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SYNTHESIS AND REACTIONS OF (E)-1,1,1-TRIFLUORO-2-METHYL-2-PENTEN-4-YLIDENE-MALONODINITRILE

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SUMMARY

Condensation of (E)-1,1,1-trifluoro-2-methyl-2-penten-4-one with malonodinitrile affords mixtures of unsaturated nitriles. Attempted cyclization of these nitriles in concentrated sulfuric acid furnishes derivatives of alkylidenecyanoacetamides and alkylidenemalonodiamide.

INTRODUCTION

Cyclization of ylidenemalonodinitriles and ethyl ylidenecyanoacetates obtained from unsaturated ketones is a simple and useful route to carbocyclic o-aminonitriles and o-aminoesters. This approach has been applied for the synthesis of ethyl 2-amino-4,6-dimethylbenzoate starting from mesityl oxide [1] or for the construction of sym-octahydrophenanthrene or as-hydrindacene systems [2,3]. Schmidt and Junek have obtained a highly functionalized benzene system by cyclization of malonodinitrile derivatives synthesized from ß-keto esters [4]. Pyrolytic synthesis of N-(trimethylsilyl)aniline from trimethylsilyl (E,E)-2-cyanohexa-2,4-dienoate has been investigated by Besida and Brown [5]. The results of our

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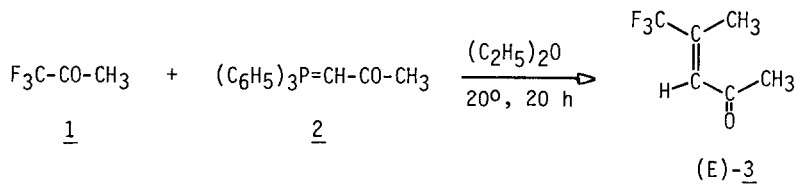
investigations on cyclization of unsaturated nitriles synthesized from mesityl oxide encouraged the author to extend this approach to 1,1,1-trifluoro-2-methyl-2-penten-4-one (3), the trifluoromethyl analog of mesityl oxide. The purpose of present research has been cyclization of the ylidenemalonodinitrile obtained from this ketone to 2-amino-4-methyl-6-(trifluoromethyl)benzene-1-carbonitrile (6). This approach would allow introduction of the trifluoromethyl group or perhaps perfluoroalkyl groups on a functionalized carbocyclic system.

RESULTS AND DISCUSSION

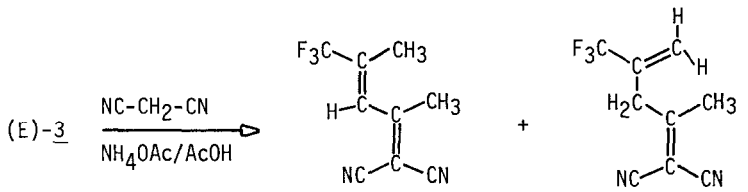
The reaction of 1,1,1-trifluoropropan-2-one (1) with 1-triphenylphosphoranylidene-2-propanone (2) was carried out at room temperature in diethyl ether. This was essentially the procedure reported by Dull and co-workers [6] with some modifications in the isolation of the final product. These authors reported on the basis of gas chromatographic analysis alone that only one geometrical isomer of the fluoroketone 3 was formed but they did not offer a structural assignment.



1 2 (E)-3

It was essential for our investigations to differentiate between the possible (E) and (Z) isomers of 1,1,1-trifluoro-2-methyl-2-penten-4-one (3), since it was assumed that only the ylidenemalonodinitrile obtained from the (E)-3 isomer would have the appropriate geometry for the ring closure leading to the o-aminonitrile 6. In the cyclization step the attack of the protonated nitrile group presumably occurs on an olefinic carbon atom generated from the methyl group previously located cis to the dinitrile moiety [1]. Similar cyclization of the ylidenemalonodinitrile obtained from (Z)-3 isomer appears less feasible. The (E) structure for the ketone 3 was assigned on the basis of ^{1}H-NMR and ^{19}F-NMR spectral data. The methyl group of 3 at the olefinic bond appeared

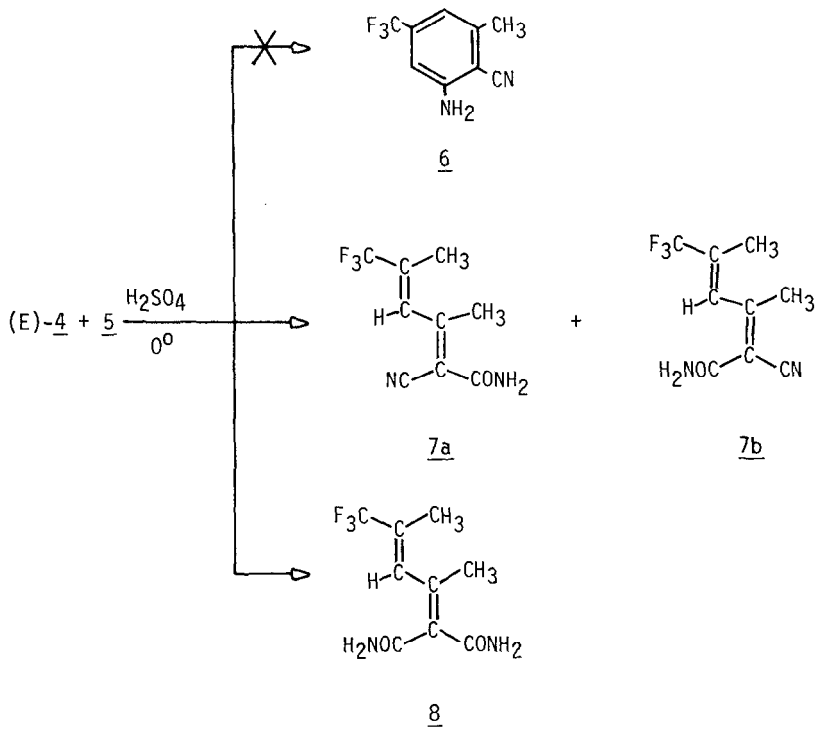
as a doublet at δ 2.17 ppm ($J_{CH_3,H}$ = 1.5 Hz). Since the value of the coupling constant $J_{CH_3,H}$ for CH_3-C=C-H (cis) and CH_3-C=C-H (trans) systems are nearly in the same range, the final assignment of the structure of the ketone 3 was based on ^{19}F-NMR data. The value of the $J_{CF_3,H}$ coupling constant (1.7 Hz) indicated the cis position of the trifluoromethyl group with respect to the vinyl proton [7,8]. Burton and co-workers [7] reported the coupling constant J_{H,CF_3} for CF_3-C=C-H (trans) systems in the range of 0-0.7 Hz. Therefore in our case the coupling constant $J_{CF_3,H}$ for (Z)-3 isomer would be expected in a similar range. The vinyl proton of 3 appeared as a multiplet at δ 6.62 ppm in the ^{1}H-NMR spectrum. This multiplet collapsed to a well resolved quartet (J_{H,CF_3}= 1.6 Hz) after decoupling of the trans methyl group. All these data as well as gas chromatographic analysis support (E)-3 structural assignment for the fluoroketone 3.



(E)-4 5

Condensation of the ketone (E)-3 with malonodinitrile was carried out under standard conditions [1,2] to give predominantly the liquid ylidenemalonodinitrile 4. The ^{1}H-NMR and ^{19}F-NMR spectra and also gas chromatographic analysis of this product revealed that beside expected ylidenemalonodinitrile (E)-4 a small amount of an isomeric dinitrile 5 was present in the reaction product (5:1 ratio). The structural assignment for 4 and 5 was carried out in a similar manner as for the ketone 3. It is interesting to note that an analog of 5 was not detected in the condensation product obtained from mesityl oxide and malonodinitrile [1].

Dissolving the mixture of nitriles 4 and 5 in ice-cold concentrated sulfuric acid followed by quenching the solution with ice afforded after purification colorless needles in low yield (28%). Spectral analysis of this product (m.p. 117-118°) revealed that a mixture of ylidenecyanoacetamides 7a and 7b was obtained instead of expected carbocyclic aromatic o-aminonitrile 6.



Neutralization of acidic filtrate gave after separation of 7a and 7b the ylidenemalonodiamide 8 (m.p. 174-174°) in very low yield (3.4%). Structural assignment of 8 was based only on MS, IR, and microanalytical data. Attempted cyclization of nitriles 4 and 5 by hot polyphosphoric acid, boron trifluoride etherate or by ethanolic sodium ethoxide was unsuccessful. Under these conditions only unchanged starting nitriles 4, 5 were isolated from reaction mixtures.

The nitrile 5 has the double bond conveniently located for the electrophilic attack of the protonated nitrile group in the ring closure step. However, it appears that the trifluoromethyl group of 5 renders the olefinic bond unsusceptible to electrophilic attack. In the same manner, the electronegative trifluoromethyl group of 4 may prevent electrophilic attack on the double bond generated in the intermediate step leading to 6 [1]. Therefore, the hydrolysis of the cyano group is predominant reaction pathway. Similar hydrolysis of cyano groups of some ylidenemalonodinitriles on attempted cyclization in sulfuric acid was reported earlier by Campaigne and co-workers [9].

EXPERIMENTAL

Melting and boiling points are uncorrected. ^{1}H-NMR spectra were obtained on a Bruker HFX-90 spectrometer with TMS as an internal standard. ^{19}F-NMR spectra were recorded on a Bruker HX-60 spectrometer with hexafluorobenzene as an internal standard and fluorine chemical shifts were converted to fluorotrichloromethane standard. The mass spectra were obtained on a Varian MATCH-5 instrument and IR spectra were recorded on a Perkin-Elmer IR-325 spectrometer.

The Reaction of 1,1,1-trifluoropropan-2-one (1) with 1-triphenylphosphoranylidene-2-propanone (2)

1-Triphenylphosphoranylidene-2-propanone (2) (10.0 g, 31 mmol) was dissolved in anhydrous diethyl ether (40 ml) in a flask equipped with efficient reflux condenser and a magnetic stirrer. The apparatus was protected from moisture and cold methanol (-15°) was circulated through the reflux condenser. Trifluoroacetone 1 (3.9 g, 35 mmol) was added to the solution and the resulting mixture was continuously stirred at room temperature for 20 h. The precipitated solid was filtered off and washed with ether. Ether solutions were combined and most of the solvent was removed by distillation under slightly reduced pressure. The remaining liquid was frozen in liquid nitrogen then all volatiles removed under high vacuum on a vacuum line into a trap cooled in liquid nitrogen. In this manner traces of triphenylphosphine oxide and starting compound 2 were efficiently separated avoiding distillation at higher temperature which usually caused decomposition of the product. Fractionation of the distillate at atmospheric pressure afforded 2.8 g (58%) of pure (E)-1,1,1-trifluoro-2-methyl-2-penten-4-one (3) as colorless liquid with characteristic pleasant smell; b.p. 108-109°; n_D^{19} = 1.3730; MS (70 eV) m/e 152(M^+, 35%),137(100),132(10),117(9),109(8),89(47),69(7),59(20); IR (neat) 1709(C=O),1653(C=C),1430,1360,1298(CF_3),1200,1175,1132,1106,968,873 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.62 (m,1$H_{vinylic}$); 2.31 (s,3H,-CH_3); 2.17 ppm (d,3H, -CH_3,J=1.5 Hz); ^{19}F-NMR ($CDCl_3$) -71.35 ppm (d,-CF_3, J=1.7 Hz), (lit., [6], b.p. 109-112°; n_D^{21} = 1.3726).

Condensation of (E)-1,1,1-trifluoro-2-methyl-2-penten-4-one (3) with malonodinitrile

The ketone (E)-3 (4.8 g, 31 mmol), malonodinitrile (2.2 g, 33 mmol), ammonium acetate (0.6 g), acetic acid (1.6 g), and anhydrous benzene (15 ml) were heated under reflux in a flask equipped with a Dean-Stark water trap until separation of water was complete (6 h). The solution was washed with water, saturated sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. Benzene was removed on a rotary evaporator and the product was fractionated under reduced pressure to afford 2.9 g (45%) of the mixture of (E)-1,1,1-trifluoro-2-methyl-2-penten-4-ylidenemalonodinitrile (4), and 2-(trifluoromethyl)-1-penten-4-ylidenemalonodinitrile (5), as yellowish oil; b.p. 76°/3 torr; n_D^{19} = 1.4448; MS (70 eV) m/e 200(M^+,20%),173(40),104(100); IR (neat) 3008,2240(CN),1594(C=C),1558,1442,1363,1307,1290,1262,1250 (br.CF_3),1057,1021,997,870 cm^{-1}; ^{1}H-NMR ($CDCl_3$), (E)-4: δ = 6.73 (m,1$H_{vinylic}$); 2.44 (s,3H,-CH_3); 2.04 ppm (d,3H,-CH_3,J=1.5 Hz); 5: δ = 5.98 (m,1$H_{vinylic}$); 5.54 (m,1$H_{vinylic}$); 3.50 (s,2H,-CH_2-); 2.30 ppm (s,3H,-CH_3); ^{19}F-NMR ($CDCl_3$), (E)-4: -70.53 ppm (d,-CF_3,J=1.7 Hz); 5: -68.44 ppm (m,-CF_3). The ratio of (E)-4 and 5 (5:1) was estimated from ^{1}H-NMR spectrum. Elemental analysis was carried out for mixture of 4 and 5. Anal. calcd for $C_9H_7F_3N_2$ (200.16): C, 54.00; H, 3.52; N, 13.99. Found: C, 54.21; H, 3.59; N, 14.12.

The reaction of ylidenemalonodinitriles 4 and 5 in concentrated sulfuric acid

The mixture of ylidenemalonodinitriles 4 and 5 (496 mg, 2.5 mmol) was slowly dissolved with stirring in ice-cold concentrated sulfuric acid (3 ml). The solution was left overnight at room temperature and then poured onto ice (50 g). A yellow oil separated and slowly solidified at room temperature. The solid was filtered off, washed with water, and sublimed in vacuo (0.05 torr). Recrystallization from n-hexane afforded 150 mg (28%) of the mixture of (E,E)-7a and (E,Z)-1,1,1-trifluoro-2-methyl-2-penten-4-ylidenecyanoacetamide (7b), as colorless needles; m.p. 117-118°; MS (70 eV) m/e 218(M^+,10%),217(8),198(11), 155(13),150(13),149(100),127(12),104(10),79(15),77(15); IR (KBr) 3416, 3218(NH_2),2220(CN),1678(C=O),1610,1447,1388,1362,1309,1185,1127(CF_3),

890,800,744 cm^{-1}; ^{1}H-NMR ($CDCl_3$), (E,E)-7a: δ = 6.67 (br.s,1$H_{vinylic}$); 6.30 (br.s,2H,-NH_2); 2.47(s,3H,-CH_3); 1.95 ppm (d,3H,-CH_3,J=1.5 Hz); (E,Z)-7b: δ = 7.05 (br.s,1$H_{vinylic}$); 6.30 (br.s,2H,-NH_2); 2.37 (s,3H,-CH_3); 1.82 ppm (d,3H,-CH_3,J=1.5 Hz); ^{19}F-NMR ($CDCl_3$), (E,E)-7a: -70.81 ppm (d,-CF_3,J=1.6 Hz); (E,Z)-7b: -70.56 ppm (d,-CF_3,J=1.7 Hz). The ratio 7a : 7b (4:1) was estimated from ^{1}H-NMR spectrum. Anal. calcd for $C_9H_9F_3N_2O$ (218.18): C, 49.55; H, 4.16; N, 12.84. Found: C, 49.47; H, 4.21; N, 12.79.

The acidic filtrate left after separation of 7a and 7b was neutralized with the solution of sodium hydroxide and concentrated by heating on a steam bath. After standing at room temperature for a few hours, the precipitated product was separated, washed with water and sublimed in vacuo. The sublimed product was extracted with hot n-hexane. The hexane soluble fraction (40 mg) was a mixture of 7a and 7b. Hexane insoluble fraction was recrystallized from chloroform to give 20 mg (3.4%) of (E)-1,1,1-trifluoro-2-methyl-2-penten-4-ylidenemalonodiamide (8), (nc), as colorless needles; m.p. 173-174°; MS (70 eV) m/e 236 (M^+,4%),204(9),202(21),192(9),191(13),168(10),167(100),151(8),150(77), 149(43),128(10),127(16),122(10),109(9),94(9),80(15),79(31),77(21); IR (KBr) 3440,3320,3215(NH_2),1655(C=O),1618,1447,1380,1359,1296,1182,1125 (CF_3),1054,880 cm^{-1}; Anal. calcd for $C_9H_{11}F_3N_2O_2$ (236.19): C, 45.77; H, 4.69; N, 11.86. Found: C, 45.64; H, 4.75; N, 11.92.

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