The Peculiar Behaviour of the Trifluoromethyl Substituent in $S_{RN}1$ Processes

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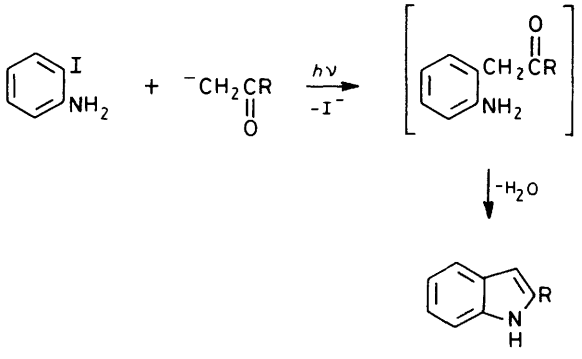
Reaction of the enolate of 3,3-dimethylbutan-2-one with α,α,α-trifluoro-*o*-iodotoluene in a $S_{RN}1$ process does not yield the expected substitution product, but a more complex molecule deriving from it. An accurate n.m.r. analysis of the products, along with other evidence, indicates a mechanism for this rearrangement, where an interaction of the trifluoromethyl group with the adjacent enolate moiety occurs, once the 'normal' $S_{RN}1$ substitution product has formed. The peculiar effect of the CF_3 substituent is not only confined to the *ortho* position. Even α,α,α-trifluoro-*p*-iodotoluene shows unusual behaviour and affords a rearranged product. A mechanistic explanation is offered, where some of the key steps are similar to those involved in the case of the *ortho* isomer.

The outcome of the $S_{RN}1$ nucleophilic substitution, carried out on aryl halides,[1] may be significantly influenced by the presence in the substrate of substituents *ortho* to the nucleofugal group.[2] Two main cases of ensuing behaviour have been documented. First, in the presence of an *ortho*-halogen[3] or an *ortho*-nitro[4] group, the reactivity of the substrate as such, or even the nature of the process, may be modified. Second, owing to the favourable *ortho* array, the substituent can react with a functional group (such as a carbonyl group) introduced in the substitution step. A spontaneous cyclization can then occur with substituents such as NH_2, CH_2NHR, or CONHR (Scheme 1). Access to a variety of heterocyclic systems is thus provided.[5,6]



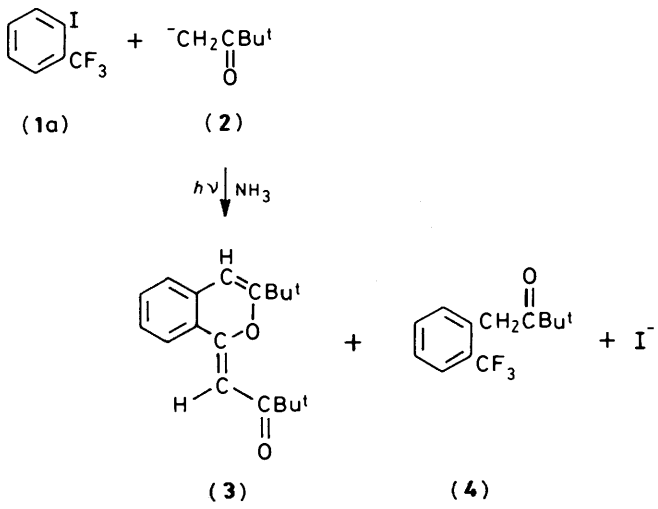
Scheme 1.

We now report on the special behaviour observed with the CF_3 substituent, which shows some analogy to the second case. It transpires, however, that this singularity of behaviour is not confined to the *ortho* position.

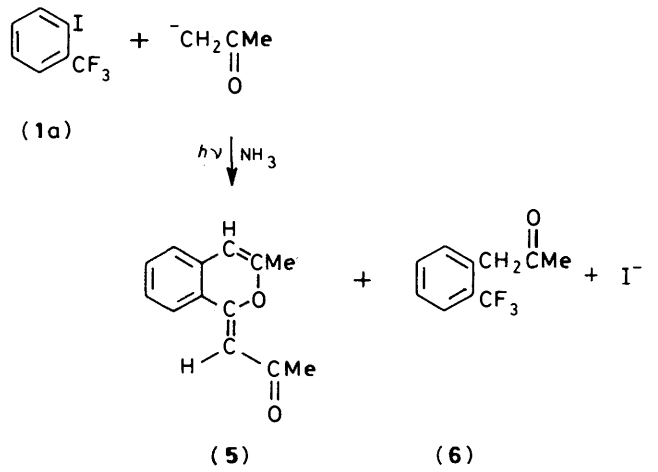
Results and Discussion

Treatment of α,α,α-trifluoro-*o*-iodotoluene (**1a**) with the enolate of 3,3-dimethylbutan-2-one (**2**) in liquid ammonia under standard photosensitisation conditions[1,2] afforded mainly (**3**) (43%) and only a minor amount (8%) of the expected substitution product (**4**) (Scheme 2). The formation of (**3**) was intriguing. However, we could confirm the finding since reaction of (**1a**) with the enolate of acetone afforded similarly, (**5**) (18%) along with (**6**) (12%) (Scheme 3).

Apparently, the CF_3 group was not stable under the reaction

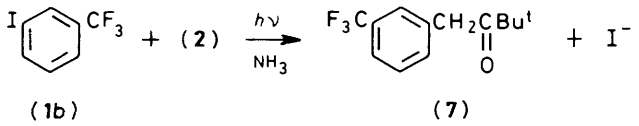


Scheme 2.



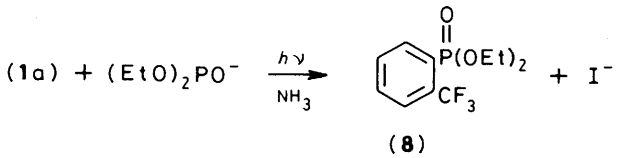
Scheme 3.

conditions but strangely enough this instability did not show up in two subsequent experiments. In the first, reaction of the *meta*-isomer (**1b**) with the enolate gave only the expected $S_{RN}1$ substitution product (**7**); (40%) (Scheme 4).[7] In the second, reaction of (**1a**) with another nucleophile, *i.e.* $(EtO)_2PO^-$,



Scheme 4.

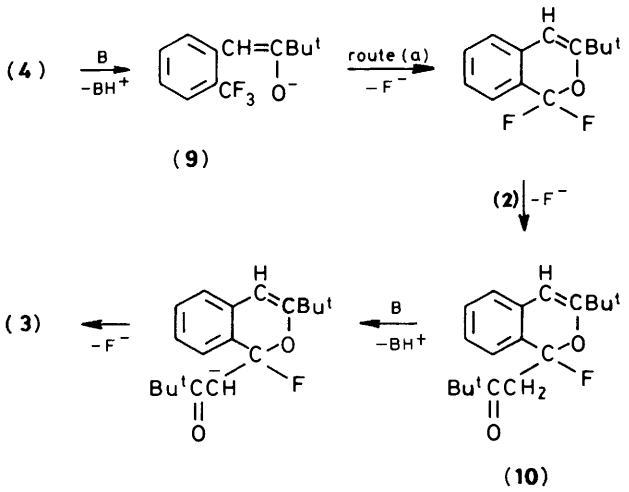
under the same experimental conditions of Scheme 2, yielded the straightforward $S_{RN}1$ substitution product (**8**); (60%) (Scheme 5). Hence, we concluded that an uncommon effect,



Scheme 5.

specifically associated with an enolate nucleophile, was operating in Schemes 2 and 3. The presence of an excess of the enolate appeared also to be of crucial importance. When the reaction in Scheme 2 was repeated with a larger excess (5 mol equiv. instead of 2.5) of (**2**), compound (**3**) became the sole reaction product and no traces of (**4**) were detected.

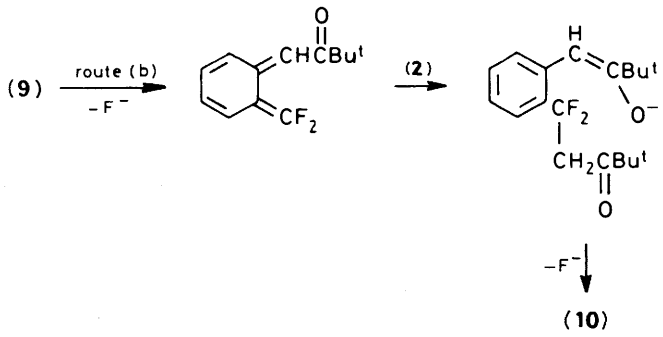
It was thought that compound (**4**), which is the product of the photo-induced $S_{RN}1$ reaction of (**1a**), could behave as an intermediate in the formation of (**3**), in a comparable way to the process exemplified in Scheme 1. Two hypotheses are likely, in our opinion, for the formation of (**3**) in Scheme 2. In both, the first two steps are (*i*) straightforward photo-induced $S_{RN}1$ substitution and (*ii*) conversion of product (**4**) into its conjugate base (**9**) by the excess of enolate present. Anion (**9**) can then [route (a)] undergo an intramolecular substitution to form a six-membered ring, due to the convenient juxtaposition of the two functionalities (Scheme 6). Further reaction with excess of



Scheme 6.

enolate would effect replacement of one fluorine and elimination of the other, leading eventually to product (**3**).

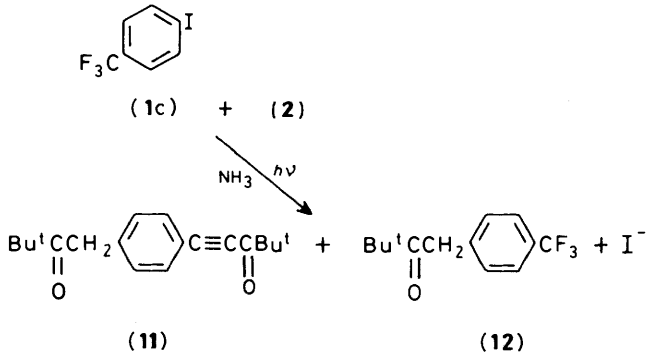
According to the second hypothesis [route (b)], a fluoride ion is eliminated from anion (**9**) in a concerted process, which shows some resemblance to a case already reported (Scheme 7).[8]



Scheme 7.

Addition of a further enolate molecule to the intermediate and subsequent intramolecular substitution would afford intermediate (**10**), common to the other route. Analogous behaviour with acetone enolate leads to the formation of (**5**) (Scheme 3). Neither of the two suggested routes are available to the *meta*-isomer (**1b**), so the formation of (**7**) as the sole product in Scheme 4 is reasonable.

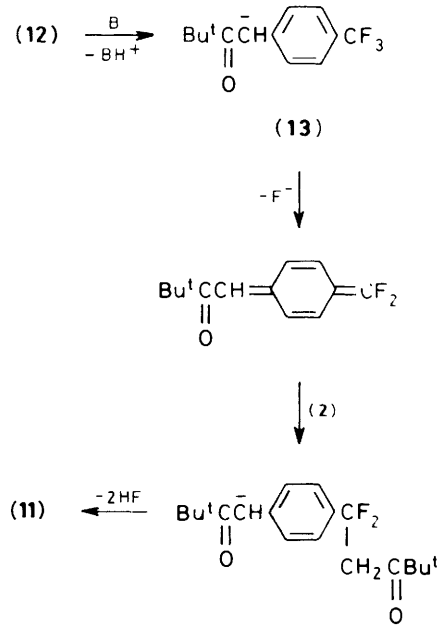
To verify our mechanistic proposal and to decide whether route (a) or (b), was operative, we treated the *para*-isomer (**1c**) with compound (**2**). Since the separation of the two functional groups should prevent reaction *via* route (a), it was expected that the concerted elimination of route (b) would play its role. Compound (**11**) (12%) was isolated that again did not contain any fluorine atoms, along with another product (**12**) (21%) arising from a straightforward $S_{RN}1$ substitution (Scheme 8).



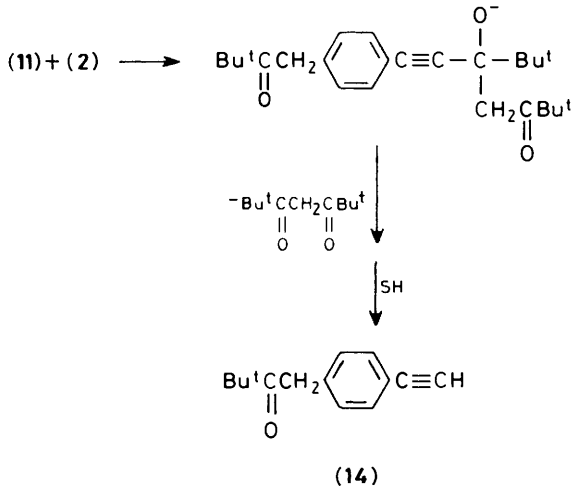
Scheme 8.

Compound (**11**) is believed to result from an intramolecular elimination of fluoride ion from the anion (**13**), subsequent conjugate addition of the enolate ion, and removal of the two molecules of hydrofluoric acid by the basic medium (Scheme 9). It was also noted that small amounts of compound (**14**), possibly arising from the cleavage of (**11**) by attack of the enolate ion, were also obtained from the reaction shown in Scheme 10.

As some of the key steps in the formation of (**11**) appear to be similar to those in route (b) to (**3**), we considered the latter to be the most probable mechanism. Products (**4**) and (**12**) then represent the 'reactive intermediates' in the formation of (**3**) and (**11**), respectively. In fact, in a separate experiment we converted quantitatively the small amount of the isolated product (**4**) into (**3**), under the same experimental conditions as those described in Scheme 2. As our mechanistic scheme implies, there was no photochemical initiation required.



Scheme 9.



Scheme 10.

Experimental

A Rayonet RPR-100 photochemical reactor fitted with 16 '350 nm' lamps was employed. G.l.c. analyses were carried out on a Hewlett Packard 5840A instrument fitted with a 10 m quartz capillary column supporting methyl silicone fluid. Mass spectra were obtained at 20 eV on a Finnigan Model 4000 instrument by direct inlet or in the g.c.—m.s. mode through a 2 m OV-101 column (100—200 °C temperature range). ^{1}H N.m.r. and ^{13}C n.m.r. spectra were obtained on a Jeol FX 100S instrument. The purification of some of the compounds was carried out by preparative g.l.c. on a Varian Aerograph A90-P3 fitted with a 2 m column of 10% UC-W98 on 80—100 mesh Chromosorb WAW DMCS.

3,3-*Dimethyl*-1-(3-*t*-*butyl*-1H-*benzo*[c]*pyran*-1-*ylidene*)*butan*-2-*one* (**3**).—The procedure now reported is typical. Irradiation of a solution of α,α,α-trifluoro-*o*-iodotoluene (**1a**) 3.25 g (12 mmol), 3,3-dimethylbutan-2-one (3.0 g, 30 mmol), and of Bu^{t}OK 4.4 g (39 mmol) in NH_3 (250 ml) for 40 min afforded compound (**3**) (1.46 g, 43%), which was isolated by column chromatography (using benzene as the eluant on silica gel), m.p. 142—143 °C (from ethanol–water), *m*/*z* 284 (M^+), 227 (M^+ − 57), 199 (M^+ − 85), 85 (Bu^{t}CO$^+$), and 57 (Bu^{t+}); $\nu_{max.}$ (CCl_4) 1 675 (conjugated carbonyl), and 1 660 cm^{-1} (vinylic ether); δ($CDCl_3$) 7.5—6.9 (m, 4H, ArH), 6.1 (s, 1 H, vinylic H), 5.7 (s, 1 H, vinylic H), 1.2 (s, 9 H, Bu^t), and 1.1 (s, 9 H, Bu^t). The ^{13}C n.m.r. spectra (see Table 2) were run in $CDCl_3$. APT and INEPT experiments[9] showed the relative multiplicity of the carbons, while an inverted gated (NNE) experiment allowed integration of the carbon atoms. The u.v.–vis (EtOH) spectrum showed four principal sharp bands: $\lambda_{max.}$ 386 (ε 14 500), 284 (ε 26 000), 275 (ε 26 000), and 204 nm (ε 26 750). (Found: C, 80.05; H, 8.64. $C_{19}H_{24}O_2$ requires C, 80.23; H, 8.52%).

Table 1. Reaction of ketone enolates with α,α,α-trifluorotolyl iodides (**1**) in liquid ammonia at −33 °C under photosensitisation.

Substrate	Photosensitisation time/min	Yields[a] (%) I$^-$	ArX left	Substitution product	Others[b]
(**1a**)	40	61	44	(**4**) 8	(**3**) 43
(**1a**)	40	55	40	(**6**) 12	(**5**) 18
(**1b**)	40	74	25	(**7**) 40	
(**1c**)	40	55	45	(**12**) 21	(**11**) 12; (**14**) traces

[a] By titration of the iodide released, by g.l.c. or by weighing. [b] Some dehalogenated product (*i.e.* α,α,α-trifluorotoluene) is formed but has not been quantitatively determined.

3,3-*Dimethyl*-1-(o-*trifluoromethylphenyl*)*butan*-2-*one* (**4**).—This compound was recovered as a pale yellow liquid (8% yield) from the column chromatography described for (**3**), *m*/*z* 244 (M^+), 187 (M^+ − 57), 159 (M^+ − 85), 85, and 57; δ ($CDCl_3$) 7.7—7.5 and 7.2—6.9 (m, 4 H, ArH), 3.9 (s, 2H, $ArCH_2CO$), and 1.1 (s, 9 H, Bu^t). The product was dissolved in liquid NH_3 in the presence of an excess of 3,3-dimethylbutan-2-one and Bu^{t}OK and stirred without photostimulation for 40 min. Solid NH_4NO_3 was added and the ammonia was evaporated. The residue was worked up with ether. G.l.c. inspection of the crude product revealed that compound (**4**) had completely disappeared and compound (**3**) had been formed.

1-(3-*Methyl*-1H-*benzo*[c]*pyran*-1-*ylidene*)*propan*-2-*one* (**5**).—This compound was obtained (18% yield) from the reaction of (**1a**) with potassium acetone enolate, and was purified by column chromatography and by preparative g.l.c., m.p. 56—58 °C, *m*/*z* 200 (M^+), 185 (M^+ − Me), 157 (M^+ − Ac), and 129; δ(CCl_4) 7.2—6.6 (m, 4 H, ArH), 5.7 (br s, 2 H, vinylic H), 2.0 (s, 3 H, Me), and 1.2 (s, 3 H, Me). The ^{13}C n.m.r. spectrum ($CDCl_3$) is reported in Table 2.

1-(o-*Trifluoromethylphenyl*)*propan*-2-*one* (**6**).—This compound was recovered, as a forerun, from the column chromatography of (**5**) as a pale yellow liquid, *m*/*z* 202 (M^+), 183 (M^+ − F), 159 (M^+ − Ac), 140, and 109. The ^{13}C n.m.r. spectrum ($CDCl_3$) is reported in Table 2.

4,4-*Dimethyl*-1-(p-*pivaloylmethylphenyl*)*pent*-1-*yn*-3-*one* (**11**).—This product was isolated by means of column chromatography from the crude product mixture from the reaction of (**1c**) with (**2**), as a liquid, *m*/*z* 285 (M^+ + 1), 227 (M^+ − 57), 200 [(M^+ + 1) − 85], 185, 171, 142, 85, and 57; δ($CDCl_3$) 7.6—7.5 and 7.2—7.1 (dd, 4 H, ArH-*p*), 3.8 (s, 2 H, $ArCH_2CO$), 1.3 (s, 9 H, Bu^t), and 1.2 (s, 9 H, Bu^t). The ^{13}C n.m.r. spectrum ($CDCl_3$) is reported in Table 2.

Table 2. ^{13}C n.m.r. characterization of reaction products (at 25 MHz).

Compd.	Carbon	δ (p.p.m. from TMS)	NNE[a]	APT[b]	INEPT[c]
(3)	*Me*$_3$C	27.4	3C	Me	
	Me$_3$*C*	43.6	1C	C or CH_2	C
	C=O	200.9	1C	C	
	=*C*HC=O or C-4	92.4	1C	CH	
	C-1 or C-3	163.4	1C	C	
	C-6, C-7, C-8	123.0	2C	CH + C	
	C-5 and	125.5	1C	CH	
	C-8a or C-4a	127.2	1C	CH	
		131.7	1C	CH	
	C-4a or C-8a	132.8	1C	C	
	C-4 or=*C*HCO	98.2	1C	CH	
	C-3 or C-1	159.9	1C	C	
	Me$_3$*C*	35.5	1C	C or CH_2	C
	Me$_3$C	27.6	3C	Me	
(5)	Carbon	δ (p.p.m. from TMS)			
	CO*Me*	32.7			
	C=O	196.8			
	=*C*HCO or C-4	100.1			
	C-1 or C-3	163.8			
	C-7, C-8, C-8a	121.1			
		124.7			
	C-4a, C-5, C-6	124.8			
		126.5			
		130.0			
		133.2			
	C-4 or =*C*HCO	101.4			
	C-3 or C-1	159.9			
	Me	24.9			
(6)	Carbon	δ (p.p.m. from TMS)			
	*Me*CO	29.4			
	C=O	204.2			
	ArCH_2	47.5			
	6 × ArC	126.3			
		127.4			
		129.9			
		132.0			
		132.9			
	CF_3	119.2			
(11)	Carbon	δ (p.p.m. from TMS)			
	2 × *Me*$_3$C 1 and 15	26.3			
	2 × Me$_3$*C* 2 and 14	44.4			
	≡C–*C*=O	193.5			
	C≡*C*–CO	92.1			
		86.0			
	ArC-C≡	118.3			
	4 × Ar*C*	129.7			
		129.8			
		132.8			
		132.9			
	ArC-CH_2	138.0			
	CH_2CO	43.0			
	C=O	211.2			
(14)	Carbon	δ (p.p.m. from TMS)	APT[b]	INEPT[c]	OFR[c]
	≡CH	77.0	CH or C	CH or C	CH
	≡*C*Ar	84.2	CH or C	CH or C	C
	Arc-C≡	120.6	C		
	4 × ArC	129.3	CH		
		129.5	CH		
		132.0	CH		
		132.3	CH		
	ArC-CH_2	135.9	C		
	CH_2CO	43.1	CH_2 or C	CH_2	
	C=O	211.8	C		
	Me$_3$*C*	44.6	C or CH_2	C	
	Me$_3$C	26.3	Me		

[a] Gives the number of carbon atoms under that signal. [b] Allows multiplicity of that carbon atom to be established. [c] Additional experiment to clarify multiplicity of ambiguous cases.

3,3-*Dimethyl*-1-(p-*trifluoromethylphenyl*)*butan*-2-*one* (**12**).—This product was recovered as a forerun from the column chromatography of (**11**), *m/z* 244 (M^+), 187 ($M^+ - 57$), 159 ($M^+ - 85$), 145, 85, and 57; δ($CDCl_3$) 7.5—7.4 and 7.2—7.1 (dd, 4 H, ArH-*p*), 3.5 (s, 2 H, $ArCH_2CO$), and 1.2 (s, 9 H, Bu^t).

3,3-*Dimethyl*-1-(p-*ethynylphenyl*)*butan*-2-*one* (**14**).—This product was also isolated from the column chromatography of (**11**). *m/z* 200 (M^+), 143 ($M^+ - 57$), 115 ($M^+ - 85$), 101, 85, and 57. The ^{13}C n.m.r. data ($CDCl_3$) are reported in Table 2. APT and INEPT experiments gave some indications of the relative multiplicity of the carbons, and an off-resonance (OFR) experiment allowed unambiguous assignments of the acetylenic carbons. The shielding assignments of the latter carbons are in agreement with literature data on acetylenic compounds.[10]

3,3-*Dimethyl*-1-(m-*trifluoromethylphenyl*)*butan*-2-*one* (**7**).—This product was obtained from the reaction between (**1b**) and (**2**), *m/z* 244 (M^+), 187 ($M^+ - 57$), 159 ($M^+ - 85$), 145, 85, and 57; δ($CDCl_3$) 7.9—7.7 and 7.2—7.0 (m, 4 H, ArH), 3.5 (s, 2H, $ArCH_2CO$), and 1.1 (s, 9 H, Bu^t).

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