FRIEDEL–CRAFTS ACETYLATION OF DURENE, ISODURENE AND PREHNITENE

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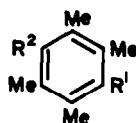School of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH, England

Abstract—Good yields of acetyl- and diacetyl-durene, acetyl- and diacetyl-isodurene, and acetylprehnitene can be obtained by Friedel–Crafts acylations. Products arising from methyl-migration prior to acetylation are also formed. A claim of the formation of diacetylprehnitene is shown to be incorrect.

The Friedel–Crafts acetylations of the tetramethylbenzenes have been studied several times, durene (Ia),[1–3] isodurene (IIa),[1,3] and prehnitene (IIIa),[1,3] giving good yields (70–80%) of the expected mono-ketones, (Ib, IIb, and IIIb), respectively. With an excess of reagents diketones (Ic and IIc) are formed.[4] Formation of diacetylprehnitene (IIIc) was also reported.[1] When durene was acetylated using an excess of aluminium chloride,[2] a product of methyl-rearrangement, diacetylisodurene (IIc), was reported as a by-product. In the acetylation of prehnitene under strenuous conditions substantial formation of diacetyldurene (Ic) was recorded.[1] In view of these anomalous reactions, the problems of steric crowding associated with the formation of hexa-substituted benzenes, known acyl-rearrangements,[2,5,6] methyl-rearrangements,[7–10] and methyl-disproportionations[5,9,11–13] in systems of this type, it was decided to reinvestigate the Friedel–Crafts acetylations of these hydrocarbons.

(a) $R^1 = R^2 = H$

(b) $R^1 = Ac$, $R^2 = H$

(c) $R^1 = R^2 = Ac$

The results from Friedel–Crafts monoacetylations of the tetramethylbenzenes are given in Table 1. The Perrier addition procedure, which avoids direct contact between the catalyst, aluminium chloride, and the substrate was mainly used. Analyses of mixtures was achieved by the use of glc. High yields of monoketones were obtained in each reaction, in particular when two moles of the preformed acetyl chloride/aluminium chloride complex were used. In most acylations trace amounts of other products were formed. In one reaction (no. 4) of durene *ca.* 2% of the isomer prehnitene was present. In another acylation (no. 8), of isodurene, the product mixture contained *ca.* 2% each of durene and prehnitene, as well as small amounts of the corresponding ketones, (Ib
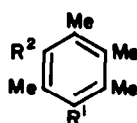
and IIIb). Analogously, in most of the acetylations of prehnitene *ca.* 3–4% of durene were formed, together with small amounts of acetyldurene (Ib) and acetylisodurene (IIb).

In an attempt to explain the formation of these by-products the isomeric tetramethylbenzenes were treated in 1,2-dichloroethane solution with the molecular complex of acetophenone/aluminium chloride for an extended duration. In this way it was hoped to simulate conditions under which rearrangements could occur in the substrates when treated with acetyl chloride/aluminium chloride. Alternative conditions, such as treatment with solid, uncomplexed catalyst would have been too harsh; and treatment with aluminium chloride in nitromethane solution would have involved a very different system in which the many basic solvent molecules would compete for the Lewis acid. The results of these stability tests are given in Table 2. Under the conditions used slow conversion (no. 17) is seen to occur of durene into prehnitene, and, rather more rapidly (no. 18), of isodurene into durene. Durene and prehnitene have been reported to be converted into isodurene, in anhydrous hydrogen fluoride (with or without addition of BF_3 or NbF_5); the two reactions were said to occur at practically the same rate.[8] Applying M.O. theory to the study of methyl transfer in polymethylbenzenes, it was concluded that these acid-catalysed rearrangements take place intramolecularly by successive 1,2-shifts.[14] The formation of by-products as given in Table 1 can, we believe, best be explained in terms of some rearrangement of the hydrocarbons accompanying the faster acetylation reactions.
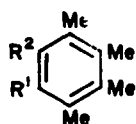
Acylations were also conducted with a view to obtaining good yields of diketones (Table 3). Diacetyldurene (Ic) and diacetylisodurene (IIc) are formed in >90% yields from the corresponding hydrocarbons, if an excess of acylating reagent (*cf* Ref. 4), and especially if an excess of catalyst over the acylating reagent, is employed (nos 20, 23). The presence of excess of (solid) aluminium chloride, however, permits the incursion of rearrangement reactions. It is evident from the high yields of diketones (Ic and IIc) obtainable that the second acetylation stage proceeds at a much faster rate than do the various rearrangements. The reported[1] formation of a high yield of acetyldurene (Ib) accompanying the diacetylation of isodurene could not be confirmed. It was found here (no. 23) that "foreign" ketones amount to no more than 1.3% of the total reaction product.

Table 1. Friedel-Crafts acetylation of the tetramethylbenzenes[1]

Reaction no.	Hydrocarbon	Solvent	Conditions[2]	Products (%)					
				(Ia)	(IIa)	(IIIa)	(Ib)	(IIb)	(IIIb)
1	(Ia)	CHCl$_3$	A				100		
2		CS$_2$	A	0.6		0.2	99.2		
3		MeNO$_2$	A	3.2			96.8		
4		CS$_2$	B	1.5		0.1	98.3[3,4]		
5		CCl$_4$	C[5]	2.3	0.1	2.3	94.6[3]		
6	(IIa)	CHCl$_3$	A		2.1			97.9	
7		MeNO$_2$	A		2.3			97.7	
8		CS$_2$	D[6]	1.8	0.6	1.9	2.2	92.8	0.7
9	(IIIa)	CHCl$_3$	A			2.3	4.1	0.7	95.3
10		CS$_2$	A			2.6	2.8	1.1	93.8
11		Me NO$_2$	A			0.7	2.1	0.5	94.8
12		CHCl$_3$	E	2.9		3.1			96.4[3]
13		CS$_2$	E	4.2					91.8[3]
14		MeNO$_2$	E	2.7	0.9	1.8	0.9	0.1	94.6[3]
15		(CH$_2$Cl)$_2$	E	4.0		2.1			93.9[3]
16		PhNO$_2$	E	3.0	0.2	0.5		0.4	95.9[3]

[1] Unless stated to the contrary, the Perrier procedure was used   [2] A: molar ratios of substrate:AcCl:AlCl$_3$ = 1:2:2, molarity of substrate = 0.7M, at 25°C/1h; B: molar ratios of substrate:Ac$_2$O:AlCl$_3$ = 1:1.9:3.5, molarity of substrate = 1.5M, using the Bouveault procedure, at 25°C/1h, then 50°C/3h; C: molar ratios of substrate:AcCl:AlCl$_3$ = 1:1:1, molarity = 1.5M, at 5°C/1h, then 25°C/1h; D: molar ratios of substrate:Ac$_2$O:AlCl$_3$ = 1:1.2:2.2, molarity of substrate = 2.5M, using the Bouveault procedure at 50°C/0.5h; E: molar ratios of substrate:AcCl:AlCl$_3$ = 1:1.1:1.1, molarity of substrate = 1.0M at 25°C/3h   [3] Product was isolated in high yield (> 80%) by crystallisation   [4] Ketone (Io)(0.1%) also formed   [5] Method of Ref 2   [6] Method of Ref. 1.

Table 2. The action of aluminium chloride/acetophenone on durene, isodurene and prehnitene in 1,2-dichloroethane solution at 20° for 15 hr[1]

Reaction no.	Hydrocarbon	Products (%)[2]		
		(Ia)	(IIa)	(IIIa)
17	(Ia)	89.4		10.6
18	(IIa)	35.8	64.2	
19	(IIIa)			81.4[3]

[1] Molar ratios of hydrocarbon: aluminium chloride: acetophenone = 1:1:1, molarity = 0.65M [2] Xylenes, mesitylene, pentamethylbenzene and hexamethylbenzene were absent [3] A compound (19% w/w) was formed, but not identified.

Table 3. Formation of diketones in the Friedel–Crafts acetylation of the tetramenthylbenzenes in carbon disulphide suspension

Reaction no.	Hydrocarbon	Conditions[1]	Products (%)							
			(Ia)	(IIa)	(IIIa)	(Ib)	(IIb)	(IIIb)	(Ic)	(IIc)
20	(Ia)	A	0.1			1.6			98.3[2]	
21		B[3]				69.6		2.9	27.5	
22	(IIa)	C					97.8			2.2
23		D[4]	0.9	2.9	0.1		3.6	1.2	0.1	91.2[2]
24	(IIIa)	D[5]			0.6	0.3	0.3	90.6	5.4	2.8
25		E				0.1	0.1	81.0	11.6	7.2
26		F			0.3			93.2	4.9	1.6
27		G						70.8	20.3	8.9

[1] A: Perrier conditions, molar ratios of substrate:AcCl:AlCl$_3$ = 1:4.3:6.8, molarity of substrate = 0.25M, 50°C/1h; B: Bouveault conditions, molar ratios = 1:1.9:3.5, molarity of substrate = 1.5M, 25°C/1h, then 50°C/3h; C: Perrier conditions, molar ratios = 1:2:2, molarity of substrate = 0.75M, 25°C/1h; D: Bouveault conditions, molar ratios of substrate:Ac$_2$O:AlCl$_3$ = 1:2.3:6, molarity of substrate = 1.0M, 50°C/2h; E: As for D, but with molar ratios = 1:6:6; F: Perrier conditions, in 1,2-dichloroethane solution, molar ratios of substrate:AcCl:AlCl$_3$ = 1:10:10, molarity of substrate = 0.5M, 50°C/40h; G: As for F, but with molar ratios = 1:40:40, 50°C/48h, then 25°C/72h [2] Isolated yield normally >80% [3] Method of Ref 2. Reported yields: 56% of (Ib) and 14% of (Ic) [4] Reported yields (Ref 1): 53% of (Ib) and 6% of (IIc) [5] Reported yields (Ref 1): 40% of (Ib) and 8% of 'diacetylprehnitene' (IIIc).

It had been reported that treatment of prehnitene (IIIa) with an excess of acetic anhydride and aluminium chloride resulted in the formation of a 40% yield of acetyldurene and an 8% yield of a diketone (with acceptable C, H analyses), m.p. 113°, called "diacetylprehnitene". The evidence advanced for its structure was very slender; on the basis of our results (nos 24–27) the diketone isolated[1] was probably impure diacetyldurene (Ic). In the presence of an excess (up to 40×) of reagents, in carbon disulphide or 1,2-dichloroethane media, the main product was the monoketone (IIIa). There was no evidence of the formation of a new diketone, but the isomers (Ic) and (IIc) were indeed formed, up to a total of ca. 30%. The ratios of diketones (Ic)/(IIc) were reasonably constant, 1.6–1.9 in carbon disulphide, or 2.3–3.1 in 1,2-dichloroethane.

The non-formation of diacetylprehnitene (IIIc) is not, perhaps surprising. The formation of the diketones (Ic and IIc) indicates that there is no inherent difficulty in obtaining hexasubstituted benzenes by the Friedel–Crafts reaction. The introduction of a first acetyl-group, as in (Ib or IIb), does not cause major deactivation of the nucleus, as can be seen, e.g. from our data (nos 4 and 23), where diketones are already being formed even

though the starting hydrocarbons are still available and competing for the acylating reagent (cf acetylation of mesitylene[6]). The probable reason is that two ortho-Me groups induce a rotation of the acetyl-group to a near orthogonal position,[15] and deactivation by conjugative interaction ($-\underline{M}$) is severely curtailed.

The reactivity in Friedel–Crafts acetylation of prehnitene was found to be about the same as that of isodurene.[3] In acetylprehnitene (IIIa) the reactivity of the free position will be substantially reduced, since there is a single methyl-group ortho to the acetyl group, which will rotate away from the aromatic plane by no more than ca. 30°,[16] and which will offer more hindrance to attack by an acetyl reagent than would two flanking methyl groups.

Since previously the ketones formed were often of unstated purity their physical constants are here recorded in some detail.

EXPERIMENTAL

General. Temps are in °C. All m.ps are uncorrected. IR spectra were recorded, unless otherwise stated, for discs in KBr. PMR and ^{13}C-NMR spectra were obtained, unless otherwise stated, for solutions in CDCl$_3$. Glc analyses were conducted using (i) for

monoacetylation products, a column 2 m × 6 mm of 3% O.V. 17 on 60–80 mesh diatomite "C", acid washed and silanised with DMCS, at 150°, (ii) for diacetylation products, a column 2 m × 6 mm of 5% O.V. 17 on 80–100 mesh diatomite "C", acid washed and silanised with DMCS, at 180°, and (iii) a column 1 m × 0.25 mm, WCOT with O.V. 17 coating, at 150°, all using N_2 as carrier gas and a flame ionisation detector.

Hydrocarbons. Commercial 1,2,3,4-tetramethylbenzene (86% by glc) was converted into its picrate, m.p. 86–87° (lit.[17] m.p. 92–95°); IR 1175 (OH), 1370 (NO_2) and 1540 cm^{-1} (NO_2). Regeneration from the picrate gave 1,2,3,4-tetramethylbenzene (> 99.4%), b.p. 46–46.5° at 1.5 mm Hg, n_D^{21} 1.5240 (lit.[18] b.p. 96.5° at 25 mmHg, n_D^{20} 1.5202); IR (film) 810 (C–C) and 1480 cm^{-1} (C–H); PMR δ 2.50 (s, 1- and 4-CH_3), 2.98 (s, 2- and 3-CH_3), and 7.15 (s, 5- and 6-H); ^{13}C-NMR (CCl$_4$) δ 19.0 (CH_3), 131.0 (3- and 6-C), 132.9 (1-, 2-, 4- and 5-C) ppm.

1,2,3,5-Tetramethylbenzene(91% pure) gave a picrate, m.p. 90–91°; IR 1166 (OH), 1343 (NO_2) and 1530 cm^{-1} (NO_2). It gave 1,2,3,5-tetramethylbenzene (>99%), b.p. 35–35.5° at 0.7 mmHg, n_D^{20} 1.5131 (lit.[19] b.p. 104.5° at 30 mmHg, n_D^{20} 1.5130); IR (film) 860 (C–C) and 1494 cm^{-1} (C–H); PMR δ 1.99 (s, 2-CH_3), 2.05 (s, 5-CH_3), 2.10 (s, 1- and 3-CH_3), 6.72 (s, 4- and 6-H); ^{13}C-NMR (CCl$_4$) δ 14.7 (2-CH_3), 20.4 (1- and 2-CH_3), 21.0 (5-CH_3), 128.8 (4- and 6-C), 131.4 (2-C), 134.2 (5-C), 135.8 (1- and 3-C) ppm. Another specimen was obtained from 2,4,6-trimethylbenzaldehyde,[20] b.p. 130–132° at 18 mm Hg, n_D^{20} 1.5540 (lit.[20] b.p. 118–121° at 16 mm Hg) by reduction[21] (yield 92%). The hydrocarbon had b.p. 35–36° at 0.7 mm Hg, n_D^{18} 1.5146, showed a single peak by glc (>99.5%) and was identical (IR) with the above product.

Commercially "pure" 1,2,4,5-tetramethylbenzene (96% pure by glc) was recrystallised repeatedly (EtOH) to give crystals (> 99.7%), m.p. 79.5–80° (lit.[20] m.p. 79.2°); IR 870 (C–C) and 1465 cm^{-1} (C–H); PMR δ 2.10 (s, CH_3) and 6.88 (s, 3- and 6-H).

Friedel–Crafts acylations

(i) *General.* The components were brought together in the chosen solvent in the usual way, with final addition of the hydrocarbon (Perrier procedure) or of the acyl component (Bouveault procedure).

(ii) *Acetylation of 1,2,3,4-tetramethylbenzene* (method of Ref. 1; no. 24).—Aluminium chloride (29.6 g) was added to a stirred suspension of 1,2,3,4-tetramethylbenzene (5.0 g) in carbon disulphide (37 ml) at 20°, followed by dropwise addition during 15 min of AcO (8.7 g). The mixture was then gently boiled for 2 hr, then cooled, and poured into ice-water. Working up in the usual way a dark-brown liquid (7 g) was obtained, which deposited a solid (2.2 g) on standing. Crystallisation from ether afforded (i) 1,4-diacetyl-2,3,5,6-tetramethylbenzene (0.13 g), m.p. and mixed m.p. 177–178°, identical (IR, PMR) with an authentic specimen, and (ii) 1,3-diacetyl-2,4,5,6-tetramethylbenzene (0.50 g), m.p. and mixed m.p. 120°, identical (IR, PMR) with an authentic specimen.

Physical properties of ketones. 2,3,4,5-Tetramethylacetophenone had b.p. 83–83.5° at 0.2 mmHg (lit.[1] b.p. 122–124° at 8 mmHg). A sample, after preparative glc was >99.7% pure, and had n_D^{20} 1.5320, IR (film) 1692 cm^{-1} (C=O) (lit.[12] 1694 cm^{-1}). Bulk purification was achieved by regeneration of the picrate, m.p. 115–115.5°; IR 1165 (OH), 1338 (NO_2), 1540 (NO_2) and 1640 cm^{-1} (C=O), followed by redistillation (> 99.7% pure); PMR δ 2.13 (s, 3- and 4-CH_3), 2.20 (s, 5-CH_3), 2.25 (s, 2-CH_3), 2.43 (s, COCH_3), 7.11 (s, arom-H); (reported[12] PMR δ 2.09, 2.23, 2.35, 2.45, and 7.23); ^{13}C-NMR δ 18.0 (3-CH_3), 18.4 (4-CH_3), 19.0 (2-CH_3), 22.8 (5-CH_3), 32.2 (COCH_3), 129.3 (3-C), 134.8 (4-C), 135.5 (5-C), 139.0 (2-C), 139.9 (6-C), 140.7 (1-C), 206.1 (C=O) ppm.

2,3,4,6-Tetramethylacetophenone, prepared by the literature method,[1] had b.p. 102–104° at 3.5 mmHg, and was 97.9% pure by glc. It gave a picrate, m.p. 122–123°, IR 1150 (OH), 1340 (NO_2), 1551 (NO_2) and 1662 cm^{-1} (C=O); the recovered ketone (99.7%

pure) had b.p. 84.5–85.5° at 0.7 mmHg, n_D^{20} 1.5262 (lit.[1] b.p. 135–137° at 16 mmHg); IR (film) 1703 cm^{-1} (C=O) (lit.[12] 1695 cm^{-1}); PMR δ 2.11 (s, 3- and 4-CH_3), 2.15 (s, 2-CH_3), 2.21 (s, 6-CH_3), 2.39 (s, COCH_3), 6.81 (s, 5-H) (lit.[12] PMR δ 2.08, 2.13, 2.20, 2.30, 6.78); ^{13}C-NMR δ (CCl$_4$) 15.9 (3-CH_3), 17.9 (4-CH_3), 19.8 (2-CH_3), 21.6 (6-CH_3), 33.3 (COCH_3), 130.0 (3-C), 131.0 (4-C), 131.6 (2-C), 134.0 (5-C), 137.5 (6-C), 142.9 (1-C), 208.4 (C=O) ppm.

2,3,5,6-Tetramethylacetophenone formed crystals, m.p. 69–69.5° (lit.[2] m.p. 73°); IR 1692 cm^{-1} (C=O); PMR δ 2.09 (s, 3- and 5-CH_3), 2.28 (s, 2- and 6-CH_3), 2.47 (s, COCH_3), 6.86 (s, 4-H); ^{13}C-NMR δ (CCl$_4$) 15.6 (2- and 6-CH_3), 19.4 (3- and 5-CH_3), 32.2 (COCH_3), 127.3 (2- and 6-C), 131.2 (4-C), 133.8 (3- and 5-C), 143.6 (1-C), 206.4 (C=O) ppm.

1,3-Diacetyl-2,4,5,6-tetramethylbenzene had m.p. 119–119.5° (lit.[4] m.p. 119.5°); IR 1696 cm^{-1} (C=O); PMR δ 2.19 (s, 5-CH_3), 2.29 (s, 2-, 4- and 6-CH_3),[22] 2.63 (s, COCH_3).

1,4-Diacetyl-2,3,5,6-tetramethylbenzene had m.p. 177–177.5° (lit.[4] m.p. 177–178.5°); IR 1699 cm^{-1} (C=O); PMR δ 2.08 (s, arom-CH_3) and 2.42 (s, COCH_3) (lit.[15] PMR 2.10 and 2.44); ^{13}C-NMR δ 16.0 (CH_3), 32.6 (COCH_3), 128.5 (2-, 3-, 5-, and 6-C), 143.4 (1- and 4-C), 208.5 (C=O) ppm.

The action of solvated aluminium chloride on the tetramethylbenzenes. Using aliquots from standard solutions prepared in 1,2-dichloroethane solution, prehnitene (0.168 g) was added at 20° to a solution of acetophenone (0.150 g) and anhydrous aluminium chloride (0.167 g) in the solvent (1.93 ml), and the homogeneous mixture resulting kept at 20° for 15 hr. Working up of the mixture and preparation of the product for glc analysis was carried out in the usual way. For the other tetramethylbenzenes the same molarity (0.650 M) of reactants was employed, but the scale of the reactions varied, within the range 0.97–1.25 mmol.

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