Tetrahedron Vol. 46, No. 8, pp. 2707-2714, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

THE NITRATION OF PIVALOPHENONE WITH NITRONIUM TETRAFLUOROBORATE IN SULFOLANE

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(*Received in USA* 4 *October* 1989)

ABSTRACT The nitration of pivalophenone (2,2-dimethyl-1-phenyl-propan-1-one) with NO_2BF_4 gives o-,m-, and p-nitropivalophenones in the percentage ratio of 26:45:29. Competition experiments showed that pivalophenone is ten to twenty times less reactive than benzene but two to five times more reactive than acetophenone. No evidence for ipso attack could be found.

Recently, the nitration of pivalophenone (2,2-dimethyl-1-phenyl-propan--1-one with fuming nitric acid at 0-5°C or 50% v/v HNO_3 and H_2SO_4 at -20° to 0°C was reported to give identical mixtures of o-, m-, and p-nitropivalophenones (30:44:26 percent ratios) in 95-98% combined yields.[1]

This unexpected product distribution was attributed to a combination of steric factors. First, the steric interaction between the hydrogens in the t-butyl group and the ortho ring hydrogens causes non coplanarity of the carbonyl group with the ring resulting in a decrease of ring deactivation. The second steric factor was throught to be the hindrance of nitronium ion attack of one ortho position by the bulky t-butyl group leading to a "statistical analysis" in which the ratio of o-; m-; p-nitropivalophenones would be as 25:50:25 rather than 40:40:20 percent.

While this analysis appears to correlate theory with observations there are several other considerations. The possibility of ipso[2] attack by nitronium ion at the substituent bearing aromatic carbon, followed by rearrangement to an ortho or meta position, does not appear to have been considered. A second difficulty is that high positional selectivities are a hallmark of ionic aromatic nitrations[3-5]. Even in those studies employing nitronium salts in aprotic solvents where encounter controlled rates and low substrate selectivities are observed, one still finds the usual substituent directive effects[6]. A third possibility is that the anomalous product compositions might be forming through a nitro radical-aromatic radical cation encounter pair complex along the lines suggested by Perrin[7] and examined in some detail by Eberson[8].

In his recent reviews of mechanistic studies in aromatic nitration,[9,10] Olah notes that ionic nitrations with NO_2BF_4 lost substrate selectivity but maintain positional selectivity, while free radical nitrations with N_2O_4, $C(NO_2)_4$ or chloropicrin result in low substrate and low regioselectivity[7b].

We decided to study the nitration of pivalophenone, 1, with nitronium tetrafluoroborate, 2, in sulfolane in order to verify that the o:m:p product composition is the same in aprotic media as that observed in HNO_3. The work of Coombes, Moodie & Schofield expects such a finding[6a]. Further we planned to compare the relative reactivity of pivalophenone with benzene and with nitrobenzene in an effort to assess how much ring deactivation the pivaloyl group exerts.

Results

The nitration of pivalophenone with nitronium tetrafluoroborate in sulfolane produced ortho, meta and para nitropivalophenones in the yields and isomer ratios shown in Table 1. Also shown are the results from a preparative scale nitration run in fuming HNO_3, and the literature data.[1] In general the new data agree within 3-4% with the literature. Whether the NO_2BF_4 was added to the ketone or visa versa, the o:m:p ratio was not significantly affected. See Table 2. Variation of reaction times and concentrations also did not change the product ratios. Although our yields were strongly dependent upon the quality of the NO_2BF_4, our product ratios remained in the same ±4% area. Commercial NO_2BF_4 has been shown to contain 10-12% of $NOBF_4$.[11] We were able to raise yields from 81% to 91% by washing the NO_2BF_4 with nitromethane and methylene chloride. Control experiments showed that $NOBF_4$ did not react with 1.

Table 1: The Nitration of Pivalophenone[a]

Reagent	Yield	% Ortho	% Meta	% Para
NO_2BF_4	91%	26.4	44.7	28.9
HNO_3[b]	99%	33.1	40.1	26.8
Ref. 1	100%	30	44	26

(a) Phenyl-tertbutylketone; (b) $d^{25°} = 1.476$ g/mL

In the preparative scale nitration with fuming HNO_3, separation of the o-, m-, and p- isomers of nitropivalophenone was accomplished by flash column chromatography[24]. Treatment of the individual nitropivalophenones with HNO_3/H_2SO_4 nitrating agent for 1.0 hr at -20° showed no isomerization, no proto-denitration and no proto deacylation. Treatment of the meta- and para-nitropivalophenones with HNO_3/H_2SO_4 at +27° for 20 and 22 hr gave dinitropivalophenones.

Competitive nitrations of pivalophenone and nitrobenzene with nitronium tetrafluoroborate in sulfolane were run at 25°. The products were exclusively nitropivalophenones even when the solution of aromatic substrates was added to the NO_2BF_4 solution. No dinitro-benzene could be detected by vpc with a H_2 flame-ionization detector. In contrast, treatment of nitrobenzene alone with NO_2BF_4 solution gave a mixture of dinitrobenzenes whose composition was 6.1% ortho-, 92.5% meta-, and 1.4% para dinitrobenzene. These experiments show that pivalophenone is not a ring-deactivated aromatic substrate, and led to the question of how does this ketone compare with benzene in its reaction with NO_2BF_4?

Table 2: Nitration of Pivalophenone, with Nitronium Tetrafluoroborate in Sulfolane.

Run	[1] M	[2] M	Order of Addition	Yield %	Isomer Ratios % ortho	% meta	% para
8	1.2	0.26	P	98	26.1	44.7	29.2
17	1.0	0.75	P	98	25.8	45.1	29.1
10	0.6	0.42	P	75	26.6	44.0	29.4
11	0.6	0.42	P	89	28.8	44.1	27.1
12	0.6	0.28	P	54	27.8	43.5	28.7
13	1.0	0.68	N	87	26.1	44.6	29.3
14	1.0	0.68	N	85	26.4	45.0	28.6
15	1.0	0.50	N	80	25.1	45.8	29.1
16	1.0	0.50	N	79	24.5	45.7	29.8

(a) Runs 8-14 at R.T.; 15 & 16 were at 6-9°C. Reaction times = 7-68 min.
(b) P: 1 was added dropwise into a solution of 2 N: 2 was added to 1.
(c) 2%; (d) 1.0%

Nitrations of reactive aromatics like benzene and toluene are subject to mixing control and mass diffusion effects because of the very high reactivity of the NO_2^+ ion.[12-15]. In an effort to overcome the difficulty of obtaining a homogeneous mixture of reactants, we injected 40 mL of nitronium tetrafluorobórate solutions (0.45 M) under 5 psi of dry N_2 pressure into vigorously stirred sulfolane solutions of pivalophenone and benzene (and 1 and acetophenone) during six seconds. The initial concentrations of the reactants together with relative rate constants $k_{C_6H_6}/k_{piv.}$ and $K_{piv.}/k_{aceto}$ are shown in Table 3.

In the course of the competitive nitration of acetophenone with NO_2BF_4, abnormally high proportions of ortho-nitroacetophenones were observed (40 ± 1%). Subsequent nitrations of acetophenone alone with NO_2BF_4 at 25° ±0.1°C occurred with formation of brown colored solutions and gave a low yield (28%) of nitroacetophenones with recovery of acetophenone (20%) whenever the technique of rapid injection of NO_2BF_4 solution was used. If a slow,

Table 3: Competitive Nitrations: Pivalophenone, 1, vs. Benzene, 3, and 1, vs. Acetophenone, 4.

Run No.	[1]	[3]	[4]	Temp (°C)	K_3/K_1	K_1/K_4
35	0.21	0.21		27	20	
36	0.84	0.21		26	19	
38	0.42	0.21		30	13	
41	0.136	0.136		32	10	
34	0.21		0.84	28		2.5
40	0.17		0.34	30		5.1

(a) with NO_2BF_4

dropwise addition of NO_2BF_4 solution is utilized, the acetophenone reacts almost completely (0.4% was unreacted) and the yield of aromatic ring nitrated acetophenones drops to 11.4%.

Discussion and Conclusions

The surprisingly high amounts of o- and p-nitropivalophenones obtained upon nitration of the parent ketone have been correctly attributed to steric inhibition of aromatic ring deactivation by the bulky t-butyl group. However, if the nitration of pivalophenone is to be analyzed on a purely statistical basis, surely one would have to consider the possibility of ipso[16] attack followed by rearrangement[17] or by decarbonylation.[18]

If ipso attack is occurring, substitution of the pivaloyl group by a nitro group should produce nitrobenzene. However, no nitrobenzene was found even though 0.1% could have been detected easily. While the absence of decarbonylation does not prove the absence of ipso attack, one would imagine that the ipso carbon is sterically hindered by the t-butyl group on one side and a basic carbonyl oxygen atom on the other side. If ipso attack is being followed by rearrangement to ortho- or meta nitro ketones,[19] then the rearrangement step has occurred with an unusually high precision in the o- and m- percentages in more than 30 nitration runs. Since inverse addition of reactants had no effect on product composition, ipso attack followed by rearrangement seems unlikely.

The absolute rates of nitration of nitrobenzene by NO_2BF_4 in several solvents have been measured.[20] The second order rate constants varied from 0.1 to 1.1 M^{-1} min^{-1} as the solvent was changed from CH_3CN to H_2SO_4 to CH_3SO_3H. Consequently, the observation that NO_2BF_4 reacts exclusively with pivalophenone and not at all with nitrobenzene suggests that the rate of

nitration of pivalophenone with NO_2BF_4 in sulfolane must be at least a factor of 10^2 to 10^3 times greater than that for nitrobenzene.

The fact that pivalophenone is only 10 to 20 times less reactive than benzene towards NO_2^+ in sulfolane is in line with expectations for a weakly deactivating substituent.

Our attempts to study the nitration of acetophenone with NO_2BF_4 in sulfolane encountered side reactions which lead to products other than those of electrophilic aromatic substitution. The hydrogens in the methyl group of acetophenone may be undergoing electrophilic attack by NO_2^+ ion. Indeed Olah has reported the nitration of alkanes and cycloalkanes with stable nitronium salts.[21]. The literature contains two reviews of side reactions.[22,23]

In summary, it has been established that the reactivity sequence toward NO_2BF_4 in sulfolane is benzene > pivalophenone > acetophenone >> nitrobenzene.

Experimental

Materials. Nitronium Tetrafluoroborate (NO_2BF_4, Aldrich Chemical Co.) was washed twice with nitromethane and twice with methylene chloride in a 60 l dry box under a dry nitrogen atmosphere.

Sulfolane (500 ml of Aldrich tetrahydrothiophene -1,1-dioxide) was distilled in vacuo after stirring with CaH_2 for 1 h; bp 150-151°C; lit mp 28.37°C.[25] The sulfolane was found to be free of thiophene by UV analysis.[6b]

Pivalophenone (phenyl-t-butyl ketone) was prepared by the reaction of phenylmagnesium bromide with pivalonitrile (2,2-dimethylpropane-nitrile) in 78% yield.[26]

Reference samples of ortho-, meta-, para-nitropivalophenone were isolated from a nitric acid nitration on pivalophenone with separation of the isomers by flash column chromatography over silica gel (see below).[24]

Nitrobenzene ($C_6H_5NO_2$, Baker Reagent Grade) was distilled in vacuo; bp 130°C/8.5 mm.

Reference samples of ortho-, meta-, para-dinitrobenzene were recrystallized from 95% ethanol; m-$(NO_2)_2C_6H_4$ mp 90-90.5°C; lit[27] mp 90°C; o-$(NO_2)_2C_6H_4$ mp 118-119°C; lit mp 118.5°C.[27] Para-dinitro-benzene was prepared by the reaction[28] of p-nitro-benzenediazonium tetrafluoroborate (Eastman Kodak) with aqueous sodium nitrite and copper; p-$(NO_2)_2C_6H_4$ mp 173-174°C; lit mp 174°C.[27] The diazonium salt was washed with fluoboric acid, ethanol, and ether before use.

Acetophenone ($C_6H_5COCH_3$, Baker Reagent Grade) was distilled in vacuo; 73°C/7 mm.

Reference samples of meta-, and para-nitroacetophenone were recrystallized from 95% ethanol; m-$NO_2C_6H_4COCH_3$ mp 78.5-80°C; lit[27] mp 81°C;

p-$NO_2C_6H_4COCH_3$ mp 80-82°C; lit mp 80-82°C.[27] Ortho-nitroacetophenone was recrystallized from 33% diethyl ether/pet ether at -20°C; mp 26-27°C, lit[27] p 28°C.

Benzene (C_6H_6, Fischer Scientific, spectral analyzed) was distilled from calcium hydride before use; bp 80-80.3°C.

All materials were analyzed by gas chromatography for assessment of purity before use.

Infrared spectra were taken on a Perkin-Elmer model no. 1320 spectrophotometer. Proton NMR spectra were taken on a Varian T-60A instrument. Analytical gas chromatographic analyses were done on a Hewlett Packard 5880A instrument with an eight foot OV-101 glass column and with a hydrogen flame ionization detector. Isomer ratios and yields of the product mixtures were analyzed quantitatively by the internal and external standard methods on the gas chromatograph.[29] Preliminary and less accurate results were acquired by H^1NMR integration of the t-butyl peaks in the nitropivalophenones[1]. Melting points were taken with a Meltemp instrument.

Nitrations of Pivalophenone. In the fuming nitric acid nitrations, 10 g of pivalophenone (0.062 moles) was added dropwise with stirring, over 60 min, into 20 mL of fuming HNO_3 (d^{25} = 1.475 g/mL) while keeping the temperature between 0 and 8°. The temperature was allowed to rise to 25° and stirring continued for 90 min. The reaction was hydrolyzed with water and extracted with ether.

In the nitrations with nitronium tetrafluoroborate, NO_2BF_4 solutions of the specified concentrations (Table 2) were prepared under a dry nitrogen atmosphere. The solutions were then added dropwise into a stirred solution of pivalophenone of the specified concentrations (Table 2). For the inverse addition experiments, the aromatic solution was added into the NO_2BF_4 solution. After the specified reaction time, the solution was hydrolyzed on ice and the products were isolated.

Separation of Nitropivalophenones. Three grams of the product mixture from the fuming nitric acid nitration of pivalophenone was separated on 150 g of 230-400 mesh silica gel by flash chromatography. R_f values of 0.21 and 0.17 for the three isomers were achieved on test TLC plates with 20% ethyl acetate/pet ether. Fifteen-hundred mL of 20% ethyl acetate/pet ether was eluted and twenty-six 50 mL fractions were collected. After reapplying 4 unseparated fractions and reeluting, all three isomers were separated and deemed pure by GC analysis. The ortho isomer was isolated and distilled to give a yellow oil which froze upon cooling; mp 15-17°. The meta isomer was isolated and recrystallized from 95% ethanol at -20°; mp 45-46°; lit mp

45-46°.[1] The para isomer was recrystallized from pet ether at 0°; mp 63-64°; lit mp 62-64°.

Nitration of Nitrobenzene. In the nitration of nitrobenzene, 0.5 M solutions of NO_2BF_4 (0.014 mole) were prepared and added dropwise into a 1 M solution of nitrobenzene (0.012 mole) in sulfolane at 25°. After a one hour reaction time, the solution was hydrolyzed over ice and water, and the products were secured and anlyzed by vpc.

Protodenitration. Eight mL of 50% nitric acid in sulfuric acid mixture was added dropwise into 51 mg of the individual nitro-pivalophenone (0.249 mmole) at -20° over a 10 min period. The mixture was then allowed to warm to 0° and stirred for 60 min. The reaction mixture was hydrolyzed and the products were analyzed by vpc. The experiments were repeated with 20 and 22 h reaction times at 27° and dinitration was detected chromatographically.

Competitive Nitrations. In the competitive nitrations of nitrobenzene and pivalophenone, NO_2BF_4 solutions of the specified concentrations were prepared in the dry nitrogen atmosphere of a dry box. The total molar amount of the nitrating agent was less than the molar amount of either one of the aromatics present. The solution was added dropwise into the aromatic solution under a nitrogen atmosphere.

In the inverse nitration experiments, the aromatic mixture was added to the NO_2BF_4 solution in 17 and in 10 min. In the competitive nitrations of benzene vs. pivalophenone and of acetophenone vs. pivalophenone, 0.45 M (0.018 mole) solutions of NO_2BF_4 were prepared under a dry nitrogen atmosphere and were flushed, under 5 psi of dry nitrogen, into various concentrations of aromatic solutions with vigorous, motor driven, teflon-paddle stirring. The aromatic solutions included 1:1, 2:1, and 4:1 molar excess of pivalophenone over benzene in set one, and 2:1 and 4:1 molar excess of pivalophenone over acetophenone in set two. In both cases, the minor amount of aromatic (0.019 mole) was always present in 5.5% excess of the NO_2BF_4 present. The reaction mixtures were hydrolyzed after 30 min with 50 mL water and the homogeneous reaction mixtures were analyzed before and after product isolation. The reaction mixtures were extracted with ether (3 x 70 mL). The combined ether extracts were back washed with water to remove dissolved sulfolane and dried (Na_2SO_4).

Acknowledgements

The financial support of the Camille and Henry Dreyfus Foundation and the City University of New York, Faculty Research Award No. 6-65224 is greatly appreciated.

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