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ACYLATIONS WITH PIVALYL CHLORIDE[1]

DOROTHY V. NIGHTINGALE, ROBERT L. SUBLETT, RICHARD A. CARPENTER, AND HERSCHEL D. RADFORD

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When pivalyl chloride is used as an acylating agent in the Friedel-Crafts reaction, yields of pivalophenones are usually low due to the rapid decomposition of the acid chloride into carbon monoxide, hydrogen chloride, and isobutylene (1, 2, 3).

In view of the recent interest in acylations with pivalyl chloride (3, 4), we are presenting a summary of our experience with this reagent during the last several years.

Fair yields of substituted pivalophenones were obtained from the following hydrocarbons in carbon disulfide solution at reflux temperature: toluene (20%), *o*-xylene (27%), *m*-xylene (38%) (5), mesitylene (35%), and isodurene (28%). *p*-Xylene, pseudocumene, and durene yielded only small amounts of impure ketone.

When the viscous tarry residues remaining in the distilling flasks were washed with ligroin, light colored solids remained. These solids were strongly fluorescent (blue) in ultraviolet light, and were identified by carbon and hydrogen analyses as polymethylanthracenes. The yields of purified anthracenes were 3–5%.

When the acylations were carried out at 0°, little or no ketone was formed and there was no residue.

It is of interest to note that there was some demethylation of the hydrocarbons. A tetramethylanthracene was a by-product from the acylation of mesitylene, whereas a hexamethylanthracene was obtained from pseudocumene, and hexamethylanthracenes were obtained from durene and isodurene. It was not possible to separate the polymethylanthracenes or the polymethylanthraquinones obtained from them or to determine their orientation.

The polymethylanthraquinones were best obtained by oxidation of the polymethylanthracenes in benzene solution with sodium dichromate and dilute sulfuric acid rather than by chromic anhydride in acetic acid solution.

When pivalic acid was added to *o*-, *m*-, and *p*-xylene and aluminum chloride at room temperature and then warmed on a water-bath, the amounts of polymethylanthracenes were increased but no appreciable amounts of ketones were isolated except from the reaction with *m*-xylene. Carbon and hydrogen analyses of this ketone agreed with the values for a dimethylpivalophenone, but the refractive index (n_D^{20} 1.5580) was high and the carbinol obtained by catalytic hydrogenation of the ketone was a solid, m.p. 87–88°, rather than the viscous carbinol obtained from the reduction of 2,4-dimethylpivalophenone. All efforts to oxidize the two carbinols to polycarboxylic acids led to inseparable mixtures

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[1] From the Ph.D. theses of R. L. Sublett and H. D. Radford and the Master's thesis of R. A. Carpenter.

of acids which could not be identified. The ketone may possibly be 3,5-dimethylpivalophenone.

The structure of 3,4-dimethylpivalophenone was established by its synthesis by the Grignard reagent from 4-bromo-*o*-xylene and pivalonitrile, but 2,4-dimethylpivalophenone could not by synthesized in this manner.

The structure of 2,3,4,6-tetramethylpivalophenone was established by cleavage of the ketone with sodium amide (6) to yield isodurene. The isodurene so obtained yielded dinitroisodurene, m.p. 156–157°, which did not depress the melting point of an authentic sample.

Substituted pivalophenones were formed from *o*-, *m*-, and *p*-cresol methyl ethers in yields of 75%, 23%, and 59% respectively when the acylations were done in carbon disulfide solution at a temperature range of 0° to 20°. At reflux temperature there was no acylation and the cresol ethers were recovered unchanged. No anthracenes were formed during these acylations and there was no residue.

Since Rothstein and Saville (4) reported increased yields of substituted pivalophenones when petroleum ether was used as solvent for the acylation of anisole, *tert*-butylbenzene, and some other compounds with pivalyl chloride, it was of interest to repeat some of the acylations in that solvent. Yields of substituted pivalophenones from *m*-cresol methyl ether, *o*-, *m*-, and *p*-xylene were increased to 63%, 36%, 53%, and 10% respectively, and smaller amounts of polymethylanthracenes were formed. No ketones were obtained when either durene or isodurene were acylated in petroleum ether solution; this may be due to the separation of an insoluble complex when the reagents were mixed.

The methylmethoxypivalophenones were reduced to the corresponding methylmethoxyneopentylbenzenes with hydrogen and copper-chromium oxide catalyst at 130–150° and 2200–2700 p.s.i., whereas *o*- and *p*-hydroxypropiophenone were reduced to the corresponding alkylphenols at 115–125° (7).

EXPERIMENTAL

The carbon and hydrogen analyses were done by R. A. Carpenter, R. L. Sublett, and J. S. Finney.

The acylations. (*a*) *In carbon disulfide solution.* The acylation of isodurene is typical. All reagents were anhydrous. Isodurene (35 g., 0.25 mole), 100 cc. of carbon disulfide, and 33.5 g. (0.25 mole) of aluminum chloride were stirred together in the usual apparatus. The solution was warmed to slight reflux and a solution of 30 g. (0.25 mole) of pivalyl chloride in 100 cc. of carbon disulfide was added during 30 minutes. The mixture was stirred and warmed gently for three hours more, when about half of the solvent was removed at reduced pressure. The complex was decomposed with iced hydrochloric acid, the oily layer was extracted with ether, and the ether solution was washed, dried, and distilled at 2 mm. through a small column. The following fractions were obtained: (a) 9.8 g., 60–112°; (b) 11 g., 110–117°; (c) 6.4 g., 117–119°; and (d) residue, 10 g.

Fraction a was mainly hydrocarbon.

Redistillation of fractions b and c through a small column packed with helices yielded 15 g. of 2,3,4,6-tetramethylpivalophenone, b.p. 117–119° (2 mm.), n_{D}^{25} 1.5170. This ketone would not form an oxime.

Fraction d consisted of a tar and a finely divided solid. The tar was extracted with ligroin, leaving a fluorescent solid which was recrystallized from benzene and ether. The

TABLE I

THE PIVALOPHENONES AND THEIR OXIMES

PIVALOPHENONE	n_D^{25}	B.P., °C.	KETONES						KETOXIMES					
			MM.	FORMULA	Calc'd		Found		M.P., °C.	FORMULA	Calc'd		Found	
					C	H	C	H			C	H	C	H
3,4-Dimethyl-	1.5150	102–109	2	$C_{13}H_{18}O$	82.08	9.53	81.85	9.77	202–203	$C_{13}H_{19}NO$	76.10	9.27	75.94	9.77
2,4-Dimethyl-	1.5023								153–154	$C_{13}H_{19}NO$	76.10	9.27	76.01	9.48
2,5-Dimethyl-	1.5168	76–78	2	$C_{13}H_{18}O$	82.08	9.53	82.33	9.63	162–163	$C_{13}H_{19}NO$	76.10	9.27	76.02	9.30
2,4,6-Trimethyl-	1.5150	120–122	8	$C_{14}H_{20}O$	82.3	9.87	82.22	10.33	[a]					
2,3,4,6-Tetramethyl-	1.5170	117–119	2	$C_{15}H_{22}O$	82.57	10.09	82.47	10.23	[a]					
2-Methyl-4-methoxy-	73–74[b]	126–128	4	$C_{13}H_{18}O_2$	75.66	8.75	75.37	8.53	177–178	$C_{13}H_{19}NO_2$	70.52	8.65	70.59	8.78
3-Methyl-4-methoxy	51–52[b]	127–129	4	$C_{13}H_{18}O_2$	75.66	8.75	75.15	9.03	172–173	$C_{13}H_{19}NO_2$	70.52	8.65	70.78	8.65
2-Methyl-5-methoxy-	50–51[b]	130–132	4	$C_{13}H_{18}O_2$	75.66	8.75	75.91	8.88	174–175	$C_{13}H_{19}NO_2$	70.52	8.65	70.25	8.44

[a] These ketones did not form oximes. [b] M.p., °C.

pale yellow plates (1.2 g.) melted at 269–271° and were identified as hexamethylanthracene.

Anal. Calc'd for $C_{20}H_{22}$: C, 91.61; H, 8.39.
Found: C, 91.43; H, 8.62.

The physical constants of the pivalophenones and their oximes are summarized in Table I.

The preparation of the polymethylanthraquinones. The hexamethylanthraquinone was prepared by dissolving 0.1 g. of the hexamethylanthracene from isodurene in 15 cc. of benzene and stirring this solution rapidly at room temperature with a solution of 2 g. of potassium dichromate in 50 cc. of dilute sulfuric acid. After two hours the benzene layer was concentrated to half its volume. The hexamethylanthraquinone crystallized on standing as a pale yellow solid, m.p. 200–202°.

TABLE II

REDUCTION PRODUCTS OF THE SUBSTITUTED PIVALOPHENONES

COMPOUND	B.P., C°.	MM.	n_D^{20}	FORMULA	CALC'D		FOUND	
					C	H	C	H
1-Methyl-3-methoxy-6-neopentylbenzene	93–94	4	1.4962	$C_{13}H_{20}O$	81.21	10.48	81.17	10.78
1-Methyl-2-methoxy-5-neopentylbenzene	102–104	4	1.4999	$C_{13}H_{20}O$	81.21	10.48	81.20	10.62
1-Methyl-4-methoxy-2-neopentylbenzene	92–93	4	1.4979	$C_{13}H_{20}O$	81.21	10.48	81.21	10.52
1,2,3,5-Tetramethyl-4-neopentylbenzene	96–97	2	1.5080[a]	$C_{15}H_{24}$	88.24	11.76	88.01	11.97
1,3-Dimethyl-4-neopentylbenzene	75–78	3	1.4983[a]	$C_{13}H_{20}$	88.63	11.37	88.52	11.52
(2,4-Dimethylphenyl)-*tert*-butylcarbinol	95–97	2	1.5155[a]	$C_{13}H_{20}O$	81.21	10.48	81.13	10.60
(x,x-Dimethylphenyl-*tert*-butylcarbinol(?)[b]	92–93	5	87–88[c]	$C_{13}H_{20}O$	81.21	10.48	81.13	10.31

[a] Refractive index at 25°. [b] Obtained by reduction of the ketone from the acylation of *m*-xylene with pivalic acid. [c] M.p., °C.

Anal. Calc'd for $C_{20}H_{20}O_2$: C, 82.19; H, 6.85.
Found: C, 82.15; H, 6.98.

The preparation of 3,4-dimethylpivalophenone from 4-bromo-o-xylene. The Grignard reagent was prepared from 46 g. (0.25 mole) of 4-bromo-*o*-xylene and 6 g. (0.25 mole) of magnesium in 250 cc. of ether. Pivalonitrile (21 g., 0.25 mole) was added rapidly according to the directions of Pearson (3). The solution was refluxed for two hours, then cooled and poured onto iced hydrochloric acid. The ether layer was separated, washed, dried, and distilled to yield 7.1 g. (15%) of 3,4-dimethylpivalophenone, b.p. 100–101° (3 mm.), n_D^{25} 1.5143. The oxime of this ketone melted at 202–203° and did not depress the melting point of the oxime of 3,4-dimethylpivalophenone obtained from *o*-xylene and pivalyl chloride.

(*b*) *Acylations in petroleum ether solution.* The acylation of *m*-cresol methyl ether is typical. *m*-Cresol methyl ether (24 g., 0.25 mole) in 100 cc. of petroleum ether (60–70°) was cooled to 0° in the usual apparatus, and 18.6 g. (0.14 mole) of aluminum chloride was added. The solution was maintained at 0° and stirred while a solution of 11.2 g. (0.1 mole) of pivalyl chloride in 20 cc. of petroleum ether was added during 30 minutes. The reaction mixture was stirred for one hour longer, then heated to 55–60° for an additional 15 minutes. The complex was decomposed and the ketone isolated in the usual manner. 3-Methyl-4-methoxypivalophenone, m.p. 73.5–74°, b.p. 126–128° (1 mm.) was obtained in 63% yield.

Reduction of the substituted pivalophenones. The ketones were reduced with hydrogen and copper-chromium oxide catalyst as previously described (7). Center cuts were used for physical constants and analytical samples (Table II). Yields were 89–92%.

Preparation of the ketoximes. The oximes were prepared from the ketones by the standard procedure, using hydroxylamine hydrochloride and sodium hydroxide.

Cleavage of 2,3,4,6-tetramethylpivalophenone with sodium amide (6). A mixture of 8.5 g. (0.04 mole) of 2,3,4,6-tetramethylpivalophenone, 2 g. of sodium amide, and 10 cc. of dry benzene was refluxed for eight hours. Ice was added to the solution, and the hydrocarbon layer was separated, washed, and dried. Careful fractionation of the benzene solution through a micro column yielded 1.2 g. of isodurene, b.p. 193–196°, n_D^{20} 1.5138 [literature value n_D^{20} 1.5134 (8)]. Nitration of this isodurene yielded dinitroisodurene, m.p. and mixed m.p. with an authentic sample 157–158° (9).

Reaction of m-xylene with pivalic acid. A mixture of *m*-xylene (1.6 moles) and pivalic acid (0.5 mole) was stirred while 1.1 moles of aluminum chloride was added during one hour. The mixture was stirred at room temperature for about 12 hours and then heated on a water-bath for six hours.

The complex was decomposed in the usual manner. Fractionation of the reaction product yielded the following fractions: (a) 14 g., 91–92° (5 mm.), n_D^{20} 1.5518; (b) 4.2 g., 95–102° (1 mm.), n_D^{20} 1.5598; (c) 16 g., 181–186° (3 mm.).

Analyses of fraction a corresponded to the values for a dimethylpivalophenone but the refractive index of 2,4-dimethylpivalophenone is n_D^{20} 1.5058. Reduction of this ketone with hydrogen and copper-chromium oxide catalyst yielded a white solid, m.p. 87–88°. The carbon and hydrogen analyses of this solid corresponded to the values for a (dimethylphenyl)-*tert*-butylcarbinol.

Oxidation of this carbinol with potassium permanganate in aqueous pyridine solution yielded an acid which melted at 223–225° after many recrystallizations, but carbon and hydrogen analyses and a neutral equivalent did not agree with any probable polycarboxylic acids or keto acids and indicated that the acid was a mixture.

Fraction c was a suspension of a yellow solid in a reddish oil. The oil was extracted with petroleum ether, leaving a mixture of polymethylanthracenes which melted at 234–239°.

SUMMARY

Fair to good yields of substituted pivalophenones may be obtained from the acylation of toluene, the xylenes, mesitylene, and the cresol methyl ethers with pivalyl chloride in petroleum ether solution. 2,3,4,6-Tetramethylpivalophenone was obtained in 38% yield from isodurene in carbon disulfide solution.

Polymethylanthracenes were by-products of these acylations.

Columbia, Missouri

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