[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, REED COLLEGE]

Preparation of Tertiary Amines by the Leuckart Reaction[1]

BY J. F. BUNNETT AND JEAN LOVENDAHL MARKS

Although the conversion of aldehydes and ketones to primary, secondary or tertiary amines by reductive condensation with an appropriately substituted ammonium formate or formamide has been known for several decades,[2,3] the Leuckart reaction did not come into general use as a preparative method until 1936 when Ingersoll and co-workers[4] developed a procedure by means of which 52 to 85 per cent. yields of primary amines were obtained from a variety of ketones. Novelli[5] showed that comparable yields of secondary amines could be obtained by the action of N-alkyl formamides on some substituted acetophenones according to a similar experimental procedure. There has been, however, no development of the Leuckart reaction as a general method for the synthesis of tertiary amines.

The few recorded instances of Leuckart reactions leading to tertiary amines fall into two groups: (A) those cases in which an aldehyde was caused to react with formamide or a monoalkylformamide (in these cases two or three of the alkyl groups in the tertiary amine product came from the aldehyde used) and (B) those cases in which an aldehyde or ketone reacted with a dialkylformamide. Examples of (A) are the formation of diamylaniline from valeraldehyde and formanilide,[3] of difurfurylmethylamine from furfural and methylamine formate,[6] and of tribenzylamine from benzaldehyde and formamide.[3] In group (B) fall the reaction of benzaldehyde with formylpiperidine to give N-benzylpiperidine,[3] the conversion of furfural to furfuryldimethylamine[6] and of acetophenone to N-(α-methylbenzyl)-piperidine.[7] An attempt to cause dimethylammonium formate to condense with laurophenone was unsuccessful.[8] In none of the above cases were yields reported; only Nabenhauer[6] appears to have employed the reaction as a method for the preparation of substantial amounts of tertiary amines.

In initial experiments in which the experimental procedure of Novelli[5] was followed, 14% conversion[9] of acetophenone to α-N,N-trimethylbenzylamine (I) and 5% conversion of *p*-bromoacetophenone to *p*-bromo-α,N,N-trimethylbenzylamine (II) were obtained. Shortly after these experiments were completed, there arrived in our laboratories an interesting paper by Webers and Bruce[10] in which it was shown that the acidic substances, magnesium chloride and ammonium sulfate, have a marked catalytic effect on the conversion of benzophenone to N-benzhydrylformamide (increasing it from about 40 to about 90%). We tried magnesium chloride as a catalyst in the preparation of II, and found it to have a pronounced beneficial effect. Our experiments with various catalysts are summarized in Table I.

TABLE I

EXPERIMENTS WITH VARIOUS CATALYSTS: REACTIONS OF *p*-BROMOACETOPHENONE WITH DIMETHYLFORMAMIDE

Run	Description of experiment[a]	Conversion,[9] %	Ketone recovered, %	Adjusted yield,[9] %
1	Uncatalyzed reaction	13	78	60
2	Run 1 + 1 mole pyridine formate/mole ketone	17	60	43
3	Run 1 + 1 mole formic acid/mole ketone	20	59	48
4	Run 3 + 0.15 mole $FeCl_3$/mole ketone	17	80[b]	83
5	Run 3 + 0.15 mole $ZnCl_2$/mole ketone	8	77[b]	33
6	Run 3 + 0.15 mole $MgCl_2$/mole ketone	36	51	74

[a] For detailed description, see Experimental Section. [b] The recovered ketone was oily.

It is obvious that magnesium chloride is the most satisfactory catalyst of those investigated.[10a] The most striking demonstration of its value as a catalyst was the transformation of cyclohexanone and of heptanone-2 to tertiary amines in 54% yields in the presence of magnesium chloride (see Table II); the reactions failed to give tertiary amines in the absence of the catalyst. We adopted magnesium chloride catalysis as standard procedure in subsequent runs.

Recent practice,[4,5,10] in running Leuckart reactions has been to heat the reaction mixture more or less directly to 165–190°, and to maintain the elevated temperature until distillation of water

---

[1] This research was supported in part by the Research Corporation through a Frederick Gardner Cottrell grant-in-aid, and in part by the Office of Naval Research under a contract with Reed College.

[2] Leuckart, *Ber.*, **18**, 2341 (1885); Leuckart and Bach, *ibid.*, **19**, 2128 (1886).

[3] Wallach, *Ann.*, **343**, 54 (1905).

[4] Ingersoll, Brown, Kim, Beauchamp and Jennings, THIS JOURNAL, **58**, 1808 (1936).

[5] Novelli, *ibid.*, **61**, 520 (1939).

[6] Nabenhauer, Abstracts of American Chemical Society Meeting, Chapel Hill, April, 1937.

[7] Stevens, Cowan and MacKinnon, *J. Chem. Soc.*, 2568 (1931).

[8] Crossley and Moore, *J. Org. Chem.*, **9**, 529 (1944).

[9] In this paper "conversion" refers to the yield based only on the amount of ketone introduced at the beginning of the reaction, while "adjusted yield" refers to the yield based on the amount of ketone consumed in the reaction, that is, on the amount introduced less the amount recovered.

[10] Webers and Bruce, THIS JOURNAL, **70**, 1422 (1948).

[10a] NOTE ADDED IN PROOF.—Recently I was prepared using calcium chloride catalysis with 27% conversion or 78% adjusted yield; this is better than any preparation of I by magnesium chloride catalysis, suggesting that calcium chloride may be superior in general.

TABLE II

LEUCKART SYNTHESIS OF SOME TERTIARY AMINES[a]

Tertiary amine product[b]	Conversion,[9] %	Adjusted yield,[9] %	B. p. °C.	Mm.	d^{20}_{20}	n^{20}_D	Picrate M. p., °C.	Hydrochlorides M. p., °C.	Hydrochlorides Formula	Hydrochlorides % Cl Calcd.	Hydrochlorides % Cl Found
p-Bromo-N,N,α-trimethyl-Ba. (II)[c]	36	61	120–122	14	1.2855	1.5462	152–153	251–252	$C_{10}H_{15}NBrCl$	13.40	13.42
N-Cyclohexyl Pip.[d]	54	54[e]	110–111	14	0.9250	1.4882	129–130	290–291.5[j]	$C_{11}H_{22}NCl$	17.40	17.58
N-(1-Methylhexyl) Pip.[f]	54	54[e]	110–111	14	0.8380	1.4552	114.5–115.5	167.5–168	$C_{12}H_{26}NCl$	16.13	16.18
N,N,α-Trimethyl Ba. (I)[g]	18	57	82–83	14			135–136				
N-(α-Methylbenzyl) Pip.[h]	29	49	138–139	20	0.9661	1.5272	140–141 147–148	178–178.5			
N-(*p*-Bromo-α-methylbenzyl) Pip.[i]	21	39	177	22				208–208.5	$C_{13}H_{19}NBrCl$		

[a] See experimental section for procedural details. Carbon and hydrogen analyses by Dr. Carl Tiedcke. [b] Abbreviation: Ba.—benzylamine. Pip.—piperidine. [c] From 0.5 mole *p*-bromoacetophenone. Calcd.: mol. refr., 56.65. Found: mol. refr., 56.22. Calcd. for $C_{10}H_{14}NBr$ (free amine): C, 52.64; H, 6.19. Found: C, 52.44; H, 5.69. [d] From 0.2 mole cyclohexanone. Calcd.: mol. refr., 52.72. Found: mol. refr., 52.12. Winans and Adkins, THIS JOURNAL, **54**, 306 (1932), reported for N-cyclohexyl pip. b. p. 98–100° (10 mm.); m. p. of picrate 127–127.5°. Drake and McElvain, *ibid.*, **55**, 1155 (1933), reported m. p. 292–293° (dec.) for N-cyclohexyl pip. hydrochloride. [e] No ketone could be recovered despite efforts to do so. [f] From 0.2 mole heptanone-2. Calcd.: mol. refr., 59.54. Found: mol. refr., 59.42. Calcd. for $C_{12}H_{26}NCl$ (hydrochloride): C, 65.63; H, 11.92. Found: C, 65.79; H, 11.74. [g] From 0.167 mole of acetophenone. Stevens, *J. Chem. Soc.*, 2107 (1930), reported m. p. 134–137° for N,N,α-trimethylbenzylamine picrate. [h] From 0.2 mole acetophenone. Calcd.: mol. refr., 60.55. Found: mol. refr., 60.14. Stevens, Cowan and MacKinnon, *ibid.*, 2568 (1931), reported m. p. 140–142° for N-(α-methylbenzyl)-pip. picrate. We found in our experiments that pure samples of this compound sometimes melted sharply at 140–141° and other times sharply at 147–148°. [i] From 0.1 mole *p*-bromoacetophenone. Calcd. for $C_{13}H_{19}NBrCl$ (hydrochloride): C, 51.24; H, 6.29. Found: C, 50.80; H, 6.21. [j] (Cor.).

has ceased, or for an arbitrary number of hours. In this work, yields of II obtained by this technique were variable, and only when temperature was very closely controlled were high yields obtained reproducibly. The improved procedure involves heating the reaction flask strongly enough to keep the temperature of the distilling vapors about 100° as long as possible, and then slowly increasing the temperature of the reaction mixture to 175° and maintaining the latter temperature until distillation of dimethylformamide (b.p. 154°) has virtually stopped. Other variations in reaction conditions such as the use of stirring, doubling the amount of catalyst, increasing the ratio of amide to ketone to 12:1, and use of strictly anhydrous dimethylformamide and catalyst did not improve the yield. With careful temperature control, conversions[9] in the preparation of II have run about 36%, and adjusted yields[9] about 65%. The latter figure is significant for evaluation of the reaction as a preparative method, for the recovered *p*-bromoacetophenone was pure enough for use directly in another reaction except in a few cases in which recrystallization was desirable.

Something of the general utility of the Leuckart reaction for the synthesis of tertiary amines is shown by the experiments described collectively in Table II. It will be seen from inspection of this table that we have used both aliphatic and aromatic ketones in the synthesis along with either dimethylamine or piperidine. Although the yields are not as high as might be desired, the synthesis is to be recommended for its simplicity of manipulation[11] and for the purity of the products obtained. It appears that it should be regarded as a method of choice for the conversion of ketones to tertiary amines and, as a consequence of the ready availability of some classes of ketones, as a useful method for the general synthesis of tertiary amines.

Experimental

Experiments Summarized in Table I.—Formic acid (0.4 mole) and 72.1 g. of 25% dimethylamine in water (0.4 mole of dimethylamine) were mixed in a distilling flask and about 53 ml. of water was removed by distillation. The catalyst and 19.9 g. (0.1 mole) of *p*-bromoacetophenone were added, and heat was applied sufficient to raise the temperature of the reaction gradually to 175° and to keep it there for three hours. The product was isolated from the reaction mixture as described below ("Improved Procedure for Preparation of II").

Experiments Summarized in Table II.—The molar amount of ketone used is stated in the table. Four times as many moles of formic acid and of dimethylamine (in water solution) were mixed and the water was removed by distillation. The ketone, formic acid (1 mole per mole of ketone) and magnesium chloride hexahydrate (0.15 mole per mole of ketone) were added. In the preparation of N-cyclohexylpiperidine and of N-(1-methylhexyl)-piperidine, the temperature of the reaction mixture was raised directly to 175° and held there for four hours. In the other cases, the rate of heating was adjusted to allow distillation of vapors with temperature 100° as long as possible, and then the temperature of the reaction mixture was raised to 175° and held there for about two hours. The products were isolated as described below ("Improved Procedure for Preparation of II"). Hydrochlorides and/or picrates were prepared and purified by conventional means. Samples of the amines for determination of physical constants were purified by fractional distillation or by regenerating the amine from the pure hydrochloride.

Improved Procedure for Preparation of II.—Seven hundred and twenty grams of a 25% aqueous solution of dimethylamine was added slowly to 184 g. (4 moles) of formic acid in a one-liter distilling flask cooled by an ice-bath. Upon completion of addition, 612 ml. of water was removed by distillation. To the residual dimethylformamide were added 199 g. (1 mole) of *p*-bromoacetophenone, 46 g. (1 mole) of formic acid, and 30 g. (0.15 mole) of magnesium chloride hexahydrate. The flask was placed

---

(11) In the Leuckart synthesis of primary and secondary amines the initial product is a substituted formamide which must be subjected to hydrolysis in order to get the free amine. Tertiary amines are formed directly as such, and the hydrolysis step is not required.

in an oil-bath, and the apparatus was fitted with thermometers to measure the temperatures of the bath, of the reaction mixture and of the distilling vapors. The bath temperature was raised directly to 160°, at which point boiling commenced in the reaction mixture. The further progress of the reaction is shown in Table III.

TABLE III

Total time in hours	Temperature, °C. Bath	Pot	Vapor	Remarks
0	160	110	98	Started boiling. H_2O started distilling
1.25	158	129	104	
2.25	163	143	100	
3.25	170	150	100	
4.50	177	160	88	Distillation practically stopped
5.00	180	162	90	
5.50	185	165	123	
6.50	187	170	151	Dimethylformamide started distilling
7.75	187	175	133	
8.50	187	177	91	
10.50	185	178	64	Distillation practically stopped. Shut off

Following the period of heating, the reaction mixture was allowed to cool somewhat (it solidifies if allowed to cool to room temperature) and was poured into about twice its volume of water. This gave a milky suspension of oily unreacted ketone and product; acidification with hydrochloric acid removed the milkiness. On cooling, the unreacted ketone solidified; it was removed by filtration and dried. It weighed 86.4 g. (43.5%), and was of purity sufficient so that it could be used directly in another reaction.

The solution containing the product was made strongly alkaline with sodium hydroxide and was steam-distilled. The distillate was extracted with three portions of ether, and the combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. The ether was evaporated, and the amine distilled at reduced pressure. The product was a colorless oil of b. p. 120–122° (14 mm.), and weighed 88.1 g. (38.6% conversion or 68.4% adjusted yield).

In other preparations of II according to the improved procedure, conversions[9] of 28, 46, 31, 33 and 36% and adjusted yields[9] of 73, 68, 97, 61 and 61%, respectively, have been obtained.

Preparation of II by the Eschweiler[12] Reaction.—*p*-Bromo-α-methylbenzylamine hydrochloride (0.02 mole) (prepared from *p*-bromoacetophenone by the Leuckart reaction) was sealed in a Pyrex tube with 4 g. of 40% formaldehyde solution, and the tube was heated three hours at 130°. The product was isolated as its picrate (m. p. 151.5–152°) in 34.5% yield. A mixed melting point with the picrate of II prepared from *p*-bromoacetophenone and dimethylamine was not depressed.

Acknowledgment.—To Miss Bonnie Souther the authors express their appreciation for her assistance in several of these experiments.

Summary

It is shown that the Leuckart reaction is a useful method for the synthesis of tertiary amines from ketones and dialkylformamides. Magnesium chloride catalysis is necessary.

[12] Eschweiler, German Patent 80,520 (Dec. 17, 1893); Stevens, *J. Chem. Soc.*, 2107 (1930).

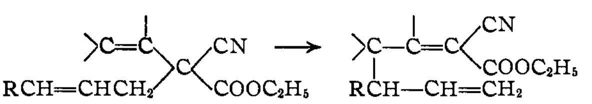
PORTLAND, OREGON RECEIVED SEPTEMBER 20, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Rearrangement of Allyl Groups in Three-Carbon Systems. V. Ethyl (3-Indenyl)-allylcyanoacetate

BY ARTHUR C. COPE AND LAMAR FIELD[1]

A number of (substituted vinyl)-allylcyanoacetic esters have been observed to rearrange in the following manner on heating at 170–200°[2]



(R = H or CH_3)

This paper reports an investigation of the rearrangement of ethyl (3-indenyl)-allylcyanoacetate (III), a crystalline ester previously prepared by Ingold and Thorpe.[3]

In the synthesis of III, 1-indanone (I) was condensed with ethyl cyanoacetate in the presence of ammonium acetate to give an ester (II) which could have either the α,β-unsaturated structure IIA or the β,γ-unsaturated structure IIB. Ingold and Thorpe considered that IIB was the correct formula because the ester formed a sodium enolate and could be alkylated to give III. It is now recognized that such evidence is inconclusive, because alkylidene cyanoacetic esters (such as IIA) can form sodium enolates by three-carbon tautomerism and can be alkylated. Comparison of the ultraviolet absorption spectra of the ester II and the alkylation product III obtained by treating II with sodium ethoxide and allyl bromide furnished convincing evidence concerning the structures of both compounds. The spectrum of III (curve 1, Fig. 2), coincides closely with the spectrum reported for indene itself,[4] which has the same conjugated system. The ester II, on the other hand, absorbs strongly at much longer wave lengths (curve 3, Fig. 2), and accordingly can be assigned structure IIA, in which the nitrile and carbethoxyl groups are included in the conjugated system.

Confirmation of the structure of III was obtained by a synthetic route, beginning with hydro-

---

[1] Socony-Vacuum Oil Co. Fellow, 1947–1948.

[2] Cope and Hardy, THIS JOURNAL, **62**, 441 (1940); Cope, Hoyle and Heyl, *ibid.*, **63**, 1843 (1941); Cope, Hofmann and Hardy, *ibid.*, **63**, 1852 (1941).

[3] Ingold and Thorpe, *J. Chem. Soc.*, **115**, 143 (1919).

[4] Morton and de Gouveia, *ibid.*, 911 (1934).