THE ROSENMUND REDUCTION OF 4-PHENYL-3-BUTENOYL CHLORIDE

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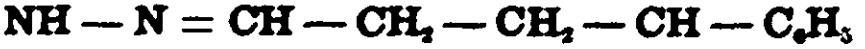
Hydrazine hydrate reacts smoothly with γ,β-unsaturated aldehydes in a condensation-cyclization process to produce pyrazoline derivatives in generally good yields (3). It is not known, however, whether β,γ-unsaturated aldehydes will undergo this reaction to yield the analogous tetrahydropyridazine derivatives. Since excellent yields of 5-phenylpyrazoline

$$NH—N = CH\text{-}CH_2 — CH—C_6H_5$$

are obtained readily from 3-phenylpropenal (cinnamaldehyde) in this reaction, 4-phenyl-3-butenal (styrylacetylaldehyde) was selected to investigate the feasibility of forming the analogous six-membered heterocycle, 6-phenyl 1, 4, 5, 6-tetrahydropyridazine,



$$NH — N = CH — CH_2 — CH_2 — CH — C_6H_5$$

Because the conjugation between the double bond and the carbonyl present in the γ,β-unsaturated aldehydes is absent in the β,γ-unsaturated compounds, the success or failure of the condensation-cyclization reaction would shed some light on the effect of conjugation in the cyclization process.

Meyer (6) has prepared 4-phenyl-3-butenal but his method, when beginning with readily available starting materials, requires the synthesis and purification of nine intermediate compounds; in addition, the overall yield is very poor. Consequently, the Rosenmund reduction of acid chlorides to the corresponding aldehydes was chosen as a shorter and perhaps more efficient route to the desired compound, since this is often the easiest means of producing an aldehyde when the corresponding acid is easily obtainable. In this case 4-phenyl-3-butenoic acid may be readily formed by the condensation of phenylacetaldehyde with malonic acid (3), so that the preparation of 4-phenyl-3-butenal by this scheme may be represented by the following equations:

$$C_6H_5CH_2CHO + CH_2(COOH)_2 \xrightarrow[\text{Ethanol}]{(C_2H_5)_2NH} C_6H_5CH{=}CHCH_2COOH + H_2O + CO_2$$

$$C_6H_5CH{=}CHCH_2COOH + SOCl_2 \longrightarrow C_6H_5CH{=}CHCH_2COCl + HCl + SO_2$$

$$C_6H_5CH{=}CHCH_2COCl + H_2 \xrightarrow[\text{poison}]{\text{Pd-BaSO}_4} C_6H_5CH{=}CHCH_2CHO + HCl$$

In the selective catalytic reduction of an acid chloride to the aldehyde, known as the Rosenmund reaction, care must be taken to avoid further reduction to the alcohol and even to the hydrocarbon. Moreover, the formation of these products of excessive reduction induces side reactions which consume the acid chloride, forming esters, acids, anhydrides, ethers, and hydrocarbons and thus further reducing the yield of aldehyde. Accordingly, a catalyst poison or regulator is usually recommended (4), although the data collected by Mosettig and Mozingo (7) in an excellent review of the Rosenmund reaction covering the literature to November, 1947, show that fully two-thirds of the reductions were conducted without the use of a regulator and with no obvious general decrease in yields.

The catalyst more commonly used is palladium supported on barium sulfate in a catalyst-acid chloride ratio from 1:5 to 1:10, and although other metals and other supports have been used, no definite advantage seems to have been achieved (7). The catalyst regulator is usually an organic sulfur compound such as thioquinanthrene, Quinoline-S (a crude preparation of thioquinanthrene), or thiourea, the satisfactory amount being about 10 mg. of regulator per gram of catalyst (4). As solvent xylene is the most favored, though benzene, toluene, tetralin, and decalin are used to a lesser extent. The reaction temperature depends of course on the solvent and acid chloride, but the optimum temperature is the lowest possible one which permits a constant evolution of hydrogen chloride. Commercial electrolytic hydrogen is satisfactory for the reduction of most acid chlorides, but the last traces of moisture and oxygen must be removed in certain cases, e.g., heterocyclic acid chlorides (8).

The yields obtainable in the Rosenmund reduction vary from zero to practically quantitative (7). However, the extent to which reducible groups other than -COCl in a given molecule may interfere with the Rosenmund reaction is not known in general. Aromatic acid chlorides containing nitro or halogen groups have been successfully reduced without affecting these groups (9). With double bonds the situation is more obscure. Cinnamoyl chloride, $C_6H_5CH{=}CHCOCl$, has given 56 to 60 per cent yields of cinnamaldehyde (10). Nevertheless, while $CH_2{=}CH(CH_2)_8COCl$ formed 55 per cent unsaturated aldehyde with significant amounts of the saturated aldehyde, $CH_3(CH_2)_9CHO$, ozonolysis disclosed that the unsaturated aldehyde product was mainly $CH_3CH{=}CH(CH_2)_7CHO$ with some $CH_3CH_2CH{=}CH(CH_2)_6CHO$ and that no $CH_2{=}CH(CH_2)_8CHO$ was formed at all. To predict what will happen to 4-phenyl-3-butenal would be at best uncertain, for although the double bond is isolated from the -COCl group, it is still conjugated with the benzene ring and is not completely isolated as in the case above.

EXPERIMENTAL

As directed by Hershberg and Cason (4) technical xylene was refluxed over sodium, decanted, distilled from a fresh supply of sodium, and finally stored over more sodium.

Thionyl chloride was purified by distilling from a mixture of the technical-grade product with quinoline, mixing this distillate with boiled linseed oil, and distilling from this latter mixture following directions by Fieser (2).

The palladium catalyst was prepared according to Weygand (11) from metallic palladium by converting it to the chloride, precipitating the hydroxide on a barium sulfate suspension by the slow addition of a slight excess of aqueous sodium carbonate, washing with distilled water by decantation, filtering with gentle suction, and drying over potassium hydroxide pellets.

The catalyst regulator, Quinoline-S, was prepared by the procedure of Hershberg and Cason (4) by refluxing a mixture of sulfur and freshly distilled Eastman Kodak C.P. quinoline. Although they reported a dark brown liquid as the product, dark brown crystals were always obtained in this work and close examination indicated the presence of three different crystalline modifications: colorless needles, light brown shiny platelets, and a dark brown powder. However, the mixture was used without further separation and was dissolved in purified xylene.

The procedure followed in preparing 4-phenyl-3-butenoic acid was essentially that suggested by Linstead and Williams (5). Matheson technical-grade phenyl-acetaldehyde (a 50 per cent ethanol solution) was freshly distilled at reduced pressure before each run but without apparent separation of alcohol and aldehyde. To a liter round-bottom flask arranged for reflux were charged 146 gm. of freshly distilled aldehyde-alcohol mixture, 61 gm. of Eimer and Amend malonic acid, an additional 160 ml. of absolute ethanol, and 12 drops of diethylamine. The mixture was refluxed for 6 hours, cooled, and poured into an excess of 2 N sodium carbonate. The resulting mixture was extracted with ether and the aqueous layer was neutralized with dilute sulfuric acid. The oil that first formed crystallized readily when the wall of the container was scratched with a glass rod. The crude white crystals melted at 78-83° and then at 83.5-85° after recrystallization from ethanol. Linstead and Williams (5) reported a melting point of 87° for 4-phenyl-3-butenoic acid and a yield of 60 per cent, noting at the same time that lower yields were sometimes caused by extensive esterification. This was borne out by the present work, for the yields of five different runs ran from 7 to 37 per cent, varying inversely with the age of the original aldehyde-alcohol solution. However, attempts to recover more acid by the alkaline hydrolysis of the material in the ether extract were either fruitless or gave negligible amounts of the acid.

Contrary to the experience of Linstead and Williams (5) only tarry products were obtained when purified thionyl chloride was added directly to 4-phenyl-3-butenoic acid, regardless of purity or dryness of the acid or the rate of addition of thionyl chloride. Subsequently, it was found that the use of a solvent, such as petroleum ether dried over anhydrous calcium chloride or thiophene-free benzene, produced an almost quantitative yield of satisfactory material. In a typical preparation 20 gm. of recrystallized acid, 125 ml. of dry petroleum ether, and 20 ml. of purified thionyl chloride were charged to a flask protected from atmospheric moisture by calcium chloride and Drierite-activated alumina drying towers. The endothermic reaction was allowed to proceed with an occasional shaking or swirling of the contents of the flask until completion, as evidenced by the disappearance of the solid acid, cessation of gas evolution, and the attainment of room temperature by the flask contents. This usually required about 3 days but it could be shortened to 36 hours by very frequent shaking. The acid chloride was recovered by removal of the solvent at about 40 mm. of mercury pressure and room temperature, the crude product melting at 39.5-41°; Linstead and Williams (5) reported a melting point of 42° for a recrystallized product.

Three different attempts (using Quinoline-S, thiourea, and no regulator at all) were made to reduce the acid chloride to the aldehyde by the Rosenmund reaction, but although 88 to 95 per cent of the expected hydrogen chloride (based on acid chloride used) was evolved, as indicated by titration with sodium hydroxide of the water solution in which it was absorbed, only trace amounts of 4-phenyl-3-butenal were obtained and then only as various derivatives. The general procedure involved bubbling commercial electrolytic hydrogen (passed through a Drierite column) through a suspension in purified xylene of the palladium-barium sulfate catalyst and catalyst regulator (if used) to displace any air in the system and reduce the catalyst to metallic palladium while the solvent was refluxed on an oil bath. Then heating was interrupted, the stream of hydrogen was shut off, and a solution of 4-phenyl-3-butenoyl chloride in sufficient purified xylene to give a concentration of about 0.15-0.26 gm. per ml. of xylene when mixed with the contents of the reaction flask was added. The oil-bath temperature was raised to about 150° and the bubbling of hydrogen was resumed again, producing almost instantaneously a darkening of the solution in all runs. The reaction mixture was cooled when evolution of hydrogen chloride ceased (3 to 10 hours), filtered, and carefully subjected to flash distillation at diminished pressure and a temperature of 95-102° in order to remove the xylene, which required about 5 hours.

Examination of the residue after removal of xylene disclosed no alcohol, i.e., acetyl chloride and xanthate tests were negative, only trace amounts of aldehyde (not identified), and, except when thiourea was used, small amounts (less than 10 per cent) of 4-phenyl-3-butenoic acid, which was identified by its melting point and that of the amide prepared from it. The combined stripped solvent fractions were carefully fractionated with a Snyder 3-ball column to remove the large quantity of xylene and the 5-ml. residue was charged together with 10 ml. of *n*-butyl phthalate as a booster liquid to a Todd semimicro fractionating column. A 1-ml. cut boiling at 172-172.5° was obtained which resembled phenylcyclopropane in odor and boiling point but differed significantly from it in density (0.876 at 30°) and refractive index (1.5273 at 28°). Since some 4-phenyl-3-butenal was found to be present (see below) and its density and refractive index are not known, so that its effect on the properties of the mixture cannot be indicated, the identity of the hydrocarbon, apparently the major constituent of this cut, cannot be suggested with any certainty. Likely possibilities include phenylcyclopropane, 1-phenyl-1-propene, 1-phenyl-1-butene, and phenylcyclobutane with the first two being most probable from considerations of their physical properties although each differs markedly from this cut in at least one physical property.

Treatment of portions of this cut with appropriate reagents yielded a semicarbazone melting at 213.6-214.2°, a 2,4-dinitrophenylhydrazone melting at 237° with decomposition, a liquid phenylhydrazone, and a methone melting at 192.8-193.2°. The xanthene derivative was prepared by cyclizing the methone with a drop of concentrated hydrochloric acid, and after one recrystallization from methanol it melted at 202.8-203.2°. Since the only previously reported derivative of 4-phenyl-3-butenal was the semicarbazone with a melting point of 212-214° (6), the close agreement of the above value with this one constitutes strong evidence for the presence of this aldehyde in the cut.

Consequently, it seems that the Rosenmund reduction of 4-phenyl-4-butenoyl chloride to 4-phenyl-3-butenal under the conditions described above is far from satisfactory as a method of preparation because of the extremely small amounts of desired product obtained. Although working at lower temperatures, under reduced pressure, and with lower-boiling solvents would probably increase the yield, it is doubtful that it would be enough to warrant its use as a preparative method. Four new derivatives of 4-phenyl-3-butenal were prepared and sharp melting points were obtained for the three solid compounds: the 2,4-dinitrophenylhydrazone (237° d.), the methone (192.8-193.2°), and the xanthene (202.8-203.2°), the phenylhydrazone being a liquid. However, in the course of this work an improved method for making acid chlorides from acids with thionyl chloride was devised involving no heating, an anhydrous system, and the use of a solvent (where none had been used before) so that yields were increased to nearly quantitative ones.

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