Highly selective *N*- and *O*-functionalization of adamantane utilizing nitrogen oxides. Kyodai-nitration of aliphatic hydrocarbons

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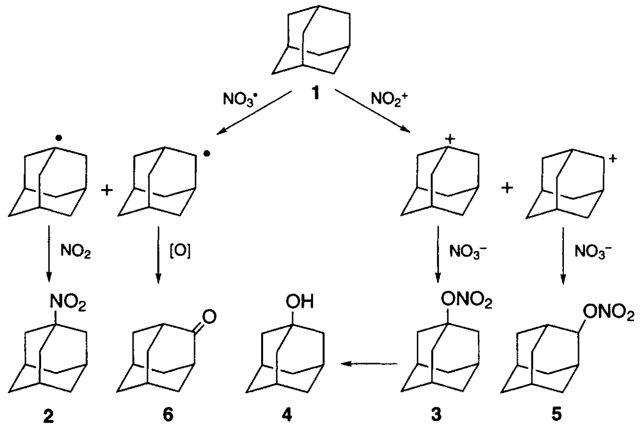
In the presence of ozone at −78 °C, nitrogen dioxide selectively reacts rapidly with adamantane at the bridgehead position to give the corresponding nitration product, while in the presence of methanesulfonic acid at 0 °C, dinitrogen pentoxide readily reacts with this hydrocarbon at the same position exclusively to afford the corresponding nitrooxylation product, the yields of both products being quite satisfactory.

Aliphatic hydrocarbons are inert towards conventional nitrating agents under ambient conditions. Under forced conditions, they undergo cleavage of the C–C bond to give a complex mixture of oxidation products and lower nitro alkanes. Recently we have found that nitrogen dioxide is activated in the presence of ozone and joins the aromatic moiety as a nitro group at low temperatures (kyodai–nitration).[1] This reaction has been of wide use and is now the subject of industrial research. As an extension to the aliphatic series, we report here the highly selective *N*- and *O*-functionalization of adamantane **1** based on the nitration methodology. Because of the symmetrical nature and high stability of the carbon framework, hydrocarbon **1** is a good model compound for examining the behaviour of alkanes toward the kyodai–nitration.

Previously, the nitration of adamantane has been carried out using nitronium hexafluorophosphate[2] and tetrafluoroborate,[3] nitric acid,[4] and dinitrogen pentoxide.[5] Except for the early literature reports which lack detailed product analysis, the products are a mixture of several compounds arising from the *N*- and *O*-attacks at the secondary and tertiary positions.

When an ozonized oxygen was bubbled slowly into a stirred solution of hydrocarbon **1** in dichloromethane containing excess nitrogen dioxide at low temperatures, the nitration occurred with unexpected ease and high positional selectivity at the bridgehead to give 1-nitroadamantane **2** as the major product. Accompanying minor products included adamant-1-yl nitrate **3**, adamantan-1-ol **4**, adamant-2-yl nitrate **5** and adamantanone **6** (Table 1). The best result was obtained from the reaction carried out at −78 °C in the presence of a large excess of nitrogen dioxide, where the tertiary/secondary positional selectivity reached as high as 100. Noteworthy is that the reaction proceeded increasingly faster as the reaction temperature was lowered.

A typical experimental procedure is as follows: to a stirred mixture of hydrocarbon **1** (0.27 g, 2.0 mmol) and dichloromethane (30 cm^3) was added liquid nitrogen dioxide (2.0 cm^3, 60 mmol) at −78 °C and then ozonized oxygen was bubbled through at a low flow rate.[‡] After 0.5 h, the reaction was quenched with aq. $NaHCO_3$. The organic phase was separated, washed and dried with Na_2SO_4. GC analysis revealed the composition of the crude product to be **1**:**2**:**3**:**4**:**5**:**6** = 0:93.9:4.2:1.9:0:0. Removal of the solvent under reduced pressure left a white solid residue which was chromatographed on deactivated alumina using hexane–ethyl acetate as eluent to



Scheme 1

Table 1 Reaction of adamantane **1** with nitrogen dioxide–ozone[a]

T/°C	NO_2/ mmol	Reaction time/h	Product composition (%)[b] 2	3	4	5	6	1
−78	60	0.5	95	4	1	—	—	—
−78	30	0.5	92	6	1	< 1	< 1	< 1
−78	15	0.5	84	14	< 1	< 1	2	< 1
−78	6	0.5	76	6	16	—	2	—
−30	30	0.5	50	3	< 1	1	1	45
−30	30	1.0	87	6	1	1	2	3
0	30	0.5	23	3	1	1	< 1	72
0	60[d]	1.0	51	10	1	2	1	35
0	60[d]	1.5	66	26	< 1	2	1	4
−78[c]	30	0.5	92	5	< 1	1	—	2
0[c]	60[d]	1.5	44	46	7	1	2	—

[a] The reaction was carried out using hydrocarbon **1** (2 mmol) and CH_2Cl_2 (30 cm^3). [b] Determined on a Shimazu GC-14A gas chromatograph using a J & W Scientific DB-5 capillary column. [c] $MeSO_3H$ (5 equiv.) was added. [d] Half the amount was introduced at the start of the reaction and the remaining half was added after 0.5 h.

Table 2 Reaction of adamantane **1** with various nitrating agents[a]

	Selectivity		Product composition (%)[b]					
Reagents and conditions	3°/2°	**2**/(**3** + **4**)	**2**	**3**	**4**	**5**	**6**	**1**
NO_2–O_3, −78 °C, 0.5 h[c]	100	13	92	6	1	< 1	< 1	< 1
$AcONO_2$ (8 equiv.), room temp., 8 h[c]	20	4.3	73	17	—	4	—	6
N_2O_5 (3.5 equiv.), 0 °C, 1 h	25	0.25	19	75	1	4	—	< 1
N_2O_5 (3.5 equiv.), $MeSO_3H$ (5 equiv.) 0 °C, 1 h	∞	0.01	1	91	8	—	—	—
fuming HNO_3, H_2SO_4, room temp., 20 h	∞	0	—	70	1	—	—	29

[a] The reaction was carried out using **1** (2 mmol) and CH_2Cl_2 (10 cm^3) under the given conditions. [b] See footnote *b* in Table 1. [c] See footnote *a* in Table 1.

give the pure nitro derivative **2** (0.32 g, 90%), mp 162–163 °C (lit.,[6] 159 °C).

In order to probe into the mechanistic pathway, the reaction of hydrocarbon **1** and a variety of nitrating agents was investigated as to the dependence of the product distribution on the reaction conditions. The relative product ratios varied over a wide range depending on the reagent and temperature employed (Table 2). At −78 °C, however, all nitrating agents except the nitrogen dioxide–ozone system failed to react with compound **1**, thus substantiating the crucial role of the *in situ* generated nitrogen trioxide as an initial reactive species. Under the typical ionic conditions based on the use of HNO_3–H_2SO_4 or N_2O_5–$MeSO_3H$, the reaction occurred exclusively at the tertiary position of **1** *via* *O*-attack to give the nitrate **3**. The active species involved therein is presumably the nitronium ion, which makes preferential electrophilic attack at the bridgehead C–H bond to generate the adamant-1-yl cation,[2] eventually leading to nitrate **3**. Thus the classical nitration based on the nitronium ion provides a convenient means to introduce the oxygen function into the bridgehead position of the adamantane nucleus. The reaction with acetyl nitrate or dinitrogen pentoxide produced the nitro derivative **2** and nitrates **3** and **5** in varying ratios depending on the conditions employed, presumably due to the competition between the concurrent ionic and radical processes involving the nitronium ion and nitrogen trioxide as the respective attacking species.

The low temperature kyodai–nitration of **1** is highly likely to proceed *via* the abstraction of the bridgehead hydrogen by nitrogen trioxide. The tertiary adamantyl radical thus formed is rapidly trapped by nitrogen dioxide to form nitro compound **2**. No skeletal rearrangement was observed.

Although the reported tertiary/secondary positional selectivity of the hydrogen abstraction by nitrogen trioxide falls within the range 3–14 at ambient temperature,[5,7,8] the corresponding value of the kyodai–nitration reached 100 at −78 °C. The remarkably high selectivity is in accordance with the strongly electron–defficient nature of nitrogen trioxide ($E°$ 2.3 V *vs.* normal hydrogen electrode),[9] which should prefer the more electron–rich tertiary C–H bond over the secondary one. Formation of nitrates **3** and **5** may in part be attributed to the oxidation of the initially formed adamantyl radicals to carbocations followed by coupling with the nitrate ion, and also in part to the reaction of adamantyl radicals with nitrogen dioxide and subsequent oxidation of the resulting nitrites. Alcohol **4** probably arose from nitrate **3** during aqueous work-up. Slowing down of the reaction with the rise of reaction temperature may be attributed to the increase in trapping efficiency of nitrogen trioxide by nitrogen dioxide at elevated temperatures.

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Footnotes

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† A Nippon Ozone Co. Ltd., type ON-1-2 apparatus was used for the generation of ozone. The machine produced ozone at the rate of 10 mmol h^{-1} under the following conditions: oxygen flow 10 dm^3 h^{-1}; applied voltage 80 V.

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