Ring Closures with α-Chloroazines

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Two series of unsymmetrical 3,6-disubstituted 1,2,3,4-tetrahydro-1,2,4,5-tetrazines and 3,5-disubstituted 4-amino-2,3-dihydro-1,2,4-triazoles were synthesized from unsymmetrical 1,4-disubstituted 1-chloroazines with hydrazine, 1-methylhydrazine, and 1,2-dimethylhydrazine. These partially reduced heterocycles belong to little known and less accessible classes of heterocycles.

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Stolle *et al.* [1,2] and others [3,4] have shown the usefulness of symmetrically disubstituted α-chloroazines in the synthesis of nitrogen heterocycles because of the ease with which the chlorides undergo nucleophilic displacement followed by cyclization.

Thermolysis of 4-chloro-2-(1-chloro-2,2,2-trifluoroethyl)-1-thia-2,3-diazaspiro[4.5]dec-3-ene 1,1-dioxide [5] in refluxing toluene gave *N*-[(2,2,2-trifluoroethylidene)amino]-1-cyclohexene-1-carboximidolyl chloride **Ia**, a reactive, unsymmetrical 1,4-disubstituted-1-chlorazine. Reaction of **Ia** with water and dimethylamine gave the expected acyclic reaction products [5]. This observation appeared to offer a practical method for the preparation of partially hydrogenated five- and six-membered heterocyclic ring systems from **Ia** and related α-chloroazines by reaction with 1,1- and 1,2-dinucleophilic reagents. Of particular interest would be the preparation of novel 1,2,3,4-tetrahydro-*s*-tetrazines having a redox relationship with the 1,4-dihydro-*s*-tetrazines and *s*-tetrazines [6], thereby acting as redox herbicides [7].

The present investigation demonstrates the feasibility and explores the scope of this synthetic method.

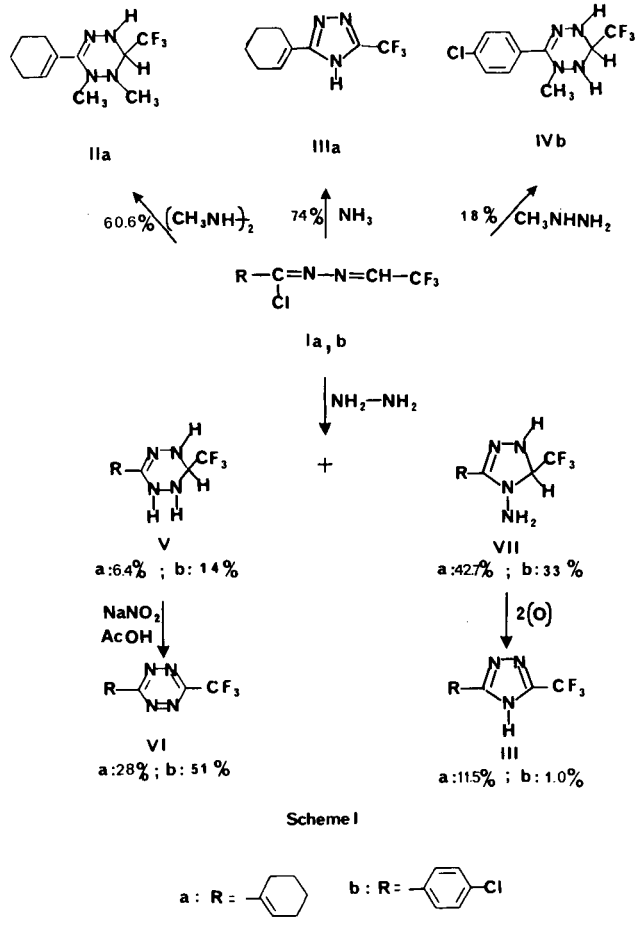
Results and Discussion.

1-Chloroazine **Ia** reacted smoothly and rapidly at ambient temperature with 1,2-dimethylhydrazine to give the 1,2,3,4-tetrahydro-*s*-tetrazine **IIa** in 61% yield.

With ammonia and **Ia**, *s*-triazole **IIIa** was obtained as a white crystalline solid in 74% yield.

With two molar equivalents of hydrazine, **Ia** afforded a mixture of triazole **IIIa** (12%), 4-amino-2,3-dihydro-1,2,4-triazole **VIIa** (43%), and 1,2,3,4-tetrahydro-*s*-tetrazine **Va** (6.4%), which were separated by silica chromatography.

Oxidation of **VIIa** with sodium nitrite in glacial acetic acid gave a product **IIIa** that is identical with authentic **IIIa**, obtained from **Ia** and ammonia. On the other hand, the white solid **Va** with nitrite in acetic acid was converted into the red *s*-tetrazine **VIa** in 28% yield (Scheme 1).



Scheme I

The analogous reaction of 1-chloroazine **Ib** with methylhydrazine gave the tetrahydro-*s*-tetrazine **IVb** in 18% yield.

Reaction of **Ib** with hydrazine gave three products which were separated by silica chromatography. The major fraction (33%) consisted of the white solid 4-amino-2,3-dihydro-1,2,4-triazole derivative **VIIb**. A second product was identified as the *s*-triazole **IIIb** (1.0%). Compound **VIIb** was converted into **IIIb** by oxidative deamination with sodium nitrite in acetic acid. The third compound which was isolated in 14% yield was identified

as the tetrahydro-*s*-tetrazine **Vb**. This white solid was readily oxidized (sodium nitrite, acetic acid) to the known [7] *s*-tetrazine **VIb**. On melting, **Vb** was observed to resolidify and then, at a higher temperature (180-182°), remelt; behavior which suggests the occurrence of a facile ring contraction (-NH-NH- → >N-NH_2), a well-known property of certain saturated six-membered 1,2-diazaheterocycles, including dihydro-*s*-tetrazines.

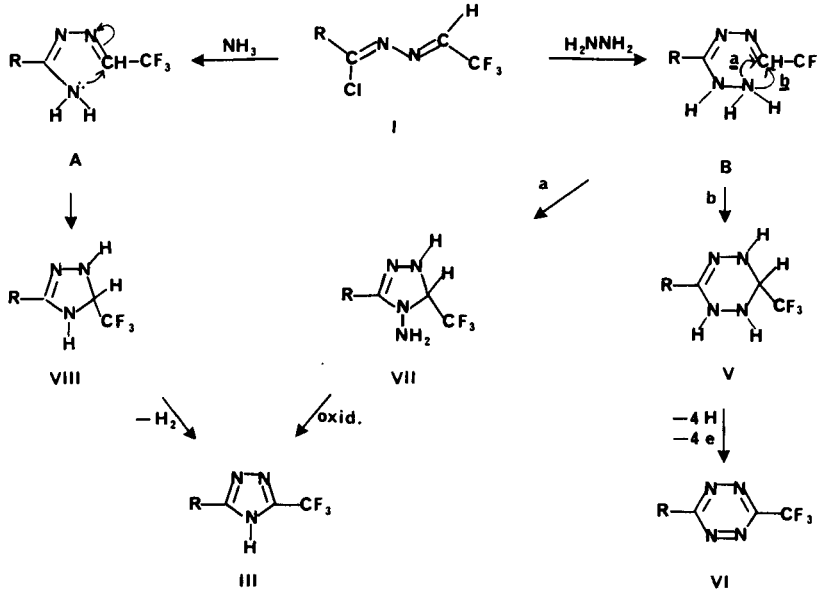
2,3-Dihydro-*s*-triazoles **VII**, in which an amino-substituent is present on N-4, appear to be less prone to undergo dehydrogenation to *s*-triazoles than the **VIII** compounds carrying hydrogen on N-4 as evidenced by the failure to isolate the 2,3-dihydro-1,2,4-triazole **VIII** (R = 1-cyclohexen-1-yl) from the reaction of **Ia** with ammonia leading to **IIIa**. However, treatment of **VII** with nitrite in glacial acetic acid led to dehydrogenation-deamination to give **III** identical with the reaction product of **I** with ammonia. When the tetrahydro-*s*-tetrazines **V** were treated with nitrite in acetic acid, the purple-red *s*-tetrazines **VI** were isolated. The oxidation of 4-amino-2,3-dihydro-1,2,4-triazoles, **VII**, and isomeric tetrahydro-*s*-tetrazines, **I**, to white *s*-triazoles, **III**, and purple-red *s*-tetrazines, **VI**, respectively, provides unambiguous chemical proof of both structures.

Dihydro-*s*-triazoles, **VII**, and *unsymmetrically* disubstituted-1,2,3,4-tetrahydro-*s*-tetrazines, **V**, are the first examples of these types of compounds. Synthesis of *symmetrically* disubstituted-1,2,3,4-tetrahydro-*s*-tetrazines has been achieved in only one case. The procedure reported [8] for this type of tetrahydro-*s*-tetrazine is the sulfide reduction of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine which was obtained by oxidation of the corresponding hexahydro-*s*-tetrazine.

Dihydro-1,2,4,5-tetrazines are usually differentiated from 4-amino-1,2,4-triazoles by oxidation of the former to highly colored 1,2,4,5-tetrazines [9]. A further reliable basis of differentiation is their ^{1}H nmr spectra [10]. The nitrogen protons of dihydro-*s*-tetrazines appear at much lower field (δ 9.1-8.18) than do those of isomeric 4-amino-1,2,4-triazoles (δ 6.22-5.74). Comparison of the ^{1}H nmr spectra of the isomeric **Va**, m/z = 234 (M+) and **VIIa**, m/z = 234 (M+), compounds shows the nitrogen protons of the tetrahydro-*s*-tetrazines appear at lower field than those of the 4-amino-2,3-dihydro-1,2,4-triazoles. However, the differences appear too small to be of general value.

All aspects of the chemistry of 1-chloroazines, such as **I** are consistent with a pronounced susceptibility to nucleophilic displacement of chloride. We propose initial *N*-imidoylation by **I** to give intermediates of the general structure **A** and **B** as the only reasonable common step in reactions of **I** with ammonia and hydrazine, respectively (Scheme 2). The above transformations with ammonia of unsymmetrically disubstituted-1-chlorazines, **I**, leading to **III**, may proceed through stage **A** (1-aminoazine) and **VIII** (2,3-dihydro-1,2,4-triazole). Our findings that unsymmetrically disubstituted-1-chloroazines, **I** undergo reaction with ammonia under very mild conditions (0-20°) suggest that the reaction sequence involved nucleophilic substitution (stage **A**) followed by conjugate addition (stage **VIII**) and dehydrogenation (aromatization) (stage **III**).

The formation of both 4-amino-2,3-dihydro-1,2,4-triazoles **VII** and 1,2,3,4-tetrahydro-1,2,4,5-tetrazines **V**



Scheme II

from reactions of **I** with hydrazine allows the suggestion of a common intermediate, **B**, in the early stage of these cyclizations. Thus, the suggested mechanism for the formation of **VII** and **V** involves the intermediate formation of 1-hydrazinoazine, **B**, hydrazine acting both as a 1,1-dinucleophile (path *a*) and as a 1,2-dinucleophile (path *b*). Disproportionation reactions [3] have not been observed for the **I** compounds as evidenced by the failure to detect symmetrically disubstituted reaction products (azines, *s*-triazoles, *s*-tetrazines).

EXPERIMENTAL

General Methods.

Melting and boiling points are uncorrected. The ^{1}H nmr spectra were recorded at 60 MHz on a Varian EM-360 spectrometer with TMS as an internal standard. The ^{13}C nmr chemical shifts were determined on a Bruker WP-60 spectrometer operating at 15.08 MHz. Electron impact mass spectra were determined at 70 eV on a Finnigan 3200 mass spectrometer by direct introduction *via* solid probe. Chemical ionization mass spectra were obtained at 70 eV on a Finnigan 4000 mass spectrometer. A Finnigan 6110 Data System was used for data acquisition.

6-(1-Cyclohexen-1-yl)-1,2,3,4-tetrahydro-1,2-dimethyl-3-(trifluoromethyl)-1,2,4,5-tetrazine (**IIa**).

To a stirred solution of 2.4 g (40 mmoles) of 1,2-dimethylhydrazine in 25 ml of THF was added dropwise 4.8 g (20 mmoles) of *N*-((2,2,2-trifluoroethylidene)amino)-1-cyclohexene-1-carboximidoyl chloride, **Ia** [5]. After 24 hours at room temperature, the light yellow colored solution was diluted with 50 ml of ice water and extracted with three 50 ml-portions of ether. The combined extracts were washed with cold water, dried and concentrated to give 5.4 g of yellow syrup. Purification by silica chromatography (solvent system (by volume): hexane (80), tetrahydrofuran (4), ethyl acetate (16)) gave 3.2 g (61%) of colorless solid; mp 67-69°; ^{1}H nmr (deuteriochloroform): δ 1.6 and 2.15 (8H, $(CH_2)_4$), 2.65 and 2.85 (6H, $(CH_3)_2$), 4.1 (1H, CH), 5.1 (1H, NH), and 5.9 (1H, CH=); ir (potassium bromide): ν 3240 cm^{-1} (NH); ei/ms: (m/z) 262 (M^+), 203 (M^+-$(CH_3N)_2H^+$), 122 ($C_6H_9CNNH^+$), 81 ($C_6H_9^+$), 59 ($CH_3NNHCH_3^+$); ^{1}H nmr (DMSO-d_6): δ 1.56 (4H, m, $(CH_2)_2$), 1.9-2.3 (4H, m, $(CH_2)_2$), 2.44 (3H, s, CH_3), 2.51 (3H, s, CH_3), 3.32 (1H, d, NH), 4.50 (1H, m, CH), and 5.81 (1H, s, CH=).

Anal. Calcd. for $C_{11}H_{17}F_3N_4$ (262.28): C, 50.4; H, 6.5; N, 21.4. Found: C, 50.4; H, 6.5; N, 21.3.

Reaction of **Ia** with Hydrazine. Preparation of **IIIa**, **Va** and **VIIa**.

To a stirred solution of 1.4 g (44 mmoles) of hydrazine in 25 ml of THF was added dropwise 4.8 g (20 mmoles) of **Ia** causing the internal temperature to increase from 10° to 45°. After 18 hours at room temperature, the reaction mixture was diluted with 100 ml of water and extracted with three 100 ml-portions of ether. The ethereal extracts were washed with water, dried and concentrated to 4.8 g of light yellow oil. Silica chromatography of the crude product [solvent: tetrahydrofuran (4%), hexane (80%), ethyl acetate (16%) (vvv)] gave 0.5 g (12%) of light tan solid **IIIa**, mp 181-184° (from ether-hexane); ^{1}H nmr (DMSO-d_6): δ 1.65 (2H, m, CH_2), 1.71 (2H, m, CH_2), 2.22 (2H, m, CH_2), 2.40 (2H, m, CH_2), 3.45 (1H, m, NH) and 6.81 (1H, m, CH=); ei/ms (m/z) 217 (M^+), 202 (M^+-NH), 198 (M^+-F), 188 (M^+-N_2H), 151, 138, 118, 91, 79, 67, 53.

Anal. Calcd. for $C_9H_{10}F_3N_3$ (217.19): C, 49.8; H, 4.6; N, 19.3. Found: C, 49.7; H, 4.6; N, 19.2.

A second fraction consisted of 0.3 g (6.4%) of tan solid **Va**, mp 110-113°; ir (potassium bromide): ν 3260 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.6 (4H, $(CH_2)_2$), 215 (4H, $(CH_2)_2$), 4.05 (1H, NH), 4.9 (2H, $(NH)_2$), and 6.05 ppm (1H, CH=); ^{1}H nmr (DMSO-d_6): δ 1.54 (4H, s, $(CH_2)_2$), 2.05 and 2.13 (4H, s, $(CH_2)_2$), 3.35 (3H, s, $(NH)_3$), 4.25 (1H, m, CH), and 6.04 (1H, s, CH=); ei/ms: (m/z) 234 (M^+), 203 (M^+-N_2H_3), 165 (M^+-CF_3), 123, 108, 81 ($C_6H_9^+$), 79, 67, 53.

Anal. Calcd. for $C_9H_{13}F_3N_4$ (234.22): C, 46.2; H, 5.6; N, 23.9. Found: C, 45.8; H, 5.5; N, 23.6.

A third fraction consisted of 2.0 g (43%) of cream colored solid **VIIa**, mp 92-95°; ir (potassium bromide): 3300 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.65 (4H, $(CH_2)_2$), 2.25 (4H, $(CH_2)_2$), 4.0 (2H, NH_2), 5.0 (1H, NH), 5.3 (1H, CH), and 6.45 (1H, CH=); ^{1}H nmr (DMSO-d_6): δ 1.57 (4H, $(CH_2)_2$), 2.0-2.5 (4H, $(CH_2)_2$), 3.33 (2H, NH_2), 4.68 (1H, NH), 5.0 (1H, CH), 6.5 (1H, CH=); ei/ms: (m/z) 234 (M^+), 217 (M^+-NH_3), 165 (M^+-CF_3).

Anal. Calcd. for $C_9H_{13}F_3N_4$ (234.22): C, 46.2; H, 5.6; N, 23.9. Found: C, 45.9; H, 5.5; N, 23.7.

Compound **VIIa** decomposes when subjected to the conditions of gc/ms leading to fragments that are the result of dehydrogenation (aromatization) and a combination of dehydrogenation-deamination conditions.

3-(1-Cyclohexen-1-yl)-6-(trifluoromethyl)-1,2,4,5-tetrazine **VIa**.

To a cooled (10°) and stirred solution of 0.2 g (0.85 mmole) of **Va** in 5 ml of glacial acetic acid was added dropwise an excess of saturated aqueous sodium nitrite, changing the reaction mixture from colorless to cherry red. The reaction mixture was extracted with ether. The combined extracts were washed with two 10 ml-portions of saturated sodium bicarbonate and then with water, dried over anhydrous magnesium sulfate, filtered and concentrated under rotary evaporation at 25° (0.5 mm) to give 90 mg of red oil. The crude tetrazine which contained about 20% of cyclohexenylcarbonitrile, m/z 107 (M+), was purified by silica chromatography [solvent system (by volume): hexane (96) and tetrahydrofuran (4)] to give 55 mg (28%) of red oil; ei/ms: (m/z) 230 (M^+), 203 (M^+-HCN), 137 (M^+-C_6H_9C), 107 ($C_6H_9CN^+$), 92 ($C_6H_8C^+$), 80 (m/z/ 107-HCN), 66, 54.

Anal. Calcd. for $C_9H_9N_4F_3$ (230.19): C, 47.0; H, 3.9; N, 24.3. Found: C, 47.2; H, 3.8; N, 24.3.

Reaction of **Ia** with Ammonia. Preparation of **IIIa**.

To a cooled (0°) solution of 2.0 g (0.133 mole) of ammonia in 50 ml of ether was added a solution of 4.0 g (0.017 mole) of **Ia** in 10 ml of ether. After 2 days at ambient temperature, the reaction mixture was washed with 30 ml of 10% cold hydrochloric acid. The organic layer was dried and concentrated to give 3.15 g of cherry red liquid. Silica chromatography gave 2.7 g (74%) of **IIIa**, mp 177-180° (from ether-hexane); ir (potassium bromide): 3000 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform + DMSO-d_6): δ 1.7 (4, $(CH_2)_2$), 2.4 (4, (CH_2), 6.8 (1, CH=); ^{13}C nmr: δ 21.44 (CH_2), 21.79 (CH_2), 25.13 (CH_2), 24.87 (CH_2), 120.44 (CF_3), 125.15 (CH=), 132.08 (C=), and 157.82 (C=), ei/ms: (m/z) 217 (M^+), 202, 188, 151, 91, 79, 69, 53.

Anal. Calcd. for $C_9H_{10}F_3N_3$ (217.19): C, 49.8; H, 4.6; N, 19.3. Found: C, 49.3; H, 4.6; N, 19.3.

1-Chloro-1-(4-chlorophenyl)-4-(trifluoromethyl)azine (**Ib**).

A solution of 72.0 g (0.29 mole) of trifluoroacetaldehyde-4-chlorobenzoylhydrazone [6] in 500 ml of thionyl chloride containing 10 drops of DMF was stirred and heated to reflux for 18 hours. The excess of thionyl chloride was removed under rotary evaporation. The crude chloroazine, 74.2 g, distilled at 80-85° (0.1 mm) to give 36.0 g (50%) of yellow oil; ir (potassium bromide): ν 1000 (C=) and 1180 (CF_3) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.0 (4, (CH=)$_4$) and 8.0 (1, CH=); ei/ms: (m/z) 268 (M^+), 233 (M^+-Cl), 137 ($ClC_6H_4CN^+$), 69 (CF_3^+).

Anal. Calcd. for $C_9H_5Cl_2F_3N_2$ (269.05): C, 40.2; H, 1.9; N, 10.4. Found: C, 40.0; H, 2.0; N, 10.3.

6-(4-Chlorophenyl)-1,2,3,4-tetrahydro-1-methyl-3-(trifluoromethyl)-1,2,4,5-tetrazine (**IVb**).

To a stirred and cooled (-30°) solution of 9.2 g (0.2 mole) of methylhydrazine in 150 ml of tetrahydrofuran was added dropwise (20 minutes) a solution of 26.9 g (0.10 mole) of **Ib** in 100 ml of tetrahydrofuran. The mixture was stirred at -30° for 0.5 hour and then at 0° for 0.5 hour, and then was heated to 56° for 0.5 hour. The solvent was removed by rotary evaporation. The residue was diluted with ether, extracted with 3 x 250

ml of water, dried, and purified by silica chromatography [solvent system (by volume): hexane (80), tetrahydrofuran (16), ethyl acetate (4)] to give 5.0 g (18%) of **IVb**, mp 121-124°; ir (potassium bromide): 3250 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.70 (3, CH_3), 4.52 (1, CH), 5.66 and 7.29 (2, $(NH)_2$), 7.47 (4, $(CH=)_4$); ei/ms: (m/z) 278 (M^+) (1 Cl), 233 (M^+-CH_3NHNH_2), 209 (M^+-CF_3), 152 ($ClC_6H_9CNNH^+$), 137 ($ClC_6H_4CN^+$), 111 ($C_6H_4Cl^+$), 102, 75, 69 (CF_3^+), 63, 50, 45.

Anal. Calcd. for $C_{10}H_{10}ClF_3N_4$: C, 43.1; H, 3.6; N, 20.1. Found: C, 43.4; H, 3.6; N, 20.2.

Reaction of **Ib** with Hydrazine. Preparation of **Vb**, **IIIb**, and **VIIb**.

To a stirred and cooled solution of 5.5 g (162 mmoles) of 95% hydrazine in 150 ml of tetrahydrofuran was added dropwise a solution of 21.8 g (81 mmoles) of **Ib** in 50 ml of tetrahydrofuran. After two hours, the reaction mixture was poured into water and filtered. The filter cake was absorbed on silica gel and chromatographed as described under **IVb** (above) to give 7.0 g (33%) of colorless solid **VIIb**, mp 102-105°. The analytical sample melted at 104-105° (from ether-hexane); ir (potassium bromide): ν 3230 and 3380 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.98 (2H, s, NH_2), 5.05 (1H, m, CH), 5.45 (1H, d, NH), and 7.4 and 7.75 ppm (4H, q, $(CH=)_4$); ei/ms: (m/z) 264 (M^+), 247 (M^+-NH_3), 195 (M^+-CF_3).

Anal. Calcd. for $C_9H_8ClF_3N_4$ (264.64): C, 40.8; H, 3.0; N, 21.2. Found: C, 41.0; H, 3.1; N, 21.0.

A second fraction consisted of 0.2 g (1%) of **IIIb**, an off-white solid; mp 176-179°; ei/ms: (m/z) 247 (M^+), 228, 199, 152, 138.

Anal. Calcd. for $C_9H_5ClF_3N_3$ (247.61): C, 43.6; H, 2.0; N, 17.0. Found: C, 43.9; H, 2.0; N, 17.0.

The third fraction, 3.0 g (14%) consisted of **Vd**, a colorless solid, mp 174-175°, resolidifies and melts at 180-182°; ir (potassium bromide): ν 3290 and 3200 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.33 and 3.36 (3H, $(NH)_3$), 4.41 (1H, m, CH), 7.41 (2H, q, $(CH=)_2$) and 7.62 ppm (2H, q, $(CH=)_2$); ei/ms: (m/z) 264 (M^+), 249 (M^+-NH), 195 (M^+-CF_3), 137 ($ClC_6H_9CN^+$), 111 ($C_6H_9Cl^+$), 102 (m/z 137-Cl), 75, 69 (CF_3^+), 50.

Anal. Calcd. for $C_9H_8ClF_3N_4$ (264.64): C, 40.8; H, 3.0; N, 21.2. Found: C, 40.9; H, 2.9; N, 21.2.

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