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THE ARNDT-EISTERT SYNTHESIS OF UNSATURATED ACIDS[1]

JOHN H. WOTIZ AND STEPHEN N. BUCO

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The Arndt-Eistert synthesis consists of the reaction of acid chlorides with diazomethane and the rearrangement (Wolf rearrangement) of the formed diazoketone into the next higher homologous acid or acid derivative. The literature contains only one reference of the successful formation of an unsaturated acid by this method, (2-methylcyclohexenyl)acetyl chloride was thus converted into β-(2-methylcyclohexenyl)propionic acid (1). This paper deals with the scope of this reaction using unsaturated acid chlorides (olefinic, acetylenic, and an allenic) and noting the limitations because of the location of the unsaturation with respect to the acid chloride functional group.

Unsaturated acid chlorides contain two sites of reactivity toward diazomethane. The reaction at the point of unsaturation to form heterocyclic compounds must be at a minimum if a successful Arndt-Eistert synthesis is to be accomplished. This was found to be the case when the unsaturation was in a position other than α,β. Even in the presence of an excess of diazomethane at $-10°$, diazoketones were formed in high yields. These diazoketones were stable at room temperature but resisted crystallization. They were rearranged into methyl esters using the improved method which employs the triethylamine-silver benzoate catalyst described by Newman and Beal (2). In this manner, methyl 7-nonynoate ($CH_3C{\equiv}C(CH_2)_5CO_2CH_3$), methyl 8-nonynoate ($HC{\equiv}C(CH_2)_6CO_2CH_3$), and methyl 11-dodecenoate ($CH_2{=}CH(CH_2)_9CO_2CH_3$), were prepared in 80, 75, and 78% yields, respectively, based on the quantity of the starting acid chloride. When the conventional silver oxide catalyst was used (3) in the Wolf rearrangement, methyl 7-nonynoate was formed only in a 65% yield. All of the Wolf rearrangements were followed by collecting the evolved nitrogen. In the above mentioned reactions 90% to 96% of the theoretical amount (based on the amount of acid chloride consumed) of nitrogen was evolved. For the purpose of characterization and identification, the esters were converted into the corresponding acids and amides. The melting points of mixtures of the nonynoic acids and amides with samples prepared by a different method (4) were not depressed. The formed 11-dodecenoic acid which melted at 17–18°, was a known compound, whose physical properties were in accord with the ones in the literature (5). This acid also was converted into the amide which, mixed with 10-undecenamide, showed a depression of the melting point.

The reactions of crotonyl chloride ($CH_3CH{=}CHCOCl$), 2-heptynoyl chloride ($C_4H_9C{\equiv}CCOCl$), phenylpropynoyl chloride, ($C_6H_5C{\equiv}CCOCl$), and, 2-butylbutadienoyl chloride, ($CH_2{=}C{=}C(C_4H_9)COCl$), with diazomethane yielded products which decomposed with an evolution of a gas even at $-10°$. The changing of the acid chloride-diazomethane ratio, lowering of the reaction

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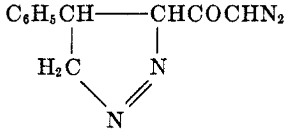
temperature to −78°, or the changing of solvents did not produce more stable products. The rearrangement of these crude diazoketones yielded small quantities of products which contained nitrogen and resisted purification by distillation or crystallization. When cinnamoyl chloride was reacted with diazomethane, using experimental conditions which were successful in the reaction of acid chlorides which were not α,β-unsaturated, one of the products was 4-phenyl-5-diazoacetyl-pyrazoline (m.p. 76°).



This structure was proposed previously (6) and it was partly confirmed by noting the characteristic infrared absorption band (Fig. 1, Curve A) of diazoketones near 4.8 μ. The mother liquor from this pyrazoline also yielded a small quantity of the desired 1-diazo-4-phenyl-3-butenone ($C_6H_5CH{=}CHCOCHN_2$, m.p. 173°) (Fig. 1, Curve B). It was possible to increase the yield of this compound by increasing the dilution of the reagents in ether. When this diazoketone was rearranged, 90% of the theoretical amount of nitrogen was collected, but the product did not distill under 200° at 2 mm. It was likely that the product was

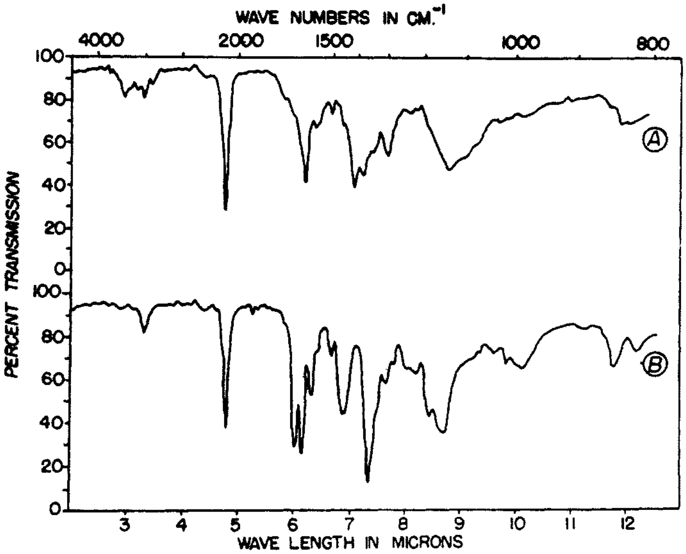
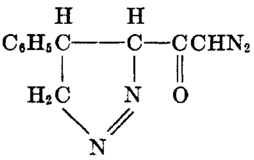
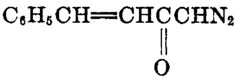


FIG. 1. INFRARED SPECTRA OF COMPOUNDS OBTAINED FROM THE REACTION OF DIAZOMETHANE WITH CINNAMOYL CHLORIDE (IN $CHCl_3$ SOLUTION).

A.



B.



$$C_6H_5CH{=}CH\underset{\overset{\|}{O}}{C}CHN_2$$

polymerized methyl styrylacetate. The only isolated product (66% yield) in the reaction of *p*-methoxycinnamoyl chloride and diazomethane was 4-(*p*-methoxyphenyl)-5-diazoacetylpyrazoline. No attempt was made to rearrange this product. *p*-Nitrocinnamoyl chloride and diazomethane reacted to form a product which decomposed (evolved a gas) during the process of isolation. No product was isolated upon the rearrangement of the crude diazoketone.

EXPERIMENTAL

6-Octynoyl chloride. A solution of 50 g. (0.36 mole) of 6-octynoic acid (7) and 50 g. (0.41 mole) of thionyl chloride in 60 ml. of dry benzene was refluxed for two hours. Distillation gave 54 g. of product (95% yield), b.p. 79–80° at 6 mm., n_D^{25} 1.4653.

Anal. Calc'd for $C_8H_{11}ClO$: C, 60.5; H, 7.0; Cl, 22.4.

Found: C, 60.7; H, 7.1; Cl, 22.3.

Similarly *7-octynoyl chloride* was obtained in a 93% yield. B.p. 82–83° at 9 mm., n_D^{25} 1.4563.

Anal. Calc'd for $C_8H_{11}ClO$: C, 60.5; H, 7.0; Cl, 22.4.

Found: C, 60.9; H, 6.9; Cl, 22.2.

2-Heptynoyl chloride was obtained in a 95% yield and was a known compound (8). Found: b.p. 70–71° at 5 mm., n_D^{25} 1.4638.

Phenylpropynoyl chloride was obtained in a 82% yield and was a known compound (9). Found: b.p. 104–106° at 4 mm.

2-Butylbutadienoyl chloride was prepared from sodium 2-butylbutadienoate and oxalyl chloride. A more detailed description will appear shortly (10).

Methyl 7-nonynoate. A solution containing about 0.15 mole of diazomethane in 150 ml. of dry ether was placed in a 1000-ml. three-necked round-bottomed flask fitted with a condenser, mechanical stirrer, and a dropping-funnel, and was cooled to −10°. To this was added a solution of 8 g. (0.05 mole) of 7-octynoyl chloride in 50 ml. of dry ether. After stirring for one hour, the solvent and excess of diazomethane were removed under reduced pressure at room temperature. The yellow oily residue did not solidify on cooling in attempted crystallization. It was therefore dissolved in 70 ml. of methanol and placed in a 500-ml. three-necked round-bottomed flask fitted with a mercury-sealed mechanical stirrer, a dropping-funnel, and a condenser connected to an azotometer. A solution of 1 g. of dry silver benzoate (prepared by mixing equivalent portions of silver nitrate and sodium benzoate) in 9 g. of triethylamine was then added dropwise over a period of 90 minutes. The reaction mixture turned black and the evolution of nitrogen commenced immediately. A total of 93% of the theoretical amount of gas was collected. The reaction mixture then was refluxed for five minutes and filtered. Most of the alcohol was removed under a vacuum, and the residue was dissolved in ether, and washed successively with hydrochloric acid, sodium hydroxide, and water. After drying over magnesium sulfate, distillation yielded 13 g. (80%) of product, b.p. 97–100° at 8 mm. On redistillation the fraction boiling at 97° at 8 mm. with n_D^{25} 1.4480 was analyzed.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6.

Found: C, 70.8; H, 9.2.

This ester was converted into *7-nonynoic acid*, m.p. 50–52°, and *7-nonynamide*, m.p. 83–84° which did not depress the melting points when mixed, respectively, with independently prepared samples (4).

Methyl 8-nonynoate was prepared in a similar manner, from 8 g. (0.05 mole) of 7-octynoyl chloride. The evolution of nitrogen was 90% of theory, and 6.3 g. (75% yield) of product was obtained, b.p. 98 to 103° at 6 mm. The fraction boiling at 100° at 6 mm. was redistilled and analyzed.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6.

Found: C, 70.8; H, 10.1.

This ester was converted into *8-nonynoic acid*, m.p. 18–19°, and *8-nonynamide*, m.p. 84–85°, which did not depress the melting points when mixed, respectively, with independently prepared samples (4).

Methyl 11-dodecenoate was prepared in a similar manner from 9.2 g. (0.05 mole) of 10-undecenoyl chloride. The yield was 8.3 g. (78%), b.p. 119–120° at 2 mm. Literature (5): b.p. 121–123° at 3 mm. This ester was saponified with 5% potassium hydroxide, and on acidification *11-dodecenoic acid* was obtained, b.p. 140–142° at 2 mm., n_D^{20} 1.4516, m.p. 17–18°. Literature (5): b.p. 143–144° at 3 mm., n_D^{20} 1.4510, m.p. 19°. This acid was converted into *11-dodecenamide*, m.p. 86–87°.

Anal. Calc'd for $C_{12}H_{23}NO$: N, 7.1. Found: N, 7.3.

A mixture of this amide with 10-undecenamide (m.p. 84–85°) melted at 82–84°.

4-Phenyl-5-diazoacetylpyrazoline was prepared from 8.4 g. (0.05 mole) of cinnamoyl chloride in 50 ml. of ether, at −10°. The formed yellow-orange solid (8.4 g.) was separated by filtration. Recrystallization from carbon tetrachloride yielded 4.1 g. (36%) of the pale yellow pyrazoline, m.p. 75–76°. Literature (6): m.p. 79–80°.

Anal. Calc'd for $C_{11}H_{10}N_4O$: C, 61.7; H, 4.9, N, 26.1.

Found: C, 61.2; H, 4.7: N, 25.9.

Its infrared spectrum is Curve A in Fig. 1. Evaporation of the ether filtrate under reduced pressure at room temperature yielded an orange solid. Crystallization from ethyl acetate produced 1 g. of 1-diazo-4-phenyl-3-butenone-2, m.p. 173–174°.

1-Diazo-4-phenyl-3-butenone-2 was prepared from 84 g. (0.5 mole) of cinnamoyl chloride in 250 ml. of ether and about 1.5 mole of diazomethane in 3 liters of ether at −10°. There was no suspended solid after the completion of addition of the reactants. The ether was evaporated under a vacuum at room temperature, and 71 g. of an orange residue was obtained. Recrystallization from ethyl acetate yielded 26 g. (24%) of the product, m.p. 172–174° (decomp).

Anal. Calc'd for $C_{10}H_8N_2O$: C, 69.8; H, 4.7; N, 16.2.

Found: C, 69.9; H, 4.8; N, 15.9.

Its infrared spectrum is Curve B in Fig. 1.

The reaction with methanol in the presence of silver benzoate-triethylamine catalyst resulted in a 92% of theory evolution of nitrogen. After filtration and removal of the alcohol, the residue did not distill under 200° at 2 mm. It was therefore treated with a 25% solution of sodium hydroxide, and the remaining orange solid was digested with hydrochloric acid, filtered, washed with water, and dried. The resulting pale amorphous solid charred when heated above 360°. When digested with nitric acid, the aqueous solution gave a positive test for the presence of silver ions. The solid also showed the presence of sodium (flame test).

Anal. Found: C, 53.8; H, 4.3; Ash, 35.1.

4-(p-Methoxyphenyl)-5-diazoacetylpyrazoline was prepared from 9.6 g. (0.05 mole) of *p*-methoxycinnamoyl chloride in 25 ml. of ether and about 0.05 mole of diazomethane in petroleum ether (30–60°). The yield of the pale yellow solid was 8.1 g. (66%), m.p. 81–82° from a mixture of benzene and ether.

Anal. Calc'd for $C_{12}H_{12}N_4O_2$: N, 23.0. Found: N, 22.7.

SUMMARY

The Arndt-Eistert synthesis was satisfactorily applied in converting olefinic and acetylenic acids (containing a terminal and nonterminal triple bond) into their next higher homologs. The over-all yields were 75 to 80%. Acids containing the unsaturation in the α,β-positions usually formed heterocyclic products. Using higher dilution of solvents, cinnamoyl chloride reacted with diazomethane only at the acid chloride functional group.

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