Alkyl Exchange Reactions in Trifluoroacetic Acid. t-Butyl Trifluoroacetate, an Efficient Alkylation Agent for Aromatic Compounds

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Activated aromatic compounds are rapidly alkylated by t-butyl trifluoroacetate in trifluoroacetic acid. The reaction proceeds in quantitative yield and is conveniently carried out by mixing the reagents at room temperature and evaporating the solvent after a few hours. The reaction is accelerated by strong acids, and in the presence of the latter *ortho*-substituted anisoles rearrange to the *para*-isomers. Debutylation of *ortho*-t-butylphenols occurs readily at room temperature in neat trifluoroacetic acid. A kinetic isotope effect, k_H/k_D = 5·5, was found for the dealkylation of 2,4,6-tri-t-butylphenol. No dealkylation of the corresponding anisole was observed under comparable conditions and a mechanism for the debutylation is proposed which involves ketonisation to give the cyclohexa-2,4-dienone.

In strongly acidic media, t-butylation and debutylation of aromatic compounds proceed readily.[1] These reactions, as well as migrations[2,3] of t-butyl groups are believed to take place with the intermediate formation of the t-butyl cation. Thus, the mechanism of debutylation of an aromatic compound in strong acid involves an initial protonation of the ring followed by the loss of the t-butyl cation. During our investigation[4] of the protonation behaviour of phenols and alkyl aryl ethers in acidic media, we observed the rapid rearrangement of 2,6-di-t-butylphenol (2,6-DBP) in trifluoroacetic acid (TFA) at room temperature. Recent studies have shown that neat TFA is not sufficiently acidic to protonate even water.[5] In view of the latter fact, the very ready alkylation–dealkylation reaction was surprising. The observation suggested that the weakly acidic nature of the medium might be of value in carrying out alkylation and dealkylation of compounds which cannot survive the strongly acidic conditions under which such reactions are normally conducted. The results of t-butylation and debutylation of a number of aromatic compounds in TFA are summarised here.

EXPERIMENTAL

Reagents.—Trifluoroacetic acid, sulphuric acid, methanesulphonic acid, and t-butyl alcohol were all of commercial reagent grade and used without further purification. Substrates for the alkylation reactions as well as the t-butylphenols were either of commercial reagent grade or prepared by published procedures.

Spectra.—The ^{1}H n.m.r. spectra were recorded at 60 MHz on a Varian A-60A spectrometer equipped with a variable temperature controller (V6040). The i.r. spectra were recorded on a Perkin-Elmer 337 Grating Infrared Spectrometer.

Alkylation Reactions.—The alkylation reactions were carried out at room temperature usually with 10% solutions of equimolar amounts of substrate and t-butyl alcohol in TFA. The reactions were followed by ^{1}H n.m.r. spectral changes, and when they were complete the solvent was removed under reduced pressure. Products of high purity were obtained directly. When strong acid catalyst was used, the crude product was dissolved in dichloromethane and washed first with water and then with saturated sodium hydrogen carbonate solution. The products were obtained after drying ($MgSO_4$) and evaporation. A typical example is the t-butylation of phenol.

t-Butylation of phenol. Phenol (376 mg, 4·0 mmol) and t-butyl alcohol (300 mg, 4·05 mmol) were dissolved in TFA (5·0 ml) at room temperature; after 2 h the ^{1}H n.m.r. spectrum of the solution showed the presence of a single compound: τ 2·96 (AA'BB' pattern) and 8·71 (s, Bu^t). Removal of the TFA under an aspirator at 30° left a white crystalline compound (650 mg, 98%) the ^{1}H n.m.r., i.r., and mass spectra of which were identical with those of authentic 4-t-butylphenol.

Debutylation Products.—All products were isolated and characterised by i.r. and ^{1}H n.m.r. spectra.

Kinetic Measurements.—The substrate (50 mg) was placed in an n.m.r. tube which was equilibrated in a bath at the temperature of the kinetic run. TFA (0·5 ml) was pipetted from a container also kept in the bath, and added to the substrate. Immediately after mixing, the tube was placed in the spectrometer probe and measurements were started. Pseudo-first-order rate constants were determined graphically from changes in the intensity of the signals from the t-butyl (product and t-butyl trifluoroacetate) protons. Good straight line plots were obtained for at least one half-life. Curvature was observed at longer times ($t > t_{\frac{1}{2}}$) due to the reversibility of the reactions. The following example illustrates the procedure.

Debutylation of 2,4,6-tri-t-butylphenol to 2,4-di-t-butylphenol at 0°. The initial concentration of substrate was expressed as I_p (the intensity of the signal due to the *p*-butyl protons), and the concentration at time t as $I_p - I_{ac}$ (where I_{ac} is the intensity of the signal from the t-butyl protons of t-butyl trifluoroacetate). The rate constant was then obtained from the slope of a plot of $I_p/(I_p - I_{ac})$ *versus* $t/2{\cdot}303$. Rate constants are summarised in Table 4.

RESULTS

Behaviour of t-Butyl Alcohol in TFA.—When t-butyl alcohol and TFA were rapidly mixed at room temperature and the ^{1}H n.m.r. spectrum was measured immediately, a small signal at τ 8·62 due to the t-butyl groups of the alcohol was observed. This signal rapidly disappeared leaving only the signal at τ 8·40 due to the t-butyl groups of the ester. At 0° the conversion of alcohol into ester was much

[1] For a general review, see 'Friedel-Crafts and Related Reactions,' ed. G. A. Olah, Wiley, New York, 1964, vol. II, part 1.

[2] G. A. Olah, M. W. Meyer, and N. A. Overchuk, *J. Org. Chem.*, 1964, **29**, 2310.

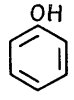
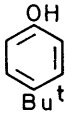
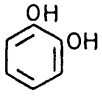
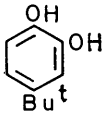
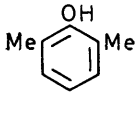
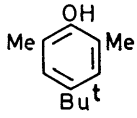
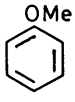
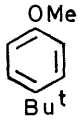
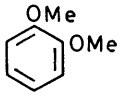
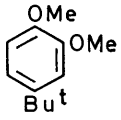
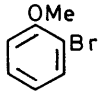
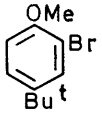
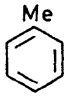
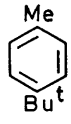
[3] G. A. Olah, C. G. Carlson, and J. C. Lapierre, *J. Org. Chem.*, 1964, **29**, 2687.

[4] U. Svanholm and V. D. Parker, *J.C.S. Perkin II*, 1972, 962.

[5] M. J. Harris and J. B. Milne, *Canad. J. Chem.*, 1971, **49**, 3612.

TABLE 1

Products of t-butylation reactions in trifluoroacetic acid

Substrate	Product	^{1}H N.m.r. data [a]	Isolated yields (%) [b,c]
		1·27 (9H), 4·83 (1H) 6·45 (2H, d), 7·4 (2H, d), *J* 8·5	79
		1·15 (9H), 5·88 (2H), 6·75 (3H, m)	68
		1·27 (9H), 2·22 (6H), 4·18 (1H), 6·93 (2H)	86
		1·28 (9H), 3·73 (3H), 6·53 (2H, d), 7·47 (2H, d), *J* 9·0	68
		1·28 (9H), 3·8 (3H), 3·83 (3H), 6·83 (3H, m)	70
		1·27 (9H), 3·82 (3H), 6·75 (d, *J* 8·5), 7·48 (d, *J* 2), 7·22 (dd, *J* 8·5 and 2)	80
		1·28 (9H), 2·28 (3H), 6·97 (2H, d), 7·3 (2H, d), *J* 8·5	59

[a] Measured in $CDCl_3$ at 60 MHz; δ in p.p.m. relative to internal Me_4Si; *J* in Hz; singlet signals unless otherwise indicated. [b] Substrate (500 mg) and t-butyl alcohol (500 μl) in TFA (5 ml) containing conc. H_2SO_4 (100 μl). [c] In the absence of added acid catalyst, n.m.r. analysis of reaction mixtures indicated essentially quantitative conversion of the substrates into the corresponding t-butyl derivatives, and isolation gave greater than 90% yield in all cases. In some cases the reaction was inconveniently slow, *i.e.* reaction was not complete in 5 days with toluene in TFA at room temperature.

slower, requiring about 45 min for complete reaction. Nearly identical spectra were observed in [^{2}H]TFA, indicating that exchange of hydrogen with deuterium in the t-butyl groups does not occur.

Alkylation Reactions.—Aromatic compounds react with t-butyl trifluoroacetate in TFA at rates depending on the degree of activation by electron-donating substituents. In the absence of added catalyst, the reaction with benzene is almost immeasurably slow, whereas those with anisole and phenol are very rapid. Products of t-butylation of aromatic compounds in TFA are summarised in Table 1. The effect of added acids on the *para*/*ortho* product ratio is given in Table 2. Table 3 is a summary of the extent of reaction at 25° after 5 min in TFA containing sulphuric acid ($9·4 \times 10^{-2}$ M) as a function of substitution on phenols and anisoles.

Dealkylation of t-Butylphenols.—2,6-DBP rapidly and quantitatively rearranged to 2,4-DBP upon dissolution in TFA at room temperature. The progress of the reaction was followed by ^{1}H n.m.r. spectral changes in the aromatic and t-butyl regions (2,6-DBP showed a single signal at δ 1·43 p.p.m. whereas signals of equal intensity at δ 1·3 and 1·43 p.p.m. were observed for the t-butyl protons of 2,4-DBP). No change was observed in the spectrum of 4-t-butylphenol in TFA over several days. On dissolution of 2,4,6-tri-t-butyl phenol (TBP) in TFA, the first species observed were 2,6-DBP and t-butyl trifluoroacetate. As before, 2,6-DBP rearranged to 2,4-DBP. 2,6-Di-t-butyl-*p*-cresol (2,6-DBC) was rapidly converted into 2-t-butyl-*p*-cresol (2-BC) upon dissolution in TFA at room temperature.

Rates of Debutylation.—First-order rate constants for dialkylation of the t-butylphenols are summarised in Table 4. The loss of the first t-butyl group from TBP was too rapid to be followed at room temperature. At 0° TBP was dealkylated fifty times faster than 2,4-DBP in TFA. The reaction of TBP in [^{2}H]TFA at 0° was slower by a factor of 5·5. The rate of loss of the *ortho*-t-butyl group of 2,4-DBP and 2-BC was followed at 40° in TFA, with the former reacting 1·75 times faster than the latter. A deuterium kinetic isotope effect of 5·5 was also observed for the reaction of 2,4-DBP.

2,4,6-*Tri-t-butylanisole in TFA.*—No change was observed in the ^{1}H n.m.r. spectrum of 2,4,6-TBA in TFA over several days.

Deuterium–Hydrogen Exchange in [^{2}H]TFA.—Products obtained from dealkylation of the t-butylphenols in [^{2}H]TFA contained deuterium in the positions vacated by the t-butyl groups. Slow exchange of the *ortho* and *para*-hydrogen atoms of phenol and the *ortho*-hydrogen atoms of

TABLE 2

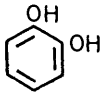
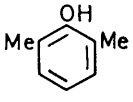
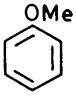
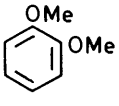
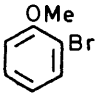
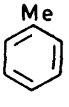
Effect of acid catalysis on the t-butylation of anisole in trifluoroacetic acid *

	No catalyst		H_2SO_4 ($1·9 \times 10^{-2}$ M)		H_2SO_4 ($3·8 \times 10^{-2}$ M)		H_2SO_4 ($7·5 \times 10^{-2}$ M)		$MeSO_3H$ ($6·2 \times 10^{-2}$ M)	
Time (min)	*p*/*o*	conv. (%)	*p*/*o*	conv. (%)	*p*/*o*	conv. (%)	*p*/*o*	conv. (%)	*p*/*o*	conv. (%)
5	2·07	10·5	1·79	41·5	2·57	55·3	2·94	68·6	2·17	56·1
10	2·0	19·0	2·39	63·9	4·16	73·6	5·49	85·7	3·52	76·1
15	2·14	28·3	3·40	75·7	5·95	86·0	7·71	95·0	4·85	87·7
20	2·22	36·0	4·43	82·0	7·41	89·9	9·22	96·4	6·02	94·1
25	2·26	42·9	5·32	87·4	8·29	93·5	10·54	99·2	7·21	97·0
30	2·33	48·8	6·27	91·4	9·39	95·8	11·81	100	8·43	98·6
1 day	6·32	*ca.* 100								

* Runs carried out in the n.m.r. probe at 36°. Anisole (50 μl) was dissolved in TFA (500 μl) containing t-butyl alcohol (50 μl) and in some cases conc. acid. The *para*/*ortho* ratio (*p*/*o*) was determined from the intensity of the t-butyl signals at δ 1·3 and 1·42 p.p.m., respectively. The % conversion was determined by comparison of the spectra with that of the same solution left at room temperature for several hours.

TABLE 3

t-Butylation reactivity of aromatic compounds in TFA

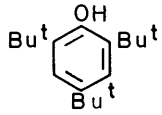
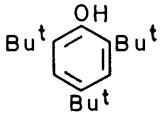
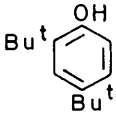
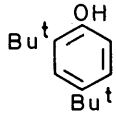
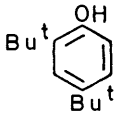
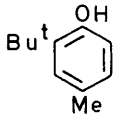
Compound	$\Sigma\sigma$ [a]	$\Sigma\sigma^+$ [a]	% Conversion [b]
	−0·36	−0·92	62·9
	−0·36		61·6
	−0·50		74
	−0·27	−0·76	65·7
	−0·15	−0·71	28·6
	+0·12	−0·37	12·4
	−0·17	−0·31	22·6
			6·6

[a] Substituent constants summed for the position of substitution. [b] Measured after 5·0 min at 36°; substrate (50 mg) in TFA (500 μl) containing t-butyl alcohol (50 μl) and sulphuric acid ($9·4 \times 10^{-2}$M).

seen by comparing the results in Table 1 with those in Table 5 taken from an exhaustive compilation of data on alkylation with alcohols.[6] In general, the yields reported for t-butylation of phenol, anisole, and related

TABLE 4

Rate constants for debutylation of phenols in trifluoroacetic acid *

Compound	T/°C	Solvent	10^2k/min^{-1}
	0	TFA	2·3
	0	[^{2}H]TFA	0·42
	0	TFA	0·046
	40	TFA	1·6
	40	[^{2}H]TFA	0·29
	40	TFA	0·92

* First-order rate constants were determined from the decrease in intensity of the appropriate t-butyl ^{1}H n.m.r. signal and are the average of at least five runs except in the deuteriated solvent in which duplicate runs were carried out. All kinetic runs were carried out in the probe of the spectrometer and the temperature was controlled to within ±1°.

TABLE 5

Strong acid catalysed alkylation reactions of phenol and related compounds [a]

Substrate	Alcohol	Catalyst	Temp. (°C)	Time (h)	Yield (%) of 4-subst.	Ref.
Phenol	t-Butyl	70% $HClO_4$	60	0·15—20	5—48	*b*
Phenol	t-Pentyl	$ZnCl_2$ (2 mol. equiv.)	180		65	*c*
Phenol	t-Pentyl	$AlCl_3$ (0·5 mol. equiv.)	25—30	3—4	45—60	*d*
Anisole	t-Butyl	$TiCl_4$ (0·25—1 mol. equiv.)	1—40	10—40	53—67	*e*
o-Cresol	t-Butyl	100% H_3PO_4	60—65	8	63·4	*f*

[a] A. Schriesheim, ch. XVIII in ref. 1. [b] C. A. Sears, jun., *J. Org. Chem.*, 1948, **13**, 120. [c] B. Fischer and B. Grutzner, *Ber.*, 1893, **26**, 1646. [d] R. C. Huston and T. J. Hsieh, *J. Amer. Chem. Soc.*, 1936, **58**, 439. [e] N. M. Cullinane and D. M. Leyshan, *J. Chem. Soc.*, 1957, 2952. [f] H. Hart and E. A. Haglund, *J. Org. Chem.*, 1956, **15**, 396.

p-cresol with deuterium was observed during measurements of the ^{1}H n.m.r. spectra in [^{2}H]TFA at room temperature over 2 days. Under comparable conditions, no exchange was observed for anisole.

DISCUSSION

The advantage of using TFA as medium and catalyst for the t-butylation of aromatic compounds is readily compounds in the presence of t-butyl alcohol and strong acid catalyst are 60% or lower and in many cases require elevated temperatures and large amounts of catalyst. The yields in TFA are nearly quantitative and the reactions require short times at room temperature.

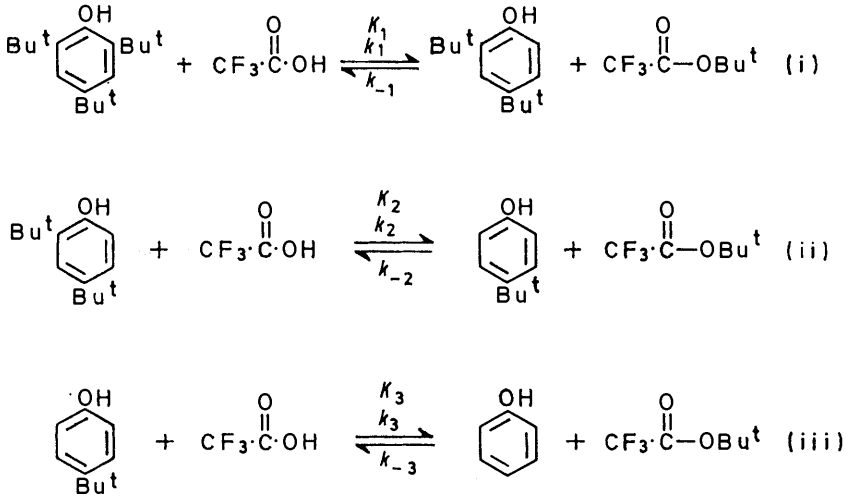
[6] H. C. Brown, D. Gintis, and L. Domash, *J. Amer. Chem. Soc.*, 1956, **78**, 5387.

These features, along with the ease of product isolation, make TFA the medium of choice for t-butylation.

Strong acids, sulphuric and methanesulphonic in this work, greatly accelerate t-butylation reactions in TFA. The latter effect is shown in Table 2 in which conversion of anisole is tabulated as a function of nature and concentration of catalyst. While only 10% conversion was observed after 5 min without catalyst, 40—70% was observed in the presence of strong acid. The *p*/*o* ratio is nearly independent of time in the absence but markedly increases with time in the presence of catalyst. The latter indicates that isomerisation (*ortho* to *para*) of t-butylanisoles in TFA is a ready reaction only if a low concentration, after the solution was refluxed for some time. This indicates that K_3 is larger at higher temperature.

The driving force for debutylation is presumably relief of steric strain; for example, the strain energy in *o*-t-butyltoluene has been estimated to be *ca.* 4—6 kcal mol^{-1}.[6] The fact that k_1 is about fifty times greater than k_2 suggests, as expected, that 2,4-DBP is considerably less strained than 2,4,6-TBP since the hydroxy-group in the former is free to rotate away from the bulky *ortho*-t-butyl group.

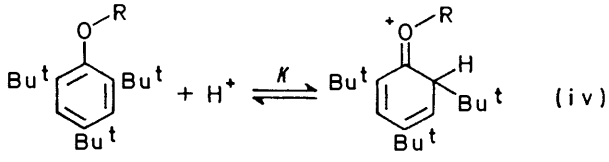
The first step in relieving the strain could be *C*-protonation [equation (iv)]; this being the case one



catalyst is present. Thus, true isomer ratios are obtainable in the absence of catalyst.

Relative rates of t-butylation of several aromatic compounds in TFA are summarised in Table 3. The relative reactivity is that expected for an electrophilic substitution reaction. Although a detailed mechanistic study was not carried out, it appears clear that the mechanism of t-butylation in TFA involves electrophilic attack on the aromatic substrate, probably by a protonated form of t-butyl trifluoroacetate, although dissociation to the t-butyl cation could precede reaction with the substrate.

Debutylation of t-Butylphenols.—Dealkylation of 2,4,6-TBP takes place stepwise, with each subsequent step becoming less favourable. The processes that occur may be summed up by the three equilibria in equations (i)—(iii). Of the three equilibrium constants, only K_2 is readily measurable and was found to be 0·04 at 36°. The first equilibrium (i) lies far to the right, no 2,4,6-TBF being detectable from the ^{1}H n.m.r. spectrum of the solution shortly after mixing at room temperature. Further reaction of 2,4-DBP precludes the existence of an equilibrium mixture containing 2,4,6-TBP and 2,4-DBP. On the other hand, K_3 is very small; no t-butyl trifluoroacetate was detected in a solution of 4-BP in TFA at 36°. The equilibrium does indeed exist, since the ester was readily detected, although in would expect that 2,4,6-tri-t-butylanisole (2,4,6-TBA) should be even more reactive than 2,4,6-TBP, since the

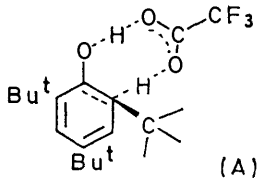


anisole is more basic and more steric relief would be gained when R = Me [equation (iv)]. However, 2,4,6-TBA is stable in TFA; no dealkylation was observed even after several days at room temperature. Furthermore, an equilibrium such as equation (iv) preceding rate-determining elimination of the t-butyl group would predict a solvent kinetic isotope effect of less than 1·0, since equilibrium (iv) would lie further to the right in the deuteriated solvent.[7] Thus, the large value of k_H/k_D (5·5) implicates the breaking of an O–H(D) bond in the rate-determining step.

The failure of the ether (TBA) to undergo debutylation in TFA under the conditions where the corresponding phenol (TBP) reacts rapidly, suggests that ketonisation is a crucial step in the reaction. Thus, it appears either that ketonisation is rate-determining or

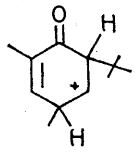
[7] P. M. Laughton and R. E. Robertson, in ' Solute-Solvent Interactions,' eds. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, New York, 1969, ch. 7.

that rapid ketonisation is followed by rate-determining protonation. The deuterium kinetic isotope effect requires that simple protonation is not the rate-determining step, since, as already pointed out, equilibria



(A)

such as (iv) would lie further to the right in the deuteriated acid. Transition state (A) does account for the results, *i.e.* failure of TBA to react and the large isotope effect. The essential feature of this mechanism is that hydrogen bonding between the phenol and TFA gives rise to a favourable geometry for concerted ketonisation. The anisole could not react by this mechanism. The kinetic isotope effect then is that expected for catalysis by a weak acid.* In an alternative mechanism, ketonisation is not rate-determining but rather, rate-determining



(B)

protonation occurs after rapid ketonisation to give species (B) which is then debutylated.†

[2/2207 *Received*, 21*st September*, 1972]

* A pertinent example is the transfer of a proton from acetic acid to the enolate ion of methylacetylacetone.[8]

† The latter mechanism was suggested by a referee. In the opinion of the authors, the magnitude of the kinetic isotope effect ($k_H/k_D = 5{\cdot}5$) is too great for the latter mechanism. In a related case, the *ortho*-Claisen rearrangement of allyl phenyl ethers in TFA,[9] a much smaller deuterium kinetic isotope effect ($k_H/k_D = 1{\cdot}4$) was observed.[10]

[8] F. A. Long and D. Watson, *J. Chem. Soc.*, 1958, 2019.
[9] U. Svanholm and V. D. Parker, *J.C.S. Chem. Comm.*, 1972, 645.
[10] U. Svanholm and V. D. Parker, submitted for publication.