Journal of Fluorine Chemistry, 55 (1991) 215–219

New fluorinated halomethyl isoxazoles*

Alexander Klausener and Bernd Baasner
Bayer AG, Central Research Department, W-5090 Leverkusen (Germany)

(Received July 27, 1991; accepted September 16, 1991)

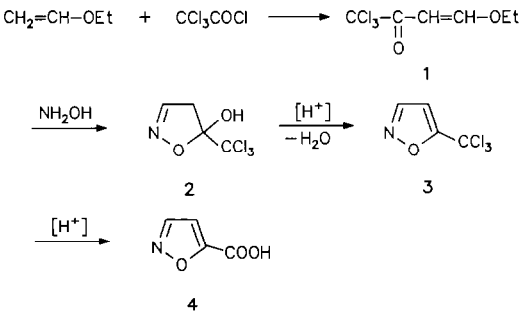
Abstract

New fluorinated 5-halomethyl isoxazoles may be prepared from easily accessible 5-trichloromethylisoxazole by chlorine–fluorine exchange reactions. The reaction products may be ring-opened to enolates of 3-oxo-4,4,4-trihalobutyronitriles, which are useful as halogenated C_3 synthons.

Introduction

5-Trichloromethyl isoxazole (**3**) is an important intermediate for the preparation of isoxazole-5-carboxylic acid (**4**), which is used as a starting material in the synthesis of fungicides [1]. This compound is obtained by the dehydration of the easily accessible 5-hydroxy-5-trichloromethyl-Δ^2-isoxazoline (**2**) by treatment with concentrated sulphuric acid [2] (see Scheme 1).

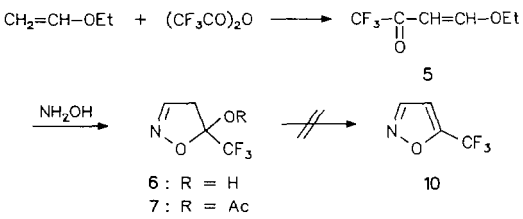
In a similar manner as described for **2**, 5-hydroxy-5-trifluoromethyl-Δ^2-isoxazoline (**6**) may be prepared by the reaction of hydroxylamine and the enol ether **5**, which is formed in quantitative yield by treatment of 2-ethoxy ethene with trifluoroacetic anhydride [3]. All attempts to convert this compound into the 5-trifluoromethyl isoxazole (**10**) in an economical way have failed



Scheme 1.

*Dedicated to Professor Karl-Heinz Büchel on the occasion of his 60th birthday.

0022-1139/91/$3.50



Scheme 2.

or resulted in low yields*. While sulphuric acid causes no dehydration of the substrate, the action of acetic anhydride leads to the formation of the acetoxy derivative **7** (see Scheme 2).

Experimental

The NMR spectra of all new compounds were recorded with a Bruker WP 80 FT spectrometer at 80 MHz (^{1}H) and 75.39 MHz (^{19}F). TMS was used as the internal standard for the ^{1}H NMR spectra and trifluoroacetic acid as the external standard for the ^{19}F NMR spectra. The MS data were recorded on a Finnegan MAT 112 spectrometer (EI mode, 70 eV). The melting points and boiling points listed are not corrected.

5-Hydroxy-5-trifluoromethyl-Δ^2-isoxazoline (6)

A solution of hydroxylamine hydrochloride (3.47 g, 50.0 mmol) in water (5.0 ml) was added dropwise over a period of 15 min to a stirred solution of the enol ether **5** (9.10 g, 50.0 mmol) in tetrahydrofuran (10 ml). The temperature was maintained at 15 °C by occasional external cooling. After the addition was complete the reaction mixture was stirred for several hours at ambient temperature and then concentrated under reduced pressure at a bath temperature of not more than 30 °C. The residue was taken up in diethyl ether, dried over anhydrous sodium sulphate, filtered and concentrated. Yield 6.85 g (88.3%); colourless solid; m.p., 50–52 °C (a small sample after sublimation showed the same m.p.). ^{1}H NMR (DMSO-d_6/$CDCl_3$ 1:1): δ 3.10 (d, 1H; H-4A), 3.33 (d, 1H; H-4B), 7.37 (s, 1H; H-3), 3.10 (bs, 1H; OH); $H_{4A,\,4B}$ = 19.0 Hz. Analysis: $C_4H_4F_3NO_2$ (155.08): C, 30.92 (30.98); H, 2.50 (2.60); F, 36.59 (36.75); N, 8.98 (9.03)%.

5-Acetoxy-5-trifluoromethyl-Δ^2-isoxazoline (7)

A mixture of **6** (6.0 g, 38.7 mmol) and of acetic anhydride (30 ml) was heated under reflux for 5 h. After evaporation under reduced pressure, the residue was recrystallized from ethyl acetate/n-hexane. The reaction product

*During the preparation of this manuscript, Gerus *et al.* [4] reported the successful dehydration of 5-hydroxy-5-trifluoromethyl-Δ^2-isoxazoline (**6**) to 5-trifluoromethyl isoxazole (**10**) by treatment with a large excess of phosphorus pentoxide.

contained 1 equiv. acetic acid. Yield 5.13 g (67.3%); colourless solid; m.p., 75–76 °C. ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H; CH_3/OAc), 2.40 (s, 3H; CH_3/AcOH), 5.70–5.90 (m, 2H; H-4A, B), 8.25 (bs, 1H; OH/AcOH), 8.60–8.70 (m, 1H; H-3). Analysis: $C_8H_{10}F_3NO_5$ (257.172): C, 37.27 (37.37); H, 10.10 (10.08); F, 22.08 (22.16); N, 5.55 (5.45)%.

5-Dichlorofluoromethyl isoxazole (8)

Into a stainless-steel autoclave containing anhydrous liquid hydrogen fluoride (120 ml) was added dropwise 5-trichloromethyl isoxazole (**3**) (93.25 g, 0.50 mol) with cooling (0–3 °C) and gentle stirring over 1 h. The autoclave was closed and the reaction mixture was pressurised under nitrogen (5 bar). During a period of 5.5 h the temperature of the mixture was raised to 115 °C, at which point the pressure was 12 bar. After cooling the autoclave was depressurised and hydrogen fluoride was removed under reduced pressure (150 mbar). The crude reaction product was first flash-distilled (10 mbar), washed with water (2×200 ml), dried over anhydrous magnesium sulphate and distilled under reduced pressure. Yield 57.0 g (67.0%); colourless liquid; b.p., 52–54 °C (20 mbar); n_D^{20}, 1.4550. ^{1}H NMR ($CDCl_3$): δ 6.68 (d, 1H; H-3), 8.35 (d, 1H; H-4). ^{19}F NMR ($CDCl_3$): δ −27.42 (−$CFCl_2$). Mass spectrum (*m/e*): 169/171 (M^+), 134/136 (base peak, $M^+ - Cl$). Analysis: $C_4H_2Cl_2FNO$ (169.974): C, 28.35 (28.27); H, 1.25 (1.19); Cl, 40.79 (41.72); F, 11.20 (11.18); N, 8.25 (8.24)%.

5-Chlorodifluoromethyl isoxazole (9)

Into a steel autoclave containing anhydrous liquid hydrogen fluoride (180 ml) and antimony pentachloride (0.5 ml) was added dropwise 5-trichloromethyl isoxazole (**3**) (93.25 g, 0.50 mol) with cooling (−5 to 0 °C) and gentle stirring over 1 h. The autoclave was closed and the reaction mixture was pressurised under nitrogen (18 bar). The temperature of the reaction mixture was raised to 150 °C over a period of 3 h and stirring was continued at this temperature for one further hour. After cooling the autoclave was depressurised and hydrogen fluoride was removed under reduced pressure (150 mbar). The crude reaction product was washed with water (3×200 ml), dried over anhydrous magnesium sulphate and distilled under atmospheric pressure. Yield 43.2 g (56.5%); colourless liquid; b.p., 92–93 °C; n_D^{20}, 1.4033. ^{1}H NMR ($CDCl_3$): δ 6.68 (d, 1H; H-3), 8.32 (d, 1H; H-4). ^{19}F NMR ($CDCl_3$): δ −27.40 (−CF_2Cl). Mass spectrum (*m/e*): 153/155 (M^+), 134/136 ($M^+ - F$), 118 (base peak, $M^+ - Cl$). Analysis: $C_4H_2ClF_2NO$ (153.519): C, 31.63 (31.30); H, 1.33 (1.31); Cl, 23.23 (23.09); F, 25.08 (24.75); N, 9.11 (9.12)%.

5-Trifluoromethyl isoxazole (10)

A mixture of 5-trichloromethyl isoxazole (**3**) (56.0 g, 0.3 mol), antimony trifluoride (80.0 g, 0.45 mol) and antimony pentachloride (1.0 ml) was slowly heated to 140 °C, during which time gentle reflux began. The reaction mixture was allowed to react for a further 90 min under reflux. After this time the

volatile products were distilled off under normal pressure (70–120 °C). The crude reaction product was redistilled over a 10-cm packed column. Yield 26.8 g (65.2%); colourless liquid; b.p., 79–80 °C; n_D^{20}, 1.3433. ^{1}H NMR ($CDCl_3$): δ 6.76 (d, 1H; H-3), 8.38 (d, 1H; H-4). ^{19}F NMR ($CDCl_3$): δ −14.39 (−CF_3). Mass spectrum (*m/e*): 137 (base peak, M^+), 118 ($M^+ - F$). Analysis: $C_4H_2F_3NO$ (137.064): C, 35.28 (35.05); H, 1.52 (1.47); F, 42.05 (41.58); N, 10.26 (10.22)%.

*Piperidinium salt of 3-oxo-4,4,4-trichlorobutyronitrile (**11a**)*

Piperidine (8.52 g, 0.1 mol) was added dropwise to a cooled solution of 5-trichloromethyl isoxazole (**3**) (18.64 g, 0.1 mol) in ethanol (80 ml) with stirring, which was continued at 0 °C for a further 2 h and then at room temperature overnight. After evaporation (first 10 mbar, then at 10^{-2} bar), a residue was obtained which was recrystallised from ethyl acetate/n-hexane. Yield 20.13 g (74.1%); m.p. 85–86 °C. ^{1}H NMR ($CDCl_3$): δ 1.55–1.70 (m, 2H; H-4,4′/piperidinium), 1.72–1.90 (m, 4H; H-3,3′,5,5′/piperidinium), 3.21–3.26 (m, 4H; H-2,2′,6,6′/piperidinium), 4.86 (s, 1H; H-2), 8.64 (s, 2H; NH_2^+/piperidinium). Analysis: $C_9H_{13}Cl_3N_2O$ (271.584): C, 39.90 (39.81); H, 4.72 (4.83); Cl, 39.05 (39.16); N, 10.28 (10.28)%.

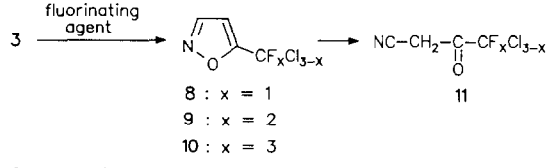
*Piperidinium salt of 3-oxo-4,4,4-trifluorobutyronitrile (**11b**)*

The procedure as described for **11a** was followed. Compound **11b** was obtained from 5-trifluoromethyl isoxazole (**10**) (6.50 g, 47.42 mmol) and piperidine (4.04 g, 47.42 mmol). Yield 6.80 g (64.5%); m.p. 36–40 °C. ^{1}H NMR ($CDCl_3$): δ 1.64–1.75 (m, 6H; H-3,3′,4,4′,5,5′/piperidinium), 3.10–3.14 (m, 4H; H-2,2′,6,6′/piperidinium), 4.40 (s, 1H; H-2), 8.31 (s, 2H; NH_2^+/piperidinium). Analysis: $C_9H_{13}F_3N_2O$ (222.219): C, 48.44 (48.65); H, 5.92 (5.90); F, 25.47 (25.65); N, 12.65 (12.61)%.

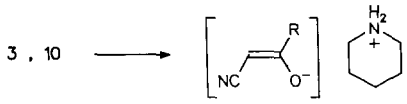
Results and discussion

Treatment of 5-trichloromethyl isoxazole (**3**) with certain fluorinating agents allows the easy and selective preparation of fluorinated 5-halomethyl isoxazoles **8, 9** and **10** (see Scheme 3).

On studying the action of anhydrous hydrogen fluoride on 5-trichloromethyl isoxazole (**3**), it was found that depending on the reaction temperature and pressure, the presence of a catalyst, and the proportion of substrate/HF, one or two of the chlorine atoms were easily exchanged to yield **8** or



Scheme 3.



11a : R = CCl_3
11b : R = CF_3

Scheme 4.

9, respectively. In these cases hydrogen fluoride serves simultaneously as a solvent and as a reagent. The reactions were carried out in stainless-steel autoclaves as indicated in the experimental section. The selective substitution of two chlorine atoms was improved by the addition of a catalytic amount of antimony pentachloride to the reaction mixture. The use of antimony trifluoride as a fluorinating agent in the presence of catalytic quantities of antimony pentafluoride allowed complete chlorine–fluorine exchange under normal pressure at 140 °C. The reaction product **10** was isolated by fractionating over a short packed column.

Isoxazoles, which carry no substituent in the 3-position, are easily ring-cleaved under the action of bases, leading to 3-oxonitriles. These compounds are versatile synthons, *e.g.* in the preparation of heterocycles [5], and may be isolated and stored as salts. Treatment of the isoxazoles **3** and **10** separately with 1 equiv. piperidine led to the piperidinium salts of 3-oxo-4,4,4-trichloro- (**11a**) and 3-oxo-4,4,4-trifluoro-butyronitrile (**11b**) being isolated (Scheme 4).

References

1 B. Zeeh, H. Theobald, E. Ammermann and E.-H. Pommer (to BASF A.G.), *DOS 2 940 189* (1979).

2 (a) W. Spiegler and N. Götz (to BASF A.G.), *DOS 3 212 136* (1982), (b) W. Spiegler and N. Götz (to BASF A.G.), *DOS 3 212 137* (1982), (c) W. Spiegler and N. Götz, *Synthesis*, (1986) 69.

3 (a) M. Hojo, R. Masuda, Y. Kokuryo, H. Shioda and S. Matsuo, *Chem. Lett.*, (1976) 499; (b) Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobushi and T. Nishigaki, *Synthesis*, (1986) 340.

4 I. L. Gerus, M. G. Gorbunova, S. I. Vdovenko, Y. L. Yagupolskii and V. P. Kukhar, *Zh. Org. Khim.*, *26* (1990) 1877.

5 (a) L. Claisen, *Ber.*, *25* (1886) 1776; (b) L. Claisen, *Ber.*, *42* (1909) 59; (c) A. Quilico, in A. Weissberger (ed.), *The Chemistry of Heterocyclic Compounds*, Vol. 17, Wiley, New York, 1962; (d) N. K. Kochetkov and S. D. Sokolov, *Adv. Heterocycl. Chem.*, *2* (1963) 365; (e) H. Dahn and H. Hauth, *Helv. Chim. Acta*, *47* (1964) 1424; (f) A. I. Meyers, *Heterocycles in Organic Synthesis*, Wiley, New York, 1963; (g) J. F. Blount, D. L. Coffen and D. A. Katonak, *J. Org. Chem.*, *43* (1978) 3821; (h) B. J. Wakefield and D. J. Wright, *Adv. Heterocycl. Chem.*, *25* (1979) 147; (i) A. Alberola, A. M. Gonzales, D. Guerra and F. J. Pulido, *J. Heterocycl. Chem.*, *19* (1982) 1073; (j) A. Alberola, L. F. Antolin, A. M. Gonzales, M. A. Laguna and F. J. Pulido, *J. Heterocycl. Chem.*, *23* (1986) 1035; (k) P. Ooms, A. Klausener, B. Baasner, B. Becker, W. Behrenz and B. Homeyer (to Bayer A.G.), *Eur. Pat. 285 947* (1988).