Mild and Selective Nitration by "Claycop"

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A one-pot nitration of aromatic compounds by "claycop", a reagent consisting of an acidic montmorillonite clay impregnated with anhydrous cupric nitrate, is reported. Simply by varying the conditions, it is possible to drive the reaction at will toward either mono- or polynitration. Both the yields and selectivities are superior to those obtained under homogeneous reaction conditions.

We report here a one-pot procedure for the mono- or polynitration of aromatic compounds by the reagent "claycop", an acidic montmorillonite clay impregnated with anhydrous cupric nitrate. Both the yields and selectivities of this method are superior to those obtained under homogeneous reaction conditions.

Quantitative and selective mononitration of aromatic hydrocarbons can be accomplished by a clay impregnated with cupric nitrate or ferric nitrate, under Menke conditions, i.e. in the presence of acetic anhydride.[1-4] Under such conditions, the likely nitrating species is acetyl nitrate.[5]

It proved more difficult to accomplish polynitrations under such mild conditions. We report here conditions that are applicable to a wide range of unactivated, activated and deactivated aromatic substrates. The yields are high, and as a rule are nearly quantitative. These novel procedures are also highly selective and contamination by oxidation side-products is avoided. Moreover, in mixed-acid nitration reactions, the products can undergo violent oxidative degradation since nitric acid is a powerful oxidizing agent, especially at high temperatures. This risk is minimized under the room temperature conditions of our procedure. Furthermore, we would like to emphasize that mono- or polynitration products can be obtained at will simply by adjusting the reaction conditions. In addition, the workup is simplified, because product separation requires only a simple filtration to remove the spent "claycop" reagent.

Results and Discussion

The reaction procedure was applied to benzene, as well as the following substrates: "activated" aromatic compounds such as toluene, naphthalene, 5-*tert*-butyl-1,3-dimethylbenzene, 5-*tert*-butyl-1,2,3-trimethylbenzene, and dehydroabietic acid; "strongly activated" aromatic compounds such as phenol, cresol, anisole or aniline; and "deactivated" compounds such as chlorobenzene and benzaldehyde.

Polynitration of Benzene and of Activated Aromatic Compounds. The procedure for nitration of aromatic hydrocarbons with "claycop" reported earlier[2] was extended to the polynitration of benzene and activated aromatic compounds by the use of significantly greater amounts of claycop (48-fold) and, whenever necessary, by adding small amounts of fuming nitric acid after cooling the reaction mixture to 0–5 °C. Generally, these reactions proceed satisfactorily at room temperature, with good to excellent yields of the polynitrated products (Table 1).

The nitration of toluene by the present procedure produced at least a 9:1 mixture of 2,4- and 2,6-dinitrotoluenes, compared to 8:2 with mixed acid.[6,7] With naphthalene, yields of 1,5- and 1,8-dinitronaphthalenes are comparable to those presently obtained in industry either by direct mixed acid nitration of naphthalene, or by nitration of 1-nitronaphthalene[8,9] with the advantage of much lower reaction temperatures. This new and efficient method was also applied to the polynitration of 5-*tert*-butylxylene and of 5-*tert*-butyl-1,2,3-trimethylbenzene to give good yields of two important musklike odoriferous compounds,[10] musk xylene and musk tibetene, respectively, which are used in the perfume industry and are usually prepared by nitration with a sulfo-nitric mixture.[11] Good yields (80% or higher) were also obtained for the preparation of 12,14-dinitrodehy-

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Table 1. Polynitration of Benzene and Activated and Strongly Activated Aromatic Compounds and Mononitration of Deactivated Aromatic Compounds with "Claycop", Improved by the Addition of Fuming Nitric Acid[a]

substrate	fuming HNO_3 (mL/mmol)	time (h)	molar yield (%)	product distribution (%)[b]
benzene	2	8	92	nitrobenzene (40) 1,3-dinitrobenzene (60)
toluene	0.75	4	95	2,4-dinitrotoluene (86) 2,6-dinitrotoluene (13)
naphthalene	0.75	3	97	1,8-dinitronaphthalene (70) 1,5-dinitronaphthalene (23) 1,6-dinitronaphthalene (4) 1,7-dinitronaphthalene (3)
5-*t*-Bu-1,3-$(CH_3)_2C_6H_3$	3.5	20	90	2,4-$(NO_2)_2$-5-*t*-Bu-1,3-$(CH_3)_2C_6H$ (19) 2,4,6-$(NO_2)_3$-5-*t*-Bu-1,3-$(CH_3)_2C_6$ (82)
5-*t*-Bu-1,2,3-$(CH_3)_3C_6H_2$ (5-*t* -Bu-hemimellitene)	0.5	2	92	4,6-$(NO_2)_2$-5-*t*-Bu-1,2,3-$(CH_3)_3C_6$ (93)[c]
dehydroabietic acid	0.5	2	85	12,14-dinitrodehydroabietic acid (80)[c]
phenol	0	0.75	90	2,4-dinitrophenol (80)[c]
2-methylphenol (*o*-cresol)	0.5	1	89	4,6-dinitro-2-methylphenol (80)[c]
4-methylphenol (*p*-cresol)	0.1	0.75	90	2,6-dinitro-4-methylphenol (93)[c]
anisole	0.25	1.5	95	2,4-dinitroanisole (90)[c]
aniline	1	2.5	98	2,4-dinitroacetanilide (98)[c]
chlorobenzene	1.5	24	98	*o*-nitrochlorobenzene (13) *p*-nitrochlorobenzene (85)
benzaldehyde	1.0	6	99	*o*-nitrobenzaldehyde (26) *m*-nitrobenzaldehyde (41) *p*-nitrobenzaldehyde (27)

[a] Claycop: 480 mg/mmol; Ac_2O: 1.5 mL/mmol; CCl_4: 3 mL /mmol. [b] Unless otherwise noted, yields were determined by GC before the isolation of the products. [c] Isolated yield.

Table 2 . Mononitration of Strongly Activated Aromatic Compounds with "Claycop"[a]

substrate	time (min)	molar yield (%)	product distribution (%)[c]
phenol	5	92	2-nitrophenol (86) 4-nitrophenol (6)
2-methylphenol (*o*-cresol)	4	95	6-nitro-2-methylphenol (85)[d]
3-methylphenol (*m*-cresol)	5	90	2-nitro-5-methylphenol (55) (6-nitro-*m*-cresol) 4-nitro-3-methylphenol (15)
4-methylphenol (*p*-cresol)	5	95	2-nitro-4-methylphenol (92)[d]
anisole	15	98	2-nitroanisole (44) 4-nitroanisole (52)
aniline[b]	30	100	2-nitroacetanilide (98)

[a] Claycop: 240 mg/mmol; Ac_2O: 0.75 mL/mmol; CCl_4: 1.5 mL/mmol. [b] Claycop: 480 mg/mmol; Ac_2O: 1.5 mL/mmol; CCl_4: 3 mL/mmol. [c] Unless otherwise noted, yields were determined by GC before the isolation of the products. [d] Isolated yield.

droabietic acid. Both the amounts of fuming nitric acid required and the reaction times depend upon the reactivity of the aromatic substrate and the degree of nitration desired (Table 1).

The addition of fuming nitric acid facilitates the nitration process by increasing both the rate of reaction and the yield of nitrated product. This improvement is probably due not only to the lower temperature that helps to maintain the concentration of the nitrating agent, ($AcONO_2$, bp_{70} 22 °C)[12] but also to an increase in the rate of nitration upon lowering the temperature, an unusual effect already observed by Bonner[13] and Coombes[14] for the nitration of aromatics in solution, particularly in carbon tetrachloride.

The increased selectivities in the dinitration of toluene (Table 1), as compared to classical homogeneous conditions, result from the high *para*-regioselectivity obtained for mononitration,[1] in which a likely role of the acidic support (K 10 montmorillonite clay) is to favor a radical multistep mechanism through the $ArH^{\bullet+}$ radical cation.[15,16]

Nitration and Dinitration of Strongly Activated Compounds. Earlier work[3] on the nitration of phenol and derivatives with "clayfen" (K10-supported anhydrous ferric nitrate) in various solvents gave improved *para* selectivity, mononitration, and good to excellent yields. We report here the use of "claycop" as the nitrating agent in the presence of acetic anhydride, with carbon tetrachloride as solvent. This alternative method provides nitrated phenols directly, in short reaction times and in high yields (Table 2).

As shown in Table 2, preferential *ortho*-nitration prevailed except with anisole. The difference in regioselectivity when using "claycop" with acetic anhydride or "clayfen"[3] might be due to the formation, in the former case, of an intermediate ester which lowers electronic density in the ring, particularly in the *para* position, decreasing its vulnerability toward electrophilic substitution.

With both phenols and cresols, intermediate acetylated derivatives formed, as determined both by GC/MS analyses and isolation, and underwent *in situ* hydrolysis due to the acidity of the clay.

Aniline followed a different pathway, selectively forming the *ortho* isomer 2-nitroacetanilide, in high yield

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(Table 2). In this case, we did not observe hydrolysis of the acetylated product, which usually requires prolonged heating.[17]

Our procedure is also applicable to the dinitration of strongly-activated aromatic substrates in excellent yields, by either using a larger amount of "claycop" (480 mg/mmol) or by adding fuming nitric acid, depending upon the reactivity of the substrate (Table 1). The process showed high selectivity for all the substrates studied.

This procedure has the advantage of providing direct nitration or dinitration of aromatic compounds such as aniline, phenol, and derivatives, depending on the amount of claycop used. For full dinitration, the addition of fuming nitric acid improves the yield and shortens reaction times.

Nitration of Deactivated Aromatic Compounds. Halobenzenes traditionally[6] give *ca.* 35:1:64 mixtures of *o*, *m*, *p* nitro derivatives. We obtained in the present study a quantitative yield of nitrochlorobenzene, as a mixture of *o*- and *p*-isomers (13:85), using carbon tetrachloride as the solvent, and by the addition of fuming nitric acid (1.5 mL/mmol) (Table 1). By this method we achieved in a shorter time (6 h) a regioselectivity similar to that shown earlier[13] with "claycop" in hexane after 48 h.

Our process, when applied to benzaldehyde, provided nitrobenzaldehyde in 90% overall yield (3 h), as a mixture of *o*-, *m*-, *p*-isomers (26:41:27) (Table 1), to be compared to the selectivity (20:80:0) of the conventional nitration.[18] The increase in *para*-isomer reflects the increased electron-attracting nature of the acylal group, $CH(OCOMe)_2$, which is readily hydrolyzed during the reaction.

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Experimental Section

General. GLC analyses were performed using a J&W DB-1 fused silica capillary column, 15 m, 0.25 μ film thickness. Reagents were of analytical grade and used without further purification. "Claycop", cupric nitrate trihydrate (11 g) supported on clay (10 g), was prepared and used under Menke conditions, previously reported for regioselective mononitrations.[1,2]

General Procedure for the Polynitration of Benzene and Activated and Strongly Activated Benzene Derivatives and Mononitration of Deactivated Benzene Derivatives. General Procedure I. The aromatic substrate (10 mmol) was added to a suspension of claycop (4.8 g) in carbon tetrachloride (30 mL) and acetic anhydride (15 mL). The mixture was stirred vigorously at room temperature and followed by GLC. The reaction mixture was then cooled in an ice bath and fuming nitric acid (100%) (see Table 1) was added dropwise. After addition, the reaction mixture was kept at room temperature with vigorous stirring until completion and then filtered. The filter cake was washed with a suitable solvent, and the combined organic portions were washed with water and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The nitro compounds were separated by crystallization or by column chromatography on silica gel, using mixtures of hexane and ethyl acetate of increasing polarity as eluents. The products were identified by comparison (TLC; capillary GLC, mp, IR, or NMR) with authentic samples.

General Procedure for the Nitration of Strongly Activated Benzene Derivatives. General Procedure II. The aromatic substrate (10 mmol) was added to a suspension of claycop (2.4 g) in carbon tetrachloride (30 mL) and acetic anhydride (7.5 mL). The mixture was stirred vigorously at room temperature, followed by GLC (for reaction times see Table 2), and then filtered. Workup of the reaction mixture and characterization of products was as described above.

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