A New and Efficient Heterogeneous System for the Phthalimide *N*-Oxyl (PINO) Radical Generation

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Sodium periodate/wet silica gel in the presence of dichloromethane is an efficient reagent at room temperature for the phthalimide *N*-oxyl (PINO) radical generation from its precursor *N*-hydroxyphthalimide (NHPI). PINO reactions with cycloalkenes occur exclusively by a "pure" radical mecha-

nism, contrasting with PINO's behavior when it is generated using lead tetraacetate.

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Introduction

The stable nitroxyl radicals have found important applications as spin labels in biology and, based on their propensity to scavenge free radicals, as powerful inhibitors of free radical chain processes such as autooxidation and polymerization. They are often added as the amine precursor, which is converted in situ to the corresponding nitroxyl radical. In contrast to the stable dialkylnitroxyl radicals, which inhibit free radical autooxidations, *N*-hydroxyphthalimide (NHPI) catalyzes autooxidations by the formation of the phthalimide *N*-oxyl radical (PINO). PINO is attracting continuous attention due to its role in the aerobic oxidation of a wide variety of organic substrates[1] (aliphatic hydrocarbons,[2] alkylbenzenes,[3] alcohols,[4] benzylamines,[5] and *N*-alkylamides[6]).

NHPI was first used in 1977 by Grochowski and coworkers[7] to catalyse the reaction of ethers with azodicarboxylate and the oxidation of 2-propanol with *m*-chloroperbenzoic acid. The reactions were assumed to involve the intermediacy of the PINO radical, which had already been described in 1968.[8] These oxidative processes, involving NHPI as a precursor for the PINO generation, under mild reaction conditions,[9,10] occur via an intermediate carbon-centered radical, which is the result of the hydrogen atom abstraction by the PINO radical generated in situ (see Scheme 1).

There are reported several methods to generate the PINO radical from its precursor NHPI. In 1983, Masui et al.[11] carried out a pioneering work on the synthetic application of NHPI as mediator in the electrochemical oxidation of secondary alcohols to ketones and showed that PINO,
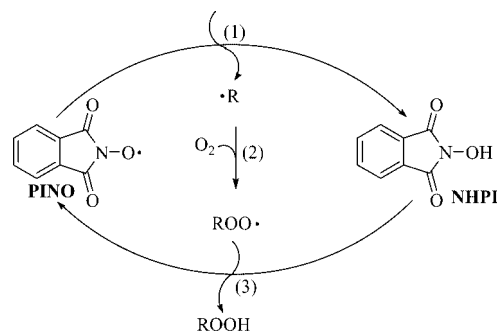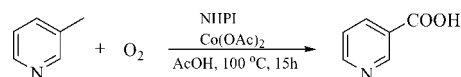

Scheme 1.

formed by an electrochemical oxidation of NHPI, abstracts selectively hydrogens atoms from the alcohols leading to ketones. Ishii et al.[1a,12,13] reasoned that combination of NHPI with the heteropolyanion $(NH_4)_5H_6PV_8Mo_4O_{40}$ could produce an effective catalyst for the aerobic oxidation of alcohols. Subsequently, Ishii et al.[1b,14] showed that the combination of NHPI with a variable-valence metal ion (what has become known as the "Ishii catalyst"), notably cobalt, afford an effective catalytic system for the autooxidation of a broad range of organic substrates, e.g., alkanes[2] and alkylaromatic compounds.[3a] For example, the selective autooxidation of adamantane to adamantanediol[2] in the presence of a catalyst consisting of NHPI (10 mol-%) and Co(oacac)$_2$ in acetic acid, has been commercialized by the Daicel Chemical Company. The products are used in the manufacture of photoresistant polymers.[14] The oxidation of β-picoline in the presence of NHPI (10 mol-%) and Co-

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.
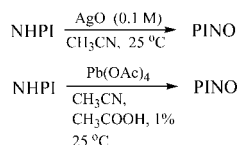

Scheme 2.

(OAc)$_2$ (1.5 mol-%) under dioxygen (1 atm) in acetic acid afforded nicotinic acid in 76% yield at 82% conversion, under mild conditions[15] (Scheme 2).

Nicotinic acid is used as a precursor of vitamin B$_3$ and is commercially manufactured on a large scale by nitric acid oxidation of 5-ethyl-2-methylpyridine.[16] Einhorn et al.[17] reported the oxidation of various hydroaromatic and benzylic compounds with oxygen at room temperature in the presence of NHPI and acetaldehyde and they concluded that the active species is PINO formed by the reaction of NHPI with an acetylperoxy radical, Scheme 3.
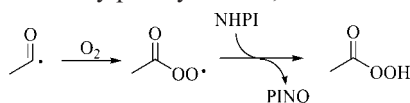
Scheme 3.

PINO can be easily generated as well upon treating NHPI with a one-electron oxidant like AgO or Pb(OAc)$_4$[18] (Scheme 4).
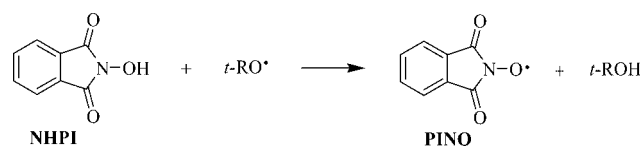

Scheme 4.

More recently,[19] NHPI also has been utilized as a catalyst for the aerobic oxidation of benzyl alcohols to aldehydes in combination with the enzyme laccase. The function of laccase would be similar to that of the Co salt in the NHPI/Co(OAc)$_2$ system. An interesting organocatalytic system of anthraquinones and NHPI to generate PINO radicals under mild conditions was very recently proposed[20] for the hydrocarbon oxygenation by dioxygen without photo and radical initiations.

It was revealed that PINO functions as a "carbon radical producing catalyst" (CRPC), selectively abstracting the hydrogen atom from the carbon–hydrogen bond of organic substrates under mild conditions to produce carbon radicals, and reverting itself to HNPI. Since carbon radicals are reactive chemical species, capturing them with various molecules, such as oxygen, allows the introduction of different functional groups. Various catalytic reactions using NHPI, include novel concepts that have not previously appeared in conventional synthetic organic approaches, and therefore, are a significant breakthrough in synthetic chemistry.

Results and Discussion

In a preliminary communication,[21] we reported a simple and convenient method for distinguishing between the abstraction-addition and addition-abstraction mechanisms involved in the cyclohexene/4-HydroxyTempo reaction. We have found that about 90% of the reaction products are formed by an abstraction-addition mechanism and only 10% are the result of the addition-abstraction mechanism.

We have carried this work forward,[22] by using 1,2-dideuteriocyclohexene, 1,2-dideuteriocyclooctene and (E)-3,4-dideuteriohex-3-ene in the reaction with PINO. An unexpected course of these reactions was observed, that is, the reaction products depend on the manner how the PINO radical is generated. When the PINO radical was generated by hydrogen atom abstraction from NHPI by using a tert-alkoxyl radical (t-RO') (Scheme 5), the only product for the reaction with the alkenes was the corresponding monoadduct.
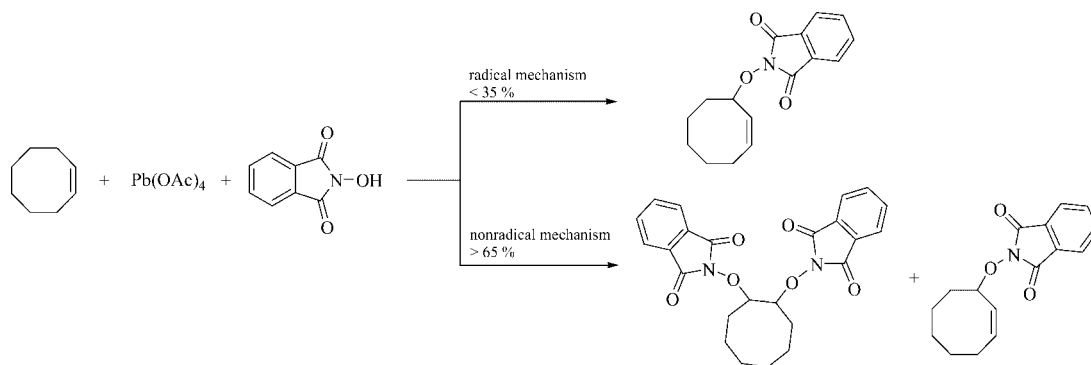

Scheme 5.

Pedulli and co-workers[23] have shown that the reaction in Scheme 5 occurs because in the presence of NHPI, photochemically generated t-RO' radicals yield the characteristic PINO EPR spectrum. The above-mentioned authors used the NHPI/t-RO' system to generate PINO, with t-RO' being generated photochemically from the peroxide t-ROOR-t. This allowed the measurement by kinetic EPR spectroscopy of the PINO/benzyl alcohol rate constant. However, it would probably not have been possible to measure the rate constant for the PINO/benzaldehyde reaction, because of benzaldehyde's strong UV absorbance.

However, the same reaction mechanism was not found when the alkenes were allowed to react with NHPI and lead tetraacetate in benzene. This is a chemical system shown to form PINO radicals as early as 1964 by Lemaire and Rassat[24] using EPR spectroscopy. Furthermore, for the NHPI/Pb(OAc)$_4$ system, a significant, even major product, was a diadduct in which two PINO moieties had added across the double bond of the alkene (Scheme 6).

Interestingly, the rate constants for the reaction of PINO with alkylaromatic compounds measured by Pedulli[13] using NHPI/t-RO' and by Espenson[25] using NHPI/Pb(OAc)$_4$ are in fair agreement. However, Espenson and co-workers, have recently reported[26] that the rate constants for hydrogen atom abstraction by PINO from p-xylene and toluene using NHPI/Co^{III} were "slightly different" from those obtained using NHPI/Pb(OAc)$_4$.

In connection with the unexpected behavior of the NHPI/cycloalkene systems, a new way to generate the PINO radical was conceived, using sodium periodate. Sodium periodate is a widely used reagent for the oxidative cleavage of 1,2-diols to carbonyl compounds.[27] Unfortunately, the use of this highly selective reagent is strongly restricted by its insolubility in organic solvents.[28] Many attempts have been reported to overcome this inconvenience, that is, the use of quaternary alkylammonium periodate in organic solvents and the use of potassium metaperiodate under phase-transfer catalysis conditions.[29–32] The concept of supported reagents,[33,34] either adsorbed on or bound to insoluble matrixes, also offered attractive solutions. To accelerate the development and optimization of

Scheme 6.

reaction conditions for solid-supported transformations, Krchnak and co-workers have designed and used dual linkers with a reference cleavage site.[35] The key feature of dual linkers is their inherent ability to provide complete cleavage of all polymer-supported reaction components. A dual linker consists of a sequence of two linkers in series cleaved by the same reagent. The second linker is attached to the polymer-supported first linker and a reference cleavage site is formed between the first and second linkers. The second linker is always cleaved from the first linker, independent of the chemical transformations performed on the second linker. Krchnak, reported the use of a dual linker in "the discovery of an unexpected side reaction" that occurs during the Mitsunobu reaction of NHPI with polymer-supported alcohols,[36] NHPI reaction with amines[37] and NHPI reaction with Wang or Sarsin resins.[38]

Silica gel supported metaperiodate was shown to oxidize smoothly 1,2-diols and hydroquinones in dichloromethane and nonpolar organic solvents. Wet silica gel is an effective support for metaperiodate. The method consists of stirring a suspension of silica gel in dichloromethane, with a freshly prepared solution of sodium periodate in water, and then NHPI is added. The PINO radical is generated according to Scheme 7.
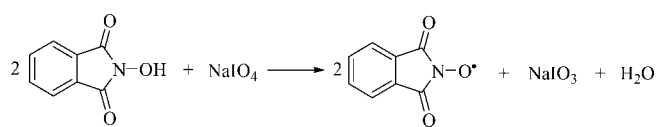
Scheme 7.

After 5 min, a cycloalkene/dichloromethane solution is added; at this point, the radical reaction between PINO and cycloalkene takes place. The reaction occurs by abstraction-addition and addition-abstraction competitive mechanisms, the final products being identical for both mechanisms in the case of symmetrical alkenes. The ratio between these two competitive reaction mechanisms was a major subject of our previous works.[21,22] Scheme 8 shows the reaction mechanism between cyclooctene and PINO; since it has been shown that cyclooctene, among all the used alkenes, yields the highest percentage (61%) in the diadduct formation with the NHPI/Pb(OAc)$_4$ system[22], the probability to detect any trace of the diadduct is obviously the highest for the cyclooctene/NHPI/sodium periodate system.

After completion of the reactions and workup (see Experimental Section), the crude products were analyzed using ^{1}H and ^{13}C NMR spectroscopy. Surprisingly, the
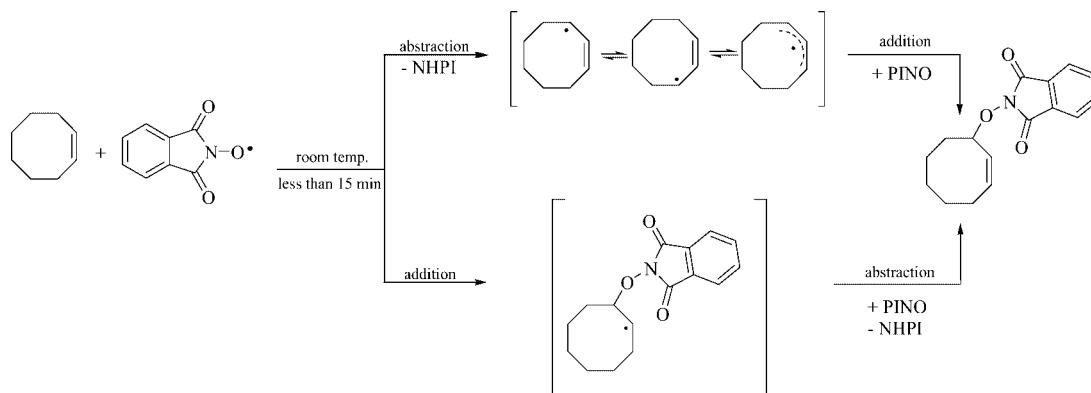
Scheme 8.

monoadduct was the only detected product for this reaction, since in the ^{1}H NMR spectra (see Supporting Information) the diadduct's characteristic peak at δ = 3.972 ppm for the two protons, bonded to the sp^3-hybridized carbon atom bearing the radical moieties, is not present. As we had expected, the monoadduct was the sole product for the cyclohexene/NHPI/sodium periodate system, according to the ^{1}H NMR spectra of the reaction product (see Supporting Information), since in the cyclohexene/NHPI/Pb(OAc)$_4$ system only 3% of diadduct was detected.[22]

The following points are found to determine a successful completion of the reaction:

(a) The T1 ratio (mass of silica gel/volume of NaIO$_4$ solution) was the most critical parameter. According to the literature,[39–41] water was absolutely required, but in our case, the suspension stability was directly dependent on the amount of aqueous solution. A T1 ratio larger than or equal to 1 ensured a suspension stability for 1 h, suitable for most reactions.

(b) Solvent polarity was also of importance; dichloromethane was the solvent of choice, since more polar solvents (ethyl acetate, ether, etc.) increased hydrate formation, and less polar solvents decreased the yields.

(c) Vigorous stirring avoided formation of colloidal silica gel.

Conclusions

We have found a new method to generate the phthalimide *N*-oxyl (PINO) radical from its precursor *N*-hydroxyphthalimide (NHPI), using the heterogeneous system sodium periodate/wet silica gel in the presence of dichloromethane. Thus generated PINO reacts by a "pure" radical mechanism with cycloalkenes, the corresponding monoadducts being the only detected products of these reactions.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ (internal standard was CHCl$_3$: δ = 7.283 ppm). The assignment of proton chemical shifts was based on decoupling experiments. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with Silica Gel 60 F$_{254}$ as the adsorbent.

Typical Experimental Procedure for the NHPI/NaIO$_4$/Cycloalkene Reaction: To a vigorously stirred suspension of chromatography-grade silica gel (15 g) in CH$_2$Cl$_2$ (100 mL) in a 250 mL Erlenmeyer flask, were added a 0.35 M aq. solution of NaIO$_4$ (10 mL) dropwise with stirring and NHPI (7 mmol). After 5 min, the cycloalkene (70 mmol) in CH$_2$Cl$_2$ (20 mL) was added, and the reaction was monitored by TLC, until it was complete, generally in less than 15 min. The mixture was then filtered through a sintered-glass funnel, and the silica gel was thoroughly washed with CH$_2$Cl$_2$ (3 × 30 mL). Evaporation of the solvent and excess cycloalkene afforded the crude product, pure enough for most purposes; yield: 88–92%. GC analysis and/or ^{1}H NMR spectroscopy revealed no diadduct formation.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for the products of cyclooc-

tene reaction with NHPI oxidized with lead tetraacetate and sodium periodate and ^{1}H NMR spectrum for the products of cyclohexene reaction with NHPI oxidized with sodium periodate.

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