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1,2,4-Triazoles, II [1] Synthesis of 1,5-Diphenyl-3-trifluoromethyl-1*H*-1,2,4-triazoles**

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Reaction of substituted phenylhydrazines **1a–f** with methyl trifluoroacetimidate **2** gives via the amidrazones **3** after treatment with benzoyl chlorides **4** the triazoles **5a–f** which showed an anti-inflammatory effect.

(Keywords: Cyclization; Anti-inflammatory effect; 1,5-Diphenyltriazole; Trifluoroacetamidrazone)

*1,2,4-Triazole, II [1]. Synthese von 1,5-Diphenyl-3-trifluoromethyl-1H-1,2,4-triazolen***

Umsetzung substituierter Phenylhydrazine **1a–f** mit Trifluoressigsäure-imidat (**2**) liefert über die Amidrazone **3** nach Ringschluß mit Benzoylchloriden **4** die Triazole **5a–f**. Sie zeigen entzündungshemmende Eigenschaften.

Introduction

Certain diaryl heterocycles of a variety of structural types [1–4] (among them trifluoromethyl-substituted ones [5, 6]) have useful anti-inflammatory activity.

On the basis of our results [1] we have become interested in developing a method for the synthesis of 1,5-diaryl-3-trifluoromethyl-1H-1,2,4-triazoles.

Results and Discussion

The methods [1, 7–11] described for the preparation of trisubstituted 1,2,4-triazoles (among them for some trifluoromethyl-substituted triazoles [12, 13]) were not useful for the synthesis of the title compounds.

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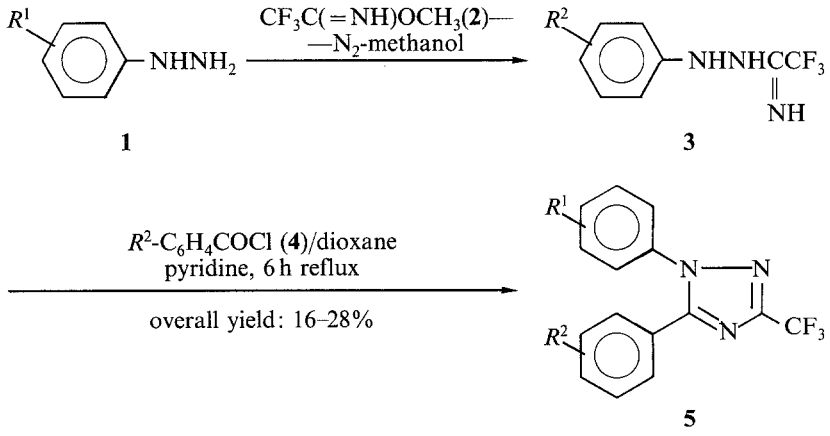
Until recently, the widely used procedure for trifluoromethyl-substituted heterocycles involved the utilization of starting materials containing the trifluoromethyl group to avoid the subsequent fluorination of a methyl group with SbF_5 [14, 15]. Another possibility would have been the reaction of a 3-halogenated diaryltriazole with methyl iodide/copper reagent [16]—but this starting material was not readily accessible.

Therefore the amidrazone route was chosen as synthetic strategy.

Methyl trifluoroacetimidate [17] **2** was found to be a conventional precursor: treatment of **2** with phenylhydrazines **1 a–f** in methanol led to the amidrazones **3**, followed by acylation with benzoyl chlorides **4** in hot dioxane/pyridine to give the desired 1,5-diphenyl-3-trifluoromethyl-1H-1,2,4-triazoles **5 a–f** (Scheme 1).

Scheme 1



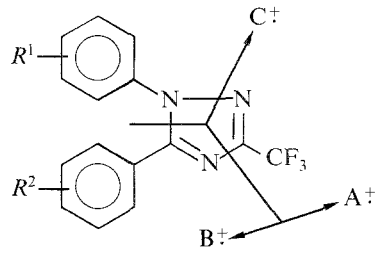
1, 3, 5	R^1	R^2
a	H	H
b	4-Cl	4-F
c	4-F	4-Cl
d	4-Cl	4-Cl
e	4-F	4-F
f	3-CF_3	4-Cl

The intermediate amidrazones **3** could be isolated in crystalline form only in the case of **3 a**.

The structure of **5** was fully characterized by satisfactory microanalyses and by mass spectral data. The IR and ^{1}H-NMR spectra were however not characteristic.

The fragmentation of the molecules is shown in Scheme 2.

Scheme 2



The most typical fragmentation route was the C_3—N_4 bond fission forming two ions A^+ and B^+, respectively, with an almost standard intensity ratio of 10 : 1. In addition, a third stable ion C^+ of high intensity (formed from the ion A^+) could also be observed.

The compounds **5** were not superior to known antiinflammatory agents.

Experimental

Melting points were determined with a Büchi apparatus and are uncorrected. Compounds were analyzed for the elements indicated and are ± 0.24% (C), 0.11% (H), 0.30% (F, N) of the calculated values. IR spectra were recorded in KBr pellets on a Bruker IFS-85 spectrophotometer, ^{1}H-NMR spectra were obtained on a Varian XL-100 spectrophotometer using *TMS* as internal standard. Mass spectra were recorded on a Varian MAT SM1 double focusing mass spectrometer. The operating parameters were: an accelerating potential of 8 kV, 70 eV electron energy, an electron current of 300 mA, a source temperature of 250 °C, a resolution of 1 250. The evaporation temperature for **5a, c, e** was 80 °C, for **5d** 95 °C, for **5f** 50 °C and for **5b** 40 °C.

N^2-Phenyl-trifluoracetamidrazone (**3a**)

A mixture of phenylhydrazine **1a** (2.0 ml, 20 mmol), methyl trifluoroacetimidate [17] **2** (3.0 ml, 28 mmol) and methanol (10 ml), is stirred under nitrogen stream for 24 h. After evaporation of the solvent, the residue is recrystallized from benzene/petrolether to give **3a**, yield: 2.4 g (64%), m.p. 69–71 °C.

$C_8H_8F_3N_3$ (203.17). Calcd. F 28.05 N 20.70.
Found F 27.93 N 20.87.

IR (KBr): 1 664 (C=N) cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 3.6–4.8 (s, 2 H), 5.5–6.4 (s, 1 H), 6.7–7.4 (m, 5 H).

3-Trifluoromethyl triazoles **5** *(General Procedure)*

To the stirred mixture of the amidrazone **3** (20 mmol) prepared above, pyridine (22 mmol) and dioxane (30 ml) is added a solution of substituted benzoyl chloride **4** (22 mmol) in dioxane (15 ml) under a nitrogen stream at room temperature. The stirred solution is boiled for 6 h, then after evaporation of dioxane the residue is taken up in dichloromethane (50 ml). The solution is successively extracted with several portion of 4% hydrochloric acid (5 × 20 ml), water (20 ml), 10% sodium carbonate solution (20 ml) and water (20 ml), dried over magnesium sulfate, and the solvent evaporated to leave the triazole **5**. Further purification is accomplished by column chromatography on silica gel (100 : 1 mixture of benzene/methanol as solvent).

1,5-Diphenyl-3-trifluoromethyl-1H-1,2,4-triazole (**5a**)

Yield: 26%, m.p. 131–132 °C (from cyclohexane).

$C_{15}H_{10}N_3F_3$ (289.25). Calcd. C 62.18 H 3.48 F 19.70 N 14.52.
Found C 62.15 H 3.50 F 19.56 N 14.32.

MS: *m/e* = 289 (M^+) (100%), *m/z* = 91 (65), 288 (32), 186 (25), 69 (13), 134.5 (7), 77 (6), 78 (5), 51 (5).

5-(4-Fluorophenyl)-1-(4-chlorophenyl)-3-trifluoromethyl-1H-1,2,4-triazole (**5b**)

Yield: 16%, m.p. 77–78 °C (from hexane).

$C_{15}H_8ClF_4N_3$ (341.69). Calcd. C 52.72 H 2.36 F 22.24 N 12.29.
Found C 52.93 H 2.41 F 22.42 N 12.31.

MS: *m/e* = 341 (M^+) (100%), *m/z* = 125 (63), 127 (62), 220 (23), 222 (8), 90 (16), 63 (5), 322 (4), 324 (1).

1-(4-Fluorophenyl)-5-(4-chlorophenyl)-3-trifluoromethyl-1H-1,2,4-triazole (**5c**)

Yield: 26%, m.p. 91–93 °C (from ethanol).

$C_{15}H_8ClF_4N_3$ (341.69). Calcd. C 52.72 H 2.36 F 22.24 N 12.29.
Found C 52.86 H 2.44 F 22.49 N 12.39.

MS: *m/e* = 341 (M^+) (68%), 343 (25%), *m/z* = 109 (100), 204 (25), 82 (14), 89 (5), 95 (4), 322 (3), 324 (1), 139 (3).

1,5-bis(4-Chlorophenyl)-3-trifluoromethyl-1H-1,2,4-triazole (**5d**)

Yield: 15%, m.p. 122–124 °C (from ethanol).

$C_{15}H_8Cl_2F_3N_3$ (358.14). Calcd. C 50.30 H 2.25 F 15.91 N 11.73.
Found C 50.20 H 2.22 F 16.03 N 11.65.

MS: *m/e* = 357 (100%), 359 (66%), 361 (12%), *m/z* = 125 (81), 127 (28), 230 (32), 222 (10), 90 (21), 63 (7), 89 (5), 111 (4), 113 (1.5), 75 (4), 131 (3), 133 (1).

1,5-bis(4-Fluorophenyl)-3-trifluoromethyl-1H-1,2,4-triazole (**5e**)

Yield: 18%, m.p. 88–90 °C (from ethanol).

$C_{15}H_8F_5N_3$ (325.23). Calcd. C 55.39 H 2.47 F 29.21 N 12.92.
Found C 55.55 H 2.38 F 29.46 N 12.95.

MS: *m/e* = 325 (66%), *m/z* = 109 (100), 204 (27), 82 (7), 306 (4), 95 (4), 89 (4), 324 (3), 121 (3).

5-(4-Chlorophenyl)-3-trifluoromethyl-1-(3-trifluoromethylphenyl)-1H-1,2,4-triazole (**5f**)

Yield: 28%, m.p. 65–66 °C (from petrolether, b.p. 120 °C).

$C_{16}H_8ClF_6N_3$ (391.70). Calcd. C 49.05 H 2.31 F 29.10 N 10.72.
Found C 49.32 H 2.37 F 29.06 N 10.70.

MS: *m/e* = 391 (58%), 393 (20%), *m/z* = 159 (100), 139 (12), 390 (9), 392 (4), 372 (7), 374 (3), 109 (9), 145 (5), 132 (5).

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