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### MODIFIED AND CONVENIENT METHODS FOR THE PREPARATION OF SOME NITRO MUSKS

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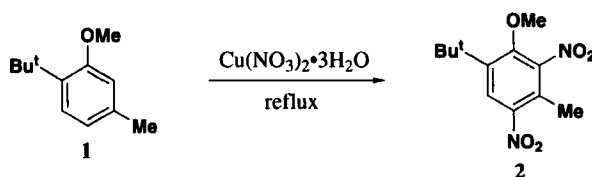
**MODIFIED AND CONVENIENT METHODS  
FOR THE PREPARATION OF SOME NITRO MUSKS**

Submitted by Javad Safaei-Ghomi\* and Abdolhamid Bamoniri  
(09/26/03)

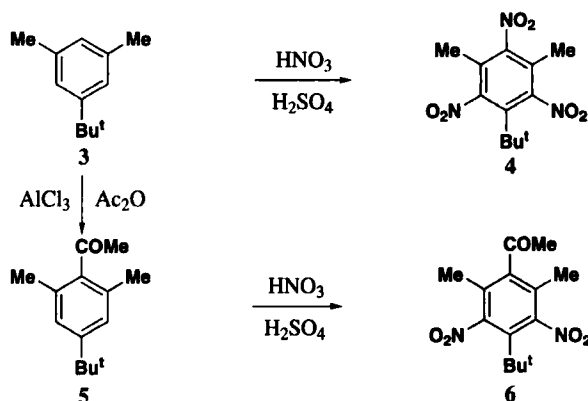
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Synthetic musks are important artificial fragrances used in large amounts in perfumes, toiletry products, detergents, fabric softeners, and medication<sup>1-3</sup> and, can roughly be divided in two main groups: nitro musks and polycyclic musks.<sup>4</sup> They are still of considerable industrial importance as substitutes for the naturally occurring musk odorants that are expensive and difficult to synthesize. Since their discovery as by-products during the development of new explosives,<sup>5</sup> much work has been done on the musk-like systems and a number of compounds with or without the nitro functionality are commercially introduced as artificial musks.<sup>4,6</sup> 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. We report here modified and improved procedures for the production of some nitro musks (aroma chemicals) by acylation and nitration in yields higher than those of existing methods.

The preparation of musk amberette (2) through the nitration of 2-*tert*-butyl-5-methylanisole (1) with conc. H<sub>2</sub>SO<sub>4</sub>/HNO<sub>3</sub> or Ac<sub>2</sub>O/HNO<sub>3</sub> or Ac<sub>2</sub>O, HOAc/HNO<sub>3</sub> in overall yields of up to 80% has been reported.<sup>7-10</sup> The nitration of activated aromatic rings such as phenols and aryl ethers using Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O in overall yields of 40-90% has been described<sup>11-15</sup> and, we found that the nitration of 1 to 2 with Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O in refluxing ethyl acetate proceeds in 82% yield.



The previously reported nitration of 3 to 4 in 92% yield with a mixture of conc. sulfuric and nitric acids<sup>16,17</sup> was improved to 97% by increasing the amount of fuming nitric acid (from 5 mL to 8 mL) and heating the reaction mixture under reflux (80-90°C).



The yield of the acetylation of **3** was increased from 50% with acetic anhydride (and no yield reported with acetyl chloride<sup>18,19</sup>) to 85% by use of excess distilled acetic anhydride and of lower temperature (-12°C); at room temperature, formation of polymeric material prevented extraction of the product. Modification of the nitration of **5**<sup>16,18-20</sup> by use of an excess of fuming nitric and conc. sulfuric acids and of lower temperature (-12°C) led to an increased yield (from 56% to 68%). The overall yield of **6** from **3** was 58%.

In conclusion, we have described more efficient syntheses of some aroma chemicals by modified procedures and that using copper (II) nitrate trihydrate may be used for the preparation of musk amberette (**2**). Although it is advantageous to use Cu(NO<sub>3</sub>)<sub>2</sub>•3H<sub>2</sub>O and ethyl acetate (short reaction time, increased yield, decreased reagent costs, reduction of hazards, and simple work-up), this reagent is effective only for strongly and moderately activated aromatic rings such as phenols and aryl ethers and could not affect the nitration of benzene rings with weakly activating groups unless the reagent was supported on clay.<sup>21</sup>

## EXPERIMENTAL SECTION

Solvents and starting materials were purchased from the Fluka and Merck chemical companies. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were obtained in CDCl<sub>3</sub> using Hitachi R-24, B-360 spectrometers at 60 MHz. Chemical shifts are reported relative to internal standard Me<sub>4</sub>Si. IR spectra were taken as KBr pellets on Perkin-Elmer 781. Compounds were purified by column chromatography using silica gel 60 (Merk; 43-60 mesh).

**2-tert-Butyl-5-methyl-4,6-dinitroanisole (2).** - To a solution of 1.40 g (7.8 mmol) of 2-tert-butyl-5-methylanisole in ethyl acetate (15 mL) in a 100 mL round-bottom flask was added 8.00 g of copper (II) nitrate trihydrate. The mixture was heated at reflux with stirring for one hour. After evaporation of the solvent, column chromatography (SiO<sub>2</sub>, petroleum ether:ethyl acetate 1:3) of the solid residue afforded 1.71 g (82%) of pure **2**, mp. 84-86°C, *lit.*<sup>11</sup> mp. 85°C. <sup>1</sup>H NMR: δ 1.4 (s, 9H), 2.4 (s, 3H), 3.8 (s, 3H), 7.9 (s, 1H). IR: 3020, 2950, 1550, 1330, 1200, 1100, 700 cm<sup>-1</sup>.

**5-tert-Butyl-1,3-dimethyl-2,4,6-trinitrobenzene (4).**- To an ice-cold mixture of 10 mL oleum and 8 mL fuming nitric acid was added slowly with stirring 1.99 g (12.3 mmol) *sym-tert-butyl-m-xylene* (**3**). After addition of **3**, the mixture was heated at reflux (80-90°C) for 0.5 hour, and then poured onto ice. The nitro compound was separated, washed with water, and recrystallized from ethanol. Compound **4** was obtained 3.53 g (97%), mp. 112-113°C, *lit.*<sup>17</sup> mp. 112°C. <sup>1</sup>H NMR: δ 1.4 (s, 9H), 2.2 (s, 6H). IR: 3020, 2950, 1550, 1500, 1400, 1350, 900, 700 cm<sup>-1</sup>.

**4-tert-Butyl-2,6-dimethylacetophenone (5).**- A mixture of 5.51 g (34 mmol) of *sym-tert-butyl-m-xylene* (**3**) and 6 mL redistilled acetic anhydride was added with stirring to a mixture of 12.00 g (90 mmol) aluminum chloride and 15 mL ethylene dichloride during 0.5 hour at -12°C. Agitation was continued for 0.5 hour at -12°C and the product mixture was quenched on ice, washed to neutrality with water, and the solvent was distilled. The recrystallized (ethanol) residual solid gave 5.92 g (85%) of compound **5**, mp. 46-47°C, *lit.*<sup>18</sup> 45.5-46.5°C. <sup>1</sup>H NMR: δ 1.3 (s, 9H), 2.2 (s, 6H), 2.4 (s, 3H), 6.9 (s, 2H). IR: 3020, 2970, 1650, 1550, 1350, 1200, 850, 750 cm<sup>-1</sup>.

**4-tert-Butyl-2,6-dimethyl-3,5-dinitroacetophenone (6).**- A solution of 2.25 g (11 mmol) of ketone **5** in 10 mL chloroform was added to a 100 mL, round-bottom flask containing 3 mL of 98% nitric acid, with vigorous agitation during 15 min. at -12°C. Sulfuric acid (5.5 mL of 98%) was then added, and agitation continued for 10 min. at -12°C. The reaction mixture was quenched on ice. The pale yellow oil was taken up in benzene, washed with 5% sodium hydroxide solution until the washes were light-colored (3 washes), then washed with water to neutralize, and the organic solvent was removed under reduced pressure. The residue was recrystallized (methanol) to give 2.19 g (68%) of **6**, mp. 135-136°C, *lit.*<sup>16</sup> mp. 136.5°C. <sup>1</sup>H NMR: δ 1.4 (s, 9H), 1.9 (s, 6H), 2.4 (s, 3H). IR: 3020, 2980, 1700, 1550, 1500, 1430, 1350, 1250, 850, 700 cm<sup>-1</sup>.

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