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APPLICATIONS OF THE FLUORINATED 1,3-DIPOLAR COMPOUNDS AS THE BUILDING BLOCKS OF THE HETEROCYCLES WITH FLUORINE GROUPS. PART XII. SYNTHESIS OF TRIFLUOROMETHYLISOXAZOLINES AND THEIR REARRANGEMENT INTO TRIFLUOROMETHYLAZIRIDINES [1]

K. TANAKA, M. OHSUGA, Y. SUGIMOTO, Y. OKAFUJI
and K. MITSUHASHI

Department of Industrial Chemistry, College of Technology
Seikei University, Musashino, Tokyo 180 (Japan)

SUMMARY

N-Methyl-C-trifluoromethylnitrone cycloadded with various alkynes to give 3-trifluoromethyl-4-isoxazolines. The isolated isoxazolines further underwent the valence rearrangement into 2-trifluoromethylaziridines under more drastic conditions. Unusual stability of both trifluoromethylisoxazolines and -aziridines is discussed on the basis of the electronic effect of trifluoromethyl group.

INTRODUCTION

It is well known that some 4-isoxazolines, derived from nitrones and alkynes, are not isolable and spontaneously rearrange to aziridines. Many aziridines are so unstable as to undergo further ring-transformation to oxazolines [2]. The isolation of aziridine is reported to be possible in the cases with electron-withdrawing substituents on the nitrogen atom and with the lack of C-5 substituents under appropriate experimental conditions [3]. So far, we have demonstrated the high potential of trifluoromethyl-1,3-dipolar compounds as building blocks of trifluoromethylheterocycles [1]. In the present paper, we wish to report the reaction of N-methyl-C-trifluoromethylnitrone (2) with various alkynes, resulting in

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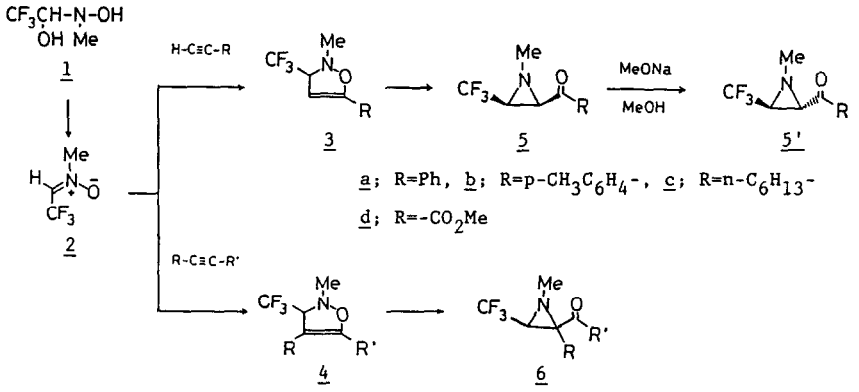
the formation of the rather stable 3-trifluoromethyl-4-isoxazolines, and the rearrangement into 2-trifluoromethyl-aziridines which are also isolable under the reaction conditions.

RESULTS AND DISCUSSION

The nitrone 2, generated by removal of water from the nitrone hydrate 1, was cycloadded with phenylacetylene in refluxing benzene to give exclusively 2-methyl-5-phenyl-3-trifluoromethyl-4-isoxazoline (3a) in a good yield. With other monosubstituted acetylenes, the reaction was carried out under the conditions shown in Table 1. Cycloadditions with p-tolyl-acetylene and 1-octyne proceeded regioselectively, affording only 5-substituted isoxazolines 3b,c, whereas methyl propiolate produced a substantial amount of regioisomer 3d' together with 3d. The nitrone 2 underwent the cycloaddition with disubstituted acetylenes to give the isoxazolines 4, as shown in Table 1. The structure of 4a was proved by a chemical conversion into the corresponding aziridine, as described later, and 4b done by ^{13}C nmr analysis indicating the long range coupling between the 5-methyl group and the ring 5-carbon. In these cases, alternative regioisomers were not detected in the reaction mixtures.



The isoxazoline 3a was then treated at an elevated temperature, resulting in rearrangement into 3-benzoyl-1-methyl-2-trifluoromethylaziridine (5a), which was epimerized in the presence of sodium methoxide to its stereoisomer 5a'. The stereochemistry of 5a and 5a' was determined on the basis of the coupling constants between 2- and 3-protons [4], 5a having the cis-configuration and 5a' the trans-configuration. The aziridine 5a is quite stable on heating at 110°C and the further ring-transformation into an oxazoline was not recognized. As shown in Table 2, compounds with 5-aryl groups (3a, 3b) underwent a smooth rearrangement to give the corresponding aziridines in fairly good yield, whereas 5-n-hexyl- or -methoxycarbonylisoxazoline 3c or 3d gave a complex mixture consisting of many products; the aziridine 5c was isolated in as low as 27% yield from 3c. 4,5-Disubstituted isoxazolines 4a,c were decomposed in refluxing toluene and, only in the case of 4a, the aziridine 6a was isolated in a yield of 8%. However, 4b was so stable under the similar conditions that it was recovered unchanged.

TABLE 1

Preparation of isoxazolines 3, 4

	React. Conditions		
Isoxazoline	Temp(°C)	Times(h)	Yields(%)
3a	80	4	91
3b	80	4	53
3c	60	4	26
3d	50	24	52†
4a	80	20	37
4b	80	5	61
4c	50	4	36

†Regioisomer 3d' was included and the ratio of 3d and 3d' was 52/48.

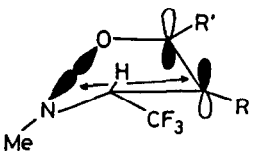
TABLE 2

Rearrangement of 3, 4 into aziridines 5, 6

Aziridine	Yield(%)†	React. Times(h)
5a	81	12
5b	91	12
5c	27	6
6a	8	6
6b	0††	18

†All runs were carried out at 110°C.
††Recovered unchanged.

From the fact that the rearrangement afforded the aziridines with the cis-configuration, the 1,3-sigmatropic process illustrated below seems to be reasonable, as proposed by Carrié and his co-worker [3c]. The stability of 3-trifluoromethyl-isoxazolines may be interpreted by the lowered energy level of the nitrogen σ-bond by the neighbouring trifluoromethyl group. Further ring-transformation of 2-trifluoromethylaziridines into the corresponding oxazolines would be retarded by the "stabilizing effect" of the trifluoromethyl group on the highly distorted small ring [5].



EXPERIMENTAL

The IR spectra were recorded on a JASCO A-100 spectrometer. The ^{1}H, ^{13}C and ^{19}F nmr spectra were measured with JEOL JNM-GX 270 and/or JNM-PMX 60 spectrometers using tetramethylsilane and trifluoroacetic acid as internal and external standards,

respectively; the chemical shifts are given in δppm downfield. All nmr spectra were measured in $CDCl_3$. Satisfactory analytical data (±0.4% for C, H, N) were obtained for 1 and 3-6.

Preparation of nitrone hydrate 1

After a mixture of N-methylhydroxylamine hydrochloride (9.45 g, 0.113 mol) and 16.5 g of sodium carbonate in 100 ml of tetrahydrofuran was stirred at room temperature for 1 h, trifluoroacetaldehyde, generated from trifluoroacetaldehyde ethylhemiacetal (23.6 g, 0.164 mol) and polyphosphoric acid (47.3 g), was bubbled into the mixture. After the bubbling, the mixture was further stirred at room temperature for 2 h. The solid was filtered off and the filtrate was evaporated to leave white solid which was recrystallized from chloroform to give 9.23 g (56%) of 1 (nc), mp 83-84°C; ^{1}H nmr δ2.6(s,3H), 4.5(m,1H), 6.5(br.s,1H), 8.0(s,1H); ^{13}C nmr δ43.1($N-CH_3$), 85.5 (CH), 123.0(CF_3); ^{19}F nmr δ-1.3; IR(KBr) 3250(OH), 1145, 1170 cm^{-1}(CF_3).

Cycloaddition of nitrone 2 with acetylenes. General Procedure.

The nitrone hydrate 1 (3.0 g, 20.7 mmol) was converted to the nitrone 2 by boiling with 50 ml of benzene in a flask fitted with an azeotropic distillation apparatus to remove water. To the mixture was added 62.1 mmol of acetylene derivative and the mixture was stirred under the conditions described in Table 1. After removal of the solvent, the product was isolated by column chromatography or distillation and further purified by recrystallization from hexane for solid or by preparative GLC for oil.

3a (nc): mp 45.5-47.5°C; ^{1}H nmr δ2.95(s,3H), 4.3(qd,J=6.6, 3.0 Hz,1H), 5.1(d,J=3.0 Hz,1H), 7.2-7.6(m,5H); ^{13}C nmr δ47.8 ($N-CH_3$), 74.0(3-C), 84.7(4-C), 124.1(CF_3), 126.0, 127.4, 128.5, 129.9(Ph), 156.9(5-C); IR(KBr) 1640(C=C), 1120 cm^{-1}(CF_3).

3b (nc): mp 74.5-76.5°C; ^{1}H nmr δ2.37(s,3H), 2.93(s,3H), 4.2 (qd,J=7.0,3.0 Hz,1H), 5.0(d,J=3.0 Hz,1H), 7.0-7.5(A_2X_2,4H);

IR(KBr) 1645, 1655(C=C), 1120, 1160 cm^{-1}(CF_3).

3c (nc): oil; ^1H nmr δ0.9(t,3H), 1.3(m,8H), 2.2(m,2H), 2.83 (s,3H), 4.1(qm,1H), 4.4(m,1H); IR(neat) 1665(C=C), 1130, 1160 cm^{-1} (CF_3).

3d (nc): oil; ^1H nmr δ2.95(s,3H), 3.86(s,3H), 4.3(qd,J=6.3, 2.9 Hz,1H), 5.7(d,J=2.9 Hz,1H); IR(neat) 1730(C=O), 1640(C=C), 1140, 1160 cm^{-1}(CF_3).

3d' (nc): oil; ^1H nmr δ2.91(s,3H), 3.79(s,3H), 4.4(qd,J=6.0, 1.6 Hz,1H), 7.6(br.s,1H).

4a (nc): oil; ^1H nmr δ2.0(br.s,3H), 2.9(s,3H), 4.0(q,1H), 7.2-7.6(m,5H).

4b (nc): mp 34-36°C; ^1H nmr δ2.27(s,3H), 2.83(s,3H), 3.73 (s,3H),4.4(q,1H); ^{13}C nmr δ12.0(5-C), 47.0($N-CH_3$), 51.1($O-CH_3$), 71.6(3-C), 94.5(4-C), 123.9(CF_3), 163.9(C=O), 168.3(5-C); IR (KBr) 1700(C=O), 1630(C=C), 1140, 1170 cm^{-1}(CF_3).

4c (nc): oil; ^1H nmr δ3.0(s,3H), 3.85(s,3H), 4.0(s,3H), 4.6(q,1H).

Rearrangement of trifluoromethylisoxazolines into trifluoromethylaziridines. General procedure.

A solution of 1.0 g of 3 or 4 in 30 ml of toluene was refluxed for the period shown in Table 2. Removal of the solvent left a residue which was chromatographed on silica gel to give 5 or 6, respectively. The further purification was carried out by recrystallization or preparative GLC.

5a (nc): mp 71.5-72.5°C; ^1H nmr δ2.4(qd,J=6.0,6.0 Hz,1H), 2.66(s,3H), 2.8(d,J=6.0 Hz,1H), 7.4-8.1(m,5H); ^{13}C nmr δ45.0 (2-C), 46.5($N-CH_3$), 47.2(3-C), 123.4(CF_3), 128.6, 133.8, 135.5 (Ph), 191.0(C=O); IR(KBr) 1685(C=O), 1130, 1160 cm^{-1}(CF_3).

5b (nc): mp 59-61°C; ^1H nmr δ2.40(s,3H), 2.45(qd,J=6.0, 6.0 Hz,1H), 2.63(s,3H), 2.9(d,J=6.0 Hz,1H), 7.1-8.0(A_2X_2,4H); IR(KBr) 1675(C=O), 1120 cm^{-1}(CF_3).

5c (nc): bp 70°C/5 mmHg; ^1H nmr δ0.9(t,3H), 1.0-1.7(m,8H), 2.3-3.2(m,4H), 2.57(s,3H); IR(neat) 1720(C=O), 1120, 1150 cm^{-1} (CF_3).

6a (nc): oil; ^1H nmr δ1.6(s,3H), 2.2(q,1H), 2.7(s,3H), 7.2-8.1(m,5H); IR(neat) 1680(C=O), 1160 cm^{-1}(CF_3).

Epimerization of 5a.

A solution of 5a (0.30 g, 1.3 mmol), 0.07 g of sodium methoxide in 10 ml of methanol was stirred at room temperature for 5.5 h. After methanol was removed, the resulting residue was extracted with ether. Extracts were washed with brine, dried over magnesium sulfate, and evaporated to leave an oil which was chromatographed (silica gel, hexane-ethyl acetate, 4:1) to give 0.16 g (53%) of 5a' (nc). The further purification was done by preparative GLC. ^{1}H nmr δ2.53(s,3H), 3.0(qd,J=5.1, 2.7 Hz,1H), 3.8(br.s,1H), 7.5-8.1(m,5H); IR(neat) 1680(C=O), 1120, 1160 cm^{-1}(CF_3).

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