[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Aromatization Studies. V. Synthesis of Alkylanilines from Alkylcyclohexenones

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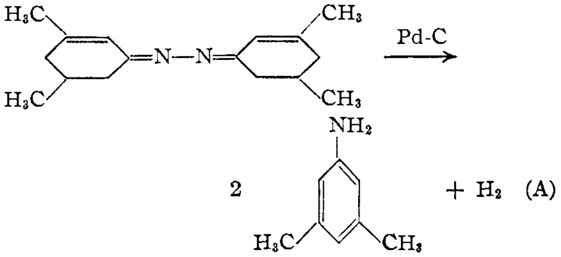
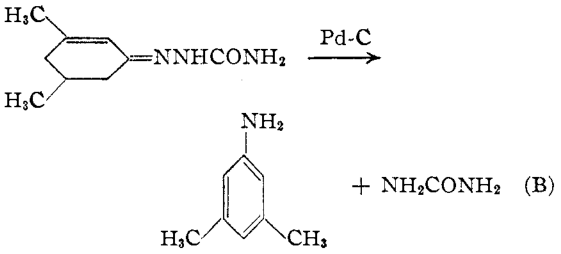
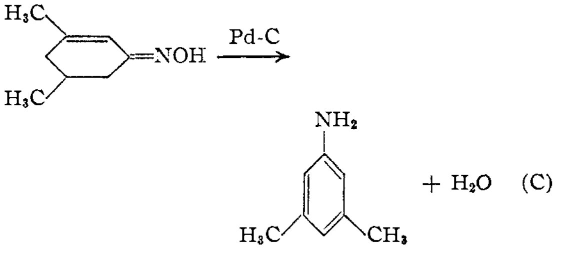
Previous studies in this series have been concerned chiefly with reactions designed to yield phenols through isomeric aromatization or dehydrogenation of hydroaromatic ketones. Both kinds of reactions are capable of proceeding rapidly and in good yield, under the influence of a palladium–carbon catalyst, but comparatively little is known of the limitations governing this general route to aromatic compounds. The present investigation was aimed at the exploration of methods for the conversion of hydroaromatic ketones to aromatic amines, by way of various carbonyl derivatives. Much of the exploratory work was carried out with derivatives of 3,5-dimethyl-2-cyclohexen-1-one.

The possible existence of reaction routes A, B and C was examined. These reactions involve the conversion of a hydroaromatic system into an aromatic one, and presumably a dehydrogenation of the alicyclic ring would be the first step in such a reaction.







It was found that reaction A could be carried out successfully, under comparatively mild conditions, using a 5% palladium–carbon catalyst, with a boiling solvent as a reaction medium. The experimental procedure was simple and straightforward; the azine and catalyst were heated under vigorous reflux in a suitable solvent for a fixed period of time, and after removal of the catalyst the amine was extracted with aqueous hydrochloric acid. The product was then converted into the corresponding alkylacetanilide. The determination of yields in the form of the acetanilide provided a more accurate basis for comparison than that afforded by isolation (by distillation) of the alkylanilines.

The results obtained at different temperatures, with varying reaction times, are noted in the experimental section. The maximum yield observed was about 50%, using triethylbenzene (b. p. 214°) as the solvent. The rate of reaction varied considerably with the temperature of the boiling medium, but even at a temperature of 136° (in ethylbenzene) the yield reached 28% in one hour. The highest temperature employed (phenyl ether, b. p. 252°) provided a yield of 44% in thirty minutes.

This reaction was extended to a series of 3-methyl-5-alkyl-2-cyclohexen-1-ones, in which the alkyl group was ethyl, *n*-propyl, isopropyl and isobutyl. The yields, under comparable conditions (triethylbenzene, thirty minute reaction time) were 50, 52, 53 and 40%, respectively.

Reaction routes B and C were also investigated, but without success. The conversion of alicyclic oximes into anilines is known to occur in a few limited instances, under the influence of acetic anhydride and hydrogen chloride, but a catalytic conversion was not observed. The aromatization of the oxime benzoate was also attempted without success.

This method of synthesis provides a route to nuclear alkylated anilines which are unavailable by the usual aromatic reaction routes. The availability of the required cyclohexenone appears at present to be the limiting factor, although information is not yet available on the influence of substituent groups in the 2- and 4-positions. An investigation of the application of this reaction to arylcyclohexenones and tetralones is now being carried out.

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Experimental

All melting points are corrected.

3,5-Dimethyl-2-cyclohexen-1-one Azine.—To 74.6 g. of 3,5-dimethyl-2-cyclohexen-1-one in 100 ml. of ethanol

TABLE I

3-METHYL-5-ALKYL-2-CYCLOHEXEN-1-ONE AZINES

5-Alkyl	Formula	Yield, %	B. p., °C.	B. p., Mm.	M. p., °C.[a]	Analyses, %, Calcd., C	Analyses, %, Calcd., H	Analyses, %, Found, C	Analyses, %, Found, H
Methyl	$C_{16}H_{24}N_2$	67	167–174	2–3	81–83	78.63	9.90	78.62	9.59
Ethyl	$C_{18}H_{28}N_2$	62	170–171	1		79.36	10.36	79.20	10.23
i-Propyl	$C_{20}H_{32}N_2$	24[b]	188–192	1–2	102–104	79.95	10.74	79.88	10.70
n-Propyl	$C_{20}H_{32}N_2$	74[c]	195–201	1–2		79.95	10.74	80.12	10.67
i-Butyl	$C_{22}H_{36}N_2$	65[c]	199–204	1–2	96–98	80.42	11.05	80.41	10.99

[a] After recrystallization from petroleum ether. [b] It was later found that this azine was not completely extracted from ether solution by dilute hydrochloric acid; this may account for the greatly decreased yield. [c] Extraction with dilute hydrochloric acid was omitted from the procedure.

TABLE II

3-METHYL-5-ALKYLACETANILIDES

5-Alkyl	Formula	Yield, %	M. p., °C.	Analyses, %, Calcd., C	Analyses, %, Calcd., H	Analyses, %, Found, C	Analyses, %, Found, H
Methyl	$C_{10}H_{13}ON$	50	140–140.5				
Ethyl	$C_{11}H_{15}ON$	50	107–109[a]	74.54	8.53	74.60	8.54
i-Propyl	$C_{12}H_{17}ON$	53	86–87[b]	75.35	8.95	75.48	8.97
n-Propyl	$C_{12}H_{17}ON$	52	75–76[b]	75.35	8.95	75.45	8.75
i-Butyl	$C_{13}H_{19}ON$	40	92–93[a]	76.05	9.33	75.96	9.27

[a] Recrystallized from cyclohexane. [b] Recrystallized from ethyl acetate–petroleum ether.

(95%) were added 21.0 g. of 85% hydrazine hydrate and 3 drops of concentrated hydrochloric acid. The solution was heated under reflux for one hour, and poured into 500 ml. of water. The azine was extracted with ether, using one 200-ml. portion and two 100-ml. portions. The combined ether extracts were extracted with one 200-ml. portion and three 100-ml. portions of 5% hydrochloric acid. The acid extracts were combined, chilled and made alkaline with 10% sodium hydroxide solution. The azine, which separated in crystalline form, was removed by extraction with one 150-ml. portion and two 50-ml. portions of ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and distilled. The azine was distilled under reduced pressure; there was obtained 49.5 g. (67%) of yellow crystalline product, boiling at 167–174°(2–3 mm.), m. p. 79–82°.

Recrystallization was effected from petroleum ether (35–60°), in 95% recovery, by chilling with Dry Ice.

Experimental data for other 3-methyl-5-alkyl-2-cyclohexen-1-one azines are in Table I.

Aromatization of Azines.—Numerous experiments were carried out with the aim of determining the optimum conditions for aromatization of these azines. The reactions were carried out in boiling solvents, with a palladium–carbon catalyst. In preliminary experiments with 3,5-dimethyl-2-cyclohexen-1-one azine, it was found advantageous to isolate the product as 3,5-dimethylacetanilide, rather than to attempt to distil 3,5-dimethylaniline. This procedure was followed in all later experiments. The best results were obtained with a reflux period of thirty minutes in triethylbenzene, and this particular experiment is described below.

To 15 ml. of triethylbenzene there was added 5.00 g. of 3,5-dimethyl-2-cyclohexen-1-one azine and 1.5 g. of 5% palladium–carbon catalyst.[1] The mixture was maintained under vigorous reflux for thirty minutes. After cooling to about 50°, the catalyst was removed by filtration, and washed with 20 ml. of warm benzene. The benzene–triethylbenzene solution was extracted with one 40-ml. portion and two 20-ml. portions of 5% hydrochloric acid. Ten per cent. sodium hydroxide solution was added to the acid solution until turbidity was produced; 10–15 ml. of 5% hydrochloric acid was then added, and the solution was diluted by the addition of 100 ml. of water. Fifteen milliliters of acetic anhydride was added, the flask was shaken vigorously, and a solution of 20 g. of sodium acetate trihydrate in 80 ml. of water was added. The mixture was chilled overnight and the crystalline anilide removed by filtration, washed well with water, and dried *in vacuo*. The yield was 3.36 g. (50%), m. p. 139.5–140°.

Recrystallization from ethyl acetate–petroleum ether yielded colorless needles, m. p. 140–140.5° in agreement with the literature.[2]

The effect of variations in the temperature and time of reaction on the aromatization of 3,5-dimethyl-2-cyclohexen-1-one azine was investigated with the following results: Ethylbenzene (b. p. 136°), with sixty-minute reaction time, gave a yield of 28%. Isopropylbenzene (b. p. 153°), with a sixty-minute reaction time, gave a yield of 46%. Cymene (b. p. 177°), with reaction times of 30, 60, and 120 minutes, gave yields of 41, 42 and 36%, respectively. Triethylbenzene (b. p. 214°), with reaction times of 30 and 60 minutes, gave yields of 50 and 43%, respectively. Phenyl ether (b. p. 252°), with reaction times of 30 and 60 minutes, gave yields of 44 and 39%, respectively. These yields were based on crude, dried products, none of which melted over more than 1° range at 138 or 139°.

Other 3-methyl-5-alkylacetanilides were obtained by following the procedure described, with a reaction period of thirty minutes in triethylbenzene. The experimental data are in Table II.

Other Aromatization Experiments.—In separate experiments, using triethylbenzene as a solvent with reaction periods of one to two hours, the effect of a palladium–carbon catalyst on the oxime,[3] oxime benzoate,[3] and semicarbazone[4] of 3,5-dimethyl-2-cyclohexen-1-one was examined. No aniline fraction was detected.

Summary

Azines of 3-methyl-5-alkyl-2-cyclohexen-1-ones have been aromatized to the corresponding 3-methyl-5-alkylanilines by a palladium–carbon catalyst. The reaction has been carried out in boiling solvents at temperatures from 136–252°. The best conversion (50%) was obtained in triethylbenzene (b. p. 214°) with a reaction period of thirty minutes.

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[1] Prepared according to Hartung's method, "Organic Syntheses," **26**, 77 (1946).

[2] Thöl, *Ber.*, **18**, 362 (1885); Wolff, *Ann.*, **322**, 382 (1902).

[3] Knoevenagel, *ibid.*, **281**, 104 (1894).

[4] Mazurewitsch, *J. Russ. Phys.-Chem. Soc.*, **45**, 1925 (1913).