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Journal of Fluorine Chemistry 76 (1996) 177–180

JOURNAL OF FLUORINE CHEMISTRY

Synthesis of trifluoromethyl *N*-vinylaziridines

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Received 18 July 1995; accepted 28 September 1995

Abstract

Novel classes of trifluoromethylvinylaziridines have been prepared. Addition of dimethylacetylenedicarboxylate to a 2-trifluoromethylaziridine gives 2(2-trifluoromethylaziridin-1-yl)fumarate. Vinylic substitution of different β-chlorotrifluoroenones produces 4-aziridin-1-yl-1,1,1-trifluorobut-3-en-2-one or 3-trifluoromethyl-3-aziridin-1-yl enone. The relative configuration of these compounds was established by NOE. A low rotation was observed around the carbon–nitrogen bond of the tetrasubstituted aziridine ring.

Keywords: β-Chloroenones; β-Chlorotrifluoromethyl group; *N*-Vinylaziridines; NMR spectroscopy; Nuclear Overhauser effect; Mass spectrometry

1. Introduction

Interest in the chemistry of trifluoromethyl-substituted heterocycles has increased considerably over the past several years. Much current activity has focused on the development of methods for the regioselective synthesis of such compounds [1]. Vinylaziridines are often used as starting materials for the synthesis of heterocyclic compounds [2–4]. In view of our general interest in the synthesis of trifluoromethylaziridines [5] and other trifluoromethylated heterocyclic compounds [6], we examined the synthesis of vinylaziridines bearing a trifluoromethyl substituent in different positions.

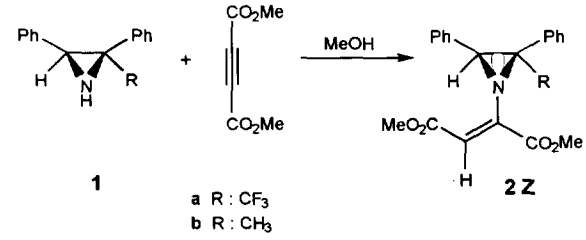
In the literature, conjugated addition has been described for the preparation of vinylaziridines. For example, Truce and Onken [7] used Michael addition of ethylenimine to acetylenic sulphones and, more recently, Barick et al. [3] prepared some 1-aziridinyl-1,2-dibenzoylalkenes by the addition of alkyl- or aryl-substituted aziridines to dibenzoylacetylene. Recently, we synthesized trifluoromethylaziridines [5] and so we decided to study Michael addition of these aziridines to obtain 2-(2-trifluoromethylaziridin-1-yl)fumarate (**2**).

Sovenko et al. [8] have shown that nucleophilic displacement of vinyl chlorides could lead to arylvinylaziridines. We have proposed the synthesis of β-chloroenones or acroleins with a trifluoromethyl group in different positions via a Vilsmeier reaction [9]; these compounds could be good starting materials for producing 3-trifluoromethyl-3-aziridin-1-yl enone (**5**) or 4-aziridin-1-yl-1,1,1-trifluorobut-3-en-2-one [7].

2. Results and discussion

The reaction of dimethyl acetylenedicarboxylate (DMAD) in methanol and 2-trifluoromethyl-2,3-diphenylaziridine (**1a**) afforded vinylaziridine (*Z*-**2a**) as the only product (Scheme 1). The *Z* stereochemistry was inferred from the ^{1}H NMR spectrum of the compound, which showed that the chemical shift of the vinylic proton (δ 6.33 ppm) is typical for the *Z* configuration in such compounds [4].

The NMR spectra show only a singlet for the aziridinyl proton and only a singlet for the trifluoromethyl signal. Hence, fast rotation must take place around the carbon–nitrogen bond. The same reaction occurred with aziridine **1b** to produce the compound *Z*-**2b**. The two *cis* phenyl groups in *Z*-**2** require the formation of only one invertomer around the nitrogen atom.



Scheme 1.

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SSDI 0022-1139(95)03361-0

The *E,Z* β-chloro-β-trifluoromethyl-acrolein (**3**) reacted in high yield with *cis*-2,3-diphenylaziridine (**4**) (Scheme 2).

5 exists as a mixture of two stereoisomers, *Z* (82%) and *E* (18%). The *Z* configuration was assigned from an NOE experiment: irradiation of the vinylic proton leaves the intensity of the aziridinyl protons unchanged, with only the intensity of the *ortho* protons of the phenyl group being increased. With the minor isomer **5**, the intensity of the aziridinyl protons is increased by 20% when an NOE experiment is applied to the vinyl proton, so that the *E* configuration is attributed to this isomer.

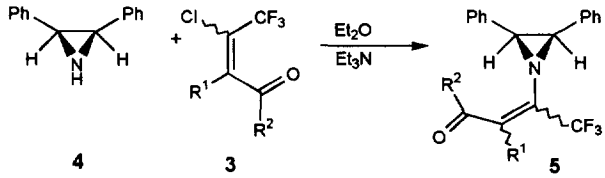
Aziridine **4** also reacted in high yield (72%) with 1,1,1-trifluoro-4-chloro-4-phenyl-3-buten-2-one (**6**) (Scheme 3).

NOE experiments on the vinyl hydrogens led to the assignment of the *Z* configuration to the major isomer. For the minor, irradiation of the vinyl hydrogen increased the intensity of the two aziridinyl protons (by 13.7%), and so the *E* configuration was assigned to the minor and the *Z* to the major isomer. In the two stereoisomers, the two aziridinyl hydrogens appear as a singlet in the NMR spectra (*E*-**7**, δ 3.72 ppm; *Z*-**7**, δ 3.78 ppm) as a result of free rotation around the C–N bond.

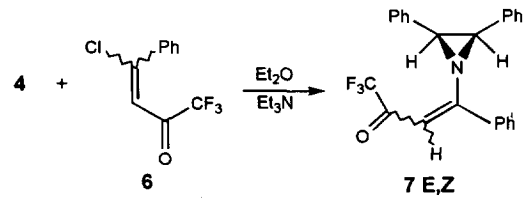
The β-chloroenone **6** and the *cis*-2,3-dimethyl-2,3-diphenylaziridine **8** (Scheme 4) produced the vinylaziridines *E,Z*-**9** in poor yield (15%) with a low stereoselectivity (*Z*/*E* = 58:42).

The *Z* configuration was attributed to the major stereoisomer on the basis of an NOE between the vinylic proton and the two *ortho* protons of the phenyl group bonded to the vinyl carbon (NOE 20.1%). In the other stereoisomer, an NOE appears between the vinylic proton and the two methyl groups, in agreement with an *E* configuration for the minor stereoisomer.

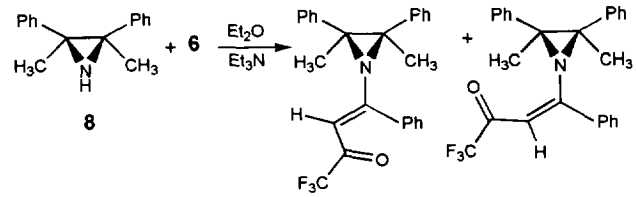
Of greater interest are the NMR signals of the two stereoisomers of compound **9**. For each isomer, the vinylic proton and the trifluoromethyl signals appear as a singlet, but the two methyl groups are different. Two methyl singlets appear



Scheme 2.



Scheme 3.



Scheme 4.

for each isomer (δ 1.18 ppm and 1.74 ppm for the major, and δ 1.30 and 1.90 ppm for the minor). This means that C–N rotation is slow and coalescence is not observed for the two methyl groups as for the two hydrogen atoms of compound **7**.

For compound *E*-**9**, saturation of the vinylic hydrogen shows an NOE of 3.5% for one methyl signal and 2.8% for the other. The reason for this NOE with the two methyl groups lies in the differing scales for the NOE and the coalescence phenomena. The rotation around the C–N bond remain sufficiently fast to lead to near equalization of the methyl signal enhancement associated with saturation of the vinylic proton resonance, but this rotation is far below the coalescence temperature of the two lines. The reason for this, of course, lies in the differing time scales of the NOE and coalescence phenomena; some examples are described in the literature [10].

3. Experimental details

Melting points are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were measured as solutions in $CDCl_3$ with a Bruker AM 200 instrument (200 MHz) using TMS or $CFCl_3$ as internal standards. Mass spectra were obtained on a Nermag R10-105 instrument via GLC–MS. Column chromatography was performed with Siligugel 60 (230–400 mesh, Merck). Starting materials were obtained by literature procedures: **1** [5], **4** [11], **3** and **6** [9] and **8** [12].

3.1. Preparation of trifluoromethyl-N-vinylaziridines **2** *– general procedure*

To a solution of aziridine **1a,b** (2.5 mmol) in methanol (20 ml) was added DMAD (2.5 mmol). The mixture was stirred at room temperature for 36 h. Removal of the solvent under reduced pressure gave a solid residue which was recrystallized.

cis-2-Trifluoromethyl-2,3-diphenyl-1-(1′,2′-dicarbomethoxy ethene)aziridine) (**2a**): yield, 0.88 g (87.0%); m.p. 86–87 °C (recrystallized from petroleum ether). ^{1}H NMR ($CDCl_3$) δ: 3.23 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.08 (s, 2H, CH); 6.33 (s, 1H, =CH); 7.04–7.50 (m, 10H, ArH) ppm. ^{19}F NMR ($CDCl_3$) δ: −66.5 (s, CF_3) ppm. ^{13}C NMR δ: 50.7 (CH); 51.4 (OCH_3); 52.9 (OCH_3); 54.3 (q, *C*–CF_3, $^{2}J_{CF}$ = 31.7 Hz); 108.1 (=*C*H); 124.5 (q, *C*F_3, $^{1}J_{CF}$ = 282.3 Hz); 127.0, 127.7, 127.8, 128,5, 129.5, 130.0, 133.6, 147.2 (=*C*–N); 163.9 (*C*=O); 164.9 (*C*=O) ppm. MS *m/z*: 404

(M − H, 100); 346 (M − CO_2CH_3, 55); 314 (M − $C_6H_5CH_2$, 49); 286 (51); 285 (51); 224 (43); 193 (52); 178 (49); 121 (51); 90 (C_6H_5CH, 47); 89 (56); 59 (45).

Cis-2-Methyl-2,3-diphenyl-1-(1′,2′-dicarbomethoxy ethenyl)aziridine (**2b**): yield, 0.77 g (87.8%); m.p. 135–136 °C (recrystallized from petroleum ether). ^{1}H NMR ($CDCl_3$) δ: 1.64 (s, 3H, CH_3); 3.23 (s, 3H, OCH_3); 3.42 (s, 1H, CH); 3.80 (s, 3H, OCH_3); 6.34 (s, 1H, =CH); 7.07–7.40 (m, 10H, ArH) ppm. ^{13}C NMR ($CDCl_3$) δ: 22.0 (*C*H_3); 51.2 (O*C*H_3); 52.7 (OCH_3); 54.8 (Ph–*C*–CH_3); 56.7 (*C*H); 108.8 (=*C*H); 126.6, 126.9, 127.4, 127.5, 128.1, 136.1, 138.5, 149.9 (=*C*–N); 165.0 (C=O); 165.7 (C=O) ppm. MS *m/z*: 320 (M − OCH_3, 14); 319 (M − CH_3OH, 86); 259 (39); 258 (73); 231 (100%); 230 (42); 202 (26); 77 (20).

3.2. Preparation of trifluoromethyl N-vinylaziridines 5, 7 and 9 – general procedure

A solution of aziridine **4** or **8** (3 mmol), triethylamine (0.5 ml) and the appropriate enone **3** or **6** (3 mmol) in dry ether (10 ml) were stirred at room temperature for 24 h. The precipitated triethylamine hydrochloride was filtered off. The solvent was then removed and the residue chromatographed on aluminium oxide using petroleum ether/CH_2Cl_2 (2:1) as eluent. The crude product was recrystallized from petroleum ether.

cis-2,3-Diphenyl-1-(1′,1′,1′-trifluoro-4-phenyl-2-buten-4-one)aziridine (**5**): yield, 91 g (77.3%); m.p. 116–119 °C (*Z,E* mixture).

(a) Major isomer (*Z*): ^{1}H NMR ($CDCl_3$) δ: 3.79 (s, 2H, CH); 6.81 (s, 1H, =CH); 7.07–7.52 (m, 13H, ArH); 7.83–7.87 (m, 2H, *o*-ArH) ppm. ^{19}F NMR ($CDCl_3$) δ: −66.8 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 50.7 (*C*H); 108.8 (=*C*H); 121.6 (q, *C*F_3, $^1J_{CF}$ = 277.9 Hz); 149.4 (q, =*C*–CF_3, $^2J_{CF}$ = 29.8 Hz); 188.9 (C=O); 127.6, 127.7, 128.0, 128.4, 128.6, 128.9, 133.1, 133.3, 133.4, 137.9 (*C*–Ar) ppm. NOE: irradiation at 6.81 ppm, 14.4% increase at 7.83–7.87 ppm.

(b) Minor isomer (*E*): ^{1}H NMR ($CDCl_3$) δ: 3.74 (s, 2H, CH); 6.46 (s, 1H, =CH); 7.07–7.52 (m, 13H, ArH); 7.92–7.96 (m, 2H, *o*-ArH) ppm. ^{19}F NMR ($CDCl_3$) δ: −63.5 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 49.2 (*C*H); 108.6 (=*C*H); 122.3 (q, *C*F_3, $^1J_{CF}$ = 271.9 Hz); 148.2 (q, =*C*–CF_3, $^2J_{CF}$ = 30.6 Hz); 189.1 (C=O); 127.6, 127.7, 128.0, 128.4, 128.6, 128.9, 133.1, 133,4, 137.9 (*C*–Ar) ppm. NOE: irradiation at 6.46 ppm, 20% increase at 3.74 ppm and 10.5% increase at 7.92–7.96 ppm.

MS *m/z*: 393 (M^+, 19); 288 (M − PhCO, 30); 165 (15); 115 (17); 105 (PhCO, 100); 77 (42); 51 (15) (for the mixture of the two isomers).

cis-2,3-Diphenyl-1-(4′,4′,4′-trifluoro-1′-phenyl-1-buten-3-one)aziridine (**7**): yield, 0.85 g (72.0%); m.p. 146–150 °C (*Z,E* mixture).

(a) Major isomer (*Z*): ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 2H, CH); 6.32 (s, 1H, =CH); 7.04–7.40 (m, 13H, ArH); 7.60–7.64 (m, 2H, *o*-ArH) ppm. ^{19}F NMR ($CDCl_3$) δ: −77.9 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 53.4 (*C*H); 100.4 (=*C*H); 116.7 (q, *C*F_3, $^1J_{CF}$ = 292.6 Hz); 173.6 (=*C*–N); 176.4 (q, *C*=O, $^1J_{CF}$ = 33.3 Hz); 127.2, 127.5, 127.6, 127.8, 128.0, 128.2, 128.5, 128.8, 130.7, 131.0, 133.3, 134.3, 134.6, 137.7 (*C*–Ar) ppm. NOE: irradiation at 6.32 ppm, 18.2% increase at 7.60–7.64 ppm.

(b) Minor isomer (*E*): ^{1}H NMR ($CDCl_3$) δ: 3.72 (s, 2H, CH); 6.20 (s, 1H, =CH); 7.04–7.40 (m, 13H, ArH); 7.50–7.55 (m, 2H, *o*-ArH) ppm. ^{19}F NMR ($CDCl_3$) δ: −78.5 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 49.7 (*C*H); 99.6 (=*C*H); 115.2 (q, *C*F_3, $^2J_{CF}$ = 285.6 Hz); 170.9 (=*C*–N); 176.6 (q, *C*=O, $^2J_{CF}$ = 34.1 Hz); 127.2, 127.5, 127.6, 127.8, 128.0, 128.2, 128.5, 128.8, 130.7, 131.0, 133.3, 134.3, 134.6, 137.7 (*C*–Ar) ppm. NOE: irradiation at 6.20 ppm, 13.7% increase at 3.72 ppm.

MS *m/z*: 393 (M^+, 19); 302 (8); 296 (M − CF_3CO, 100); 178 (17); 104 (8); 77 (5); 51 (5) (for the mixture of the two isomers).

cis-2,3-Dimethyl-2,3-diphenyl-1-(4′,4′,4′-trifluoro-1′-phenyl-1-buten-3-one)aziridine (**9**): yield, 0.19 g (15.2%); m.p. 172–175 °C (mixture).

(a) Major isomer (*Z*): ^{1}H NMR ($CDCl_3$) δ: 1.18 (s, 3H, CH_3); 1.74 (s, 3H, CH_3); 6.26 (s, 1H, =CH); 6.95–7.41 (m, 13H, ArH); 7.63–7.67 (m, 2H, *o*-ArH) ppm. ^{19}F NMR ($CDCl_3$) δ: −77.6 (s, CF_3) ppm. ^{13}C NMR ($CDCl_3$) δ: 17.4 (*C*H_3); 19.8 (*C*H_3); 54.2 (Cq); 59.3 (Cq); 99.7 (=*C*H); 170.4 (=*C*–N); 175.4 (q, *C*=O, $^2J_{CF}$ = 30.9 Hz); 126.1, 126.5, 126.6, 126.8, 126.9, 127.1, 127.2, 127.4, 127.6, 128.0, 128.1, 128.3, 128.4, 128.8, 130.4, 135.0, 139.3, 140.2, 140.4 (*C*–Ar and *C*F_3) ppm. NOE: irradiation at 6.26 ppm, 20.1% increase at 7.63–7.67 ppm; irradiation at 1.18 ppm, 3.9% increase at 7.15–7.17 ppm; irradiation at 1.74 ppm, 2.9% increase at 7.32–7.34 ppm.

(b) Minor isomer (*E*): ^{1}H NMR ($CDCl_3$) δ: 1.30 (s, 3H, CH_3); 1.9 (s, 3H, CH_3); 5.98 (s, 1H, =CH); 6.95–7.41 (m, 13H, ArH); 7.56–7.61 (m, 2H, *o*-ArH) ppm. NOE: irradiation at 5.98 ppm, 2.9% increase at 1.30 ppm and 3.5% increase at 1.90 ppm; irradiation at 1.30 ppm, 4.4% increase at 5.98 ppm and 4.4% increase at 7.06–7.10 ppm; irradiation at 1.90 ppm, 6.3% increase at 5.98 ppm and 10.5% increase at 7.05–7.12 ppm.

MS *m/z*: 223 (M − PhC=CCOCF_3, 64); 222 (M − PhCH=CCOCF_3, 100); 207 (19); 165 (11); 105 (PhCHCH_3, 60); 104 (80); 103 (54); 97 (CF_3CO, 3); 78 (33); 77 (60); 51 (24).

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