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## Efficient Catalytic Alkane Nitration with $\text{NO}_2$ under Air Assisted by *N*-Hydroxyphthalimide\*\*

Satoshi Sakaguchi, Yoshiki Nishiwaki, Takaaki Kitamura, and Yasutaka Ishii\*

In contrast to the nitration of aromatic hydrocarbons, which is easily performed using nitric acid in the presence of sulfuric acid, the selective nitration of aliphatic hydrocarbons is very difficult because of the exceedingly low reactivity of the latter. Currently, nitrations of aliphatic hydrocarbons are carried out at fairly high temperatures (250–400 °C) using nitrogen dioxide or nitric acid, and they proceed by free radical chain

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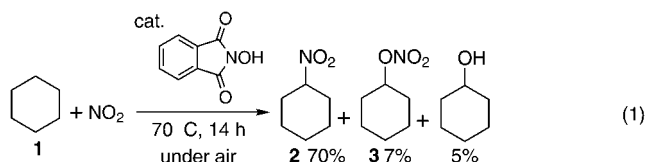
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reactions involving C–H bond homolysis.<sup>[1, 2]</sup> Under such high temperatures, higher alkanes undergo not only homolysis of C–H bonds but also cleavage of the C–C skeleton. Therefore, large-scale nitration of alkanes has been limited to lower alkanes such as methane and ethane.<sup>[2]</sup> For instance, the nitration of propane produces all of the possible nitroparaffins, namely, nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane.<sup>[1, 3]</sup> The development of selective nitration of cyclohexane is very attractive, since nitrocyclohexane is easily converted into cyclohexanone oxime, the raw material of  $\epsilon$ -caprolactam, which in turn leads to nylon-6.<sup>[4–6]</sup>

Recently we developed a catalytic method for the generation of alkyl radicals from saturated hydrocarbons using *N*-hydroxyphthalimide (NHPI), which serves as the radical catalyst.<sup>[7]</sup> The phthalimide *N*-oxyl (PINO) radical generated in situ from NHPI and  $\text{O}_2$ , which lies in a triplet state, abstracts the hydrogen atom from the saturated hydrocarbons, forming the corresponding alkyl radicals. These radicals are readily trapped by  $\text{O}_2$  under aerobic conditions to give oxygen-containing compounds such as alcohols, ketones, and carboxylic acids. These results led us to become interested in the nitration of alkanes with  $\text{NO}_2$  by the use of NHPI as a catalyst.

In the first trial, NHPI was added at room temperature to a stirred benzene solution containing dissolved  $\text{NO}_2$ . The ESR measurement of the solution indicated a triplet signal, which is assigned to the PINO radical.<sup>[8]</sup> This is believed to be due to the fact that  $\text{NO}_2$  is a stronger oxidant than  $\text{O}_2$ . Thus, the nitration of cyclohexane (**1**) was examined using  $\text{NO}_2$  in the presence of a catalytic amount of NHPI under several reaction conditions ([Eq. (1)], Table 1).



The nitration of **1** with  $\text{NO}_2$  by NHPI proceeded smoothly at 70 °C to give nitrocyclohexane (**2**, 70% based on  $\text{NO}_2$  used; Table 1, run 1) and cyclohexyl nitrite (**3**, 7%) along with a small amount of an oxygenated product, cyclohexanol (5%).

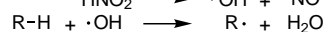
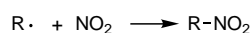
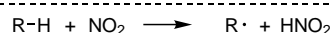
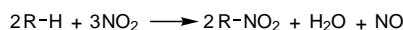
Table 1. NHPI-catalyzed nitration of **1** with  $\text{NO}_2$  under selected conditions.<sup>[a]</sup>

Run	NHPI [mmol]	$T$ [°C]	Yield of <b>2</b> [%] <sup>[b]</sup>
1	0.6	70	70
2 <sup>[c]</sup>	0.6	70	43
3	–	70	< 2
4	0.6	60	58
5	0.6	50	39
6	0.3	70	56
7 <sup>[d]</sup>	0.6	70	63
8 <sup>[e]</sup>	9	70	53

[a] Reactions were run as described in the Experimental Section. [b] Yields are average values obtained from several runs and are based on  $\text{NO}_2$  used. [c] Under argon. [d] Recovered catalyst from run 1 was used. [e] The reaction was carried out using **1** (50 mL) and  $\text{NO}_2$  (33 mmol). The yield of **2** is based on isolated product.

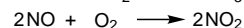
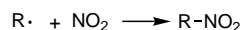
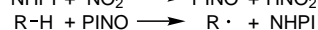
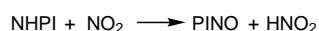
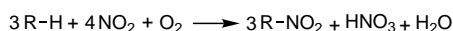
As discussed below, it is important that the NHPI-catalyzed nitration is conducted under air, since NO generated in the course of the reaction can be reoxidized to NO<sub>2</sub> by O<sub>2</sub>. For the analogous nitration of **1** in the absence of air, the yield of **2** decreased to 43% (run 2). Needless to say, the nitration of **1** was difficult to carry out without NHPI under these conditions (run 3). The nitration took place even at 50 °C to give **2** in 39% yield (run 5). When the amount of NHPI was halved (0.3 mmol), **2** was formed in slightly lower yield (56%, run 6). The nitration of **1** using recovered NHPI produced **2** in 63% yield (run 7). The large-scale nitration allowed the isolation of **2** in 53% yield (run 8).

Scheme 1 shows the reaction pathway for the vapor-phase nitration of alkanes by NO<sub>2</sub>.<sup>[2]</sup> According to this mechanism, one-third of the NO<sub>2</sub> employed is converted into NO via



Scheme 1. The reaction pathway for the conventional alkane nitration with NO<sub>2</sub>.

HNO<sub>2</sub>. Hence, the maximum yield of nitroalkanes by this method cannot, in theory, be higher than 66.7%. In fact, the nitration of **1** by NO<sub>2</sub> under argon led to **2** in 43% yield (Table 1, run 2). It is noteworthy that the present nitration of **1** by NO<sub>2</sub> (under air, catalyzed by NHPI) afforded **2** in 70% yield, that is, greater than the theoretical yield of 66.7% for the conventional nitration by NO<sub>2</sub> alone. Owing to the complexities of the present nitration, the reaction pathway is uncertain at this stage. A plausible pathway is proposed in Scheme 2.



Scheme 2. A possible reaction pathway for the NHPI-catalyzed alkane nitration with NO<sub>2</sub> under air.


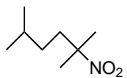


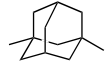
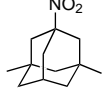
The nitration may be initiated by hydrogen-atom abstraction from the hydroxyimide group of NHPI by NO<sub>2</sub> to generate a PINO radical as described previously. The PINO radical readily abstracts the hydrogen atom from an alkane to form an alkyl radical, which undergoes nitration with NO<sub>2</sub> to give a nitroalkane. It has been reported that HNO<sub>2</sub> is converted into HNO<sub>3</sub>, H<sub>2</sub>O, and NO.<sup>[9]</sup> Under our conditions, the NO formed is expected to be oxidized by O<sub>2</sub> to NO<sub>2</sub>, and the generated NO<sub>2</sub> is reused in the nitration. Therefore, the yield of nitrocyclohexane is over 66.7%. In fact, when the reaction mixture was extracted with water after the reaction,

the aqueous phase was acidic, probably because of the formation of HNO<sub>3</sub>.

The most promising feature of the NHPI-catalyzed nitration of alkanes by NO<sub>2</sub> is that the nitration is conducted in the presence of air (O<sub>2</sub>) under mild conditions. Owing to the higher concentration of NO<sub>2</sub> than air, the alkyl radicals formed can react selectively with NO<sub>2</sub> rather than O<sub>2</sub> to give nitroalkanes in preference to oxygenated products. In contrast, the conventional nitration is difficult to carry out in the presence of air, since under the high temperatures used (250–400 °C) the resulting alkyl radicals react not only with NO<sub>2</sub> but also with O<sub>2</sub> to provide a complex mixture of products.<sup>[2b]</sup>

The results of the nitration of other alkanes by the present method are shown in Table 2. The reaction of cyclooctane (**4**) afforded nitrocyclooctane (**5**, 50%; run 1) and cyclooctyl nitrate (2%) along with oxygenated products, such as cyclo-

Table 2. NHPI-catalyzed nitration of alkanes with NO<sub>2</sub> under selected conditions.<sup>[a]</sup>

Run	Substrate	Product	Method	Yield [%]
1	cyclooctane ( <b>4</b> )	nitrocyclooctane ( <b>5</b> )	A	50
2 <sup>[b]</sup>	cyclooctane ( <b>4</b> )	nitrocyclooctane ( <b>5</b> )	A	44
3	<i>n</i> -hexane	nitrohexane	A	54 <sup>[c]</sup>
4	isobutane	2-methyl-2-nitropropane	B	46
5			C	46
6			C	66
7			C	70

[a] Reactions were carried out under air (1 atm) at 70 °C for 14 h. Method A: Alkane (5 mL), NO<sub>2</sub> (115 mg, 2.5 mmol), and NHPI (0.6 mmol) were used. Method B: Isobutane (2 mL) was treated with NO<sub>2</sub> (2.5 mmol) in the presence of NHPI (0.6 mmol) in PhCF<sub>3</sub> (3 mL) in a glass autoclave. Method C: The alkanes (3 mmol) were allowed to react with NO<sub>2</sub> (3.3 mmol) in the presence of NHPI (0.6 mmol) in PhCF<sub>3</sub> (5 mL). Yields are based on alkanes used. [b] Under argon. [c] 1-Nitrohexane:2-nitrohexane:3-nitrohexane = 3:53:44.

octanone (**6**, 17%) and cyclooctanol (**7**, 7%). Owing to the potent oxidizing ability of NO<sub>2</sub> and the susceptibility of **4** to oxidation, the nitration of **4** with NO<sub>2</sub> led to oxygenated products **6** (8%) and **7** (5%), even in the absence of air.<sup>[10]</sup> Hexane afforded a 3:53:44 regioisomeric mixture of 1-nitrohexane, 2-nitrohexane, and 3-nitrohexane in 54% yield (run 3) and the corresponding hexylnitrites (10%). Only the tertiary position was attacked in the nitration of substituted alkanes such as isobutane, 2,5-dimethylhexane, and adamantanes to form the corresponding nitroalkanes (runs 4–7).

In conclusion, we have achieved the first catalytic nitration of higher alkanes with nitrogen dioxide under air using NHPI as a catalyst. This is the first procedure for catalytic nitration under mild conditions, and by further improvement of the methodology it may become possible to change the industrial process for alkane nitration.

## Experimental Section

Representative procedure: NO<sub>2</sub> was used as a liquid at 0 °C. To a pear-shaped flask (100 mL) were added NHPI (98 mg, 0.6 mmol) and cyclohexane (5 mL). The flask was closed with a glass stopper and weighed. Then NO<sub>2</sub> (0.75 mL) was quickly added using a Hamilton gas-tight syringe, and the flask was reclosed with the glass stopper. The flask was weighed again in order to measure the NO<sub>2</sub> added (115 mg, 2.5 mmol). The flask was cooled in an ice bath and then quickly attached to a condenser, and the mixture was stirred at 70 °C for 14 h. After the reaction, GC and GC-MS analyses were performed. The yields of the products were estimated from the peak areas based on the internal standard technique using GC. The products were isolated by column chromatography on silica gel with hexane/ethyl acetate (10/1–3/1, v/v), and were identified by comparison of their analytical data with those of authentic samples.

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## Immobilization of Redox-Active Ligands on an Electrode: The Dendrimer Route\*\*

Franck Le Derf, Eric Levillain, Gaëlle Trippé, Alain Gorgues, Marc Sallé,\* Rosa-María Sebastián, Anne-Marie Caminade, and Jean-Pierre Majoral\*

Macrocyclic systems that respond electrochemically when interacting with a guest ion have been extensively studied,<sup>[1]</sup> notably in connection with their potential applications as chemosensors. In such host molecules, the complexing ability of the ligand can be tuned by the electrochemical potential applied. Most of these compounds are built by covalent grafting of a receptor subunit onto a redox-active component. Thus, in the case of metal-cation recognition, various ligating fragments, for example, crown ethers, have been attached to an electroactive moiety such as a metallocene or a quinone derivative.<sup>[1]</sup> Alternatively, the ability of the tetrathiafulvalene (TTF) core to act as the redox-active subunit is now well established.<sup>[2]</sup> Indeed, TTF derivatives are able to exist in three different stable redox stages (neutral, radical cation, and dication) and therefore allow the electrochemical release of metallic cations to be controlled.

A further exciting challenge, less explored, lies in the preparation of sensing devices that can transfer the above-mentioned recognition properties, observed in solution, at the interface of a solid electrode and a liquid.<sup>[3]</sup> Results in this direction have been obtained thanks to a) electropolymerization of suitably substituted redox-responsive ligands (e.g., a pyrrole- or a thiophene-based monomer),<sup>[3, 4]</sup> and b) preparation of self-assembled monolayers.<sup>[5]</sup> Modified electrodes were also recently obtained by Casado et al. by electrodeposition of organometallic-containing silicon dendrimers.<sup>[6]</sup> On the other hand, TTF dendrimers, possessing 21 TTF moieties in the highest generation, were described by Bryce et al.,<sup>[7]</sup> but no mention was made of their immobilization on an electrode surface.

We describe here the synthesis of a series of dendrimers with up to 96 redox-active TTF moieties on the periphery, which allow the generation of polycationic species bearing up to 192 positive charges on the surface. Modified electrodes incorporating these electroactive TTF dendrimers were

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