to sp^3 during the addition and loses the π component of the C_a−C and C_a−N bonds in the ring, as evident from the increase in these bond distances. (Compare the bond lengths displayed in Figures 1 and 3.) The C_a atom also displays valence angles close to the tetrahedral angle in the addition products. For example, in the addition to the para carbon atom, the C−C_a−C angle of the ring is reduced from 118.5 in the reactant to 109.9° in the product, and the C−C_a−H angles are reduced from >120 to 112.3 and 110.6°, respectively.

In conclusion, our calculated ionization potential for ethoxide and electron affinity for quinoline *N*-oxide indicates that electron transfer from the alkoxide to the *N*-oxide should be feasible. Furthermore, the favorable addition of ethoxide to quinoline *N*-oxide (pathway *a*, Scheme 4) found in the present DFT calculations suggests that the resulting addition product (**I**, Scheme 4) could be a starting point for this electron transfer (pathway *b*, Scheme 4).

Improvement of the Method, Milder Conditions. Benzyl alcohol was tried as a reaction medium in an effort to perform the deoxygenation under milder conditions. Initially, two different deoxygenation experiments using quinoline *N*-oxide (**5**) and *iso*-quinoline *N*-oxide (**7**)-were carried out at the elevated reaction temperature (160 °C) with sodium hydroxide and sodium ethoxide as the bases. In each of these two experiments (entries 14 and 15), benzoic acid was determined to be present, and a ratio of *N*-heteroarene/benzoic acid of 1:0.5 was found. In each case, the *N*-heteroarene was obtained in practically quantitative yields. In an attempt to evaluate milder conditions, an experiment was conducted at 120 °C to achieve a yield of 92% *N*-heteroarene, still with excellent

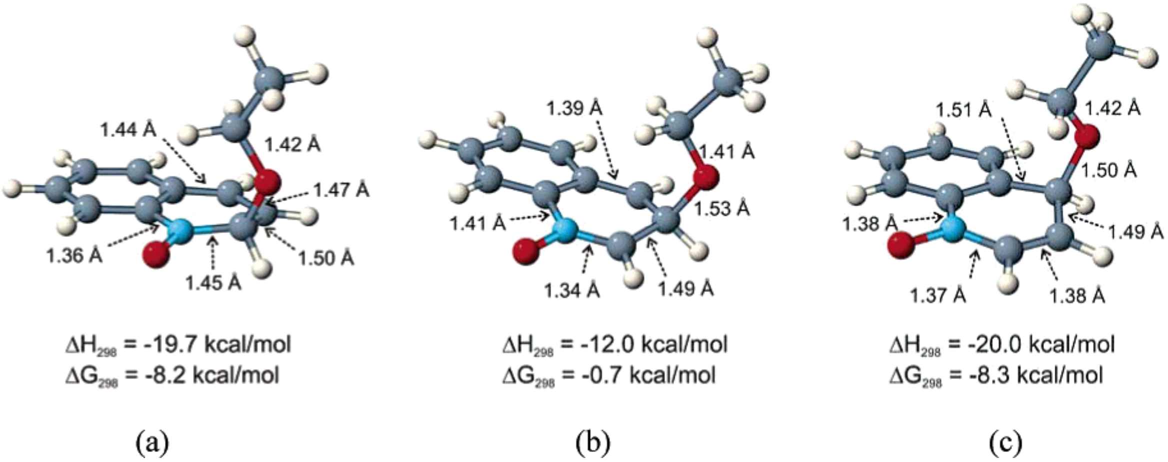
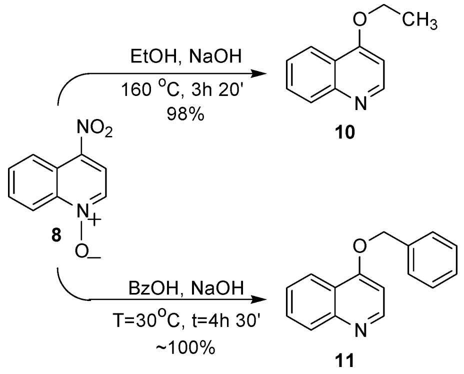


FIGURE 3. Ortho (a), meta (b), and para (c) ground-state spin singlet complexes between quinoline *N*-oxide and ethoxide as optimized using DFT calculations. Energies are given relative to separated reactants, quinoline *N*-oxide and ethoxide. Color coding: C - dark gray, H - light gray, N - blue, O - red.

SCHEME 5



selectivity (~100%). However, this experiment provided only a very small quantity of benzoic acid (~12% referred to the quantity of the *N*-heteroarene). In addition, a rather large quantity of benzaldehyde (80% referred to the quantity of the *N*-heteroarene) was obtained. Encouraged by this result, we performed new trials at successively decreasing temperatures, 80 and 30 °C. For both of the trials, quantitative yields of the *N*-heteroarene were observed along with benzaldehyde in a ratio of 1:1 *N*-heteroarene/benzaldehyde. A prolonged reaction time (6 h) was, however, required when the reaction was conducted at a reaction temperature of 30 °C. On the basis of these observations, the last steps of the mechanism were outlined (see pathways *c* and *e*−*f* of Scheme 4). Pathways *a*−*b* of the outlined mechanism involve an anionic addition followed by a homolytic bond breaking and represent an example of an inner-sphere electron-transfer mechanism.[14]

The formation of benzoic acid that was determined in the experiments that were performed under the more drastic conditions (120−160 °C) with benzyl alcohol as the solvent and reagent (entries 15 and 16, Table 1) was due to the Cannizzaro reaction and thus was only a side issue of the deoxygenating process.

4-Nitroquinoline *N*-oxide (**8**) was submitted to both the drastic conditions of 160 °C with ethanol as the reaction medium and to the mild conditions of only 30 °C with benzyl alcohol as the solvent (Scheme 5).

In both cases, a complete deoxygenation proceeded along with an ipsosubstitution of the nitro group with ethoxy and benzyloxy producing 4-ethoxyquinoline (**10**, 98% yield) and 4-benzyloxyquinoline (**11**, quantitatively), respectively. The sequence of the deoxygenation and ipsosubstitution steps is not clear, but the experiment reported in entry 20 of Table 1 also revealed a small quantity of 4-nitroquinoline, which may indicate that the deoxygenation proceeds as the first step. Comparable ipsosubstitutions of the nitro group with the methoxy group by means of sodium methoxide in methanol have been demonstrated for nitrobenzenes by several researchers, for example, Hauptschein and co-workers[15] in the synthesis of 1-methoxy-3-nitro-5-trifluoromethylbenzene from 1,3-dinitro-5-trifluoromethylbenzene. Beck and coworkers[16] used a similar protocol in the synthesis of different ortho-substituted benzonitriles from the corresponding nitrobenzonitriles. Few prior works have been published describing ipsosubstitution of nitro with methoxy on *N*-heteroarenes, although two recent patents[17,18] describe ipsosubstitution of nitro with methoxy in the synthesis of Omeprazole[19] and structurally similar products.

The reactions producing *O*-ethyl- and *O*-benzyl-substituted *N*-heteroarene quinoline described here proceed smoothly and provide products **10** and **11** in excellent yields and have, to the best of our knowledge, never been demonstrated before.

Conclusions

We believe that the process now disclosed for the deoxygenation of *N*-hetroarene *N*-oxides can find application for synthetic purposes because it has advantages compared to previously established methods: (1) it operates in the absence of any metals in catalytic or stoichiometric quantities, (2) it is operated with cheap reagents and solvents, (3) it provides better selectivity and yield as compared to most of the other previously disclosed processes, (4) no toxic or hazardous reagents are required, and (5) no harmful side products are formed during the process.

By means of DFT calculations and experimental evidence, it is demonstrated that the reaction mechanism of the deoxygenation process comprises both ionic and radical reaction steps.

The investigation of the discovered deoxygenation process revealed a complementary and highly surprising effect, namely, a highly selective partial oxidation of the reaction medium, the alcohol, to the corresponding aldehyde. The stoichiometry of the oxidation was the following: 1 mol *N*-heteroarene *N*-oxides afforded 1 mol of the *N*-heteroarene and 1 mol of aldehyde. This complementary process is under study as a continuation of the present study.

Experimental Section

Procedure Preparation of the *N*-Heteroarene *N*-Oxides. All of the *N*-heteroarene *N*-oxides were prepared according to a slightly modified protocol originally disclosed by Hirota and co-workers.[13]

A solution of the *N*-heteroarene (50 mmol) in acetic acid (30 mL) was added to aqueous hydrogen peroxide (40%, 4 mL). The reaction mixture was stirred, and the temperature was maintained at 70 °C during a period of 72 h. The solvent was evaporated under vacuum, and the residue was made basic with an aqueous solution of sodium carbonate (saturated solution, 50 mL). The resulting mixture was extracted with chloroform (3 × 40 mL). The extracts were combined and dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The resulting organic residue was purified by means of standard flash chromatography (silica gel, hexane/methanol

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9:1). For 4-nitroquinoline *N*-oxide, the eluent was a mixture of ethyl acetate/methanol (99:1). The product was identified by GC−MS and ^{1}H NMR analysis and was compared to the spectra of authentic samples.

Procedure for the Deoxygenation of 3. Na metal (9.5 mmol, 0.218 g) was allowed to react with ethanol (15 mL). This solution was added to a sample of benzo[*c*]cinnoline *N*-oxide (1.89 mmol, 84%) and benzo[*c*]cinnoline (0.3 mmol, 13%). The resulting mixture was placed into a sealed-tube reactor of 50 mL capacity that was flushed with nitrogen, closed, and maintained at 160 °C for 5 h. After cooling, the reaction mixture was quenched with water (60 mL) and extracted with ethyl acetate (3 × 70 mL). The extracts were combined and dried over anhydrous sodium sulfate and filtered, and finally, the solvent was removed under vacuum to achieve an isolated yield of 96% benzo[*c*]cinnoline with a purity of 98%.

Procedure for the Deoxygenation of 4−9. The deoxygenation of the *N*-heteroarene *N*-oxide (1 mmol) was carried out in a sealed-tube reactor of 50-mL capacity under nitrogen when high temperature was utilized (160 °C). A round-bottom flask (25 mL) equipped with a reflux condenser was used for the experiments that were performed at lower temperatures (30−120 °C). The reaction mixture containing the base (5 mmol), an alcohol (8 mL) as the solvent, and the *N*-heteroarene *N*-oxide was heated by means of an oil bath with high-speed (∼1000 rpm) agitation using a magnetic stir bar. The reaction was performed at 160 °C (sealed tube) for 3 h and 20 min or at 30−120 °C for 3−6 h (round-bottom flask). The temperatures and reaction times are given in Table 1.

Workup. The reaction mixture was quenched with saturated sodium chloride solution (80 mL). The water mixture was extracted with ethyl acetate (no. 1: 80 mL and then 4 × 30 mL). The ethyl acetate extracts were combined and extracted (3 × 30 mL) with water acidified with sulfuric acid (100:4) to recover the *N*-heteroarene. The water phase was washed with ethyl acetate (15 mL) to remove residues of benzyl alcohol and then made basic by adding solid sodium carbonate until the pH was ∼9. This water solution was then extracted with ethyl acetate (no. 2: 8 × 30 mL). The ethyl acetate extracts were combined, dried with sodium sulfate and filtered, and finally, the solvent was removed under vacuum.

For the workup of quinoline (**5**) and isoquinoline (**7**), which are not soluble in water, a simpler workup was performed. The first extraction (no. 1) was performed by using only 1 × 80 mL of ethyl acetate. The second extraction (no. 2) was performed by using 3 × 30 mL of ethyl acetate. The rest of the workup procedure was similar to that described above. The isolated yields were 4-methylquinoline, 105 mg (73%); isoquinoline, 95 mg (74%); and pyridine, 55 mg (70%).

Computational Details. Geometry optimizations were performed using the three-parameter hybrid density functional method of Becke (B3LYP),[20] as implemented in the Gaussian 03 set of programs.[21] The restricted formulation was used for spin singlet systems, whereas unrestricted calculations (i.e., UB3LYP) were performed for spin triplets. Stationary points were optimized and characterized using algorithms involving the analytical calculation of the first and second derivatives of the energy. Numerical integrations were performed using the default “fine” grid of Gaussian 03, consisting of 75 radial shells and 302 angular points per shell, and the Gaussian 03 default values were chosen for the self-consistent field (SCF) and geometry optimization convergence criteria. Standard Dunning and Hay valence double-ζ basis sets plus polarization (DZP) were used for the geometry optimizations, implying [2s,1p] contracted basis sets for H atoms and [3s,2p,1d] for first-row atoms.[22] Thermochemical corrections to obtain zero-point energies, enthalpies, and free energies were computed within the harmonic-oscillator, rigid-rotor, and ideal-gas approximations using the same method and basis sets that were used in the geometry optimizations.

The B3LYP-optimized geometries were subjected to single-point (SP) energy calculations involving basis sets that were improved compared to those used in the geometry optimizations. For carbon, nitrogen, and oxygen atoms, the standard double-ζ basis set of Dunning and Hay[22] was extended with a diffuse s and p primitive[23] and two d polarization primitives[24] and contracted to [5s,3p,2d]. The hydrogen basis set was extended with a diffuse s primitive[23] and two p polarization primitives[24] and contracted to [3s,2p]. The SP calculations were performed using the fine grid described above, and the SCF procedure was converged to a rms change in the density matrix below 1.0×10^{-5}. The relative energies and molecular properties reported here are those obtained in the SP calculations.

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Supporting Information Available: General experimental information, analytical data, and copies of ^{1}H NMR spectra for compounds **3**−**9**. Cartesian coordinates of geometry-optimized species for quinoline *N*-oxide, ethoxide, the quinoline *N*-oxide-ethoxide ortho addition product, the quinoline *N*-oxide-ethoxide meta addition product, and the quinoline *N*-oxide-ethoxide para addition product. This material is available free of charge via the Internet at http://pubs.acs.org.

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