Methyl *vs.* Methylene Condensation of Aromatic Aldehydes with 1,1,1-Trifluoroacetylacetone

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From the slow Knoevenagel condensations of 1,1,1-trifluoroacetylacetone (**4**) with aromatic aldehydes in benzene in the presence of piperidine–AcOH, low yields of three products were isolated: the enol form of the methyl-condensation product $ArCH{=}CHCOCH{=}C(OH)CF_3$ (**5**), the methylene-condensation product $ArCH{=}C(COCH_3)COCF_3$ (**6**), and the cleavage product $ArCH{=}CHCOCF_3$ (**7**). The effects of the bulk and the electron donating or withdrawing characteristics of the aldehyde component on the condensation at the CH_3 *vs.* the CH_2 group were investigated. Compound (**5**) is the major isolated product in the reaction of 2,4,6-trimethylbenzaldehyde. The low reactivity and the dependence of the Me *vs.* CH_2 selectivity of the diketone (**4**) on the structure of the aldehyde are ascribed to an initial formation of the enol form of the hydroxy amine $CF_3C(OH)(NC_5H_{10})CH{=}C(OH)Me$ (**12**) formed by the addition of piperidine to (**4**); (**12**) is the main product after short reaction times. The acidity of the CH_2 group of compound (**12**) is lower than that of trifluoroacetylacetone (**4**) and the approach of the aldehyde to the derived anion is more hindered than to the anion derived from Me ionization. The spectral properties of the products are discussed.

The base- or amine-catalysed condensation of active methylene compounds, such as β-diketones, with carbonyl compounds to form a carbon–carbon double bond is an important synthetic reaction. When a molecule contains two potential reaction sites the condensation usually takes place at the more acidic C–H bond; for example, the Knoevenagel condensation[1] of pentane-2,4-dione [acetylacetone(**1**)] with aldehydes occurs exclusively at the methylene carbon, giving the products (**2**) and their Michael adducts (**3**)[2] [equation (1)]. This is not surprising, as

$$\underset{(1)}{MeCOCH_2COMe} + ArCHO \xrightarrow{\text{base}} \underset{(2)}{ArCH{=}C(COMe)_2} + \underset{(3)}{ArCH[CH(COMe)_2]_2} \quad (1)$$

a; Ar = 4-$MeOC_6H_4$

the reaction proceeds *via* the intermediate monocarbanion. Owing to the two adjacent electron-withdrawing carbonyl groups and to the formation of a symmetrical carbanion, the $pK_a(H_2O)$ of the CH_2 of compound (**1**) (*ca.* 9 in H_2O)[3a] is several orders of magnitude lower than the pK_a of the Me group, which should be somewhat lower than that of acetone [$pK_a(H_2O)$ 18.9].[3b]

The primary anion derived by Me ionization is less stable and should therefore be more reactive. Indeed, the monoanions of β-diketones such as benzoylacetone and acetylacetone condense at the methylene group, while the dipotassium salt undergoes alkylation, acylation, and condensation reactions preferentially at the methyl group.[4] Other systems containing both activated methylene and methyl groups behave similarly.[4f]

We therefore expected that the Knoevenagel condensation of 2,4,6-trimethylbenzaldehyde with 1,1,1-trifluoroacetylacetone (**4**), a stronger carbon acid than (**1**) [$pK_a(H_2O) \leqslant 6.3$],[5] would be rapid and would take place exclusively at the methylene carbon. Surprisingly, this condensation in the presence of piperidine–AcOH in benzene proceeds slowly and forms mainly a condensation product of the methyl group. This finding initiated the following study of the condensation with other aldehydes.

Results

The condensation reactions of 1,1,1-trifluoroacetylacetone (**4**) with six aromatic aldehydes were conducted under Knoevenagel conditions (piperidine–AcOH as the catalyst in refluxing benzene under azeotropic distillation). The substituents in the aldehydes studied differ in their steric and electronic effects. The steric effect of the substituent should increase along the series Ar = Ph, 4-MeC_6H_4, 2,4-$Me_2C_6H_3$, whereas the electronic effect predominates in the series *p*-XC_6H_4, where X = MeO, Me, H, NO_2. The reactions were usually slow, for example 15% of the aldehyde still remained after 170 h in the reaction with *p*-tolualdehyde.

The n.m.r. spectra of the crude reaction mixtures were usually complex, showing the formation of a large number of compounds, and this was corroborated by t.l.c. For example, in the reaction with *p*-tolualdehyde more than ten Me signals were observed. Chromatography on silica gel showed that the products belong to two classes; those easily eluted with hexane–CH_2Cl_2 and those eluted with a more polar solvent (MeOH–CH_2Cl_2). The latter fraction was a highly complex mixture and difficult to separate; thus, as the first fraction contains the condensation products of interest, only those products eluted in the first fraction were separated and investigated. This fraction gave three main products which were identified by their spectral properties (Table 1) as the methyl-condensation product (**5**), existing mainly as the enol, the methylene-condensation product (**6**) and the condensation–cleavage product 3-arylidene-1,1,1-trifluoroacetone (**7**) (Scheme 1). The ratios of the products are based on the yields of the isolated compounds without correction for unchanged aldehyde. The isolated yields after 29—48 h were relatively low (16—31%, *cf.* Table 2). The highest observed yield of products (**5**)—(**7**) was 57%, from the reaction with *p*-tolualdehyde for 170 h.

The u.v. spectra of compounds (**5**) show a relatively high intensity peak at $\lambda_{max.}$ 365—375 nm which could be used for detecting small percentages of (**5**) in mixtures with compounds (**6**) and (**7**). The high $\lambda_{max.}$ value is consistent with the extended conjugation, low steric hindrance, and the bathochromic shift due to the vinylic OH of (**5**), and it excludes the keto structure (**8**); structure (**9**) is excluded since the i.r. and n.m.r. spectra resemble those of compound (**4**) where the enolization is in the direction of the $COCF_3$ group.[6,7] Compounds (**5**) show i.r.

Table 1. Spectral properties of the α,β-unsaturated ketones

Compound	$\lambda_{max.}$(EtOH)/nm (log ε)	$\nu_{max.}$($CHCl_3$)/ cm^{-1}	δ($CDCl_3$)/p.p.m.[a]	*m/z* (relative abundance %, assignment)[b]
(5a)[c]	233 sh (3.28), 360 (3.81)	1 695 sh, 1 620, 1 580, 1 460	2.30 (s, *p*-Me), 2.37 (s, 2 *o*-Me), 5.98 (s, =CH), 6.22, 7.98 (V), 6.92 (s, ArH)	284 (33, *M*), 269 (B, A), 268 (48, *M* − H_2O), 199 (31, *M* − CH_4 − CF_3 ?), 173 (57, E), 172 (38, I), 169 (34, D − H_2O), 145 (74, $Me_3C_6H_2CH$=CH), 144 (70, $Me_3C_6H_2CH$≡CH), 115 (53, $Me_3C_6H_2CH$=CH_2 − 2 Me), 105 (28, $Me_3C_6H_2$ − CH_2)
(5b)	244 (3.51), 370 (4.12)	1 690, 1 630sh, 1 600, 1 450	2.33 (s, *p*-Me), 2.41 (s, *o*-Me), 5.98 (s, =CH), 6.45, 8.04 (V), 7.04 (m, Ar), 7.50 (d, 3-H)	270 (11, *M*), 255 (78, A), 201 (62, C), 173 (B, D), 159 (93, E), 115 (60, MeC_6H_4CH=CH_2), 69 (84, CF_3)
(5c)	243 (3.88), 311 sh (4.02), 365 (4.31)	1 640, 1 615, 1 600, 1 580	2.39 (s, Me), 6.00 (s, =CH), 6.53, 7.73 (V), 7.24, 7.46 (Q)	256 (28, *M*), 241 (17, A), 187 (B, C), 159 (80, D), 145 (55, E), 141 (20, D − H_2O), 115 (56, F), 91 (35, T)
(5d)	243 (3.81), 379 (4.19)	1 650, 1 605, 1 595, 1 520	3.87 (s, OMe), 6.00 (s, =CH), 6.46, 7.75 (V), 6.95, 7.54 (Q)	272 (41, *M*), 230 (10, *M* − CH_2CO), 203 (65, C), 185 (5, D − H_2O), 175 (49, D), 161 (B, E), 146 (4, E − Me), 133 (38, F), 118 (16), 103 (11), 89 (17)
(6b)	260 (3.80), 300 (3.89)	1 750, 1 720, 1 695, 1 670, 1 600, 1 380[d]	2.32 (s, AcO), 2.38 (s, Me), 2.45 (s, Me), 6.98—7.08 (m, Ar), 8.06 (s, =CH)	270 (3, *M*), 255 (14, A), 229 (4), 213 (4, *M* − J), 201 (6, C), 173 (11, D), 159 (B, E), 158 (11, I), 133 (11), 131 (25, D − COMe), 119 (39), 116 (24, D − COMe − Me), 115 (36), 91 (31, T)
(6c)	260 (4.10), 304 (4.31)	1 750, 1 720, 1 700, 1 690, 1 665, 1 605[d]	2.36, 2.38 (2s, Ac), 2.45 (s, Me), 7.75 (s, =CH), 7.24, 7.28 (Q)	256 (21, *M*), 241 (99, A), 213 (5, G), 191 (9), 187 (26, C), 163 (11), 145 (B,E), 117 (29, C_7H_7CH=CH), 115 (65), 91 (16, T), 69 (13, CF_3)
(6e)	251sh (3.57), 295 (4.00)	1 750, 1 700, 1 620, 1 600[d]	2.34 (s, Ac), 2.49 (s, Ac), 7.3—7.8 (m, Ar + =CH)	
(6f)[e]	270 (4.07), 290 (4.00)	1 710, 1 690, 1 520, 1 350	2.44, 2.55 (2s, in a 3:2 ratio, Ac), 7.4—7.9 (m, Ar + =CH)	
(7b)[f]	240 (3.68), 333 (4.09)	1 715, 1 695, 1 300, 1 265[d]	2.35 (s, *p*-Me), 2.44 (s, *o*-Me), 6.92, 8.28 (V), 7.07 (s, Ar), 7.58 (d, 3-H)	228 (16, *M*), 213 (58, A), 159 (B, C), 131 (63, D), 129 (34), 116 (75, I), 103 (16), 91 (77, T)
(7c)	240 (3.78), 254 (3.79), 324 (4.24)	1 715, 1 695 1 600, 1 590[d]	2.41 (s, Me), 6.98, 7.95 (V), 7.25, 7.54 (Q)	214 (49, *M*), 155 (B, A), 117 (53, MeC_6H_4CH=CH), 115 (65, $MeC_6H_4C_2$), 91 (37, T)
(7d)	245 (3.71), 349 (4.33)	1 725, 1 600, 1 520, 1 470	3.88 (s, MeO), 6.89, 7.95 (V), 6.96, 7.92 (Q)	230 (45, *M*), 199 (6, *M* − MeO), 161 (B, C), 133 (42, D), 118 (17, I), 102 (8, PhC≡C), 90 (13)
(7e)	233 (3.78), 248 (3.59), 311 (4.26)	1 715, 1 610, 1 595, 1 430[d]	7.02, 7.95 (V), 7.3—7.7 (m, Ar)	200 (41, *M*), 131 (B, C), 103 (85, D), 77 (56, Ph)
(7f)	246 (3.54), 298 (4.22)	1 725, 1 700, 1 615, 1 600	7.13, 7.98 (V), 7.82, 8.32 (Q)	176 (B, C), 150 (27, *M* − CF_3 − C_2H_2 ?), 130 (51, *M* − CF_3 − NO_2), 102 (87, D − NO_2), 69 (55, CF_3)
(11a)[g]	286 (3.40)	1 720, 1 705, 1 680, 1 625	1.93 (s, Ac), 2.17 (s, *o*-Me), 2.28 (s, *p*-Me), 2.41 (s, Ac), 6.88 (s, Ar), 7.71 (s, =CH)	215 (B, A), 187 (20, G), 173 (18, H), 145 (11, *M* − $COCH_2COMe$), 129 (16, *M* − 2COMe − Me), 128 (19), 106 (13)
(11b)	248 (3.54) 307 (3.37)	1 740, 1 720 1 650, 1 610	(i) 2.12 (s, *p*-Me), 2.15 (s, Me), 6.66 (s, $Me_3C_6H_2$), 7.30—7.60 (m, Ar), 8.24 (s, =CH)[h] (ii) 2.29 (s, *p*-Me), 2.23 (s, *o*-Me), 6.89 (s, $Me_3C_6H_2$), 7.40—7.92 (m, ArH)[h]	346 (2, *M*), 331 (21, A), 277 (21, C), 269 (7, *M* − Ph), 249 (15, D), 172 (9, *M* − Ph − $COCF_3$), 105 (B, PhCO), 77 (71, Ph)
(2a)	225 (3.85), 318 (4.29)	1 720, 1 695, 1 610, 1 580	2.32 (s, Ac), 2.41 (s, Ac), 3.84 (s, Me), 7.43 (s, =CH), 6.90, 7.37 (Q)	218 (41, *M*), 203 (37, A), 187 (22, *M* − MeO), 175 (26, G), 162 (B, *M* − CHCOMe), 133 (31, *M* − 2COMe), 43 (86, COMe)

[a] The integrations are consistent with the assignments. V = CH=CH, q, *J* 16 ± 0.6 Hz; Q = aromatic ABq, *J* 8.6 ± 0.4 Hz. [b] A = *M* − Me; C = *M* − CF_3; D = *M* − $COCF_3$; E = *M* − CH_2COCF_3; F = *M* − $COCH_2COCF_3$; G = *M* − COMe; J = *M* − CH_2COMe; I = *M* − Me − $COCF_3$; T = tropylium ion. [c] δ_F($CDCl_3$) −77.19 (relative to $CFCl_3$). δ_C($CDCl_3$) 21.04 (q, *p*, Me), 21.19 (q, *o*-Me), 95.45 (d, C-3), 116.83 (q, CF_3, J_{CF} 285 Hz), 125.74 (d, α-C), 129.61 (d, Ar C-3), 130.56 (s, Ar C-1), 137.48 (s, Ar C-2), 139.49 (s, Ar C-4), 142.48 (d, β-C), 180.26 (q, $COCF_3$, J_{CF} 36 Hz), 181.46 p.p.m. (s, COMe). [d] Neat. [e] Could not be purified by t.l.c. [f] δ_C($CDCl_3$) 19.60 (q, *p*-Me), 21.49 (q, *o*-Me), 116.24 (d, Ar C-5), 116.53 (q, CF_3, J_{CF} 291.6 Hz), 126.94 (d, α-C), 127.54 (d, Ar C-6), 129.55 (s, Ar C-1), 132.12 (d, Ar C-3), 139.70 (s, Ar C-2), 143.05 (s, Ar C-4), 147.58 (s, β-C), 180.80 p.p.m. (q, CO, J_{CF} 36 Hz). [g] δ_C($CDCl_3$) 26.24 (q, Me), 31.51 (q, Me), 55.33 (q, MeO), 114.51 (d, Ar C-3), 131.53 (s, Ar C-1), 131.78 (d, Ar C-2), 139.64 (d, β-C), 140.73 (s, α-C), 161.74 (s, Ar C-4), 196.34 (s, CO), 206.5 p.p.m. (s, CO). [h] (i) and (ii) are the major and the minor isomers, respectively.

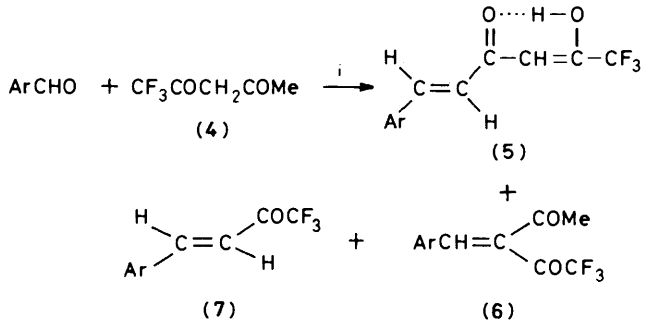
bands at 1 695—1 650 and 1 630—1 605 cm^{-1}; the former bands are consistent with structure (**5**) but not with (**8**) since $\nu_{C=O}$ in the polyfluoro ketones R_FCOR at 1760—1775 cm^{-1} [8a] is higher than that in non-fluorinated ketones.[8b] Likewise, the strong absorption of compound (**4**) at 1650 cm^{-1} is probably due to the presence of the enol form. In the i.r. spectra of compounds (**5**) the OH stretches are weak or absent, while in the ^1H n.m.r. spectra ^3J(HC=CH) = 16.0 ± 0.6 Hz, indicating the presence of the less hindered *E* isomers. The sharp singlet at δ *ca.* 6.0 is attributed to the vinylic proton which appears at δ 5.8—5.9 in the enol form of compound (**4**);[6] δ(OH) should be < 12.[6a] No evidence for the enolization of the COMe moiety was found.

The ^{13}C n.m.r. spectrum of compound (**4**) shows it to exist in the enol form at the $COCF_3$ group in non-polar solvents. There is no evidence for the suggested[9] O–H–F hydrogen bonding. In the ^{13}C n.m.r. spectrum of compound (**5a**) the δ values of C-2 (180.26 p.p.m.) and C-3 (95.45 p.p.m.) are close to the corresponding values of δ 176.6 and 96.6 p.p.m. for compound (**4**).[10]

Table 2. Reaction conditions and product distributions in the Knoevenagel reaction of aromatic aldehydes with trifluoroacetylacetone (**4**)

ArCHO Ar	[ArCHO](mM)/ [(**4**)](mM)/ [$C_5H_{10}NH$](ml) [AcOH](ml)/ [C_6H_6](ml)	Reaction time (h)	Yield product (%)[a] (**5**)	(**6**)	(**7**)
4-$MeOC_6H_4$	13/15.6/0.4/0.5/50	20	14		2
2,4,6-$Me_3C_6H_2$	39/40/1.0/1.3/100	20	23		
		60	(75)	(15)	(10)[b,d]
2,4-$Me_2C_6H_3$	11/13/0.4/0.4/50	16	7	20	4
4-MeC_6H_4	50/55/1.0/1.3/100	18		24 (41[c])	1
		48	(6)	(85)	(5)[b]
		80	(8)	(85)	(5)[b]
		170	(14)	(82)	(6)[b]
Ph	20/23/0.4/0.5/100	40		21	6
4-$O_2NC_6H_4$	13/15.6/0.4/0.5/100	48		18	1

[a] Yields of the isolated product. [b] Distribution of (**5**)—(**7**) from the n.m.r. spectrum. [c] From the n.m.r. spectrum of the crude mixture before distillation. [d] The assignment of (**6**) and (**7**) is only tentative.



a; Ar = 2,4,6-$Me_3C_6H_2$ **b**; Ar = 2,4-$Me_2C_6H_3$ **c**; Ar = 4-MeC_6H_4
d; Ar = 4-$MeOC_6H_4$ **e**; Ar = C_6H_5 **f**; Ar = 4-$O_2NC_6H_4$

Scheme 1. *Reagents:* i, piperidine–AcOH, C_6H_6

The ($M - CH_2COCF_3$) peak is abundant, and is sometimes the base peak in the mass spectra, as expected from the presence of the CH=C(OH)CF_3 moiety in compound (**5**).

The cross-conjugated compounds (**6**) have lower $\lambda_{max.}$ values than (**5**), probably reflecting their non-planarity due to the steric interference of the three bulky substituents. The steric effect is also evident in the lower ε values for the crowded compounds (**11a**) and (**11b**). There are four CO absorptions for compounds (**6b**) and (**6c**) at 1 750, 1 720, 1 700 (1 695), and 1 690 (1 670) cm^{-1}. The higher values are ascribed to the CH=C(COMe) group of the *E* and the *Z* isomers. Only two peaks at > 1 690 cm^{-1} were observed for compounds (**6e**) and (**6f**) and, since the presence of a single isomer is inconsistent with the n.m.r. spectrum, this may be due to a substituent-induced shift to a lower value of $\nu_{max.}$. Compounds (**6c**) and (**6e**) showed two COMe groups in the ^1H n.m.r. spectrum, suggesting the formation of both isomers. The single COMe signal observed for compound (**6b**) may reflect the formation of a single isomer or an accidental overlap of the signals of the two isomers.

The u.v. spectra of compounds (**7**) show that a bathochromic shift results from a change from a COMe group to a $COCF_3$ group: for ArCH=CHCOCF$_3$, $\lambda_{max.}$ (EtOH) = 311 nm (log ε 4.26) when Ar = Ph, and 324 nm (4.24) when Ar = *p*-MeC_6H_4, whereas the $\lambda_{max.}$ (EtOH) values for ArCH=CHCOMe are 286 nm (log ε 4.35) for Ar = Ph[11] and 322 nm (4.27) for Ar = *p*-MeC_6H_4.[12] Likewise, $\lambda_{max.}$ = 284 nm for trifluoroacetylacetone (**4**) which is more extensively enolized[13] than compound (**1**) ($\lambda_{max.}$ 274 nm). Compounds (**7**) have two CO absorptions at

1 725—1 715 and at 1 715—1 695 cm^{-1}, and they are shown to have the *E* structures by their ^3J(HC=CH) values of 16.0 ± 0.6 Hz.

Several conclusions can be drawn from the relative yields of those products which were isolated from similar experiments using different reagents (Table 2). First, the overall yields after moderate reaction times are rather low. This is partly due to the slowness of the reaction, to loss of some trifluoroacetylacetone (**4**) by cleavage, and to the formation of some benzoic acid from the aldehyde, but also to the formation of substantial amounts of other unidentified (and probably higher molecular weight, as judged by their chromatographic behaviour) compounds. As these may be derived from further reactions of compounds (**5**)—(**7**), the product ratios are only approximate.

Secondly, assuming that formation of the unidentified compounds does not radically change the kinetic product distributions of compounds (**5**) and (**6**), both steric and electronic effects govern the selectivity at the CH_2 *vs.* Me sites. The highest yield of the methyl-condensation product (**5**) is observed with the sterically hindered 2,4,6-trimethylbenzaldehyde: compound (**5a**) is the exclusive product at moderate reaction times, although after longer reaction times up to 15% of (**6a**) and up to 10% of (**7a**) were formed. The yield of compound (**5b**) [from 2,4-dimethylbenzaldehyde (**4b**)] is lower and the main isolated product is (**6b**). When either the steric effect around the CO group or the electron-donating ability of the aryl ring is reduced, as in *p*-XC_6H_4CHO (X = H, Me, NO_2), compound (**5**) is not formed, although (**5d**) was the main product when X = MeO.

Thirdly, the yields of the cleavage product (**7**) are low and show no discernible order.

Fourthly, electron withdrawal apparently slows the overall reaction since longer reaction times were required when X = H, NO_2.

All three products were isolated under standard reaction conditions from the reactions of both 4-methyl- and 2,4-dimethyl-benzaldehyde. Prolonged reaction with *p*-tolualdehyde resulted in an increase in the relative proportion of product (**5c**) at the expense of (**6c**) (Table 2). The ratio may be affected by the loss of the catalyst during the reaction, and indeed reaction for 40 h without azeotropic distillation gave a 2:1:1 ratio of (**5c**):(**6c**):(**7c**). Hence, the initially formed product (**6c**) may decompose to (**7c**) or rearrange to (**5c**), and

Table 3. Condensation of 2,4,6-trimethylbenzaldehyde with (**4**)

Catalyst/solvent	Reflux time (h)	Product yield (%) 2,4,6-$Me_3C_6H_2CHO$	(**5a**)	Others
Piperidine/AcOH/benzene	20	?	23[a]	
Piperidine/AcOH/benzene	60		75[b]	10,15[b,c]
Piperidine/benzene	48	25[b]	50[b]	10[d]
Piperidine/H_2O–dioxane	20	100[b]		
Piperidine/EtOH	72[e]	100[f]		
NaH/ether	20	100		
Et_3N/benzene	24	100		
Et_3N/AcOH/benzene	60	100		
TsOH/benzene	40	100		
(**12**)/benzene[g]	48	50	40	

[a] Isolated yield from chromatography. [b] Percentage of the products, from the n.m.r. spectrum. [c] *Cf.* Table 2. [d] Not identified. Possibly (**6a**). [e] At room temperature. [f] Traces of an unidentified product were formed. [g] Reaction of (**12**) without a catalyst.

$PhCOCH_2COCF_3$ (**10**)

2,4,6-$Me_3C_6H_2CH=C(COR)(COR')$ (**11**)
a; R = R′ = Me
b; R = Ph; R′ = CF_3

$CF_3C(OH)CH=C(OH)Me$ (**12**)
NC_5H_{10}

$CF_3C(OH)CH_2COMe$ (**13**)
NC_5H_{10}

$CF_3C=CHCOMe$ (**14**)
NC_5H_{10}

when (**6c**) (*E*,*Z*-mixture) in benzene was treated with piperidine and AcOH and then refluxed for 16 h it disappeared completely and (**7c**) (5%) and (**5c**) (11%) were isolated.

The (**6**)⇌(**5**) transformation is reversible but slow. Reflux of compound (**5a**) for 20 h in the presence of piperidine gave *ca.* 10% of new compounds which by n.m.r. were tentatively proposed to be a mixture of (**6a**) and (**7a**). On reflux of 2,4,6-trimethylbenzaldehyde, trifluoroacetylacetone, and piperidine for 60 h, the same signals were again observed in the ratio 3:15:2 [(**5a**):(**6a**):(**7a**)].

The effect of piperidine, AcOH, and the solvent on the condensation of 2,4,6-trimethylbenzaldehyde with compound (**4**) is shown in Table 3. The presence of AcOH is not essential as compound (**5a**) is formed in its absence; however, the presence of piperidine is necessary as (**5a**) was not formed in the presence of Et_3N even after prolonged reaction. The anion of compound (**4**), formed with NaH in ether, does not give (**5a**), and with toluene-*p*-sulphonic acid or piperidine condensation in ethanol or in aqueous dioxane does not take place. 2,4-Dimethylbenzaldehyde does not react with compound (**4**) in the absence of piperidine.

In order to distinguish the low reactivity from the Me *vs.* CH_2 selectivity, 2,4,6-trimethylbenzaldehyde was condensed with the diketones (**1**) and (**10**) under the same reaction conditions. Condensation with compound (**1**) for 20 h gave 41% of (**11a**) and 15% of unchanged aldehyde; reaction with the diketone (**10**) gave little product after 20 h, but after reflux for 88 h, the n.m.r. spectrum showed the formation of *ca.* 40% of a 4:1 *E*:*Z* mixture of two isomers of (**11b**), and 35% of unchanged aldehyde.

Reactions of 2,4,6-*Trimethylbenzaldehyde and Compound* (**4**) *with Piperidine.*—2,4,6-Trimethylbenzaldehyde and piperidine do not give the aminal 2,4,6-$Me_3C_6H_2CH(NC_5H_{10})_2$ under the reaction conditions. The reaction of equimolar concentrations of (**4**) and piperidine in benzene at room temperature is exothermic and the enol form of the adduct carbinolamine, (**12**), is formed in 95% yield after 30 min. It was identified on the basis of a broad signal at ν_{OH} 3 500—2 800 cm^{-1}, a broad concentration-dependent OH signal at δ 8.22 in the ^1H n.m.r. spectrum and the signal at 93.18 p.p.m. (CH=, d at off-resonance) in the ^{13}C n.m.r. spectrum. As there is no CH_2 signal in the n.m.r. spectra and the OH signal integrates for two protons, any contribution from the ketonic structure (**13**) must be small. The signal at $\lambda_{max.}$(cyclohexane) 286 nm (log ε 3.9) is higher than expected for an unconjugated enol. The shift to a higher $\lambda_{max.}$ value on increasing the solvent polarity and basicity [$\lambda_{max.}$(EtOH) 294 nm (log ε 4.19)] may reflect that some ionization to the anion (**17**), which presumably has a higher $\lambda_{max.}$, has taken place.

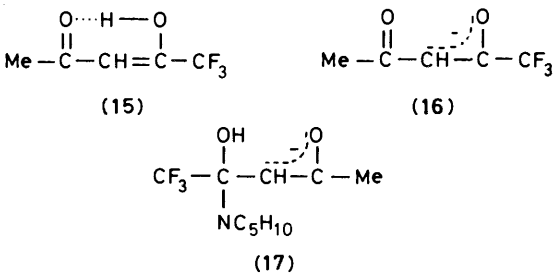
Compound (**12**) is stable at room temperature but on reflux in dry benzene for 72 h under azeotropic distillation it gives the enamine (**14**) (88%) in a similar reaction to that of aniline with trifluoroacetone.[14] Reflux of a mixture of piperidine with trifluoroacetylacetone for 18 h results in the formation of a mixture of (**12**) and (**14**) (4:1).

Reflux of compound (**12**) with 2,4,6-trimethylbenzaldehyde in benzene for 48 h gave compound (**5a**) (40%), recovered aldehyde (50%), and unidentified products (10%).

Discussion

Our results raise three related mechanistic questions: first, why is the reaction so slow in spite of the high acidity of the CH_2 group of compound (**4**)? Secondly, why does condensation occur at the Me group when it is much less acidic than the CH_2 group in trifluoroacetylacetone (**4**)? Thirdly, what are the factors which determine the CH_2 *vs.* Me selectivity in the condensation?

Several anomalies in the behaviour of (**4**) and related compounds are relevant to the first question. Comparison of the water-catalysed relative detritiation rates of compounds (**1**), (**4**) and $(CF_3CO)_2CH_2$ (4:2:0.9) with their pK_a values (8.00, 6.79, and 5.33 at 25 °C, respectively) show that fluorine substitution increases the thermodynamic acidity but reduces the kinetic acidity.[15] This was ascribed to the large extent of hydration which reduces the acidity of the C–H group. Indeed, $(CF_3CO)_2CH_2$ exists in water mainly as the dihydrate which



(15) (16) (17)

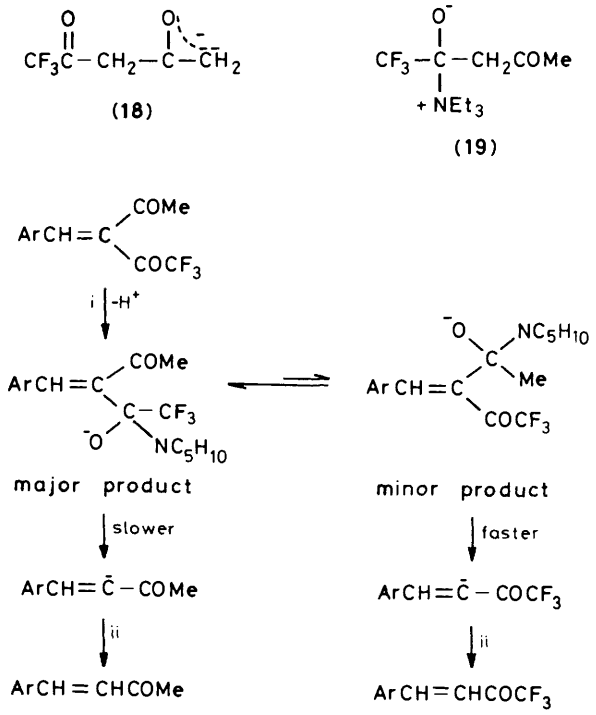
ionizes slowly even in 1M-NaOH.[16] The condensation of 1,3-β-diketones with diazobenzene-4-sulphonic acid is first order in both the substrate and the anion of the diketone, and a log k_2 *vs.* pK_a (diketone) plot is linear; however, compound (**4**) and 1,1,1-trifluoro-4-thienylbutane-2,4-dione (TTA) are much less reactive than expected from their pK_a values,[17] probably owing to hydration. Trifluoromethyl ketones, for example CF_3COPh,[18] CF_3COMe,[19a] and TTA,[19b] commonly undergo hydration and for (**4**), K = [Hydrate]/[(**4**)] = 77.2 in water.[20]

The slow reaction and the attack at the Me group are connected with the presence of the $COCF_3$ group. The non-fluorinated diketone (**1**) condenses exclusively at the CH_2 group in a reaction which is qualitatively faster than that of trifluoroacetylacetone (**4**). The more acidic compound (**10**), with no COMe group, reacts even more slowly than compound (**4**).

The lack of reactivity of trifluoroacetylacetone (**4**) with 2,4-dimethylbenzaldehyde in spite of the presence of an appreciable concentration of the anion (**16**) even in neutral solution suggests that, owing to the extensive charge dispersal, the nucleophilicity of (**16**) toward the aldehyde is very low. We suggest that the species undergoing the condensation is not trifluoroacetylacetone (**4**) but the enolate ion (**17**) derived from compound (**12**) in the basic solution. As shown above, compound (**4**) is converted in benzene–piperidine almost exclusively into compound (**12**) at a much higher rate than the condensation rate. This is consistent with the equilibrium constants for the formation of carbinolamines from aldehydes and amines.[21] Although we have no unequivocal proof that compound (**12**) lies on the reaction co-ordinate for condensation, the observed reactivity and selectivity are consistent with this fact.

The 'methylene group'* of compound (**12**) is much less acidic than that of trifluoroacetylacetone (**4**) since it is no longer activated by two CO groups, but instead by one CO and by α-OH and α-NR groups. The acidities of the Me and CH_2 groups in butan-2-one are nearly identical.[22] The effect due to the OH and NR groups is composed of inductive electron withdrawal, lone-pair repulsions, and hyperconjugative stabilization of the anion. The first two effects should destabilize the anion (**17**) since unshared electron pairs on the α-substituents reduce significantly the rate of carbanion formation.[23] The amine-catalysed deprotonation of $MeOCH_2COMe$ occurs faster at the CH_3 than at the CH_2 group.[24] However, MO calculations on the stability of $\ddot{X}CH_2\bar{C}H_2$ carbanions indicate a net stabilisation.[25] We expect an overall appreciable reduction in the CH_2 acidity of compound (**12**). This is supported by the slow exchange of the CH_2 group of hexafluoroacetylacetone hydrate in strong base,[16b] and by the pK_a values of carbonyl compounds and their hydrates.[26]

The change from compound (**4**) to (**12**) affects the acidity of the remote Me group much less, and the acidities of the CH_2 and Me groups are much closer in the latter compound. If a gap of two or three pK_a units remains, a small percentage of the primary carbanion (**18**), which is inherently more reactive than the anion (**17**), should be formed in the basic solution. Steric effects would then be important in the reaction with the bulky aromatic aldehydes. Hine suggested that 'addition of almost anything to a C=O bond gives a new group that is less electron-withdrawing and more space-filling than the original CO group'.[27] The fact that the anion (**18**) is less crowded than (**17**) at the reaction sites is therefore consistent with a lower selectivity for attack at the Me site on decreasing the number of *o*-Me groups in the aldehyde and with the lack of reactivity of 4-methoxy-4′-nitrobenzophenone with (**4**).



(18) (19)

major product minor product

Scheme 2. *Reagents*: i, piperidine; ii, H^+

Electronic effects in the aldehydes result in the predominant formation of compounds (**5**) with electron-donating substituents and of (**6**) with electron-withdrawing ones. This is consistent with the steric argument since an earlier and a looser transition state in the product-forming condensation step will be favoured by a more electrophilic aldehyde.

The lack of reaction in the presence of Et_3N may be ascribed to the formation of the zwitterion (**19**), which for electrostatic reasons is less prone to ionization than (**12**). It was also suggested that the amine in the Knoevenagel reaction forms the reactive Schiff base from the carbonyl compound.[28] Hence, in addition to the formation of compound (**12**), the piperidine may convert some of the aldehyde into the more reactive and bulkier, and hence more selective, Schiff base which then condenses with the anion (**17**) or (**18**). Likewise, it is also possible that the enamine (**14**) is involved in the reaction, although its slow formation and the lack of effect of AcOH [which should catalyse the (**12**)→(**14**) dehydration] suggest that it is not a main reaction intermediate.

Formation of Compound (**7**).—For an accurate determination of the Me *vs.* CH_2 selectivity, knowledge of the origin of the cleavage product (**7**) is needed. Initial nucleophilic attack at the CO in compound (**4**), (**5**), or (**6**) should occur nearly exclusively

* In order to retain the 'CH_2 *vs.* Me' terminology we use the term 'methylene group' although compound (**12**) is predominantly enolic. This terminology is used for discussion of reactions of active methylene compounds even when they are mainly enolic.

on the more nucleophilic CO group adjacent to the CF_3 group (as observed in the reaction of TTA·H_2O with NaOH[29]) and should give 3-arylideneacetones. As only compound (**7**) was formed, the minor attack of piperidine on the COMe group, followed by cleavage of the tetrahedral species formed to give the CF_3-stabilized enolate of (**7**), is suggested. Cleavage of the main product of attack on the $COCF_3$ group would give the less stable acetone enolate ion and therefore does not take place.

Cleavage of compound (**5**) to give the enolate of (**7**) is excluded since it requires an extensive rearrangement and since (**7**) is not formed in the early steps of the reaction with 2,4,6-trimethylbenzaldehyde. The formation of only (**5a**) after long reaction times suggests that compound (**4**) decomposes rather slowly, possibly because it is present as (**12**), although TTA·H_2O cleaves faster in basic solution than TTA.[29] As compound (**6c**) gives (**7c**) under the basic reaction conditions in a relatively high yield, (**7**) is probably formed *via* the route in Scheme 2. The *N*-acetylpiperidine is not observed since it remains in the aqueous phase.

Thus, the Me *vs.* CH_2 selectivity is given by the (**5**):(**6**) + (**7**) ratio. Fortunately, the proportion of (**7**) is low and its formation does not affect the above discussion of selectivity.

Reversibility of the Reaction.—The formation of compound (**5c**) from (**6c**) and the possible formation of (**6a**) from (**5a**) are probably due to the reversibility of the initial reaction with condensation occurring at the alternative reaction site, and not to a direct rearrangement.

Conclusions

The slow piperidine-catalysed condensation of compound (**4**) with aromatic aldehydes in benzene proceeds *via* the formation of the carbinolamine enol (**12**). In a basic medium, ionization of both the CH_2 and the Me sites generates the corresponding carbanions which condense with the aldehyde to give products (**5**) and (**6**). Judging by the isolated products, the Me *vs.* CH_2 selectivity increases with the crowding around the CO centre and with the electron-donating ability of the aldehyde, indicating the importance of steric effects. Cleavage of compound (**6**) generates the α,β-unsaturated ketones (**7**).

Experimental

M.p.s are uncorrected. U.v. spectra were determined with a Gilford 2400-S spectrophotometer, and i.r. spectra with a Perkin-Elmer 157G spectrophotometer. ^1H and ^{13}C N.m.r. spectra were recorded on a Bruker WH-300 pulsed FT spectrometer operating at 300.133 and 75.46 MHz for ^1H and ^{13}C, respectively. Mass spectra were recorded with a MAT 311 instrument.

Solvents and Materials.—Trifluoroacetylacetone (Pierce Chemicals) was distilled at 105 °C before use; $\lambda_{max.}$(EtOH) 284 nm (log ε 3.93); $\nu_{max.}$(neat) 1 750 (s) and 1 650 cm^{-1} (s); $\delta_H(CDCl_3)$ 2.21 (3 H, s, Me), 5.92 (1 H, s, CH=); $\delta_C(CDCl_3)$ 24.42 (s, C-5), 96.23 (s, C-3), 117.09 (q, J_{CF} 283 Hz, C-1), 175.83 (q, J_{CF} 36 Hz, C-2), and 194.43 (s, C-4). Acetylacetone (B.D.H.), $\lambda_{max.}$(EtOH) 274 nm (log ε 4.00), the aldehydes (Aldrich), and piperidine (Aldrich) were used without further purification. Benzene (Frutarom) was dried over sodium and distilled. Hexane, CH_2Cl_2, and $CHCl_3$ (Frutarom) for chromatography were used without purification. The silica gel used for the chromatography was 35—70 Mesh (Merck) or dry silica (Woelm-Pharma). Ether refers to diethyl ether.

General Condensation Procedure.—The aldehyde (usually 10—20 mmol) and trifluoroacetylacetone (**4**) (1.1 mol equiv., usually 11—22 mmol) were dissolved in dry benzene (100 ml). Piperidine (0.4 ml) and acetic acid (0.5 ml) were added and the mixture was refluxed in a Dean–Stark azeotropic distillation apparatus for 16—20 h. Water was then added, the phases were separated, and the benzene phase was washed first with dilute HCl, then with water, dried ($MgSO_4$), filtered, and evaporated. The remaining oil was chromatographed on dry silica gel (2.5 × 40 cm column) using hexane–CH_2Cl_2 as the eluant.

Compounds (**7**) were usually eluted first, followed by (**5**) and then by (**6**). The recovered aldehyde usually had an R_F value between those of (**5**) and (**6**), and a second chromatography was sometimes needed. Complete separation of the (*E*)- and (*Z*)-isomers of (**6**) was not achieved, although enrichment by one isomer was sometimes observed; *e.g.*, a 2:1 isomer mixture of compound (**6c**) was obtained. On standing or on trituration

Table 4. Physical and analytical data for the α,β-unsaturated ketones

Compound	M.p. (°C)	Colour	Purification[a]	R_F[b]	Formula	Analysis (%) Calc. C	Calc. H	Calc. F	Found C	Found H	Found F
(**2a**)	45[c]	Yellow-green	H		$C_{13}H_{14}O_3$	71.55	6.42		71.2	6.7	
(**5a**)[d]	46	Yellow	H	0.6	$C_{15}H_{15}F_3O_2$	63.38	5.28	20.07	63.5	5.5	19.9
(**5b**)[d]	*e*	Red	C	0.6	$C_{14}H_{13}F_3O_2$	62.22	4.81		62.5	4.9	
(**5c**)	35	Yellow	C	0.45	$C_{13}H_{11}F_3O_2$	60.93	4.29		61.2	4.4	
(**5d**)	43	Green-yellow	C	0.4	$C_{13}H_{11}F_3O_3$	57.35	4.04		57.5	4.3	
(**6b**)	*e*	Red	C	0.5	$C_{14}H_{13}F_3O_2$	62.22	4.81		62.45	4.9	
(**6c**)	*f*	Yellow	C,D	0.4	$C_{13}H_{11}F_3O_2$	60.93	4.29	22.26	61.25	4.3	21.6
(**6e**)	*e*	Light red	C	0.4	$C_{12}H_{10}F_3O_2$	59.26	4.11		59.4	4.0	
(**7b**)[f]	*e*	Yellow	C	0.8	$C_{12}H_{11}F_3O$	63.15	4.82	25.00	63.5	5.3	24.6
(**7c**)	37	Yellow	C	0.6	$C_{11}H_9F_3O$	61.68	4.20	26.63	61.2	4.4	23.5
(**7d**)	38	Yellow	C	0.7	$C_{11}H_9F_3O_2$	57.39	3.91		57.6	4.1	
(**7e**)	*e*	Yellow	C	0.8	$C_{10}H_7F_3O$	60.00	3.50		60.1	4.1	
(**7f**)	46	Colourless	C	0.5	$C_{10}H_6F_3NO_3$	48.98	2.45	*g*	48.75	2.6	*g*
(**11a**)	40[h]	Colourless	H	0.3	$C_{15}H_{18}O_2$	78.26	7.83		78.1	7.6	

[a] C: from chromatography; D: by distillation; H: by crystallization from hexane. [b] In 1:1 hexane–CH_2Cl_2. [c] No colour change with methanolic $FeCl_3$ solution. [d] The compounds give red colour with methanolic $FeCl_3$ solution. [e] Oil. [f] B.p. 120 °C/5 mmHg. [g] Found: N, 5.61. Calc. N, 5.71%. [h] B.p. 160 °C/25 mmHg.

with hexane, several of the compounds solidified to low melting solids. The yields of the isolated compounds are given in Table 2 and their spectroscopic and analytical data are given in Tables 1 and 4.

In a reaction on a larger scale, *p*-tolualdehyde (6 g, 50 mmol), compound (**4**) (9.2 g, 55 mmol), piperidine (1 ml), and AcOH (1.3 ml) in dry benzene (50 ml) were refluxed in a Dean–Stark azeotropic apparatus. After 48, 80, and 170 h the following (**5c**):(**6c**):(**7c**) ratios were observed by ^{1}H n.m.r.: 6:85:5, 8:85:5; and 14:82:6, together with *p*-tolualdehyde and *p*-toluic acid. After chromatography and separation of compound (**5c**) (1.2 g), (**7c**) (0.8 g), *p*-tolualdehyde (0.9 g) and *p*-toluic acid (0.45 g), the remaining light-red oil was distilled at 120 °C/5 mmHg to give compound (**6c**) (3.5 g) as a light-yellow oil. The overall yield of compounds (**5**)—(**7**) was 57%. A similar reaction without an azeotropic distillation gave a 50:25:25 mixture of (**5c**):(**6c**):(**7c**) after 40 h.

When a mixture of 2,4,6-trimethylbenzaldehyde (0.58 g, 4 mmol), trifluoroacetylacetone (**4**) (0.62 g, 3.9 mmol), piperidine (0.3 ml), and AcOH (0.4 ml) in dry benzene (50 ml) was refluxed under azeotropic distillation for 60 h and then worked-up as usual, n.m.r. spectroscopy showed that the aldehyde had disappeared. The main product (by n.m.r.) was (**5a**), but, in addition, singlets at δ 8.1 (CH=) and 6.86 (Ar) with *ca.* 30% of the intensity of (**5a**) were formed. These may be due to compound (**5b**).

When a mixture of 2,4-dimethylbenzaldehyde (1.2 g, 9 mmol) and trifluoroacetylacetone (**4**) (1.5 g, 10 mmol) in toluene (50 ml) was refluxed for 40 h in the absence of an added acid or base, the starting material was recovered after work-up.

Reaction of 2,4,6-*Trimethylbenzaldehyde with* 4,4,4-*Trifluoro*-1-*phenylbutane*-1,3-*dione*.—A mixture of the aldehyde (1.5 g, 10 mmol), 4,4,4-trifluoro-1-phenylbutane-1,3-dione (2.5 g, 11 mmol), piperidine (0.5 ml), and AcOH (0.6 ml) in dry benzene (50 ml) was refluxed for 88 h with azeotropic distillation. The orange oil obtained after the usual work-up, contained (by n.m.r.) 25% of the aldehyde, 35% of the diketone, and 40% of a 4:1 *E*:*Z* or *Z*:*E* mixture of the condensation products. Chromatography on dry silica using 7:3 hexane–$CHCl_3$ as the eluant followed by a second separation on a preparative t.l.c. plate, gave the minor isomer as a white solid (90 mg, 3%), m.p. 41 °C. We were unable to separate the main isomer from the starting materials. The spectral data are given in Table 1.

Reaction of Compound (**4**) *with* 4-*Methoxy*-4′-*nitrobenzophenone*.—(*a*) A mixture of the benzophenone (1.53 g, 6 mmol), (**4**) (1.1 g, 7 mmol), piperidine (0.3 ml), and AcOH (0.4 ml) in benzene (50 ml) was refluxed in a Dean–Stark apparatus for 90 h. After work-up only the benzophenone was recovered.

(*b*) To the same composition of reagents, NaH (50% in hexane; 330 mg, 7 mmol) in dry ether (100 ml) was added, and the mixture was stirred for 90 h at room temperature. Work-up as usual gave only the benzophenone.

Condensation of Aldehydes with Acetylacetone.—(*a*) *Anisaldehyde*. A mixture of anisaldehyde (1.8 g, 13 mmol), acetylacetone (1.6 g, 16 mmol) in dry benzene, piperidine (0.4 ml), and AcOH (0.5 ml) was refluxed with azeotropic distillation for 5 h. The mixture was washed with dilute HCl (50 ml) and then with water (30 ml), dried ($MgSO_4$), filtered and the solvent was evaporated. The orange oil was chromatographed on dry silica and eluted with CH_2Cl_2–hexane, giving unchanged anisaldehyde (0.4 g) and an oil (0.7 g). Trituration with hexane gave yellowish-green crystals of 3-*p*-methoxybenzylidenepentane-1,4-dione (**2a**) (0.6 g, 21%), m.p. 45 °C, which did not show colouration with methanolic $FeCl_3$. The data are given in Tables 1 and 4.

(*b*) 2,4,6-*Trimethylbenzaldehyde*. A mixture of 2,4,6-trimethylbenzaldehyde (2.7 g, 18 mmol), acetylacetone (2.5 g, 25 mmol), piperidine (0.5 ml), and AcOH (0.6 ml) was refluxed for 20 h in a Dean–Stark apparatus, and, after 40 h at room temperature, worked up as described above. The oil obtained solidified on standing, giving 3-(2,4,6-trimethylbenzylidene)pentane-2,4-dione (**11a**), (1.3 g, 31%), m.p. 40 °C. After distillation of the aldehyde at 160 °C/25 mmHg, further product (0.49; total yield 41%) was obtained. The compound did not show a molecular peak in the mass spectrum. The n.m.r. spectrum shows two COMe signals 0.49 p.p.m. apart. The singlets at δ 2.17 (*o*-Me) and 2.28 (*p*-Me) are wider than other Me signals, even after irradiation of the aromatic signal. The data are given in Tables 1 and 4.

Stability of 1,1,1-*Trifluoro*-3-(4-*methylbenzylidene*)*pentane*-2,4-*dione* (**6c**) *under the Reaction Conditions*.—(*a*) Compound (**6c**) (0.3 g, 1.2 mmol) in benzene (50 ml) was refluxed under azeotropic distillation for 16 h. Only the starting material was recovered.

(*b*) When piperidine (0.3 ml) and AcOH (0.4 ml) were added and the mixture was refluxed for an additional 26 h a red viscous oil was obtained after work-up. The n.m.r. spectrum showed the absence of (**6c**) and the presence of a small quantity of 1,1,1-trifluoro-3-(4-methylbenzylidene)acetone (**7c**) but the main product was 1,1,1-trifluoro-2-hydroxy-5-(4-methylbenzylidene)pent-2-en-4-one (**5c**).

(*c*) A mixture of (**6c**) (1.5 g, 5.9 mmol), piperidine (0.5 ml), and AcOH (0.6 ml) in benzene (100 ml) was refluxed for 7 h in a Dean–Stark apparatus. The reaction did not reach completion (n.m.r.). Chromatography over 30—70 mesh silica, using 20% $CHCl_3$–hexane gave (**7c**) (60 mg, 5%) followed by (**5c**) as light-yellow crystals, m.p. 35 °C (170 mg, 11%). The final fraction was a mixture of (**5c**), (**6c**), and the aldehyde. The data are in Tables 1 and 4.

Attempted Decomposition of 1,1,1-*Trifluoro*-2-*hydroxy*-5-(2,4,6-*trimethylbenzylidene*)*pent*-2-*en*-4-*one* (**5a**).—(*a*) A mixture of (**5a**) (200 mg, 2.4 mmol), piperidine (0.4 ml), and AcOH (0.6 ml) in dry benzene (100 ml) was refluxed for 22 h. After the usual work-up only the starting material was detected by t.l.c. and n.m.r. spectroscopy.

(*b*) A mixture of (**5a**) (310 mg, 1.1 mmol) and piperidine (150 mg, 1.8 mmol) in benzene (50 ml) was refluxed for 20 h. Work-up gave a solid whose n.m.r. spectrum showed it to be mainly (**5a**), admixed with 10% of a new material [δ($CDCl_3$) 2.16, 2.32, 2.38 (9 H, 3 Me), 6.33, 7.68 (2 H, AB q, *J* 16.7 Hz, CH=CH), 6.90 (2 H, s, Ar)], which was either (**6a**) or (**7a**).

Reaction of 2,4,6-*Trimethylbenzaldehyde with Piperidine*.—A mixture of the aldehyde (0.9 g, 6.4 mmol) and piperidine (1.1 g, 12.9 mmol) in benzene (100 ml) was refluxed for 20 h in a Dean–Stark apparatus. The oil obtained after removal of the solvent was identified by t.l.c. and n.m.r. spectroscopy as the aldehyde. No signal corresponding to the aminal $ArCH(NC_5H_{10})_2$ was observed.

Reaction of 1,1,1-*Trifluoroacetylacetone with Piperidine*.—(*a*) To (**4**) (3 g, 19.5 mmol) was added piperidine (1.5 g, 20.3 mmol). Heat was evolved and a viscous oil was obtained. Trituration with benzene after 30 min gave a white solid (4.3 g, 95%), m.p. 40 °C, which was identified as the enol form, 1,1,1-trifluoro-2,4-dihydroxy-2-piperidinopent-3-ene, of the carbinolamine (**12**): $\lambda_{max.}$ cyclohexane 286 (log ε 3.91); $\lambda_{max.}$(EtOH) 294 nm (log ε 4.19); $\nu_{max.}$($CHCl_3$) 3 500—2 800 (br, OH, CH), 1 630 (C=O), 1 500, 1 440, 1 350, 1 280—1 160 cm^{-1}; δ_H($CDCl_3$) 1.64 (6 H, m, β- and γ-piperidine-H), 2.0 (3 H, s, Me), 3.03 (4 H, br t, α-piperidine-H), 5.53 (1 H, s, =CH), and 8.22 (concentration-

dependent, 2 H, br s, OH); $\delta_C(CDCl_3)$ 22.12 (s, piperidine γ-C; t at off-resonance), 22.36 (s, piperidine β-C, t at off-resonance), 29.79 (s, C-5, q at off-resonance), 44.26 (s, piperidine α-C, t at off-resonance), 93.18 (s, C-3, d at off-resonance), 119.36 (q, J_{CF} 289 Hz, C-1, q at off-resonance), 167.9 (q, J_{CF} 29.3 Hz, C-2, q at off-resonance), and 195.81 p.p.m. (s, C-4, s at off-resonance); *m/z* no molecular peak, 221 (33%, $M - H_2O$), 154 (22, $M -$ Me $- H - CF_3$), 152 (57, $M - H_2O - CF_3$), 124 (92, $M - H_2O - CF_3$), 85 (B, $C_5H_{10}NH$), and 84 (98, C_5H_{10}) (Found: C, 50.0; H, 6.6; N, 6.0. Calc. for $C_{10}H_{16}F_3NO_2$: C, 50.20; H, 6.69; N, 5.86%).

(*b*) The carbinolamine (**12**) (2.8 g, 11.7 mmol) was refluxed in dry benzene (50 ml) for 3 days in a Dean–Stark apparatus. Evaporation of the solvent gave a light brown viscous oil (2.3 g, 90%) which (by n.m.r.) consisted of (**12**) 2% and the enamine (**14**) (88%); $\lambda_{max.}$(EtOH) 324 nm (log ε 4.40); $\nu_{max.}$(neat) 2 970, 2 930 (C–H), 1 660 (C=O, sh), 1 640, 1 550, 1 460, and 1 390 cm^{-1}; $\delta(CDCl_3)$ 1.69 (6 H, m, β-, γ-piperidine-H), 2.62 (3 H, s, Me), 3.53 (4 H, m, α-piperidine-H), and 5.36 (1 H, s, =CH); *m/z* 221 (59%, *M*), 204 (11%, $M - OH$), 152 (B, $M - CF_3$), 124 (92, $M - CO - CF_3$ or $M - C_5H_{10}N - CH$), and 84 (5.4, $C_5H_{10}N^+$) (Found: C, 54.55; H, 6.22; N, 6.56. Calc. for $C_{10}H_{14}F_3NO$: C, 54.30; H, 6.33; N, 6.33%).

When the mixture of piperidine with (**4**) was refluxed for 18 h, an oil was obtained which, on the basis of the ^1H n.m.r. spectrum, consists of a 4:1 ratio of (**12**) to (**14**). Most of the material decomposed on distillation at 70 °C/25 mmHg.

Condensation of Compound (**12**) *with* 2,4,6-*Trimethylbenzaldehyde*.—A mixture of the aldehyde (0.6 g, 4 mmol) and (**12**) (0.96 g, 4 mmol) in dry benzene (50 ml) was refluxed for 50 h. The solvent was evaporated and the n.m.r. spectrum of the red viscous oil showed unchanged aldehyde (*ca.* 50%), (**5a**) (40%), and several other compounds (*ca.* 10%) which may include (**7a**), (**14**), and the methyl-condensation product of the enamine.

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