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ELECTROPHILIC SUBSTITUTION OF BENZENES WITH STRONG ELECTRON-WITHDRAWING GROUPS IN SUPER ACID MEDIA ; FRIEDEL-CRAFTS ALKYLATION OF ACETOPHENONE

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In the presence of HF-SbF_5 super acid, the alkylation of acetophenone with various alkyl chlorides was investigated. The products were found to be those of m-alkylated acetophenone derivatives and their related compounds in fairly good yields. The relative reactivity of alkyl chlorides was in the order of EtCl > n-, iso-PrCl, n-, s-BuCl>> iso-BuCl>> t-BuCl. The formation of olefinic, alcoholic, and condensation products observed in the reaction with propyl chlorides, and skeletal isomerization products obtained in the reaction with butyl chlorides was also discussed.

The presence of strong electron-attracting groups such as acyl, carboxyl, cyano, and nitro on aromatic nucleus greatly reduces the nucleophilicity of aromatic rings. Therefore, it is not surprising that no noteworthy examples were found in the literatures of electrophilic alkylation reactions, i.e., acid-catalyzed Friedel-Crafts alkylation of benzenes.[1,2] Hitherto, every acid system used as Friedel-Crafts catalyst appears to be unable to activate alkylating agents such as alkyl halides in the electrophilic alkylation of aromatic nucleus bearing strong electron-withdrawing groups.

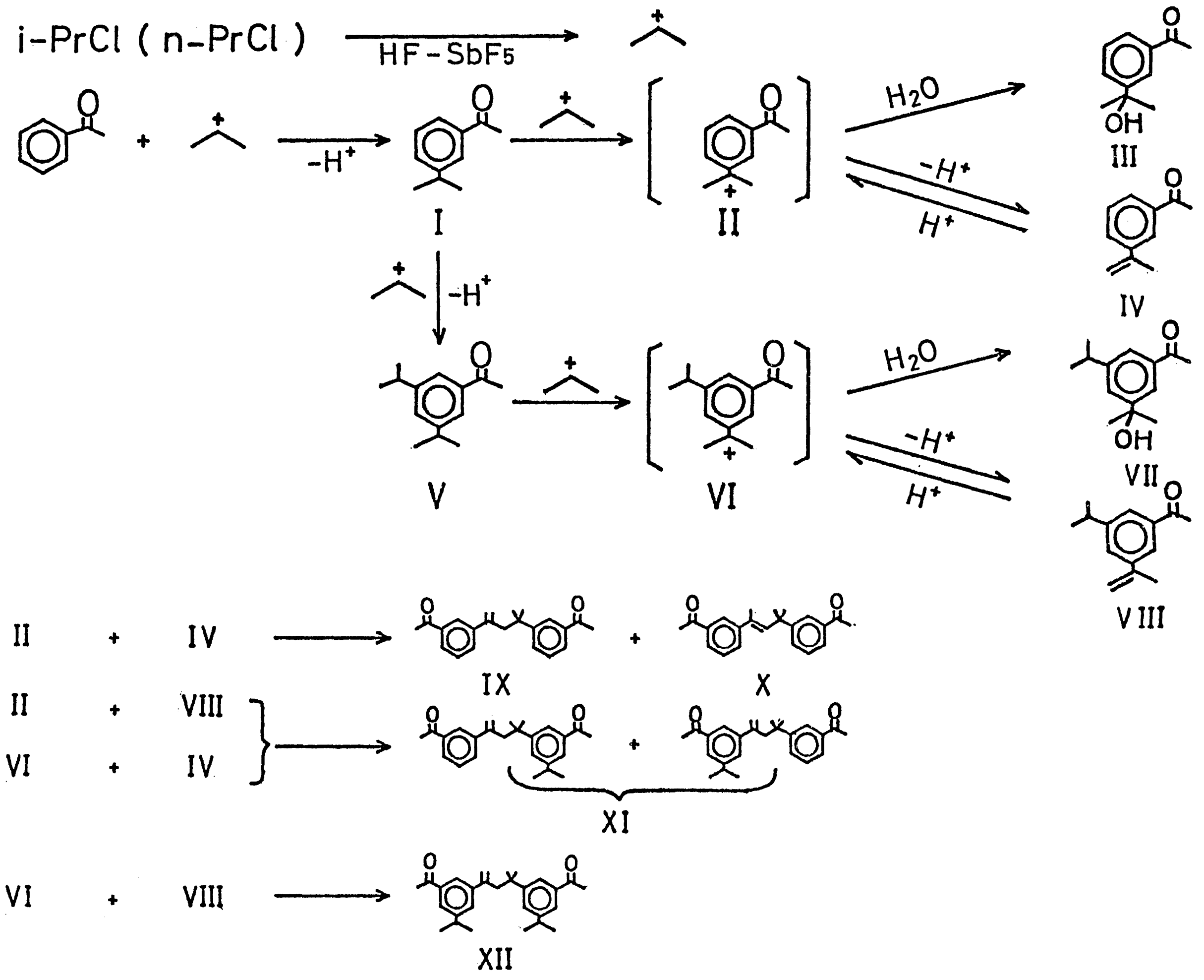
On the other hand, the discovery and development of super acid systems consisting of strong acids and weakly nucleophilic solvents such as HF-SbF_5, FSO_3H-SbF_5-SO_2ClF or SbF_5-SO_2ClF have made it possible to give long life stable alkyl cations from corresponding alkyl halides.[3] These cations are considered to be powerful electrophiles for such inactive benzenes.

We wish to report here the electrophilic alkylation of acetophenone with alkyl halides in HF-SbF_5 super acid. A solution of the substrate dissolved in the super acid media was placed into a two-necked 100-ml Kel-F reaction vessel. An appropriate alkyl halide was then added dropwise into the reaction mixture under sufficient stirring at desired temperatures and duration. The products obtained by working-up in the usual manner were identified by spectroscopic methods. Some of the experimental results are listed in the table.

The products were found to be those of m-alkylated acetophenone derivatives and related compounds in good yields. It is well known that Friedel-Crafts alkylation generally occurs most readily with tertiary, more readily with secondary and least readily with primary alkyl halides.[4] However, judging from the yields of alkylated products, the present alkylation was found to take place in the following order: ethyl chloride > n-, and i-propyl, n-, and s-butyl chlorides >> isobutyl chloride >> t-butyl chloride. The observed reactivity order of alkyl chlorides is consistent with the expected order of electrophilicity of alkyl cations derived from the corresponding alkyl halides, except for isobutyl chloride.

Another interesting result is the structure of alkylates. In the case of ethyl chloride, alkylated products are those having well expected structures. On the contrary, propyl chloride and isopropyl chloride gave considerable amounts of olefinic, alcoholic, and condensed products together with the usual Friedel-Crafts products.

The formation of these products may be accounted by the reaction routes shown in Scheme 1.

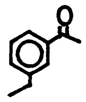
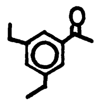
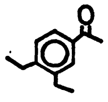
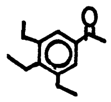
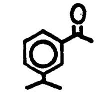
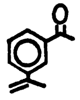
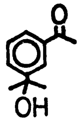
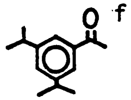
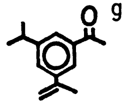
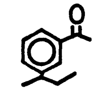
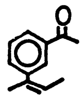
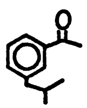
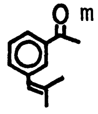
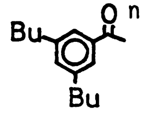
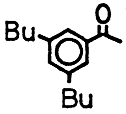
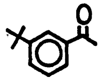


Scheme 1

A tertiary C-H bond of the isopropyl group in the initially alkylated products (I or V) can be expected to easily remove as a hydride ion by attack of electrophiles such as isopropyl cation.5) Such a hydride transfer reaction would give the carbenium ions represented as II or VI, which may be considered to be the key intermediate for the formation of III, IV, VII, VIII and IX-XII. These cations can be in an equilibrium with isopropenyl benzene derivatives, or would subsequently react with water to give alcoholic products during the working-up of the reaction mixture. Furthermore, these cations and olefinic products combine together to give condensed products (IX-XII).

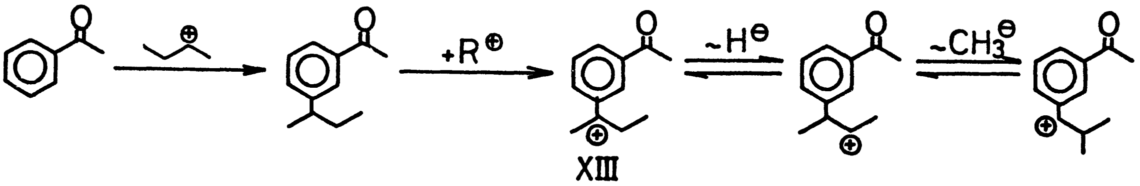
Secondary butyl cations derived from 1- and 2-butyl chlorides react with acetophenoen to give

Reaction of Acetophenone with Alkyl Chloride in HF-SbF_5 Super Acid

RCl	React. Condts.[a]		Yield[b] (%)	Product distribution (%)[c]						
	Temp. °C	Time min								
										
EtCl	0	2	~100	78	14	4	4			
					 [d]	 [e]	 [f]	 [g]	(IX[h]+X[i])[p]	XI[j]
n-PrCl	0	2	57	45	20	6	1	5	16	7
i-PrCl	0	2	55	50	19	4	1	3	16	7
					 [k]	 [l]	 [m]	 [n]	 [o]	
n-BuCl	-20	5	55	15	3	55	7	6	14	
s-BuCl	-20	5	58	17	some	57	7	7	12	
i-BuCl	-20	5	5	21	9	67	3	–	–	
										
t-BuCl	0	60	3		~100					

a) Acetophenone 9 mmol, RCl 3 mmol, SbF_5 20-25 mmol, HF 135-180 mmol. b) Based on RCl. c) Products shown in the Table include those more than 95-98% of all products. d) MS (m/e): 160 (M^+), 160, 145, 115, 28. IR (neat, cm^{-1}): 1690, 1635, 1605, 1585, 900, 800, 695. NMR (CCl_4, ppm, Ho=90 MHz): 2.19 (s, 3H), 2.52 (s, 3H), 5.12-5.4 (m, 2H), 7.29-8.0 (m, 4H). e) MS (m/e): 178 (M^+), 163, 160, 145, 115, 43, 28. IR (neat, cm^{-1}): 3600-3200, 1690, 1604, 1590, 800, 698. NMR (CCl_4, ppm, Ho=90 MHz): 1.55 (s, 6H), 2.53 (s, 3H), 7.35-8.1 (m, 4H). f) MS (m/e): 204 (M^+), 189, 43. IR (neat, cm^{-1}): 1695, 1608, 880, 700. NMR (CCl_4, ppm, Ho=90 MHz): 1.28 (d, 12H), 2.5 (s, 3H), 2.93 (m, 2H), 7.15-7.52 (m, 3H). g) MS (m/e): 202 (M^+), 197, 160, 145, 28. IR (neat, cm^{-1}): 1695, 1640, 1605, 880, 695. NMR (CCl_4, ppm, Ho=90 MHz): 1.29 (d, 6H), 2.19 (s, 3H), 2.52 (s, 3H), 2.95 (m, 1H), 5.12-5.38 (m, 2H), 7.42-7.78 (m, 3H). h) MS (m/e): 320 (M^+), 161, 43, 28. IR (neat, cm^{-1}): 1690, 1640, 1605, 1585, 900, 800, 695. NMR (CCl_4, ppm, Ho=90 MHz): 1.35 (s, 6H), 2.4 (s, 3H), 2.45 (s, 3H), 2.9 (s, 2H), 4.95-5.15 (m, 2H), 7.1-7.8 (m, 8H). i) NMR (CCl_4, ppm, Ho=90 MHz): 1.36 (s, 6H), 2.09 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 5.9 (m, 1H), 7.2-7.8 (m, 8H). j) MS (m/e): 362 (M^+), 161, 43, 28. NMR (CCl4, ppm, Ho=90 MHz): 1.15-1.20 (2d, 6H), 1.33 (s, 6H), 2.42 (2s, 6H), 2.89 (m, 2H), 4.97-5.15 (m, 2H), 7.02-7.78 (m, 7H). k) NMR (CCl4, ppm, Ho=90 MHz): 1.85 (d, 3H), 2.1 (s, 3H), 2.51 (s, 3H), 5.9-6.3 (m, 1H), 7.2-7.8 (m, 4H). l) NMR (CCl_4, ppm, Ho=90 MHz): 0.94 (d, 6H), 1.9 (m, 1H), 2.51 (s, 3H), 2.55 (m, 2H), 7.1-7.8 (m, 4H). m) NMR (CCl4, ppm, Ho=90 MHz): 1.90 (d, 6H), 2.52 (s, 3H), 6.3 (m, 1H), 7.3-7.8 (m, 4H). n) NMR (CCl_4, ppm, Ho=90 MHz): 0.94-1.25 (m, 12H), 2.48 (m, 2H), 2.51 (s, 3H), 7.05-7.85 (m, 3H). o) NMR (CCl4, ppm, Ho=90 MHz): 0.98-1.27 (m, 6H), 1.90 (m, 7H), 2.51 (m, 2H), 2.53 (s, 3H), 6.3 (m, 1H), 7.05-7.85 (m, 3H). p) IX>>X.

m-*s*-butylacetophenone derivatives together with *m*-isobutylacetophenone derivatives as major products.[6)] The rearrangement of *s*-butylbenzene to isobutylbenzene by aluminum chloride is known at temperatures above 50°.[7)] In the present reaction, however, the formation of considerable amounts of isobutyl derivatives was observed even at -20°. This result suggests that hydride transfer reaction between the initiallyformed *m*-*s*-butylacetophenone and alkyl cation may be readily take place under such super acidic conditions to give the cation (XIII) which in turn rearranges into isobutyl derivatives as shown in Scheme 2.



Scheme 2

An evidence to support the above reaction route was obtained as follows: treatment of *p*-*s*-butylacetophenone with a catalytic amount of isopropyl chloride in HF-SbF$_5$ at -20°C for 10 min. resulted in an almost complete conversion to *p*-isobutylacetophenone and its derivatives, while no reaction was observed without any addition of isopropyl chloride under the same conditions.

On the other hand, isobutyl chloride gave a poor yield of alkylated products under such conditions. Furthermore, it was found that *t*-butyl chloride hardly reacts with acetophenone to give the corresponding alkylates. This results suggests that an electropositive charge appearing in *t*-butyl cation seems to be not strong enough to attack the aromatic nucleus. Thus, isobutyl cation derived from isobutyl chloride can be considered to rearrange so rapidly to a more stable but rather weak electrophile, i.e., tert-butyl cation, leading the result that no substantial amount of alkylated products can be yielded under the conditions.

Scope and limitation of the electrophilic substitution of benzenes with strong electron-withdrawing groups, other than acetyl group, are under investigation.

References and Notes

1) N. Yoneda, Y. Takahashi, A. Suzuki, Chem. Lett., 231 (1978).
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b) R. Oda, J. Synthetic Organic Chem., Japan, 36, 467 (1978).
3) G. A. Olah, "Carbocation and Electrophilic Reactions", Verlag Chemie, Wiley (1973).
4) G. A. Olah ed., "Friedel-Crafts and Related Reactions", Vol. II p 428 (1964).
5) The formation of propane was observed.
6) Condensed products such as IX-XII obtained in the reaction of PrCl were not detected in this case.
7) R. M. Roberts, Intra-Science Chem. Rept., 6, 89 (1972).

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