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PREPARATION OF TRIFLUOROMETHYL-PYRAZOLES AND -PYRAZOLINES BY THE REACTION OF 2,2,2-TRIFLUORODIAZOETHANE WITH CARBON-CARBON MULTIPLE BONDS

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SUMMARY

1,3-Dipolar addition of 2,2,2-trifluorodiazoethane to a series of alkenes and alkynes gives good yields of the corresponding pyrazolines and pyrazoles. Chloromethyl and bromomethyl substituents activate the multiple bond more than does a phenyl substituent. A combination of electronic effects and steric hindrance accounts for the reactivity of 3,3,3-trichloropropene, methyl methacrylate, and allyl formate.

INTRODUCTION

It has previously been shown [1] that in the absence of light, 2,2,2-trifluorodiazoethane reacts as a 1,3-dipole with alkenes and alkynes to give pyrazolines and pyrazoles respectively. The reaction is slow with ethylene or acetylene, but is accelerated slightly by bromine or chlorine substituents on the multiple-bonded carbon, and markedly by a trifluoromethyl group, 3,3,3-trifluoropropene reacting some 20 times faster than ethylene. In a competition reaction, methyl propiolate, containing the highly activating methoxycarbonyl group, reacted only 2-3 times faster than 3,3,3-trifluoropropyne.

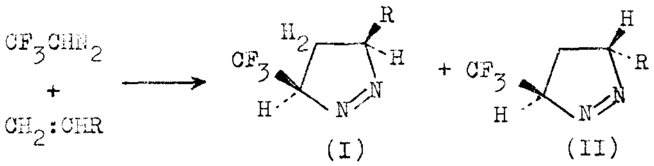
We report here the reactions of 2,2,2-trifluorodiazoethane with a further selection of alkenes and alkynes.

RESULTS AND DISCUSSION

Reactions with alkenes

Allyl chloride and 2,2,2-trifluorodiazoethane reacted readily in the dark at room temperature to give a mixture of 3-chloromethyl-5-trifluoromethylpyrazolines in 91% yield. When an excess of the olefin was present, the reaction was readily followed visually by the disappearance of the yellow colour of the diazoethane, and was complete after 2 days, but it proved difficult to separate the high-boiling olefin from the pyrazolines. Use of an excess of the volatile diazoalkane, however, avoided this difficulty. The absence of any N-H stretch from the i.r. spectrum showed that no isomerisation of the initial Δ^1-pyrazolines had occurred, and both ^1H and ^{19}F n.m.r. spectra suggested a ca. 3:2 ratio of cis- and trans-isomers, the appearance of the 4-methylene group as a deceptively simple triplet for the trans-isomer and as the AB part of an ABXY pattern for the cis-isomer being particularly useful.

The pyrazoline mixture decomposed too readily when it was either heated gently or exposed to the atmosphere for separation of the geometric isomers to be possible, rapidly producing a brown tar. Attempts at pyrolysis to the cyclopropanes were completely unsuccessful, as

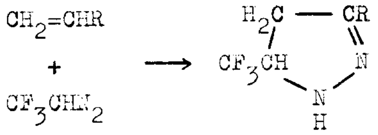


a; $R=CH_2Cl$ b; $R=CCl_3$

has been found [1] with other 1-pyrazolines derived from trifluorodiazoethane. Ultraviolet irradiation of a mixture of allyl chloride and the diazoethane also failed to produce the cyclopropanes. Although reaction was complete in 4 hours, the products were again the *cis*- and *trans*-isomers (Ia) and (IIa) in 80% yield, the faster reaction compared with that taking place in the dark probably being due to the increased reaction temperature in front of the lamp rather than to photochemical activation of the reactants. The yield of nitrogen showed that only a maximum of 17% of trifluoromethylcarbene could have been formed, and the isolation of trifluoroethylene (8%) and 1,1,1,4,4,4-hexafluoro-*trans*-but-2-ene (10%) readily accounted for all of it.

3,3,3-Trichloropropene reacted more slowly than allyl chloride (11 days), and the highly unstable product was identified spectroscopically as a 1:3 mixture of the *cis*- and *trans*- Δ^1-pyrazolines, (Ib) and (IIb), the deceptively simple triplet for the C-4 methylene group of the *trans*-isomer being much stronger than in the ^{1}H spectrum of the products from allyl chloride.

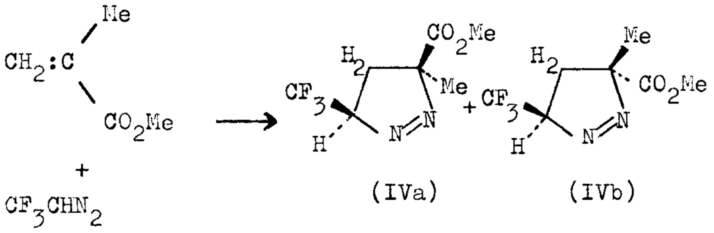
Acrylonitrile and methyl acrylate both reacted completely with the diazoethane on warming from -78°C to room temperature overnight, and these semi-quantitative experiments allow no distinction between the activating effects of the methoxycarbonyl and nitrile groups. The yields were high (87% and 98% respectively) and the products showed N-H stretching absorptions (3.01µm); the ester carbonyl absorption at 5.89µm in the spectrum of the product from methyl acrylate clearly indicated conjugation, and the products were assigned the Δ^2-pyrazoline structures (IIIa) and (IIIb).



(III) a; $R=CO_2Me$
b; $R=CN$

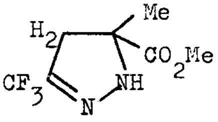
The ^{19}F n.m.r. spectra were simple doublets, but the ^{1}H spectra showed close-coupled ABX patterns, with the X part further complicated by quartet splitting from the CF_3 groups, and broad singlet N-H absorptions. No trace of the Δ^1-pyrazolines was observed in these reactions, although D'yatkin and Mochalina report [2] that in one reaction with methyl acrylate they were able to isolate the Δ-1 isomer.

Methyl methacrylate, in which the methyl group at C-2 prevents an easy 1,3-hydrogen shift to bring the ester group into conjugation with the ring, reacted more slowly (15 days), and a 98% yield of the cis- and trans- Δ^1-pyrazolines (IVa) and (IVb) obtained. The major isomer in the 3:1 mixture was tentatively assigned structure (IVa) on the basis of the ABX system observed



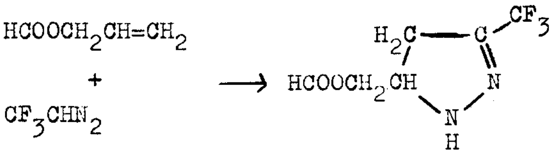
for the C-4 methylene and C-5 methine hydrogens, with a doublet for the C-4 methylene of the isomer (IVb). This is in accord with the assignment of the CF_3 absorptions made on the basis that a methoxycarbonyl group will deshield a cis-trifluoromethyl group and a methyl group will shield the cis-group, but conflicts with the predictions made on a similar basis for the methyl and methoxycarbonyl group absorptions. Re-examination of the material 1½ years later showed a singlet ^{19}F n.m.r. absorption, a broad N-H, two sharp methyl singlets, and an AB pattern for the C-4 methylene, with weak (1.5Hz) coupling to the CF_3 group, and N-H stretch in the i.r. spectrum at 2.99µm, indicating that the

C-5 hydrogen had undergone a 1,3-shift to nitrogen to form the Δ-2 isomer (V).



(V)

Allyl formate also reacted slowly with the diazoethane to give a high-boiling liquid product from which 5-formoxymethyl-3-trifluoromethyl-2-pyrazoline (VI) was obtained by distillation in 53% yield. G.l.c. prior to distillation indicated that it was formed in 75% yield.

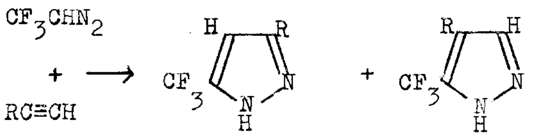


(VI)

As with (V), the N-H stretch in the infrared spectrum and ^{19}F n.m.r. singlet clearly indicate that the hydrogen of the CF_3CH group has undergone a 1,3 shift. A similar isomerisation took place when g.l.c. separation of cis- and trans-3-methyl-5-trifluoromethyl-1-pyrazolines was attempted [1], although here again the gain in stability that must provide the driving force is much less than when conjugation with a carbonyl or nitrile substituent is possible, as in the formation of (III).

Reactions with alkynes

Phenylacetylene, propyne, and 3-bromopropyne each reacted slowly with 2,2,2-trifluorodiazoethane to give almost quantitative yields of the corresponding 3(5)-substituted-5(3)-trifluoromethylpyrazole, reaction being complete in 4,8, and 2½ weeks respectively. Under similar conditions, acetylene reacts in 4 weeks, and methyl propiolate in less than 12 hours [1]. The orientation of addition was clearly indicated by the chemical shift of the ring CH, slightly to high field of benzene reference as expected for the 4-position [1,3] rather than <u>ca</u>. 1 p.p.m. to low field for the 3,5 positions; the CF_3 groups also absorb within the range expected for the 3(5)-position rather than the 4-position [1]. In previous work [1], methyl propiolate gave exclusively the 3(5)-substituted pyrazole (VIIc), but 3,3,3-trifluoropropyne and bromoacetylene, for which reaction times were 2 and 6 days respectively, gave mixtures containing 6 and 16% respectively of the corresponding 4-substituted-3-trifluoromethylpyrazoles, which were identified by independent synthesis. These results were rationalised on the basis of slow formation of the 4-substituted compound in parallel with formation of the 3(5)-substituted isomer at a rate depending on the accelerating effect of the substituent, so that with the highly activating methoxycarbonyl substituent, only (VIIc) was observed, and the proportion of (VIII) increased as the activating effect fell off. On this basis all three alkynes in the present work were expected to form mixtures of (VII) and (VIII), but in no case could any (VIII) be detected (limits estimated at less than 1%). Clearly, therefore, although we cannot at present put forward a better rationalisation, that suggested earlier is incomplete.



(VII) (VIII)

(a) $R=CF_3$
(b) $R=Br$
(c) $R=CO_2Me$
(d) $R=Ph$
(e) $R=Me$
(f) $R=CH_2Br$

The reaction times observed in the present work confirm and extend the earlier observation [1] that although mesomeric electron withdrawal, such as that by a carbonyl or nitrile group, is necessary for high activation of a carbon-carbon double or triple bond towards 1,3-dipolar addition of trifluorodiazoethane, substituents capable of withdrawing electrons inductively also provide reasonable activation. Thus the activating effect of a methoxycarbonyl group is only 4-6 times that of a chloromethyl group, and that of the bromomethyl group is almost twice the activating effect of a phenyl group. The range of reactivity of the substituted alkenes is much less for trifluorodiazoethane than the 2700 times (CO_2Me _vs._ H) quoted by Huisgen [4] for diazomethane. Presumably the smaller activation observed in the present work for the CO_2Me and CN groups is a consequence of the lower nucleophilicity of trifluorodiazoethane compared with diazomethane.

The smaller activating effect for the trichloromethyl group compared with the chloromethyl is presumably a result of the greater bulk of the trichloromethyl group, which also accounts for the increased proportion of the sterically favoured _trans_-isomer. Similar conflict between mild inductive activation and steric hindrance presumably also accounts for the deactivating effect of the formoxymethyl group. The reactivity of methyl methacrylate is low compared with ethyl acrylate and acrylonitrile, presumably due to a combination of electronic and steric deactivation by the methyl group. Although modified Courtauld models suggest that steric hindrance for the methacrylate is probably less than for trichloropropene, assessment of the extent of steric compared with electronic deactivation is not possible.

EXPERIMENTAL

2,2,2-Trifluorodiazoethane was prepared and manipulated as described previously [1]. I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer, n.m.r. spectra on a Perkin-Elmer R10 (^{19}F at 56.46 MHz, ^{1}H at 60.0 MHz) or

Varian H.A. 100 (^{19}F at 94.1 MHz, ^{1}H at 100.0 MHz) spectrometers (chemical shifts are positive to low field of external trifluoroacetic acid or external benzene reference as appropriate), and mass spectra on an A.E.I. MS2H spectrometer.

WARNING

Although the trifluoromethyl group of 2,2,2-trifluorodiazoethane makes this diazo-compound more stable than ordinary aliphatic diazo-compounds, several explosions have been experienced, both of the diazoalkane itself, and also apparently when unstable intermediates have been formed at low temperatures. Stringent safety precautions are necessary for all reactions of trifluorodiazoethane, particularly when it is used without solvent, even when apparently identical reactions have previously been carried out without incident. The energy released by explosion of 2,2,2-trifluorodiazoethane has been estimated at 50-100% of that released by an equal weight of T.N.T. [5].

Reactions of 2,2,2-Trifluorodiazoethane in the Dark

In these reactions, 2,2,2-trifluorodiazoethane and the substrate were sealed *in vacuo* in a Pyrex tube at -196°C, allowed to warm to room temperature, and kept at room temperature. The tube was examined at 6-8 h intervals, the bright yellow colour of the diazoalkane, when used in deficiency, providing a ready indicator of the extent of the reaction. Several of the reactions were then repeated using an excess of the volatile diazoethane in order to avoid problems in separation of product from the excess of high-boiling starting material.

(a) With allyl chloride

The diazoethane (1.65g, 15.0 mmol) and allyl chloride (1.93g, 25.3 mmol), after 2 days at R.T., gave allyl chloride (0.95g, 49%) and an involatile liquid mixture of cis- and trans-3-chloromethyl-5-trifluoromethyl-1-pyrazolines (2.55g, 91%), ^{19}F n.m.r. +5.95 [d, J($C\underline{F}_3$-$C\underline{H}$) 9.0 Hz] for the trans-isomer (43%) and +6.60 [d, J($C\underline{F}_3$-$C\underline{H}$) 8.5 Hz] for the cis-isomer (57%). Analysis: Found: C, 33.1; H, 3.5; N, 15.2%. Calc. for $C_5H_6F_3N_2Cl$: C, 32.2; H, 3.2; N, 15.0%.

(b) With 3,3,3-trichloropropene

Trichloropropene (1.17g, 8.0 mmol) and an excess of the diazoethane (1.10g, 10.0 mmol) after 11 weeks gave nitrogen (0.03g, 10%), recovered trifluorodiazoethane (0.17g, 15%), and a mixture of cis- and trans-3-trichloromethyl-5-trifluoromethyl-1-pyrazolines (1.83g, 90%), ^{19}F n.m.r. +6.18 p.p.m. [d, J($C\underline{F}_3$-$C\underline{H}$) 8.1 Hz] for the trans-isomer (77%) and +6.65 p.p.m. [d, J($C\underline{F}_3$-$C\underline{H}$) 7.3 Hz] for the cis-isomer (23%). The high-boiling liquid mixture rapidly gave a brown tar on gentle heating or exposure to air.

(c) With acrylonitrile

The diazoethane (1.65g, 15 mmol) and acrylonitrile (1.33g, 25 mmol) were allowed to warm to room temperature from -78°C overnight. Acrylonitrile (0.62g, 47%) was then removed *in vacuo* and the white crystalline residue was recrystallised twice (Et_2O) and sublimed *in vacuo* to give 3-cyano-5-trifluoromethyl-2-pyrazoline (nc) (2.12g, 87%), m.p., 82-83°C, ^{19}F n.m.r., +0.5 p.p.m. [d, J($C\underline{F}_3$-$C\underline{H}$) 7.5 Hz]. Analysis: Found: C, 36.8; H, 2.7; N, 25.6; F, 35.0%. $C_5H_4F_3N_3$ requires C, 36.8; H, 2.5; N, 25.8; F, 35.0%.

(d) With ethyl acrylate

The diazoethane (0.88g, 8.0 mmol) and ethyl acrylate (1.20g, 12.0 mmol) were allowed to warm from -78°C to R.T. overnight. Removal of the excess of ethyl acrylate (0.37g, 31%) and sublimation of the solid residue gave white crystals of 3-ethoxycarbonyl-5-trifluoromethyl-2-pyrazoline (nc) (1.64g, 98%), m.p., 85-86°C, ^{19}F n.m.r. +0.6 p.p.m. [d, $J(C\underline{F}_3-C\underline{H})$ 7.6Hz]. Analysis: Found: C, 40.2; H, 4.5; N, 13.5%. $C_7H_9F_3N_2O_2$ requires C, 40.0; H, 4.3; H, 13.3%.

(e) With methyl methacrylate

After 15 days the diazoethane (1.10g, 10.0 mmol) and methyl methacrylate (2.00g, 20.0 mmol) gave methyl methacrylate (0.95g, 48%) and a mixture of <u>cis</u>- and <u>trans</u>-3-methoxycarbonyl-3-methyl-5-trifluoromethyl-1-pyrazolines (2.05g, 98%), b.p., 64°C/1mmHg, ^{19}F n.m.r. +5.30 p.p.m. [d, $J(C\underline{F}_3-C\underline{H})$ 8.5 Hz] (25%) and +5.95 p.p.m. (d, $J(C\underline{F}_3-CH)$ 8.5 Hz] (75%). Analysis: Found: C, 40.3; H, 4.4; N, 13.6%. Calc. for $C_7H_9F_3N_2O_2$: C, 40.0; H, 4.3; N, 13.3% . After 18 months the Δ^1-pyrazolines had isomerized to 3-trifluoromethyl-5-methoxycarbonyl-5-methyl-2-pyrazoline, ^{19}F n.m.r. +11.0 p.p.m. (singlet).

(f) With allyl formate

After 7 weeks, allyl formate (1.29g, 15.0 mmol) and the diazoethane (1.10g, 10 mmol) gave nitrogen (0.04g, 15%), allyl formate (0.61g, 47%), and viscous, colourless 5-formoxymethyl-3-trifluoromethyl-2-pyrazoline (nc) (1.03g, 53%), b.p. 47°C/3mmHg, ^{19}F n.m.r. +9.37 p.p.m. (singlet). Analysis: Found: C, 36.7; H, 4.0; N, 14.2%. $C_6H_7F_3N_2O_2$ requires C, 36.8; H, 3.6; N, 14.3%.

(g) With 3-bromoprop-1-yne

3-Bromoprop-1-yne (1.79g, 15.0 mmol) and the diazoethane (1.10g, 10.0 mmol) were kept for 17 days to give 3-bromopropyne (0.68g, 33%) and 3(5)-bromomethyl-5(3)-trifluoromethylpyrazole (nc) (2.21g, 97%), ^{19}F n.m.r. +16.4 p.p.m. (singlet). Analysis: Found: C, 26.2; H, 1.8; N, 12.2%. $C_5H_4F_3N_2Br$ requires C, 27.0; H, 2.0; N, 12.0%.

(h) With phenylacetylene

Phenylacetylene (1.53g, 15.0 mmol) and the diazoethane (2.31g, 21.0 mmol) gave, after 4 weeks, nitrogen (0.05g, 9%), recovered trifluorodiazoethane (0.42g, 18%), and white crystalline 3(5)-phenyl-5(3)-trifluoromethylpyrazole (nc) (3.16g, 100%), m.p. 121°C, ^{19}F n.m.r., +16.5 p.p.m. (singlet). Analysis: Found: C, 56.6; H, 3.4; N, 13.2%. $C_{10}H_7F_3N_2$ requires C, 56.6; H, 3.3; N, 13.2%.

(i) With propyne

Propyne (1.15g, 28.7 mmol) and the diazoethane (2.20g, 20.0 mmol) gave, after two months, nitrogen (0.04g, 8%), recovered trifluorodiazoethane (0.24g, 11%), propyne (0.46g, 40%), and, after resublimation _in vacuo_ white crystalline 3(5)-methyl-5(3)-trifluoromethylpyrazole (nc) (2.45g, 81%), m.p., 85-86°C, ^{19}F n.m.r., +15.9 p.p.m. (singlet). Analysis: Found: C, 39.8; H, 3.6; N, 18.4%. $C_5H_5F_3N_2$ requires C, 40.0; H, 3.3; N, 18.7%.

Photochemical reaction of 2,2,2-trifluorodiazoethane with allyl chloride

The diazoethane (1.61g, 15.6 mmol) and allyl chloride (3.61g, 45.0 mmol) were sealed *in vacuo* in a silica tube (300 ml) and irradiated (Hanovia UVS 500 medium pressure mercury arc, 4 h). Fractionation *in vacuo* gave nitrogen (0.07g, 17%), allyl chloride (2.53g, 73%), a mixture of trifluoroethylene (0.10g, 8%) and 1,1,1,4,4,4-hexafluoro-*trans*-but-2-ene (0.12g, 10%), and a mixture of *cis*- and *trans*-3-chloromethyl-5-trifluoromethyl-1-pyrazoline (2.17g, 80%).

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