ELSEVIER

Journal of Fluorine Chemistry 93 (1999) 39–43

JOURNAL OF FLUORINE CHEMISTRY

Syntheses and characterization of 2-amino-5-aryl-1,3,4-oxadiazoles containing trifluoroethoxy groups

Rong Zhang, Xuhong Qian*, Zhong Li

Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, PO Box 544, 130 Meilong Road, Shanghai 200237, China

Received 3 June 1998; accepted 11 August 1998

Abstract

In order to develop an effective synthetic route to 2-amino-5-aryl-1,3,4-oxadiazoles containing trifluoroethoxy groups, a novel intermediate 2-amino-5-[4-(2′,2′,2′-trifluoroethoxy)-phenyl]-1,3,4-oxadiazole was prepared and its structure was confirmed by mass spectrometry and ^{1}H NMR spectroscopy. The chlorine atom was not substituted by trifluoroethoxy groups, when syntheses of the intermediate by direct trifluoroethoxylation of 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole was tried. The resulting product was characterized as *N*-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-chlorobenzamide. A possible reaction mechanism is suggested.

Keywords: Oxadiazole; Trifluoroethoxylation; Synthesis; Characterization; Mechanism

1. Introduction

2,5-Disubstituted-1,3,4-oxadiazoles have strong insecticidal and antibiotic activities [1,2]. Previously, we synthesized a series of *N*-(5-aryl-1,3,4-oxadiazol-2-yl)-substituted amides containing the trifluoroethoxyl group [3] and reported that trifluoroethoxy anions can even replace all the fluorine atoms of a trifluoromethyl group attached to a pyridine ring [4]. Herein, we report the alternative synthesis of 2-amino-5-[4-(2′,2′,2′-trifluoroethoxy)phenyl]-1,3,4-oxadiazole via trifluoroethoxylation by two routes. However, one line failed to give the desired product, the resulting product was identified as *N*-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-chlorobenzamide.

2. Results and discussion

In order to study an effective synthetic method for introducing trifluoroethoxy groups into 2-amino-5-aryl-1,3,4-oxadiazoles, we designed two routes to synthesize the useful intermediate 2-amino-5-[4-(2′,2′,2′-trifluoroethoxy)phenyl]-1,3,4-oxadiazole (6) via trifluoroethoxylation, and compared the reaction behavior and discussed the possible mechanism.

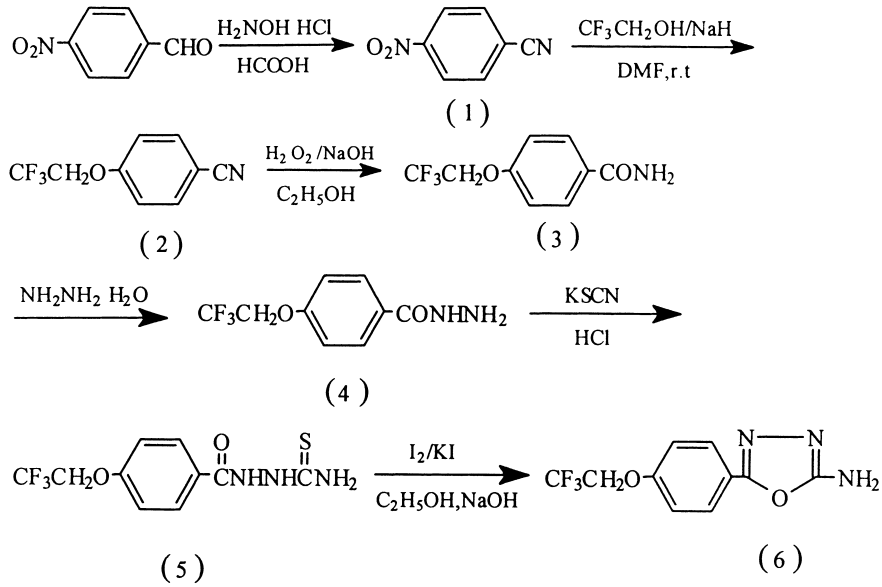
Initially, we undertook the typical procedure given in Scheme 1 and succeeded in synthesizing the desired compound. To begin with, the trifluoroethoxy group was introduced into the starting material (1) to yield (2), and then (2) took four steps through corresponding benzamide (3) benzoylhydrazide (4) and benzoylthiosemicarbazide (5), and finally by oxidative cyclization of (5) with iodine in potassium iodide solution to give the product (6).

The found elemental composition analyses were in good agreement with calculations. ^{1}H NMR spectroscopy revealed a $-CH_2-$ quartet ($J_{H,F}$=8.0 Hz) at 4.76 ppm corresponding to the trifluoroethoxy group. The protons at positions 3,5 of the phenyl ring were affected by the electron-donating ability of the neighboring trifluoroethoxy group, and their resonance values are slightly higher than the protons at positions 2,6. The amino protons could not be observed because of exchange. Mass spectra data were the most effective in elucidating the structure of this compound. We show a fragmentation pattern in Scheme 2 with the important ions observed in the mass spectra. It was in close conformity with reported results [5]. The intermediate 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole (8) had a similar result (see Section 3.2 for spectral data).

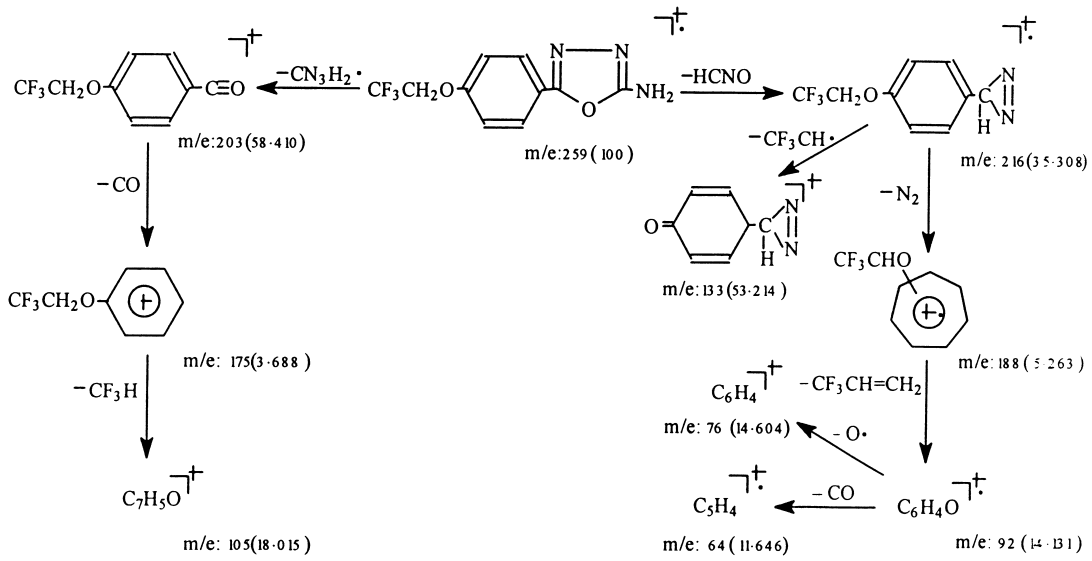
Although this route is convenient to prepare the desired oxadiazole, it was long, and gave low total yield, therefore we sought a shorter effective synthetic route. A method described in the literature [6] for the synthesis of 4-trifluoromethyl-5-ethoxyl-2-[4-(2′,2′,2′-trifluoroethoxy)phenyl]-1,

*Corresponding author. Tel.: +86-21-64252774; fax: +86-21-64251386; e-mail: xhgian@ecust.edu.cn

0022-1139/99/$ – see front matter
PII: S0022-1139(98)00269-3



Scheme 1. Route 1 for synthesis of 2-amino-5-[4-(2′,2′,2′-trifluoroethoxy)phenyl]-1,3,4-oxadiazole (6).

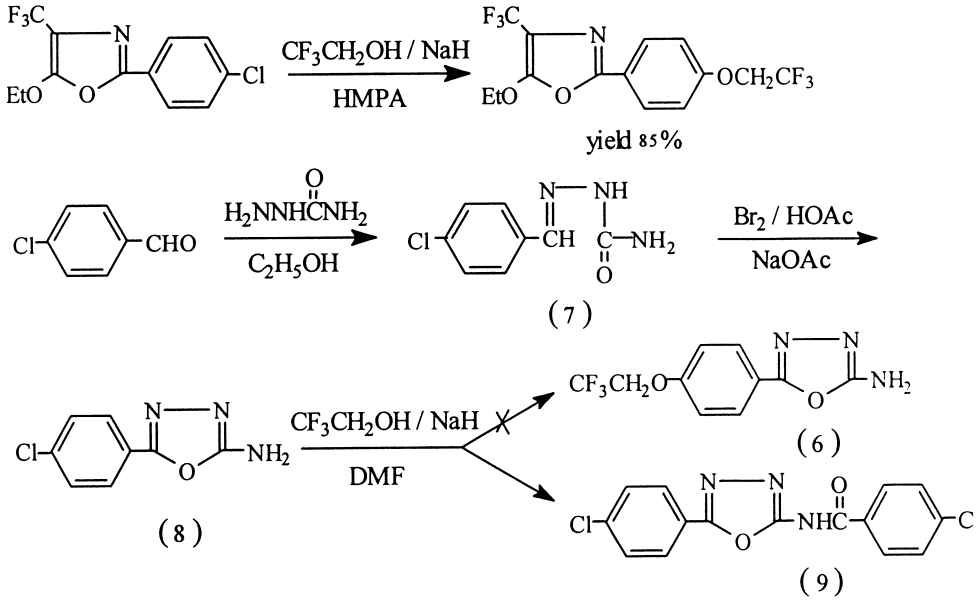


Scheme 2. Mass spectral fragmentation pattern of 2-amino-5-[4-(2′,2′,2′-trifluoroethoxy)phenyl]-1,3,4-oxadiazole (6).

3-oxazole via direct nucleophilic displacement reaction appeared to proceed via a reaction mechanism similar to that we have suggested in Scheme 3 (route 2). The major difference between routes 1 and 2 was that the trifluoroethoxy group in route 1 was introduced prior to cyclization, whereas in route 2, the reaction proceeded first by cyclization to form the 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole (8), after which the trifluoroethoxy group attempted to replace the chlorine atom in (8). However, (8) was not converted into the desired compound (6) in using the modified procedure described by Idoux et al. [6]. First of all, the isolated product did not have the same melting point as the above authentic sample (6), and the fluorine elemental analyses clearly indicated that there was no fluorine in this product. The chlorine atom had not been substituted by trifluoroethoxy group.

We have previously shown, [1,2], that the trifluoroethoxy anion was a weak nucleophilic reagent because of the strong electronegativity of the fluorine atoms, and trifluoroethoxy nucleophilic substitution could only take place where the aromatic compounds such as substituted phenyl, pyridyl, naphthyl possess an easy leaving group (e.g. NO_2, Cl) and a corresponding strong electron-attracting group such as –CN, $–NO_2$, $–COOCH_3$ etc.

Similarly comparing the reactions shown in Scheme 3, we found that the starting material 4-trifluoromethyl-5-ethoxyl-

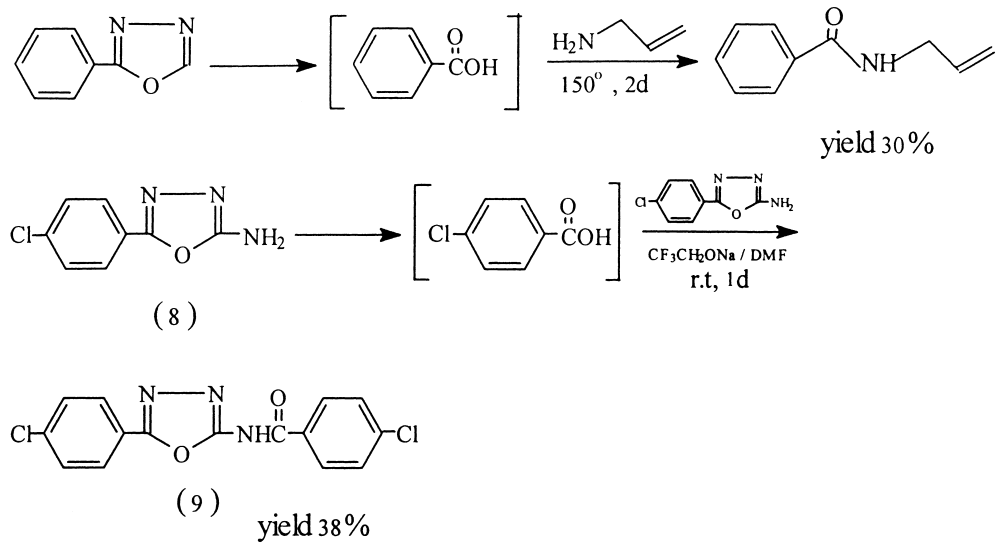


Scheme 3. Route 2 for trying to synthesis of 2-amino-5-[4-(2′,2′,2′-trifluoroethoxy)phenyl]-1,3,4-oxadiazole.

2-(4-chlorophenyl)-1,3-oxazole possesses a strongly electron-attracting trifluoromethyl group at position 4 of the 1,3-oxazole ring affecting the neighboring phenyl ring of the 1,3-oxazole ring, and resulting in decreased electron density at the chlorine atom. The chlorine atom was finally substituted by a nucleophilic reagent. On the contrary, the 1,3,4-oxadiazole ring did not have a strong electron-attracting group at position 4 instead of a strong electron-donating amino group at position 5, so the chlorine atom was in an inactivated state for substitution and could not be replaced by trifluoroethoxy group.

This isolated product was characterized as *N*-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-chlorobenzamide (9) as shown in Scheme 3, an analogue of a compound we have reported [3].

We assume that during the reaction, the starting material (8) (prepared in Section 3.2) first underwent oxadiazole ring opening and further hydrolysis to give the carboxylic acid, followed by the acylation of carboxylic acid with the amino group to give the final product (9) (Scheme 4). This could be employed to illustrate the similar reaction behavior reported by Carlsen et al. [7].



Scheme 4. A possible reaction mechanism for formation of (9).

In addition, it might be explained that the strong base sodium trifluoroethoxide in dimethylformamide played an important role for the acylation reactions in order that the reaction can proceed at room temperature smoothly during one day. It is necessary for the reported reaction to be heated in a sealed tube at 150° and for two days if the base is not present to accelerate the reaction in allylamine [7]. The product was isolated (30%) and identified as *N*-allylbenzamide by comparison with the authentic sample.

3. Experimental

Melting points were taken on a digital melting point apparatus made in Shanghai. Infrared spectra were measured on KBr using a Nicolet FT-IR-20SX instrument. Mass spectra were measured on a Hitachi M80 instrument. ^{1}H NMR spectra were obtained using a Brucker WP-100SY(100 MHz) spectrometer with $(CD_3)_2CO$ as the solvent and TMS as internal standard. Combustion analyses for elemental composition were made with an Italian MOD.1106 analyser. All reactions were monitored by TLC.

3.1.

The intermediates (1)–(4) were prepared according to our reported procedures [1,8] shown in Scheme 1, their yields and melting points are listed as follows:

- 4-Nitrobenzonitrile (1): 94.6%, m.p. 146.0–146.9°C [8].
- 4-(2′,2′,2′-Trifluoroethoxy)-benzonitrile (2): 95.0%, m.p. 60.6–61.5°C [8].
- 4-(2′,2′,2′-Trifluoroethoxy)-benzamide (3): 80%, m.p. 175.6–176.2°C [9].
- 4-(2′,2′,2′-Trifluoroethoxy)-benzoylhydrazide (4): 78%, m.p. 121.7–123.0°C [10].

3.1.1. Preparation of 4-(2′,2′,2′-trifluoroethoxy)-benzoylthiosemicarbazide (5)

This was prepared by refluxing a suspension of 2.24 g (10 mmol) 4-(2′,2′,2′-trifluoroethoxy)-benzoylhydrazide (4), 1.94 g (20 mmol) potassium thiocyanate, 10 ml of 36% hydrochloric acid and 200 ml of water for 3.5 h. After cooling, the white solid was filtered, washed with water, dried and recrystallized from ethanol to give the product, yield 78%, m.p. 214.5–216.0°C. IR (KBr): 3260 (NH); 1670 (C=O); 1350 (C=S); 1250; 1165; 930; 850; 830 cm^{-1}. Analysis: Calc. for $C_{10}H_{10}F_3N_3O_2S$ (293.26): C, 40.96; H, 3.44; N,14.33%. Found: C, 40.85; H, 3.41; N,14.37%.

3.1.2. Preparation of 2-amino-5-[4-(2′,2′,2′-trifluoroethoxy)phenyl]-1,3,4-oxadiazole (6)

To a suspension of 0.44 g (1.5 mmol) 4-(2,′2′,2′-trifluoroethoxy)benzoylthiosemicarbazide (5) in 50 ml of 95% ethanol was added 0.75 ml of sodium hydroxide (4 N) and which with stirring gave a clear solution. Iodine in potassium iodide solution (5%) was added into the solution until the colour of iodine persisted. After refluxing the mixture for 2–3 h, the reaction mixture was poured into 100 ml of ice-water, filtered and washed with water and warm carbon disulphide, and recrystallized from 75% ethanol to give white needles, yield 70%, m.p. 243.0–244.0°C. ^{1}H NMR δ: 4.76 (*q*, $J_{H,F}$=8.0 Hz, 2H, –CH_2–); 7.25 (*d*, *J*=8.0 Hz, 2H, Ar 2,6H); 7.85 (*d*, *J*=8.0 Hz, 2H, Ar 3,5H). MS (FD), (*m*/*e*, %): 259 (100) [M]; 260 (12.571) [M+1]; 216 (35.308) [M–HCNO]; 203 (58.410) [M–CN_3H_2]; 175 (3.688) [M–CN_3H_2–CO]; 133 (53.214) [M–HCNO–CF_3CH_2]; 105 (18.015) [M–CN_3H_2–CO–CF_3H]; 92 (14.131) [M–HCNO–N_2–CF_3CH=CH_2]; 76 (14.604) [M–HCNO–N_2–CF_3CH=CH_2–O]; 64 (11.646) [M–HCNO–N_2–CF_3CH=CH_2–CO]. Analysis: Calc. for $C_{10}H_8F_3N_3O_2$ (259.19): C, 46.34; H, 3.11; N, 16.21%. Found: C, 46.33; H, 3.09; N, 16.22%.

3.2.

The intermediate 4-chlorobenzaldehyde semicarbazone (7) was prepared according to the method described in [11] given in Scheme 2, yield 90%, m.p. 224.4–225.2°C; 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole (8) was prepared according to a similar procedure [12], yield 76%, m.p. 273.6–274.7°C. This agreed well with the reported data [5] and had MS (EI 70 eV), (*m*/*e*, %): 195 (100) [M]; 197 (33.557) [M+2]; 152 (84.517) [M–HCNO]; 139 (53.84) [M–CN_3H_2]; 125 (31.692) [M–HCNO–N_2]; 111 (44.519) [M–CN_3H_2–CO]; 89 (27.977) [M–HNCO–N_2–HCl]; 75 (38.361) [M–CN_3H_2–CO–HCl].

3.2.1. Preparation of N-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-chlorobenzamide (9)

0.08 g (2.7 mmol) sodium hydride (80%) was placed in 15 ml of dimethylformamide (dried over 4 Å molecular sieves) and 0.175 ml of 2,2,2-trifluoroethanol (0.24 g, 2.4 mmol) was added dropwise. After stirring for 10 min at room temperature, 0.39 g (2 mmol) 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole (8) was added and the reaction mixture stirred for one day at room temperature. After cautious addition of 35 ml of 20% hydrochloric acid, the mixture was extracted with ether (3×10 ml), washed with 3×2 ml of water, dried over magnesium sulfate, and the solvent removed in vacuo to give a yellow crude product 0.26 g in 38% yield. After recrystallization from 75% ethanol pale yellow prisms were obtained, m.p. 279.3–279.5°C. MS (EI 70 eV), (*m*/*e*, %): 333 (9.098) [M]; 335 (4.12) [M+2]; 139 (100) [M–$ClC_6H_4C_2N_2ONH$]; 141 (36.0) [M+2$ClC_6H_4C_2N_2ONH$]; 111 (34.8) [M–$ClC_6H_4C_2N_2ONH$–CO]; 113 (11.1) [M+2$ClC_6H_4C_2N_2ONH$–CO]. IR (KBr): 3400 (NH); 1740 (C=O); 1650 (C=N); 1600; 1400; 1100; 1090; 840; 750 cm^{-1}. ^{1}H NMR δ: 7.20–8.05 (m, 8H). Analysis: Calc. for $C_{15}H_9Cl_2N_3O_2$(334.16): C, 54.05; H, 2.72; N, 12.67; F, 0%. Found: C, 53.90; H, 2.75; N, 12.64; F, 0%.

Acknowledgements

We express our gratitude to the National Natural Science Foundation of China, and Shanghai Foundation of Science and Technology for the partial financial support.

References

[1] X. Qian, R. Zhang, J. Chem. Tech. Biotechnol. 67 (1996) 124.
[2] R. Zhang, X. Qian, Yingyong Huaxue 13 (1996) 5.
[3] X. Qian, R. Zhang, CN1 126 208A (1996).
[4] X. Qian, R. Zhang, J. Tang, W. Chen, J. Fluorine Chem. 67 (1994) 57.
[5] R.K. Bansal, G. Bhagchandani, J. Indian Chem. Soc. 59 (1982) 277.
[6] J.P. Idoux, C. Liu, Huaxue Shiji 16 (1994) 110.
[7] P.H.J. Carlsen, K.B. Jorgensen, J. Heterocyclic Chem. 31 (1994) 805.
[8] R. Zhang, X. Qian, W. Zhou, Org. Prep. Proced. Int. (1998), in press.
[9] C. Colon, MS Thesis, University of Central Florida, December 1983.
[10] C. Moorefield, MS Thesis, University of Central Florida, December 1983.
[11] C.C. Sigmund, A.F. Castleton, US 3 419 658 (1968).
[12] M.M. Dutta, B.N. Goswami, J.C.S. Katakey, J. Indian Chem. Soc. 67 (1990) 604.