REACTION OF ISONITRILES WITH α,β-UNSATURATED KETONES

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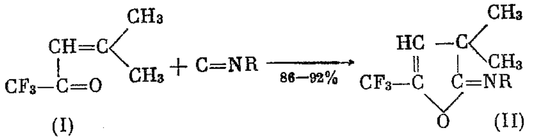
UDC 542.91:547.239.1:547.384

Isonitriles easily enter into cycloaddition reactions with bipolar, including 1,4-bipolar, compounds [1, 2]. The present paper is devoted to a study of the reaction of isonitriles with α,β-unsaturated ketones. Only one example is known of the reaction of isonitriles with an α,β-unsaturated steroid ketone. Together with other compounds, the isomerization product of the postulated intermediate cycloadduct, the γ-alkoxynitrile, was isolated in this reaction (catalyzed by BF_3) [3].

Trifluoromethyl β,β-dimethylvinyl ketone reacts with isonitriles in the absence of a catalyst to give the stable 1,4-cycloaddition products, the substituted dihydrofurans (II)



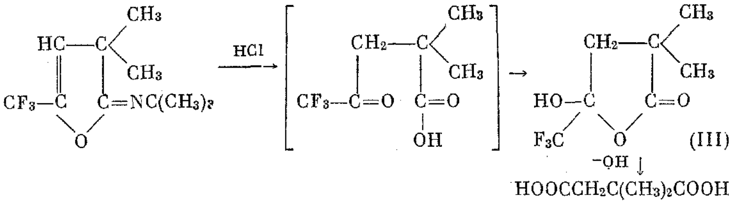
$R = C(CH_3)_3$ (a), C_6H_{11} (b)

Nucleophilic attack of the β-carbon atom of the α,β-unsaturated ketone by the isonitrile apparently plays the determining role in this reaction. A decrease in the electron density as the result of the acceptor action of the trifluoromethyl group facilitates the attack. Actually, mesityl oxide does not react with isonitrile even on long heating at 100°C.

The structure of the dihydrofurans (II) was proved by the IR, NMR and mass spectra, and also by acid hydrolysis to dimethyltrifluorolevulinic acid (III) and its amides (IV) and (V). A study of these levulinic acid derivatives (III), (IV) and (V), which became readily available, made it possible to detect some interesting differences in the properties of the fluorinated and unfluorinated analogs.

Levulinic acid is linear and only when it is heated to 100° can the presence of its cyclic form be detected [4]. α,α-Dimethyllevulinic acid contains the cyclic form even at ~20° [5]. Based on the chemical properties (haloform decomposition, preparation of linear esters), trifluorolevulinic acid was assigned a linear structure, but later an analysis of the IR spectra disclosed the presence of the cyclic form [6, 7].

The dimethyltrifluorolevulinic acid obtained by us has a cyclic structure. The equilibrium of the ring-chain tautomerism in this case is shifted so far toward the cyclic form that the linear form cannot be detected from either the IR or the ^{19}F NMR spectra. In harmony with the cyclic structure, hydroxylacetone (III) remains unchanged when refluxed with an alcohol in the presence of acid, or when treated with CH_2N_2; only on long standing with alkali does it undergo haloform decomposition to give α,α-dimethylsuccinic acid (cf. [6, 7].



Institute of Heteroorganic Compounds, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2559-2562, November, 1973. Original article submitted April 26, 1973.

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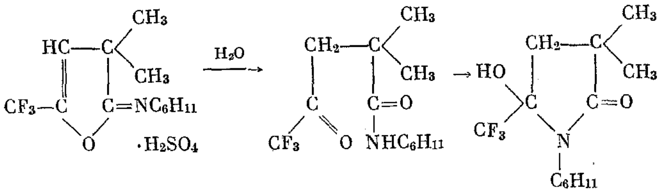
In contrast to the acid itself, in the amides of levulinic acid the equilibrium of the ring-chain tautomerism at ~20° is shifted toward the cyclic form, which changes to the linear form on heating [7-9]. Both tautomers could be isolated only in the case of the unsubstituted levulinic acid amide [8].

Depending on the conditions used to saponify dihydrofuran (IIb) we were able to obtain both the linear and the cyclic isomers of the trifluorolevulinic acid cyclohexylamide. The linear isomer (V) is formed when sulfate (IV) is treated with water at 20°. Its structure was proved by the IR and NMR spectra. Amide (V) can be stored for a long time at 0° without change, but at ~20°, and especially when heated it changes rapidly to the stable cyclic form (VI). This transformation is irreversible even at 130° (NMR spectrum). Acid and alkaline media also facilitate the cyclization. Pyrrolidone (VI) is formed exclusively when dihydrofuran (IIb) is treated with conc. HCl.



(IV) (V) (VI)

In contrast to amide (V), the absorption frequencies of the CF_3CO and RNHCO (2nd amide band) groups are absent in the IR spectra of pyrrolidone (VI). The changes in the NMR spectra are also in agreement with the cyclic structure.

Both in our study, and apparently also in [8], the liberation of the linear isomer is associated with kinetic factors. The cyclic isomers of the levulinic acid amides are thermodynamically more stable, in which connection the stability of the cyclic isomers of dimethyltrifluorolevulinic acid and its derivatives is greater than that of the unfluorinated analogs. An increase in the stability of the cyclic form when fluorine atoms are inserted is not unexpected, since the stabilizing effect of perfluoroalkyl groups on the usually unstable geminal compounds is well known [10].

EXPERIMENTAL METHOD

The IR spectra were taken on a UR-20 spectrometer, as KBr pellets for the solids. The ^{19}F NMR spectra were taken on a Hitachi instrument (56.46 MHz), using CF_3COOH as the external standard. The NMR spectra were taken on a Perkin-Elmer R-12 instrument, using HMDS as the internal standard. The chemical shifts (δ) are given in parts per million from CF_3COOH or $[(CH_3)_3Si]_2O$, respectively.

3,3-Dimethyl-5-trifluoromethyl-2-tert-butylimino-2,3-dihydrofuran (IIa). A mixture of 3 g of ketone (I) and 1.6 g of tert-butyl isonitrile was allowed to stand at ~20° for 14 days. Vacuum-distillation gave 4.24 g (92%) of dihydrofuran (IIa), bp 69° (50 mm). Infrared spectrum (ν, cm^{-1}): 1680 (C=C), 1740 (C=N). NMR spectrum: 0.82 and 0.86 (CH_3, two singlets); 5.3 (=CH, singlet). ^{19}F NMR spectrum: −7.14 (CF_3, singlet). Found: C 55.56; H 6.79; F 23.72; N 6.28%. $C_{11}H_{16}F_3NO$. Calculated: C 56.17; H 6.85; F 24.26; N 5.91%.

The same product (IIa) was obtained in 88% yield by heating a mixture of ketone (I) and tert-butyl isonitrile at 70° for 6 h.

3,3-Dimethyl-5-trifluoromethyl-2-cyclohexylimino-2,3-dihydrofuran (IIb). A mixture of 3 g of ketone (I) and 2.1 g of cyclohexyl isonitrile was allowed to stand at ~20° for 14 days. Vacuum-distillation gave 4.6 g (90%) of (IIb), bp 79° (7 mm). Infrared spectrum (ν, cm^{-1}): 1680 (C=C), 1740 (C=N). NMR spectrum: 0.8-1.7 [$(CH_2)_5$, multiplet)]; 0.9 [$(CH_3)_2$, singlet]; 3.3 (CH, multiplet); 5.4 (=CH, singlet). ^{19}F NMR spectrum: −8.0 (CF_3, singlet). Found: C 59.39; H 6.63; F 21.16; N 6.25%. $C_{13}H_{18}F_3NO$. Calculated: C 59.77; H 6.63; F 21.83; N 5.36%. Molecular weight of (IIb) = 261 (mass spectrometry). The same product (IIb) was obtained in 86% yield by heating a mixture of ketone (I) and cyclohexyl isonitrile at 100° for 5 h.

2-Trifluoromethyl-2-hydroxy-4,4-dimethyltetrahydro-5-furanone (III). A mixture of 1.2 g of dihydrofuran (IIa) and 2.8 ml of conc. HCl was refluxed for 5 h. The precipitate was filtered and washed with chilled water. We obtained 0.59 g (59.4%) of (III), mp 80-81° (from heptane). Found: C 42.16; H 4.45; F 29.59%. $C_7H_9F_3O_3$. Calculated: C 42.42; H 4.54; F 28.78%. Infrared spectrum ν, cm^{-1}: 1775 (C = O), 3240-3400 (OH). NMR spectrum (in acetone): 1.1 and 1.3 (CH_3, two singlets); 2.4 (CH_3, the center of two signals, probably the central signals of an AB system); 7.5 (OH). ^{19}NMR spectrum (in acetone): +7.5 (CF_3, singlet). Mass spectrum: 154(7), 139(53, 3), 129(10), 101(20), 85(100), 69(80). Evaporation of the filtrate gave 0.35 g (64%) of tert-butylamine hydrochloride, which was identical with an authentic sample. Lactone (III) remains unchanged when treated with excess CH_2N_2 in ether (1 day, 20°), or when refluxed (6 h) with a 20% solution of H_2SO_4 in alcohol.

Haloform Decomposition. To 0.6 g of lactone (III) was added 5 ml of 10% KOH solution and the mixture was allowed to stand for 4 days. Acidification of the reaction mixture gave 0.33 g (75%) of dimethylsuccinic acid with mp 139-141° (from water). Infrared spectrum (ν, cm^{-1}): 1695-1710 (split).

Cyclohexylamide of 1,1-Dimethyl-3,3,3-trifluorolevulinic Acid (V). With cooling, several drops of conc. H_2SO_4 were added to 0.57 g of dihydrofuran (IIb). The precipitate was filtered and washed with ether to give 0.77 g of (IV), mp 182-185° (decompn.). Infrared spectrum (ν, cm^{-1}): 1680 (C=C), 1730 (C=N). The obtained salt was mixed with 5 ml of water. After standing for 4 h the obtained crystals were filtered and washed with water. We obtained 0.52 g (86.6%) of amide (V), mp 62-65°. Infrared spectrum (ν, cm^{-1}): 1775 (C=0); 1550, 1645 (CONH), 3380 (NH). NMR spectrum (in C_6H_6): 0.93 (CH_3, singlet); 2.5 (CH_2, singlet); 3.6 (CH, multiplet). ^{19}F NMR spectrum (in C_6H_6): + (CF_3, singlet).

1-Cyclohexyl-2-hydroxy-2-trifluoromethyl-4,4-dimethyl-5-pyrrolidone (VI). a) To 1 g of dihydrofuran (IIb) was added 1.5 ml of conc. HCl. At the end of exothermic reaction the reaction mixture was poured into water. We obtained 0.9 g (80%) of (VI), mp 178-180° (from acetone). Found: C 56.07, H 7.45; N 5.23%. $C_{13}H_{20}F_3NO_2$. Calculated: C 55.95; H 7.53; N 5.01%. Infrared spectrum (ν, cm^{-1}): 1660 (C=O), 3230 (OH). NMR spectrum (in HMPO): 1.0 and 1.1 (CH_3, singlets). ^{19}NMR spectrum (in acetone): +4.3 (CF_3, singlet). Molecular weight of (VI) = 279 (mass spectrometry). Pyrrolidone (VI) remains unchanged when treated with excess CH_2N_2 in ether (2 days, 20°).

b) Pyrrolidone (VI) is formed when an acetone solution of amide (V) is allowed to stand for a long time or is refluxed for a short time.

c) To 0.1 g of amide (V) was added 2 ml of a 10% KOH solution. After 2 min the product was filtered to give 0.03 g (30%) of crystals, mp 177-180°, which were identical with those obtained in Expt. a). Acidification of the mixture gave an additional 0.05 g (50%) of the (VI) crystals, mp 181-183°.

d) Several drops of conc. H_2SO_4 were added to an acetone solution of amide (V). The ^{19}NMR spectrum, taken after 2-3 min, disclosed a sharp increase in the amount of pyrrolidone (VI).

CONCLUSIONS

1. Trifluoromethyl β,β-dimethylvinyl ketone enters with isonitriles into the uncatalyzed 1,4-dipolar cycloadditional reaction.

2. It was established for dimethyltrifluorolevulinic acid and its derivatives that the cyclic forms are more stable than the unfluorinated analogs.

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