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NEW STEREOSPECIFIC SYNTHESIS OF CIS-β,γ-UNSATURATED NITRILES FROM ACRYLONITRILE, TRIPHENYLPHOSPHINE, AND ALIPHATIC ALDEHYDES

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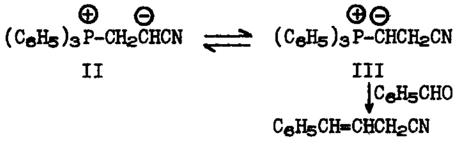
Oda and co-workers (1) recently reported that the reaction of acrylonitrile and triphenylphosphine with benzaldehyde at 140°C afforded a 23% yield of trans-4-phenyl-3-butenenitrile (I) with no mention made of the cis isomer. It was proposed that the reaction was initiated by nucleophilic addition of triphenylphosphine to acrylonitrile to form an intermediate zwitterion (II) which underwent a prototropic shift to form a ylid (III). The latter then reacted with the aldehyde in a Wittig reaction to give (I).



$$\underset{\text{II}}{(C_6H_5)_3\overset{\oplus}{P}\text{-}CH_2\overset{\ominus}{C}HCN} \rightleftharpoons \underset{\text{III}}{(C_6H_5)_3\overset{\oplus\ominus}{P\text{-}C}HCH_2CN} \xrightarrow{C_6H_5CHO} C_6H_5CH{=}CHCH_2CN$$

I

The same workers also prepared the ylid, ethyl 2-triphenylphosphoranylpropanoate, from triphenylphosphine and ethyl acrylate and trapped it by reaction with benzaldehyde. In this reaction, the presence of small amounts (10% of the weight of aldehyde) of proton donors such as benzoic acid and n-hexyl alcohol had no effect on the yield of the trapping product, trans-ethyl 4-phenyl-3-butenoate. In connection with studies on the mechanism of the triphenylphosphine catalyzed dimerization of acrylonitrile (2,3), we have in 1963-64 independently examined the reactions of acrylonitrile and triphenylphosphine with various aldehydes. In contrast to the results of Oda, we report here that when the reaction is carried out in t-butyl alcohol solvent at 165-175°C, the yields of trapping product are high (73-85%) at good conversion[a] (60-67%) of the reactants. Of much greater importance, stereochemically, is the observation that when an aliphatic aldehyde

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[a] % Conversion = % acrylonitrile not recovered (yields are calculated on the basis of acrylonitrile not recovered).

is used as the trapping agent, the thermodynamically less stable *cis*-β,γ-unsaturated nitrile is obtained in a highly stereoselective (92-94%) reaction.

Reaction of equimolar amounts of propionaldehyde, acrylonitrile, and triphenylphosphine in t-butyl alcohol solvent at 175°C affords product C_6H_9N (mass spectrometry) in 74% yield at 60% conversion of either aldehyde or nitrile. Analysis by gas-liquid chromatography shows that the product contains one major component (94%), IV, and one minor one (6%). The assignment of the structure, *cis*-3-hexenenitrile, to IV is based upon a combination of physical and chemical data.

$$CH_3CH_2CH_A{=}CH_B{-}CH_2CN$$

cis, IV

Hydrogenation of IV with palladium-on-carbon catalyst in tetrahydrofuran solution at 25°C proceeds with absorption of one molar equivalent of hydrogen to give capronitrile in 84% yield. The structure of the latter was established by hydrolysis to hexanamide (75% yield) identical in all respects to an authentic sample. The infrared spectrum of IV which exhibits absorption at 4.43 μ shows that the nitrile group is not conjugated with the double bond. The NMR spectrum of IV taken at 100 MHz with tetramethylsilane as internal reference shows a triplet at $\delta = 1.00$ ppm (3H, $\underline{CH_3}CH_2$), a well-resolved quintet at 2.07 (2H, $CH_3\underline{CH_2}CH{=}$), a doublet at 3.06 (2H, $=CH\underline{CH_2}CN$), and two overlapping multiplets at 5.40 (1H, $=C\underline{H}{-}CH_2CH_3$), and at 5.60 (1H, $=C\underline{H}{-}CH_2CN$). The J_{AB} value of 10.5 Hz for the ethylenic hydrogens determined by spin decoupling experiments is in agreement with *cis* but not *trans* coupling.

When butyraldehyde is used as the trapping agent in t-butyl alcohol solvent at 175°C, product $C_7H_{11}N$ (mass spectroscopy) is obtained in 75% yield at 60% conversion of either aldehyde or nitrile. The major component, V (92%), in $C_7H_{11}N$ is identified as *cis*-3-heptenenitrile since the NMR spectrum shows the ethylenic hydrogens as two overlapping multiplets

$$CH_3CH_2CH_2CH_A{=}CH_BCH_2CN$$

cis, V

at $\delta = 5.50$ and 5.70 ppm with a J_{AB} value of 11.0 Hz. Use of benzene (dried over molecular sieve) as solvent in place of t-butyl alcohol at 175°C gives only one third the amount of $C_7H_{11}N$ (60% yield at 25% conversion of either acrylonitrile or butyraldehyde) isolated in the alcoholic medium. The *cis*- content (V) of the $C_7H_{11}N$ product is 82% in the hydrocarbon solvent.

In contrast to the results observed with aliphatic aldehydes, reaction of benzaldehyde with equimolar amounts of acrylonitrile and triphenylphosphine in t-butyl alcohol solvent at 175°C affords $C_{10}H_9N$ (mass spectroscopy) product (85% yield, 67% conversion) that contains four components instead of two. The major component (51%), the same one isolated by Oda (1), is identified as <u>trans</u>-4-phenyl-3-butenenitrile by comparison of its melting point (60°C) with that of an authentic sample (4). Two of the other components, VI (19%) and VII (22%), have been isolated in essentially pure forms by preparative gas-liquid chromatography and have been identified as <u>cis</u>- and <u>trans</u>-4-phenyl-2-butenenitrile, respectively, by spectral means. Compound VI shows the following spectral characteristics: IR, 4.51 μ (α-β-unsaturated $C\equiv N$); NMR, quartet at $\delta = 3.67$ ppm (2H, $C_6H_5\underline{CH_2}CH=$), multiplet at 5.30 (1H, $CH=\underline{CH}CN$), multiplet at 6.55 (1H, $CH_2\underline{CH}=CH$), and a multiplet at 7.23 (5H, $C_6\underline{H_5}CH_2$). The J_{AB} value of the ethylenic hydrogens is 10 Hz. Compound VII has the following spectral characteristics: IR, 4.51 μ (α-β-unsaturated $C\equiv N$); NMR, two multiplets at 5.40 and 6.40 (1H each, $J_{AB} = 15$ Hz). Although the fourth component, VIII (8%), could not be obtained in a pure form, hydrogenation of a product mixture containing 25% VIII (enriched by preparative GLC) produces only one product, 4-phenylbutanenitrile, the same compound formed on hydrogenation of pure VI or VII. Accordingly, a <u>cis</u>-4-phenyl-3-butenenitrile structure is assigned to VIII.

$C_6H_5CH_2CH=CHCN$

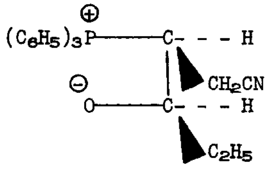
<u>cis</u>, VI; <u>trans</u>, VII

$C_6H_5CH=CHCH_2CN$

<u>cis</u>, VIII

The improvement in formation of trapping product associated with the use of t-butyl alcohol as solvent may be explained if it is assumed that the proton migration involved in proceeding from II to III is promoted by the protolytic medium. An alternative explanation is that the reaction of III with aldehyde to give V is accelerated by the presence of the alcohol (5,6). Oda attempted to promote the benzaldehyde reaction by adding small amounts of ethanol to the reaction mixture. Undoubtedly, the reason for the lower yield (23%) encountered with this procedure is that ethanol, unlike t-butyl alcohol, readily undergoes triphenylphosphine catalyzed Michael addition to acrylonitrile.

There are only a few examples in the literature (7) of the reaction of phosphorus ylides with aldehydes to afford the thermodynamically less stable <u>cis</u>-ethylenic compound in the specificity observed here. Our results must be interpreted in light of a very recent communication by Schlosser and co-workers (8) who have found, in contrast to other workers (7), that "salt-free" alkylidenetriphenylphosphoranes at 0°C tend in general toward cis-olefination. The preferential formation of cis-V in benzene solution may be accounted for if it is assumed that a "cis-effect" is operating in betaine formation. Such an effect has recently been proposed by Neureiter (9) to explain the preferential formation of cis-olefins from α-bromosulfones on treatment with base. Under salt-free conditions with a very reactive ylid, such as III, the transition state for betaine formation may come at a point along the reaction coordinate such that the attractive forces between the two eclipsing groups outweigh the repulsive forces (9). Such a transition state would afford the erythro form (IX) of the intermediate betaine which would decompose to give cis-V. In the case of ylid III, it is possible that in the highly polarized transition state, sufficient charge of opposite sign is imparted to the eclipsing groups, $-C_2H_5$ and $-CH_2CN$, to result in an additional net attraction. Increased polarity of the solvent (t-butyl alcohol) would be expected to increase this effect and, accordingly, the cis-content of the product. A great deal more experimental work on the effect of solvents on the stereochemistry of "salt-free" Wittig reactions must be carried out before the validity of the above interpretation can be secured.



IX

The observation that the product derived from the benzaldehyde reaction contains four isomers in place of the two isomers obtained from the propionaldehyde reaction may be explained by a comparison of the relative acidities of the two initially formed compounds, VIII and IV, respectively. VIII is more acidic than IV because the anion derived from VIII is stabilized by conjugation with the phenyl group. Accordingly, VIII undergoes base-catalyzed isomerization with the phosphine present (experimentally verified) but IV does not.

The following example illustrates the experimental procedure: A solution of 39.3 g (0.15 mole) of triphenylphosphine, 8.0 g (0.15 mole) of acrylonitrile, 8.7 g (0.15 mole) of propionaldehyde, and 0.1 g of hydroquinone in 100 g of t-butyl alcohol in a 350 ml glass-lined stirred autoclave sealed under nitrogen was maintained at 175 ± 1°C for eight hours. Solvent, unreacted acrylonitrile and propionaldehyde, and C_6H_9N product were removed by vacuum Claisen distillation (150-5 mm). The kettle temperature was not allowed to exceed 80°C until the end of the distillation. Analysis of the distillate by gas-liquid chromatography at 80-150°C on a 20-foot column packed with DC-710 on fluoropak showed that 3.2 g (60% conversion) of acrylonitrile and 3.5 g (60% conversion) of propionaldehyde were recovered. Analysis on a 20-foot column packed with either carbowax 20 M on fluoropak or SE-30 on chromosorb-W at 100-150°C showed the distillate contained 6.0 g (70% yield) of cis-IV and 0.4 g (4.5% yield) of trans-IV. Fractional distillation through a 2-foot spinning band column gave 5.2 g of 98% pure cis-IV, b.p. 72-73° (30 mm). Continued Claisen distillation of the reaction product gave 2.1 g, b.p. 65-100° (1.0-0.5 mm), which contained five high boiling components (GLC) that were not examined further. Recrystallization of the distillation residue (41 g) from ethyl acetate-hexane gave 15 g of triphenylphosphine oxide, m.p. 153-155°C. Further recrystallization of the residue from ethanol afforded 21.5 g of triphenylphosphine (45% conversion), m.p. 79-80°C.

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REFERENCES

1. R. Oda, T. Kawabata and S. Tanimoto, Tetrahedron Letters, 1653 (1964).
2. J. D. McClure, U. S. Patent 3,225,083 (filed in August, 1963 and issued in December, 1965).
3. M. M. Baizer and J. D. Anderson, J. Org. Chem. 30, 1357 (received in November, 1964 and published in May, 1965).
4. A. Kandiah and R. P. Linstead, J. Chem. Soc., 2139 (1929).
5. A. J. Speziale and D. E. Bissing, J. Am. Chem. Soc. 85, 3878 (1963); C. Ruchardt, S. Eichler and P. Panse, Angew. Chem. Intern. Ed. 2, 619 (1963).
6. H. O. House, V. K. Jones and G. A. Franck, J. Org. Chem. 29, 3327 (1964).
7. A. W. Johnson, Ylid Chemistry, p. 171, Academic Press, New York (1966).
8. M. Schlosser, G. Muller and K. F. Christmann, Ange. Chem. Intern. Ed. 5, 667 (1966).
9. N. P. Neureiter, J. Am. Chem. Soc. 88, 558 (1966).