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Nitration of alkanes with nitric acid catalyzed by *N*-hydroxyphthalimide

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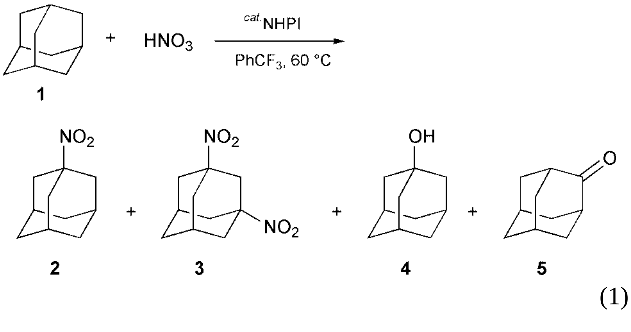
Catalytic nitration of alkanes with nitric acid was first successfully achieved by the use of *N*-hydroxyphthalimide (NHPI) under mild conditions; the key to the present nitration was found to be the *in situ* generation of NO_2 and phthalimide *N*-oxyl radical by the reaction of NHPI with nitric acid.

Nitration of saturated hydrocarbons using nitric acid is usually carried out at fairly high temperature (250–400 °C) because of difficulty in generating NO_2 from HNO_3.[1] The nitration under such severe conditions resulted in not only the homolysis of C–H bonds but also the cleavage of the C–C bonds of hydrocarbons. As a consequence, the reaction is messy and often difficult to control, and exhibits poor product selectivity. To carry out the nitration selectively, *in situ* generations of alkyl radicals from alkanes and NO_2 from HNO_3 must be achieved under mild conditions. Recently, we have developed a novel catalytic method for the nitration of aliphatic hydrocarbons with NO_2 using NHPI as the catalyst under mild conditions.[2] We now find that alkanes can be nitrated with nitric acid through the *in situ* generation of NO_2 and alkyl radicals by the use of NHPI as a catalyst under mild conditions.

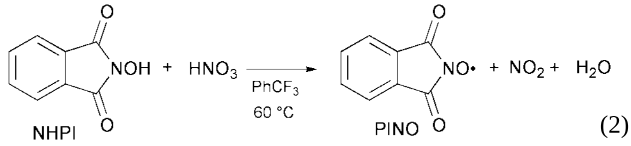
The nitration of adamantane (**1**) was chosen as a model reaction and carried out in the presence of nitric acid and a catalytic amount of NHPI in trifluorotoluene, affording 1-nitroadamantane (**2**) (64%) and 1,3-dinitroadamantane (**3**) (3%) along with oxygenated products, adamantan-1-ol (**4**) (9%) and adamantan-2-one (**5**) (5%) [eqn. (1), Table 1 entry 1]. In a previous paper, we showed that the nitration of **1** with NO_2 as a nitrating reagent affords **2** in 66% yield.[2] The nitration of **1** with HNO_3 which is easier to handle than NO_2 was found to be almost same as that with NO_2.



(1)

Table 1 shows the catalytic nitration of **1** with nitric acid by the NHPI under several reaction conditions.† Among the solvents examined, trifluorotoluene and acetic acid were found to be good solvents. Acetonitrile and ethyl acetate considerably retarded the nitration (entries 3 and 4). No reaction took place in the absence of NHPI (entry 5). The present nitration under air afforded oxygenated products, **4** and **5**, rather than nitro compounds (entry 6).

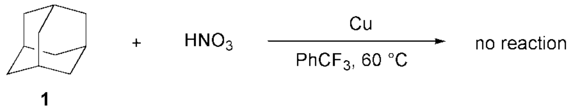
Upon treatment of NHPI with nitric acid at 60 °C, we found the evolution of brown gas attributed to NO_2. This finding suggests that the nitric acid reacts easily with the NHPI to generate NO_2 in the reaction system [eqn. (2)]. Importantly, nitric acid was easily converted into NO_2 in the presence of NHPI under relatively mild conditions, although it is known that the nitration of alkane with HNO_3 must be carried out at high temperature because of the difficulty in decomposing HNO_3 to NO_2.[1c] From EPR measurements, it was found that the phthalimide *N*-oxyl radical (PINO) was formed with the evolution of NO_2 by the reaction of the NHPI with nitric acid.‡ NHPI is known to be easily oxidized with $Pb(OAc)_4$ to the PINO.[3] In the present reaction, nitric acid serves as a good oxidizing agent of the NHPI to form the PINO and NO_2 [eqn. (2)].



(2)

In order to obtain further insight into the present nitration, **1** was allowed to react with nitric acid in the presence of copper in place of NHPI, since it is known that nitric acid reacts with copper metal, generating NO_2 according to eqn. (3).[4] However, no nitration took place, although the generation of NO_2 was observed [eqn. (4)].

$$4HNO_3 + Cu \longrightarrow Cu(NO_3)_2 + 2NO_2 + 2H_2O \qquad (3)$$



(4)

Table 2 summarizes the representative results for the nitration of various saturated hydrocarbons and their derivatives with nitric acid under the influence of the NHPI in trifluorotoluene at 60 °C for 15 h.

1,3-Dimethyladamantane (**6**) reacted with nitric acid under these conditions to give 1-nitro-3,5-dimethyladamantane (**7**) in 67% selectivity at 77% conversion (entry 1). When the NHPI used was increased from 0.1 mmol to 0.2 mmol, **7** was obtained in higher conversion and selectivity (entry 2). The nitration

Table 1 Nitration of adamantane (**1**) with HNO_3 by NHPI under various conditions[a]

			Select. (%)			
Entry	Solvent	Conv. (%)	**2**	**3**	**4**	**5**
1	$PhCF_3$	87	64	3	9	5
2	AcOH	93	62	n.d.	6	4
3	CH_3CN	55	38	n.d.	9	4
4	AcOEt	34	24	n.d.	21	3
5[b]	AcOH	>2	n.d.	n.d.	n.d.	n.d.
6[c]	$PhCF_3$	40	n.d.	n.d.	33	13

[a] **1** (1 mmol) was reacted with HNO_3 (1.5 mmol) in the presence of NHPI (0.1 mmol) at 60 °C for 15 h. [b] In the absence of NHPI. [c] Under air.

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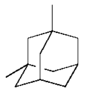
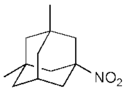
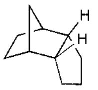
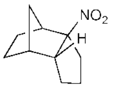
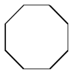
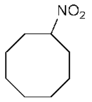
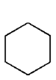
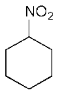
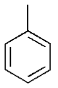
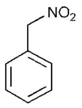
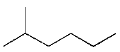
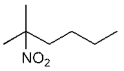
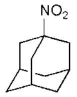
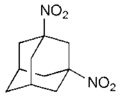
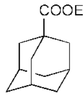
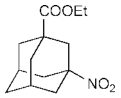
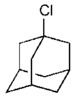
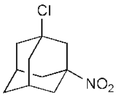
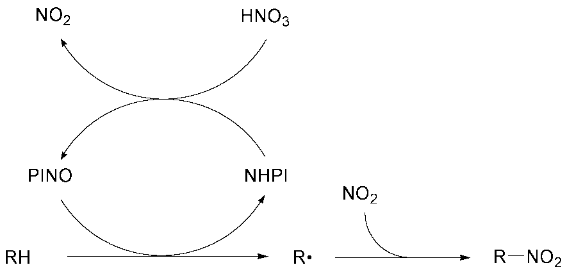
Table 2 Nitration of various substrates with HNO_3 by NHPI[a]

Entry	Substrate	Conv. (%)	Product	Select. (%)
1	 **6**	77	 **7**	67
2[b]	**6**	89	**7**	81
3[c]	**6**	50	**7**	95[d]
4	 **8**	89 (74)	 **9**	57 (47)
5		75		56[e]
6[f]		—		32[dg]
7[f]		—		60[dh]
8		80		65
9		59		61
10		73		79
11		32		91

[a] Reaction is shown in text. Parentheses show the conversion and selectivity in the nitration using NO_2 instead of HNO_3. [b] NHPI (0.2 mmol) was used. [c] Substrate (3.0 mmol) was used. [d] Based on HNO_3 used. [e] Dinitrocyclooctane (14%) and cyclooctanone (10%) were obtained. [f] Substrate (5 mL) was used. [g] Adipic acid (5%) was obtained. [h] Benzyl alcohol (21%) and benzaldehyde (19%) were obtained.

using excess **6** with respect to nitric acid resulted in **7** in excellent yield (95%). The nitration of *endo*-tricyclo-[5.2.1.0^{2,6}]decane (**8**) occurred selectively at the fused tertiary C–H bond to give the corresponding nitro compound **9** (57%). On the other hand, the nitration of **8** with NO_2 instead of HNO_3 resulted in **9** in low yield (47% selectivity, 74% conversion). Consequently, **8** was found to be nitrated with HNO_3 in higher selectivity. Cyclooctane was also nitrated to form nitrocyclooctane (56%) and a regioisomeric mixture of dinitrocyclooctane (14%) as well as a small amount of cyclooctanone (10%) at 75% conversion. Cyclohexane was difficult to nitrate selectively because of the formation of adipic acid (5%).[5] Aliphatic hydrocarbon like 2-methylhexane was nitrated at the tertiary position to lead to 2-methyl-2-nitrohexane in relatively good selectivity. Several substituted adamantanes were subjected to the nitration under these reacion conditions. Thus, 1-chloroadamantane, 1-nitroadamantane, and ethyl 1-adamantanecarboxylate were nitrated to the corresponding nitro compounds in fair to good selectivities (entries 9–11).



Scheme 1 A possible nitration path of alkanes with nitric acid by NHPI.

On the basis of these results, a possible reaction path for the present catalytic nitration of alkanes with nitric acid by the NHPI is shown in Scheme 1.

The nitration is initiated by the *in situ* generation of PINO and NO_2 from NHPI and nitric acid, respectively. The resulting PINO abstracts the hydrogen atom from alkanes to give NHPI and alkyl radicals which are readily trapped by NO_2 to form nitroalkanes.

In conclusion, the present alkane nitration with nitric acid provides a facile method for the preparation of nitroalkanes, by the use of cheap and easily available nitric acid compared with NO_2.

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Notes and references

† *A typical reaction was carried out as follows:* economic grade concentrated nitric acid (60% over) was used without any treatment. The reaction was carried out as follows: to a two necked flask was added adamantane (**1**) (1 mmol), NHPI (0.1 mmol) and nitric acid (1.5 mmol) in trifluorotoluene (3 mL), and the mixture was reacted under argon at 60 °C for 15 h. After evaporation of the solvent under reduced pressure, the reaction mixture was extracted with diisopropyl ether and the extracts were washed with aq. $NaHCO_3$. After separation of the organic phase, the mixture was subjected to silica gel chromatograph, giving 1-nitroadamantane (**2**) (57%), 1,3-dinitroadamantane (**3**) (3%) together with oxygenated products, adamantan-1-ol (**4**) (8%) and adamantan-2-one (**5**) (4%) (Table 1, entry 1).

‡ Electron paramagnetic resonance (EPR) measurements were carried out under selected conditions. To a two necked flask was added NHPI (0.1 mmol) and nitric acid (1.5 mmol) in trifluorotoluene (10 mL), and the mixture was reacted under argon at 60 °C for 1 h. The EPR spectrum attributed to PINO was clearly observed as a triplet signal based on hyperfine splitting (hfs) by the nitrogen atom (g = 2.0074, a_N = 0.46 mT). The g-value and hfs constant observed for PINO were consistent with those (g = 2.0073, a_N = 0.423 mT) reported by Mackor *et al.*[3b]

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