ELSEVIER

Journal of Fluorine Chemistry 99 (1999) 83–85

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Synthesis of trifluoromethyltetrazoles via building block strategy

Jingbo Xiao, Xiaomei Zhang, Deying Wang, Chengye Yuan*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Received 20 April 1999; accepted 31 May 1999

Abstract

A series of 1-substituted-5-trifluoromethyltetrazoles was conveniently prepared from *N*-substituted trifluoroacetimidoyl chlorides via nucleophilic replacement with azide anion followed by subsequent cyclization in moderate to excellent yield by building block strategy.

Keywords: Trifluoromethyltetrazole; Trifluoromethylated building block; Nucleophilic replacement; Cyclization

1. Introduction

A wide range of tetrazole derivatives has been patented for antihypertension activity and as angiotensin II receptor antagonists [1–3]. These are claimed to be useful for treating congestive heart failure [4] and preventing cardiac hypertrophy [5]. The tetrazole ring also features in a range of antiallergic substances which act by inhibiting the allergic histamine release [6,7]. Tetrazoles, due to their pharmaceutical importance and extensive application in organic synthesis, have aroused the interests of many synthetic chemists. On the other hand, trifluoromethylated compounds have received an increasing attention in recent years because of their enhancement effect on the biological activity of the parent molecules [8–10]. Much current effort has been devoted to the development of methods for synthesis of trifluoromethylated heterocycles, most of them are based on the building block strategy [11,12]. *N*-substituted trifluoroacetimidoyl chloride was found to be useful in the formation of trifluoromethylated nitrogen heterocycles [13]. Herein we wish to report a facile synthetic method leading to trifluoromethylated tetrazoles **3** based on building block strategy. These compounds are expected to show some potential biological activities. To the best of our knowledge, these title compounds have not been reported to date.

2. Results and discussion

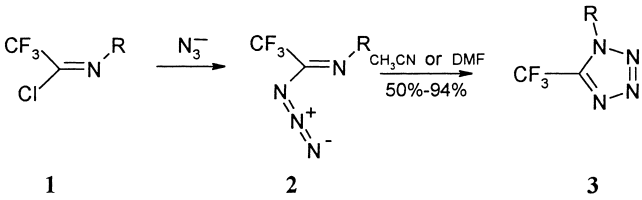
As shown in Scheme 1, *N*-substituted trifluoroacetimidoyl chlorides **1** upon nucleophilic replacement by azide ion **2** followed by subsequent cyclization give trifluoromethylated tetrazoles, namely 1-substituted-5-trifluoromethyltetrazoles **3**.

Our experimental data demonstrated that the cyclization of **2–3** proceeded smoothly in moderate to excellent yield depending on the nature of substituents on imino nitrogen. It seems that there are two structural requirements for the cyclization process. First, the lone pair of the imino nitrogen and azido group should be in *cis* configuration since some imidoyl azides in *trans* configuration were not easily cyclized to corresponding tetrazoles [14,15]. Second, a sufficient electron density is necessary on the imino nitrogen in order to form the electron withdrawing tetrazole ring. It is clear that this indirect [1–3] dipolar cycloaddition leading to the formation of the aromatic system is the driving force of this cyclization process. As shown in Table 1, the presence of an electron donating group on the *N*-substituent of **1** increases the yield dramatically, although the yield of **3c** is not so high as expected. It is necessary to point out that although Carpenter et al. [16], in their paper on fluorinated 1,2,3-triazolines, described a reaction leading to 1-benzyl-5-trifluoromethyltetrazole starting from *N*-benzyltrifluoroacetimidoyl fluoride, our method is distinguished by its availability and its wide scope of applications (see Table 2).

In summary, we describe a method for the preparation of 1-aryl(alkyl)-5-trifluoromethyltetrazoles starting from tri-

*Corresponding author.
E-mail address: yuancy@pub.sioc.ac.cn (C. Yuan)

0022-1139/99/$ – see front matter
PII: S0022-1139(99)00122-0



Scheme 1.

fluoroacetimidoyl chlorides followed by azide substitution and subsequent cyclization and discuss the effect of the substituents on the yields of the title compounds. This synthesis is convenient since the building block trifluoroacetimidoyl chlorides can be easily prepared by refluxing a mixture of trifluoroacetic acid and primary amine in carbon tetrachloride in the presence of triethylamine and triphenylphosphine [17]. The chemical reaction and the structural effect on the ^{19}F NMR chemical shift of these tetrazoles are being carried on in our laboratory. The biological investigation data will be published elsewhere.

3. Experimental

Melting points are uncorrected. IR spectra were taken on a Shimadzu-440 Spectrophotometer. ^1H NMR spectra were recorded on a JEOL FX-90Q Spectrometer. Chemical shifts for ^1H NMR spectra are reported in δ values downfield from TMS. ^{19}F NMR spectra were obtained on a Varian EM-360A Spectrometer using CF_3COOH as an external standard, positive for downfield shift. EI–MS were obtained on a HP5989A Mass Spectrometer. Elemental analysis was performed in our institute.

N-substituted trifluoroacetimidoyl chlorides were prepared by literature methods [17]. Sodium azide was purchased from Shanghai Chemical. Acetonitrile was dried by refluxing with P_2O_5, then distilled prior to use. DMF was dried by refluxing with CaH_2, then distilled.

3.1. 1-(p-methoxyphenyl)-5-trifluoromethyltetrazole (3i): typical procedure

To an oven-dried two-necked 25 ml round-bottom flask fitted with a magnetic stirring bar and charged with dry N_2 was added *N*-(*p*-methoxyphenyl)-trifluoroacetimidoyl chloride (590 mg, 2.5 mmol) and acetonitrile (4 ml) and sodium azide (177 mg, 2.5 mmol). The resulting mixture was stirred at room temperature for 10 h. Completion of reaction was monitored by TLC. The mixture was filtered and concentrated to give a crude product, which was subjected to column chromatography on silica gel (eluent: 10%

Table 1
Trifluoromethyltetrazoles prepared

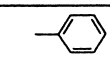
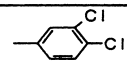
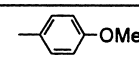
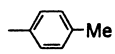
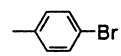
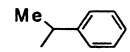
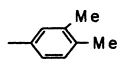
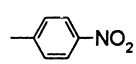
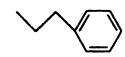
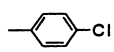
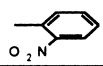
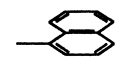
compounds	R	compounds	R	compounds	R
3a		**3e**		**3i**	
3b		**3f**		**3j**	
3c		**3g**		**3k**	
3d		**3h**		**3l**	

Table 2
Spectral characteristics of compounds **3**

Compounds	Melting point (°C)	Yield (%)	Molecular formula	IR ν (cm^{-1})	^{19}F NMR δ (ppm)	MS (*m/z*)
3a	Oil	80	$C_8H_5F_3N_4$ (214.1)	3190, 1160, 1500, 1535	−18.7	214 (M^+)
3b	Oil	91	$C_9H_7F_3N_4$ (228.2)	3050, 2920, 1165, 1510	−17.6	228 (M^+)
3c	43–45	68	$C_{10}H_9F_3N_4$ (242.2)	2960, 1160, 1510, 1530	−18.0	242 (M^+)
3d	Oil	53	$C_8H_4ClF_3N_4$ (248.6)	3090, 1170, 1490, 1530	−18.0	248 (M^+)
3e	Oil	50	$C_8H_3Cl_2F_3N_4$ (283.0)	3090, 1155, 1485, 1525	−18.0	283 (M^+)
3f	51–53	55	$C_8H_4BrF_3N_4$ (293.0)	3100, 1160, 1495, 1530	−18.4	293 (M^+)
3g	70–72	70	$C_8H_4F_3N_5O_2$ (259.1)	3080, 1150, 1495, 1525	−19.3	260 (M^++1)
3h	82–84	53	$C_8H_4F_3N_5O_2$ (259.1)	3040, 1165, 1490, 1540	−17.0	259 (M^+)
3i	Oil	94	$C_9H_7F_3N_4O$ (244.2)	3100, 2900, 1165, 1610	−17.5	244 (M^+)
3j	39–41	91	$C_{10}H_9F_3N_4$ (242.2)	2900, 1160, 1535	−17.0	242 (M^+)
3k	38–40	61	$C_{10}H_9F_3N_4$ (242.2)	3000, 1160, 1500, 1530	−16.5	242 (M^+)
3l	102–104	70	$C_{12}H_7F_3N_4$ (264.2)	3150, 1165, 1510, 1525	−17.4	264 (M^+)

Table 3
^{1}H NMR (CCl_4) δ (ppm), J (Hz) spectra of compounds **3**

Compounds	^{1}H NMR (CCl_4), δ (ppm), J (Hz)
3a	7.60–7.93 (m, 5H, Ph)
3b	7.37–7.50 (m, 4H, Ph); 2.58 (s, 3H, CH_3)
3c	7.56 (s, 3H, Ph); 2.60 (s, 3H, *p*-CH_3); 2.30 (s, 3H, *m*-CH_3)
3d	7.63 (d, 2H, $J = 8.1$ Hz, Ph); 7.48 (d, 2H, $J = 8.1$ Hz, Ph)
3e	7.26–7.82 (m, 3H, Ph)
3f	7.83 (d, 2H, $J = 9.0$ Hz, Ph); 7.47 (d, 2H, $J = 9.0$ Hz, Ph)
3g	8.59 (d, 2H, $J = 11.7$ Hz, Ph); 7.87 (d, 2H, $J = 11.7$ Hz, Ph)
3h	7.55–8.46 (m, 4H, Ph)
3i	7.45 (d, 2H, $J = 9.0$ Hz, Ph); 7.10 (d, 2H, $J = 9.0$ Hz, Ph); 3.98 (s, 3H, CH_3)
3j	7.31–7.40 (m, 5H, Ph); 5.70–5.93 (m, 1H, CH); 2.15 (d, 3H, $J = 7.2$ Hz, CH_3)
3k	7.25–7.51 (m, 5H, Ph); 4.89 (t, 2H, $J = 8.1$ Hz, N–CH_2); 3.60 (t, 2H, $J = 8.1$ Hz, CH_2–Ph)
3l	7.16–8.32 (m, 7H, naphthalene–H)

Table 4
Microanalysis data for compounds **3**

Products	Calculated (%)			Found (%)		
	C	H	N	C	H	N
3a	44.87	2.36	26.16	44.28	2.16	26.42
3b	47.38	3.09	24.55	47.07	2.75	25.07
3c	49.54	3.74	23.21	49.61	3.55	23.29
3d	38.65	1.62	22.54	38.15	1.50	22.44
3e	33.95	1.07	19.80	34.14	1.05	20.14
3f	32.79	1.38	19.12	32.63	1.21	19.33
3g	37.08	1.56	27.03	37.19	1.38	27.50
3h	37.08	1.56	27.03	36.71	1.33	27.38
3i	44.27	2.89	22.95	44.49	2.89	23.15
3j	49.59	3.75	23.13	49.59	3.58	23.35
3k	49.59	3.75	23.13	49.32	3.63	23.24
3l	54.55	2.67	21.21	54.50	2.49	21.35

EtOAc in petroleum ether v/v) to give 568 mg (94%) of pure **3i** as a light yellowish oil (see Table 3).

3.2. *1-α-naphthalene-5-trifluoromethyltetrazole (**3l**): typical procedure*

To an oven-dried two-necked 25 ml round-bottom flask fitted with a magnetic stirring bar and charged with dry N_2 was added *N*-(α-naphthalene)-trifluoroacetimidoyl chloride (858 mg, 3.05 mmol) and DMF (6 ml) and sodium azide (200 mg, 3.05 mmol). The resulting mixture was then stirred at room temperature for 24 h. Completion of reaction was monitored by TLC. The mixture was filtered and concentrated to give a yellowish crude solid, recrystallized from petroleum ether to give 562 mg (70%) of pure **3l** (m.p. 102–104°C) (see Table 4).

Acknowledgements

The authors thank the National Science Foundation of China (No. 29832052) for financial support.

References

[1] S.W. Huskey, R.R. Miller, S.H.L. Chiu, Drug. Metab. Dispos. 21 (1993) 792.
[2] K.S. Kim, L. Qian, J.E. Bird, K.E.J. Dickinson, S. Moreland, T.R. Schaeffer, T.L. Waldron, C. Delaney, H.N. Weller, A.V. Miller, J. Med. Chem. 36 (1993) 2335.
[3] W. Mederski, D. Dorsch, N. Beier, P. Schelling, I. Leus, K.O. Minck, Eur. Pat. (1993) 547 514.
[4] M.E. Pierce, D.J. Carini, G.F. Huhn, G.J. Wells, J.F. Arnett, J. Org. Chem. 58 (1993) 4642.
[5] J.W. Ellingboe, M. Nikaido, J.F. Bagli, Eur. Pat. (1993) 539 086.
[6] N.P. Peet, L.E. Baugh, S. Sunder, J.E. Lewis, E.H. Mathews, E.E. Olberding, D.N. Shah, J. Med. Chem. 29 (1986) 2403.
[7] E. Makino, N. Iwasaki, N. Yagi, T. Ohashi, H. Kato, Y. Ito, H. Azuma, Chem. Pharm. Bull. 38 (1990) 201.
[8] J. Bergman, H.C. Vanderplas, M. Simonyl, Heterocycles Bioorganic Chemistry, RSC, Cambridge, 1991.
[9] B.H. Lipshutz, Chem. Rev. 86 (1986) 795.
[10] N. Ishikawa, Biologically Active Organofluorine Compounds, CMC, Tokyo, 1990.
[11] W.S. Huang, C.Y. Yuan, Z.Q. Wang, J. Fluorine Chem. 74 (1995) 279.
[12] W.S. Huang, C.Y. Yuan, Synthesis (1996) 511.
[13] K. Uneyama, O. Morimoto, F. Yamashita, Tetrahedron Lett. 36 (1989) 4821.
[14] G. Zeccni, Synlett (1992) 858.
[15] A.F. Hegonty, M. Mullane, J. Chem. Soc., Chem. Commun. (1984) 913.
[16] W. Carpenter, A. Haymaker, D.W. More, J. Org. Chem. 31 (1966) 789.
[17] K. Tamura, H. Mizukami, K. Maeda, H. Watanabe, K. Uneyama, J. Org. Chem. 58 (1993) 32.