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Fluorinated Nitrogen Heterocycles via Cyclization. II.

3-Trifluoromethylglutarimides from Fluorinated α,β -Unsaturated Carbonyls and Cyanoacetamide.

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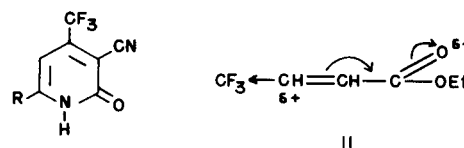
A previous paper (1) discussed the synthesis, absorption spectra, and tautomerism of trifluoromethyl-2-pyridones (Ia-e) prepared from fluorinated 1,3-dicarbonyls and cyanoacetamide. This work has now been extended to the preparation of 3-trifluoromethylglutarimides via Michael addition and ring closure by use of fluorinated α,β -unsaturated carbonyls as the fluorinated intermediates.

It has been shown by other workers (2) that the β -carbon atom of ethyl 4,4,4-trifluorocrotonate (II) is the reactive positive center in reactions with nucleophilic reagents. Addition occurred at this site, suggesting that the inductive effect of the trifluoromethyl group cannot overcome the resonance effect in the opposite direction due to the conjugated system (3). In agreement with this conclusion, it has been found in this laboratory that when the sodium salt of 2-cyanoacetamide reacts with fluorinated α,β -unsaturated carbonyls, having the general structure $\text{CF}_3(\text{R})-\text{C}=\text{CHCOOEt}$, cyclizations occur giving 3-trifluoromethylglutarimides (III, IV).

In contrast to β -trifluoromethyl substituted intermediates, no cyclization occurred utilizing methyl α -trifluoromethylacrylate under similar reaction conditions. Instead of the expected 2-cyano-4-trifluoromethylglutarimide, unreacted cyanoacetamide and a viscous, polymeric oil were isolated. This oil showed C-F absorption bands in the region 1100-1330 cm^{-1} . Reaction at low temperature and the use of piperidine in place of sodium ethoxide were also not fruitful. It can be concluded, therefore, that α -trifluoromethylacrylates do not undergo cyclization after the initial Michael addition in contrast to the β -trifluoromethyl intermediates (4). In the former case, anionic polymerization is apparently favored under these reaction conditions, possibly due to the stabilization of the anion (formed via Michael addition) by the electron-withdrawing substituents (5).

It has been observed that electron-withdrawing groups adjacent to a carbon atom carrying a nitrile group decreases the nitrile intensity (1, 6, 7), or quenches it entirely (8). This behavior has also been observed in the present case. The infrared spectra of compounds III and IV show that nitrile absorptions are entirely quenched. On conversion to their sodium salts (V, VI), however, very strong

nitrile bands appear in the regions 2165 and 2174 cm^{-1} respectively (9). These salts also exhibit N-H absorption bands of medium intensities at 3155 cm^{-1} (V) and 3205 cm^{-1} (VI). In addition, all four compounds have strong carbonyl absorptions. These observations indicate that conversion to the salt probably involves the enolization of the carbonyl adjacent to the nitrile substituent. Other strong bands, absent in III and IV, also appear in the salts V and VI in the regions 1612, 1594 and 1606, 1588 cm^{-1} respectively. These absorptions may be attributable to ring double bond stretching frequencies (10, 11).



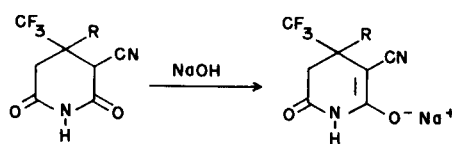
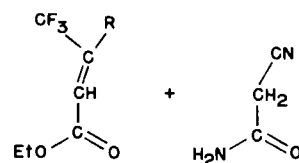
Ia, R = CH_3

Ib, R = CF_3

Ic, R = C_6H_5

Id, R = 2- $\text{C}_4\text{H}_3\text{S}$

Ie, R = OH



III, R = CH_3

V, R = CH_3

IV, R = H

VI, R = H

Difficulties were encountered in the elemental analysis of compound VI because of its decomposition on standing. This led to the preparation of the ammonium salt which also proved to be equally unstable. Unlike the ammonium salt of Ie, which is stable on long standing and at 100°/40 mm., the ammonium salt of IV evolves ammonia under similar conditions and gives the water-insoluble starting material. Treatment of III with ammonium hydroxide, also gave a white crystalline product, which behaved in a similar manner. As expected, the spectra of the ammonium salts of III and IV also show very strong nitrile absorption bands.

EXPERIMENTAL (12)

2-Cyano-3-methyl-3-trifluoromethylglutarimide (III).

Clean dry sodium metal (4.7 g., 0.21 g.-atom) was dissolved in 100 ml. of absolute alcohol. After the temperature of the solution had fallen to about 50°, cyanoacetamide (16.8 g., 0.20 mole) was added with stirring over a period of 0.5 hour and the mixture was stirred for 2 hours at 60°. Ethyl 3-methyl-4,4,4-trifluorocrotonate (36.4 g., 0.20 mole) was then added dropwise over a period of 15 minutes and the mixture was stirred for 18 hours at 70°. After the addition of 60 ml. of water, the mixture was made acidic (pH of about 2) with 40 ml. of 15% hydrochloric acid and evaporated in an air stream until about 200 ml. of mixture remained. The resulting pink-brown precipitate was removed by filtration under suction, and purification by several recrystallizations from 5% hydrochloric acid, using carbon black, gave white needles (29.0 g., 66%), m.p. 195-198°. Infrared bands appeared at 3410 w-b (13), 3205 m, 3105 s, 1735 sh, 1715 vs, 1667 sh, 1413 m, 1343 s, 1315 s, 1293 vs, 1282 vs, 1268 s, 1243 m, 1201 vs, 1183 vs, 1150 s, 1122 s, 1092 vs, 1035 w-b, 991 vw-b, 953 w, 939 w, 896 w, 857 m-b, 803 vw, and 693 w cm^{-1} .

Anal. Calcd. for $\text{C}_8\text{H}_7\text{F}_3\text{N}_2\text{O}_2$: C, 43.64; H, 3.21; F, 25.89; N, 12.73. Found: C, 43.81; H, 3.12; F, 25.34; N, 12.53.

Compound III, dissolved in a minimum of hot 10% sodium hydroxide, gave the sodium salt V on standing. Recrystallization from acetonitrile using carbon black gave white needles, hygroscopic, m.p. 317° dec.

Anal. Calcd. for $\text{C}_8\text{H}_6\text{F}_3\text{N}_2\text{NaO}_2$: C, 39.68; H, 2.50; Na, 9.49. Found: C, 39.81; H, 2.71; Na, 9.23.

2-Cyano-3-trifluoromethylglutarimide (IV).

The reaction was performed in the same manner as above, employing ethyl 4,4,4-trifluorocrotonate (33.6 g., 0.20 mole) as the fluorinated intermediate. After the addition of the crotonate, however, the mixture became very viscous on initial heating, and an additional 25 ml. of absolute alcohol was used. Several recrystallizations from 5% hydrochloric acid, using carbon black, gave white needles (28.0 g., 68%), m.p. 158.5-160°. Infrared bands were at 3390 w-b, 3175 m, 3080 m, 1747 s, 1710 vs, 1667 sh, 1342 m, 1317 s, 1300 m, 1277 vs, 1263 vs, 1241 s, 1191 vs, 1183 sh, 1163 m, 1143 s, 1130 s, 1096 w, 1058 w, 1022 w-b, 954 w, 927 s, 859 m-b, and 683 m cm^{-1} .

Anal. Calcd. for $\text{C}_7\text{H}_6\text{F}_3\text{N}_2\text{O}_2$: C, 40.79; H, 2.44; F, 27.65; N,

13.59. Found: C, 41.39; H, 2.29; F, 27.70; N, 13.66.

The sodium salt VI was prepared in a manner similar to that for V. Recrystallization from acetonitrile gave white needles, hygroscopic, m.p. 313° dec., which showed decomposition on standing (grey coloration).

Anal. Calcd. for $\text{C}_7\text{H}_4\text{F}_3\text{N}_2\text{NaO}_2$: C, 36.86; H, 1.77; Na, 10.08. Found: C, 36.55; H, 2.10; Na, 10.49.

Attempted Preparation of 2-Cyano-4-trifluoromethylglutarimide.

The reaction was performed in the same manner as that for III. Methyl α -trifluoromethylacrylate, prepared according to R. A. Darrall *et al.*, (14), was the fluorinated intermediate employed (15). Addition of water and 15% hydrochloric acid, followed by evaporation to dryness, gave a tacky brown mass. On extraction with ether, a quantitative amount of unreacted cyanoacetamide remained. Evaporation of the ether gave a very viscous oil from which no heterocyclic product could be isolated.

The reaction was also performed in the same way as that immediately above, using an ice-water bath, however, in order to keep the reaction temperature below +10° during addition of the acrylate. No product was obtained. In another run at low temperature, 10 ml. of piperidine was used as the basic catalyst but without success.

Acknowledgment.

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- (12) All melting points are uncorrected; analyses by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer with samples run as Nujol mulls.
- (13) b = broad, vw = very weak, w = weak, m = medium, s = strong, vs = very strong, sh = shoulder.
- (14) R. A. Darrall, F. Smith, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2329 (1951).
- (15) This reaction was decidedly more exothermic in comparison to reactions for the formation of III and IV.

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