

Non-acid Synthesis of Nitro Musks Based on the Ozone-Mediated Nitration Using Nitrogen Dioxide

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Abstract: Three nitro musks, musk xylol **1**, musk ketone **2** and musk ambrette **3**, were prepared in good to moderate yield by direct polynitration of the respective aromatic materials with nitrogen dioxide in the presence of ozone.

Key words: nitro musk, nitration, nitrogen dioxide, ozone, fragrance

Some highly substituted aromatic nitro compounds are characterized by a persistent musky aroma and have long been known as the nitro musks. They are still of considerable industrial importance as substitute for the naturally occurring musk odorants that are expensive and difficult to synthesize. Representative nitro musks include musk xylol **1**, musk ketone **2**, musk ambrette **3**, musk tibetene **4**, and moskene **5** (Scheme 1). Especially, the former two are used in large quantities as ingredients in inexpensive perfumes for soaps, detergents, cosmetics, and other household products as well as fixatives in blossom and fantasy compositions.

Bauer was the first to observe that certain aromatic nitro compounds imitate the odor of natural musks.¹ Since then much work has been done on the musk-like systems and numbers of compounds with or without the nitro functionality are commercially introduced as artificial musks.² Carpenter synthesized more than forty different types of musk-like odoriferous compounds and examined the rela-

tionship between the musk odor and chemical constitutions.³ The commercial method for manufacturing the nitro musks involves treatment of aromatic hydrocarbons and derivatives with ordinary or fuming nitric acid using 98% sulfuric acid, oleum, or acetic anhydride as the reaction medium. Major drawbacks of this century old procedure are the disposal of large amounts of spent acid and acidic drainage, and the toxic fumes resulting from the oxidative degradation that usually accompanies polynitration under forced conditions.

We have recently reported that nitrogen dioxide is activated in the presence of ozone to react smoothly with a wide variety of arenes, giving the corresponding nitro derivatives in high yield (*kyodai*-nitration).⁴ The combination of nitrogen dioxide and ozone exhibits a powerful nitrating ability, smoothly converting a variety of nonactivated arenes into polynitro derivatives in the presence of an appropriate acid catalyst at temperatures below 0 °C. This methodology has now been successfully applied to the direct preparation of three commercial nitro musks **1–3** from the respective aromatic materials under non-acid conditions.

Hydrocarbon **6a** was dissolved in dichloromethane or acetonitrile and exposed to ozonized oxygen in the presence of an excess of nitrogen dioxide at –10 °C for 3 h, giving the corresponding dinitro derivatives **9a** and **10** in 81–82% and 15–17% yields, respectively (Scheme). Indiffer-

Table Product Distribution in the *Kyodai*-Nitration of Compounds **6a–c** under Various Conditions^a

Substrate	Reagent	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b			
					Nitro musk	7	9	10
6a	NO ₂ -O ₃	hexane	–10	3	1 (97)	–	1	0
6a	NO ₂ -O ₃	CH ₂ Cl ₂	–10	3	1 (<1)	–	82	17
6a	NO ₂ -O ₃	MeCN	–10	3	1 (<1)	–	81	15
6a^c	NO ₂ -O ₃ / MeSO ₃ H (0.5 eq.)	CH ₂ Cl ₂	–10	3	1 (44)	–	43	0
6a	<i>fum</i> -HNO ₃ -H ₂ SO ₄	CH ₂ Cl ₂	–10	3	1 (<1)	–	57	10
6b	NO ₂ -O ₃	hexane	–10	1.5	2 (48)	<1	36	–
6b	NO ₂ -O ₃ / MeSO ₃ H (0.5 eq.)	hexane	–10	1.5	2 (55)	0	38	–
6b	NO ₂ -O ₃ /HNO ₃ (0.5 eq.)	hexane	–10	1.5	2 (60), 1 (6)	0	31	–
6b	<i>fum</i> -HNO ₃ -H ₂ SO ₄	CH ₂ Cl ₂	–10	9	2 (55)	21	23	–
6c	NO ₂ -O ₃	hexane	–10	1	3 (55)	0	22	–
6c^c	NO ₂ -O ₃ /MeSO ₃ H (0.5 eq.)	hexane	–10	1	3 (60)	0	26	–
6c^d	<i>fum</i> -HNO ₃	Ac ₂ O	10	–	3 (60)	0	21	–

^a All reactions were carried out using **6** (5 mmol) and nitrogen dioxide (1 mL) in the given solvent (25 mL)

^b Determined by ¹H NMR.

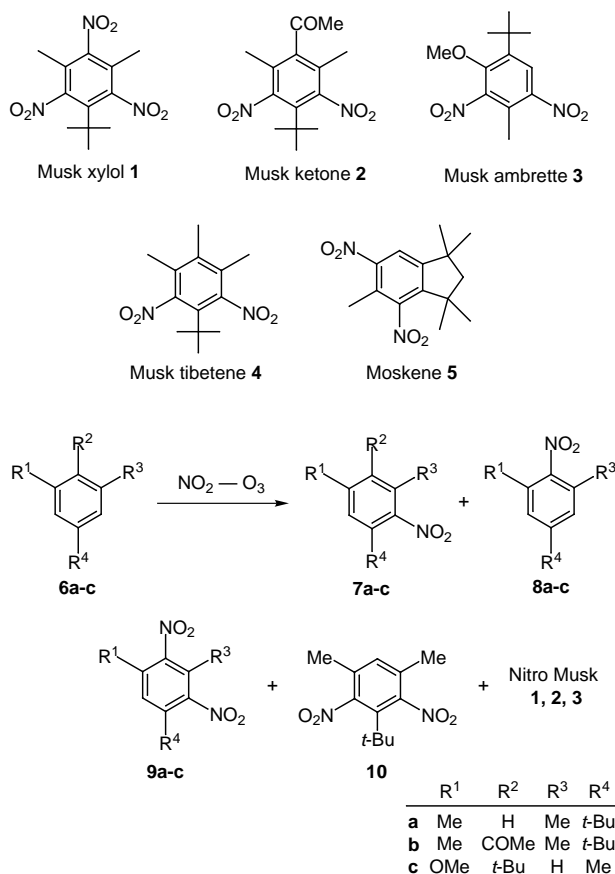
^c Determined by GLC using cyclododecane as an internal standard.

^d From ref. 3b.

ent to the solvents employed, these products were obtained in comparable yields (Table). When methanesulfonic acid was added as catalyst to the reaction system, further conversion of these dinitro derivatives was considerably facilitated and there resulted musk xylol **1**. Rather surprisingly, the reaction was found to go much more easily in hexane, resulting in the formation of trinitro compound **1** nearly as the sole product. GLC monitoring of the reaction revealed that the first and second nitration proceeded almost in parallel irrespective of the solvent polarity, but the third nitration was feasible only in hexane at moderate rate (Figure). This unexpected result may be interpreted as follows; the reaction mixture becomes heterogeneous at dinitration stage due to the low solubility of compounds **9a** and **10** in cold hexane. Dinitrogen pentaoxide, a nitronium ion precursor generated from nitrogen dioxide and ozone, is also poorly soluble in hexane. So it would be preferentially extracted into a micro-emulsion phase of more polar nitroarenes **9a** and **10** as it is formed in situ, resulting in the increased concentration of the nitrating agent at the interface. In contrast, both dinitrogen pentaoxide and products **9a/10** are soluble in dichloromethane and acetonitrile and, therefore, further nitration of these deactivated substrates would become slower under such a diluted condition as employed. Besides economy, the use of hexane as the solvent provides the additional advantage that the product **1** was separated from the reaction mixture in the form of a white solid and could be collected by simple filtration.

Better conversion of hydrocarbon **6a** to musk xylol **1** has usually been performed by a two-step procedure rather than by a single-step one that involves triple nitration under forced conditions. In the former procedure, compound **6a** is first nitrated with 68% nitric acid in 98% sulfuric acid to give mononitro derivatives **7a** and **8a**, which is then treated with fuming nitric acid in hot fuming sulfuric acid to obtain musk xylol **1**. However, the present non-acid methodology based on the combination of nitrogen dioxide and ozone can convert **6a** directly into **1** in good conversion and in a high yield.

One problem in the conventional nitration of aromatic ketone **6b** and ether **6c** to the nitro musks **2** and **3** using nitric and sulfuric acids is the partial loss of the acetyl or *tert*-butyl group during the course of polynitration. Expecting a favorable solution to this year-long but yet unsolved problem, we examined the *kyodai*-nitration of compounds **6b** and **6c** in hexane in the presence or absence of methanesulfonic acid as catalyst. Displacement of the acetyl and *tert*-butyl groups by the nitro group occurred also under our conditions to a similar extent to those observed in the conventional nitration of these substrates. Added acid catalyst was found to facilitate the reaction and somewhat improve the product yields. However, no improvement was observed as to the extent of undesired displacement of the respective substituent groups by the nitro function. Mechanistic aspect of these side reactions in the *kyodai*-nitration will be published elsewhere.



Scheme

Mps were determined on a Yanagimoto hot stage apparatus and are uncorrected. All compounds obtained are known and identified by ¹H NMR, IR and GCMS spectroscopy, or by direct comparison with the authentic samples. Reagents and solvents were all reagent-grade commercial samples. IR spectra were recorded on a Shimadzu FT-IR DR 8000/8100 infrared spectrophotometer, and only prominent peaks in the 2000–700 cm⁻¹ region were recorded. ¹H NMR spectra were obtained in CDCl₃ with a Varian Gemini 200 (200 MHz) spectrometer. Chemical ionization mass spectra were recorded on a Shimadzu GC-MS QP-5000 with DI-50 using isobutane as the reacting gas. Liquid nitrogen dioxide (99% pure; major impurities are nitrogen monoxide and small amounts of nitrogen) was purchased in a cylinder from Sumitomo Seika Co. Ltd., and used after transfer distillation. A Nippon Ozone Co. Ltd., type ON-1-2 apparatus was used for the generation of ozone. The machine generated ozone at a rate of 10 mmol h⁻¹ under an oxygen flow of 10 dm³ h⁻¹ and an applied voltage of 80 V.⁵

Kyodai-Nitration of 1-*tert*-Butyl-3,5-dimethylbenzene (**6a**) to Musk Xylol (**1**)

A solution of hydrocarbon **6a** (0.81 g, 5 mmol) and liquid nitrogen dioxide (1 mL, 30 mmol) in hexane (25 mL) was placed in a three-necked 30 mL flask fitted with a gas inlet tube and a vent. The third neck was used for withdrawing an aliquot for monitoring. The mixture was cooled to -10 °C with a cooling bath (EYELA COOL ECS-1 with two thermometers THS-40 and THD-50), while a stream of ozonized oxygen was introduced slowly under magnetic stirring through the gas inlet tube, which dipped below the surface of the liquid in the flask. At intervals of 1 h, an additional amount of nitrogen dioxide (2 x 1 mL) was added. As the reaction proceeded, the solution gradually became turbid and musk xylol **1** began to

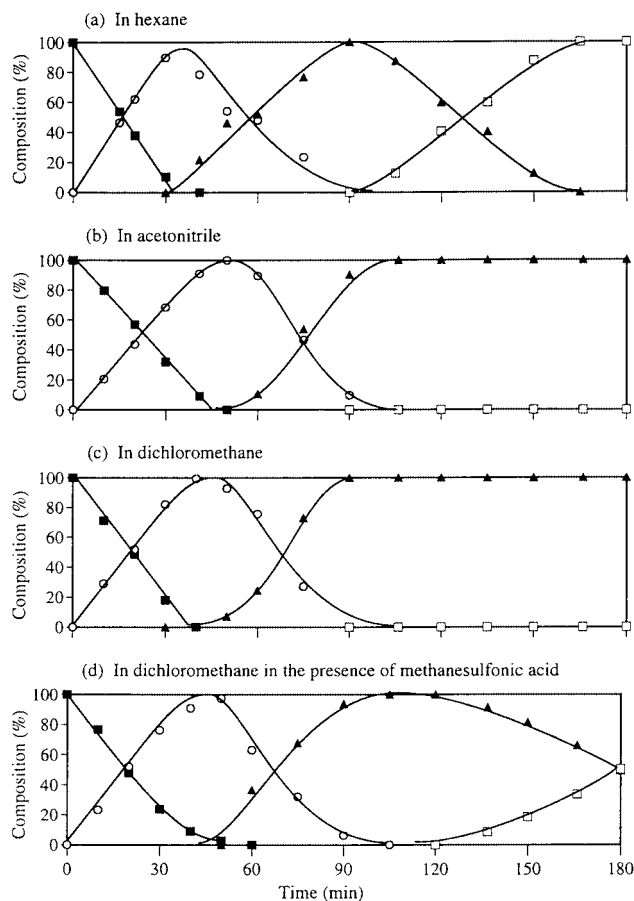


Figure. Time course of the *kyodai*-nitration of compound **6a**, determined by GLC using cyclododecane as an internal standard. For the reaction conditions, see Table. ■ Substrate **6a**; ○ mononitro derivatives **7a**, **8a**; ▲ dinitro derivatives **9a**, **10**; □ musk xylol **1**

separate as a white solid. After 3 h, unchanged nitrogen dioxide was expelled by anhyd N_2 and recovered in a cold trap for reuse. The solid product was collected by filtration. The filtrate was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to obtain the second crop. The combined crude musk xylol was recrystallized from EtOH to yield pure **1**, 1.22 g (82%). Mp 107–109 °C [Lit. ^{1a} 110 °C].

1H NMR($CDCl_3$, 200 MHz): δ = 2.17 (s, 6H), 1.46 (s, 9H).

GC-MS (CI): m/z (%) = 298 ($M^+ + 1$, 100), 282 (20), 278 (43), 253 (16).

FT-IR (KBr): ν = 1545, 1474, 1397, 1354, 1206 cm^{-1} .

Kyodai-Nitration of 4-*tert*-Butyl-2,6-dimethylacetophenone (6b) to Musk Ketone (2); Typical Procedure

4-*tert*-Butyl-2,6-dimethylacetophenone (**6b**) (1.02 g, 5 mmol) was dissolved in freshly distilled hexane (25 mL) and placed in a three-necked flask fitted with a gas inlet tube and a vent which permitted waste gas to escape. The mixture was cooled to -10 °C under stirring and liquid nitrogen dioxide (1 mL, 30 mmol) was introduced in one portion. To the resulting mixture ozonized oxygen was passed at a low flow rate. After 1 h, an additional amount of nitrogen dioxide (1 mL) was added and ozone was continuously fed for further 1.5 h. Under these conditions, the loss of nitrogen dioxide was not so significant. Then the mixture was diluted with H_2O and the organic phase was extracted with CH_2Cl_2 . The extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to leave a solid residue, which was recrystallized from EtOH to give

pure musk ketone **2** as white crystals, 0.59 g (40%). Mp 133–135 °C [lit. ^{3a} 135.5–136 °C].

1H NMR($CDCl_3$, 200 MHz): δ = 2.51 (s, 3H), 2.11 (s, 6H), 1.44 (s, 9H).

GC-MS (CI): m/z (%) = 295 ($M^+ + 1$, 100), 279 (9), 266 (25), 250 (2).

FT-IR (KBr): ν = 1713, 1539, 1474, 1372, 1350, 1242, 1125 cm^{-1} .

Musk Ambrette (3)

This compound was obtained similarly according to the above procedure. White solid (46%); mp 81–83 °C [lit. ^{3b} 85 °C].

1H NMR($CDCl_3$, 200 MHz): δ = 8.06 (s, 1H), 3.92 (s, 3H), 2.40 (s, 3H), 1.43 (s, 9H).

GC-MS (CI): m/z (%) = 269 ($M^+ + 1$, 91), 253 (7), 239 (4), 213 (100), 207 (4).

FT-IR (KBr): ν = 1617, 1541, 1534, 1350, 1271, 1246, 1062, 1052 cm^{-1} .

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