Journal of Fluorine Chemistry 132 (2011) 241–243

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Trifluoromethanesulfonamide derivatives of azoles

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ARTICLE INFO

Article history:
Received 21 December 2010
Received in revised form 17 January 2011
Accepted 18 January 2011
Available online 22 January 2011

Keywords:
Amino 1,2,4-triazoles
5-Amino tetrazole
Trifluoromethanesulfonyl fluoride
Sulfonation

ABSTRACT

Trifluoromethanesulfonamide-substituted azoles were synthesized by the reaction of 5-aminotetrazole, 3-amino-1,2,4-triazole and 3,5-diamine-1,2,4-triazole with trifluoromethanesulfonyl fluoride to prepare only monosubstituted compounds. All the compounds were fully characterized using (^{1}H, ^{19}F, ^{13}C) NMR spectroscopy, mass spectrometry (MS), and elemental analysis.

1. Introduction

There continues to be significant interest in trifluoromethanesulfonamides as they play key roles in pharmaceutical and agrochemical industries [1]. Apart from these useful applications, condensation reactions of trifluoromethanesulfonamides with carbonyl compounds lead to various heterocyclic compounds [2]. Sulfonylation of substituted and unsubstituted amines with trifluoromethanesulfonyl halide or trifluoromethanesulfonic anhydride in the presence of a base is carried out for the synthesis of the corresponding trifluoromethanesulfonamides [3]. A large number of trifluoromethanesulfonamidophenyl-substituted compounds have been found to exhibit anti-inflammatory [3,4] and anticonvulsant properties [5] which have enhanced their use in the research and development of new medicines. Trifluoromethanesulfanilides are also known to show insecticidal and nematicidal properties [6,7]. In addition to their biological properties, N-phenyl-trifluoromethanesulfonamide is used as a commercial reagent for carrying out triflation of amines, phenoxides and enolates [8–10]. Many N-substituted trifluoromethanesulfonamides which contain heterocyclic groups such as pyridinyl, quinolinyl, pyrazolyl, thiazolyl, and benzoxazolyl were found to be active herbicides and plant growth modifiers [11]. Some of these compounds such as N-trifluoromethanesulfonyl-2-aminopyridine have been cited for their anti-microbial activities as their structures show close similarity to sulfa drugs (e.g. sulfapyridine) [12]. Trifluoromethanesulfonyl-3-aminopyrrolidine has been successfully identified as an organocatalyst for Mannich reactions [13].

However, with the exception of the reactions of trifluoromethanesulfonyl chloride or pentafluoroethanesulfonyl chloride with 4-amino-1-ethyl-1H-1,2,3-triazole (or 4-amino-2-ethyl-1H-1,2,3-triazole) to form N-(1(2)-ethyl-1H-1,2,3-triazol-4-yl)trifluoromethanesulfonamide or an inseparable mixture of the mono- and disubstituted products, N-(1-ethyl-1H-1,2,3-triazol-4-yl)pentafluoro-1-ethanesulfonamide and 1-ethyl-4-bis(pentafluoroethylsulfonyl)amino-1H-1,2,3-triazole in methanol solution, no other products with 1,2,3-triazoles have been reported [14,15].

More importantly no trifluoromethanesulfonamides of 1,2,4-triazoles or tetrazoles have been studied. In this work, we have extended the series of heterocyclic N-substituted trifluoromethanesulfonamide compounds by introducing the trifluoromethanesulfonyl moiety into amino- and diamino-1,2,4-triazoles and amino tetrazole in order to form a new family of 1,2,4-triazole and tetrazole trifluorosulfonamides.

2. Results and discussion

The syntheses of trifluoromethanesulfonamides are often accomplished by the reaction of amines with trifluoromethanesulfonyl halides or the corresponding anhydride [14,15]. Sulfonylation of certain anilines with trifluoromethanesulfonic anhydride was found to proceed with the formation of mono- and bis-sulfonamides in varying amounts. Recently it was shown that a slight excess of fluorinated anhydride in the presence of excess of base was adequate for the formation of only mono-sulfonamides [16]. Trifluoromethanesulfonyl fluoride is known to give facile reactions with different amines yielding mono-sulfonamides [17]. In order to introduce the trifluoromethanesulfonyl moiety into

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doi:10.1016/j.jfluchem.2011.01.007

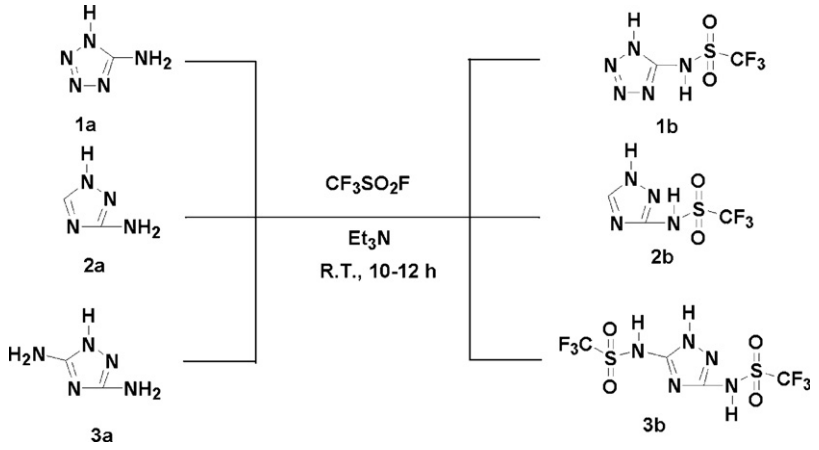

Fig. 1. Reactions of trifluoromethanesulfonyl fluoride with amino-substituted tetrazole and amino and diamino 1,2,4-triazoles.

triazoles and tetrazoles, sulfonylation reactions of 5-amino tetrazole (**1a**), 3-amino-1,2,4-triazole (**2a**) and 3,5-diamino-1,2,4-triazole (**3a**) with trifluoromethanesulfonyl fluoride were performed in the presence of an excess of triethylamine in acetonitrile at room temperature for 10–12 h with constant stirring (Fig. 1). The corresponding N-substituted mono trifluoromethanesulfonamino tetrazole [5-(trifluoromethanesulfonylamino)-1H-tetrazole] and 1,2,4-triazoles [3-(trifluoromethanesulfonylamino)-1H-1,2,4-triazole and 3,5-bis(trifluoromethanesulfonylamino)-1H-1,2,4-triazole] (**1b–3b**) were obtained in good yields. Under all conditions tried, formation of bis-sulfonamides did not occur; mono-sulfonamides were the sole products. The reaction products could be easily separated using standard procedures.

These new substituted azoles, prepared in acetonitrile in the presence of excess base, were obtained in ≥65% yields (melting points between 224 and 245 °C) which are much superior to the 24% yield obtained in the reaction of 1-ethyl-1H-1,2,3-triazole with trifluoromethanesulfonyl chloride in anhydrous methanol to form N-(1-ethyl-1H-1,2,3-triazol-4-yl)trifluoromethanesulfonamide (m.p. 133–135 °C) but measurably poorer than 89% obtained when trifluoromethanesulfonyl anhydride was allowed to react with 1H-1,2,3-benzotriazole to form 1-trifluoromethylsulfonyl-1,2,3-benzotriazole (m.p. 35 °C) in methylene chloride [14,15]. The melting points of the substituted tetrazole and 1,2,4-triazoles are significantly higher than those of the 1,2,3-triazole derivatives due in part to the presence of the ethyl substituent in the latter; however, this behavior is typical of the 1,2,4-triazole isomer vis-à-vis the 1,2,3-triazole analogue with contiguous nitrogen atoms.

3. Conclusions

In conclusion, reactions of trifluoromethanesulfonyl fluoride with 5-aminotetrazole, 3-amino-1,2,4-triazole and 3,5-diamine-1,2,4-triazole led to N-substituted trifluoromethanesulfonamide azoles (**1b–3b)** when carried out in the presence of triethylamine. Only mono-heterocylic N-substituted trifluoromethanesulfonamides were formed.

4. Experimental

Trifluoromethanesulfonyl fluoride was a gift from 3 M. 5-Amino tetrazole, 3-amino 1,2,4-triazole, and 3,5-diamino-1,2,4-triazole were obtained from Acros. All other chemicals were purchased from Aldrich or Acros and were used as received. Acetonitrile was dried using calcium hydride. A conventional Pyrex glass vacuum system equipped with a Heise-Bourdon tube gauge was used to handle gaseous and volatile compounds. Quantities of volatile materials were determined by PVT measurements assuming ideal gas behavior. A Bruker 300 MHz AMX nuclear magnetic resonance spectrometer was used to record ^{1}H, ^{13}C, and ^{19}F NMR spectra at 300.1, 75.5, and 282.4 MHz, respectively, with chemical shifts reported in ppm relative to appropriate standards – $(CH_3)_4Si$ for ^{1}H and ^{13}C nuclei, and $CFCl_3$ for ^{19}F nuclei. All NMR spectra were obtained using Me_2SO[d6] as solvent and locking solvent. Mass spectra (MS) were obtained by using direct injection with a solid probe (EI) on a Shimadzu GC–MS QP5050. DSC measurements were recorded on a TA Q10 instrument in the range of 40–400 °C at 5 °C min^{-1}. Elemental analyses (EA) data were obtained on an Exeter CE440 elemental analyzer.

4.1. General procedure for the preparation of N-substituted trifluoromethylsulfonamide azoles from sulfonylation reactions of amino azoles

All reactions were carried out on a 1.0–1.5 mmol scale under vacuum. A variety of amino azoles (**1a–3a)** were dissolved in 10–15 mL of dry acetonitrile in a 50 mL Pyrex tube equipped with a Teflon stopcock and magnetic stirring bar. Triethylamine was added in large excess (2–3 mL). By using vacuum line techniques, the required amounts of trifluoromethanesulfonyl fluoride were measured and transferred into the Pyrex reactor by condensing at −196 °C. The reaction mixture was allowed to warm to 25 °C and stirring was continued for 10–12 h. After ensuring the completion of the reaction by measuring the fluorine NMR, the solvent and excess triethylamine were first removed using a rotary evaporator and then finally under vacuum. The residue was taken up in ethyl acetate (40–50 mL). After washing (3 × 3–5 mL) with water, the organic solution was dried over sodium sulfate, and the solvent was evaporated in vacuum to leave the desired product.

4.2. Preparation of 5-(trifluoromethanesulfonylamino)-1H-tetrazole (1b)

The reaction was carried out by treatment of 5-aminotetrazole (0.08 g, 1 mmol) and triethylamine (excess ~2–3 mL) with trifluoromethanesulfonyl fluoride (1.5 mmol) in acetonitrile (10–15 mL). The product was obtained as white solid. Yield: 65%; m.p. 224 °C; ^{19}F NMR: δ −77.8 ppm (s, CF_3); ^{1}H NMR: 12.49 (brs, 1H; N–H); ^{13}C NMR: 142.3 (1C), 118.7 ppm (quart, J(C,F) = 323.7 Hz, 1C);

MS (solid probe) (EI): m/z (%): 217 $[M]^+$ (4); elemental analysis calcd (%) for $C_3H_3N_5F_3O_2S$ (217.13): C 11.06, H 0.93, N 32.25; found: C 10.69, H 0.95, N 32.34.

4.3. Preparation of 3-(trifluoromethanesulfonylamino)-1H-1,2,4-triazole (2b)

The procedure is same as for **1b** except that 3-amino-1,2,4-triazole was used as the azole. White solid. Yield: 68%; m.p. 233 °C; ^{19}F NMR: δ −78.1 ppm (s, CF_3); ^{1}H NMR: 8.40 (s, 1H; C–H), 12.56 (brs, 1H; N–H); ^{13}C NMR: 151.1 (1C), 140.6 (1C), 121.3 ppm (quart, J(C,F) = 324.5 Hz, 1C); MS (solid probe) (EI): m/z (%): 216 $[M]^+$ (16); elemental analysis calcd (%) for $C_3H_3N_4F_3O_2S$ (216.14): C 16.67, H 1.40, N 25.92; found: C 16.54, H 1.32, N 25.78.

4.4. Preparation of 3,5-bis(trifluoromethanesulfonylamino)-1H-1,2,4-triazole (3b)

The procedure is same as **1b** except that 3,5-diamino-,2,4-triazole was used as the azole. White solid. Yield 68%; m.p. 245 °C; ^{19}F NMR: δ −79.3 ppm (s, CF_3); ^{1}H NMR: 12.45–12.62 (brs, 2H; N–H); ^{13}C NMR: 151.5 (1C), 139.8 (1C), 119.8 ppm (quart, J(C,F) = 322.3 Hz, 1C), 120.5 ppm (quart, J(C,F) = 323.6 Hz, 1C); MS (solid probe) (EI): m/z (%): 364 $[M+1]^+$ (4); elemental analysis calcd (%) for $C_4H_3N_4F_6O_4S_2$ (363.21): C 13.23, H 0.83, N 19.28; found: C 13.34, H 0.80, N 18.89.

Acknowledgements

The authors gratefully acknowledge the support of DTRA (HDTRA1-07-1-0024), and ONR (N00014-10-1-0097).

References

[1] (a) J. Wagner, B.S. Avvaru, A.H. Robbins, A. Scozzafava, C.T. Supuran, R. McKenna, Bioorg. Med. Chem. 18 (2010) 4873–4878;
(b) G.W. Rewcastle, S.A. Gamage, J.U. Flanagan, A.G. Giddens, U.S. Pat. Appl. 20,100,249,099 (2010).;
(c) D.C. Kvam, U.S. Pat. Appl. 4,824,866 (1988).
(d) L. Wingard, T. Brody, J. Larner, A. Schwartz, Human Pharmacology. Mosbey-Year Book, 1991;
(e) K.N. Winzenberg, A.G. Meyer, Q. Yang, A.G. Riches, G. Andrew, U.S. Pat. Appl. 20,070,238,700 (2007).;
(f) A.G. Meyer, K.N. Winzenberg, D.G. Sawutz, A.J. Liepa, U.S. Pat. Appl. 20060281695, 2006063841 (2006).;
(g) G.G.I. Moore, J.K. Harrington, U.S. Pat. Appl. 3689553 (1972)..
[2] B.A. Shainyan, V.I. Meshcheryakov, Mini-Rev. Org. Chem. 6 (2009) 66–77.
[3] J.K. Harrington, D.C. Kvam, A. Mendel, J.E. Robertson, U.S. Pat. Appl. 3,758,688 (1969).
[4] (a) J. Delarge, B. Pirotte, J. Dogne, L.X. De Leval, F. Julemont, U.S. Pat. Appl. 20,050,020,642 (2003).
(b) J.H. Musser, A.F. Kreft, A.H.W. Reinhold, D.M. Kubrak, R.P. Carlson, J. Chang, J.M. Hand, J. Med. Chem. 32 (1989) 1176–1183.
[5] P.T. Flaherty, T.D. Greenwood, A.L. Manheim, J.F. Wolfe, J. Med. Chem. 39 (1996) 1509–1513.
[6] T. Mori, Y. Takada, M. Hatakoshi, N. Matsuo, Biosci. Biotechnol. Biochem. 68 (2004) 425–427 (and references cited therein).
[7] R.O. McCracken, A.W. Carr, W. Stillwell, K.B. Lipkowitz, R. Boisvenue, G.O.P. O'Doherty, D.I. Wickiser, Biochem. Pharm. 45 (1993) 1873–1880.
[8] J. Hendrickson, R. Bergeron, Tetrahedron Lett. 14 (1973) 4607–4610.
[9] J. McMurry, W. Scott, Tetrahedron Lett. 24 (1983) 979–982.
[10] W. Wulff, G. Peterson, W. Bauta, K.-S. Chan, K. Faron, S. Gilbertson, R. Kaesler, D. Yang, D.C.J. Murray, Org. Chem. 51 (1986) 277–279.
[11] (a) E.V. Kondrashov, E.V. Rudyakova, I.B. Rozentsveig, I.V. Ushakova, G.N. Rozentsveig, V.A. Savosik, K.A. Chernyshev, L.B. Krivdin, G.G. Levkovskaya, Russ. J. Org. Chem. 44 (2008) 86–94;
(b) R.E. Banks, U.S. Pat. Appl. 90-576291 (1993).;
(c) J.K. Harrington, D.C. Kvam, A. Mendel, J.E. Robertson, U.S. Pat. Appl. 3923810, 3920690 (1975).;
(d) J.K. Harrington, D.C. Kvam, A. Mendel, J.E. Robertson, U.S. Pat. Appl. 3758490 (1973).
[12] R. Toscano, M. Moya, C. Amabile, G. Penieres, C. Alvarez, Heteroatom Chem. 11 (2000) 308–312.
[13] M. Pouliquen, J. Blanchet, M.-C. Jerome, J. Lasne, Rouden, Org. Lett. 10 (2008) 1029–1032.
[14] V.I. Meshcheryakov, B.A. Shainyan, Russ. J. Org. Chem. 40 (2004) 390–396.
[15] V.I. Meshcheryakov, B.A. Shainyan, L.L. Tolstikova, A.I. Albanov, Russ J. Org. Chem. 39 (2003) 1517–1521.
[16] A. Greenfield, C. Grosanu, Tetrahedron Lett. 49 (2008) 6300–6303.
[17] R.D. Trepka, J.W. McConville, J. Org. Chem. 40 (1975) 428–431.