Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Fluorine Chemistry 124 (2003) 111–113
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

Direct microwave promoted trifluoroacetylation of aromatic amines with trifluoroacetic acid

José Salazar*, Simón E. López, Oscar Rebollo

Departamento de Química, Universidad Simón Bolívar, Valle de Sartenejas, Baruta, Caracas 1080-A, Apartado 89000, Venezuela

Received 13 June 2003; received in revised form 2 July 2003; accepted 17 July 2003

Abstract

A simple microwave-promoted procedure has been developed for the direct preparation of trifluoroacetanilides. An equimolar mixture of substituted anilines and trifluoroacetic acid was microwave irradiated at short reaction times, giving the corresponding anilides in high yields and purity.

Keywords: Trifluoroacetylation; Trifluoroacetic acid; Trifluoroacetanilides

1. Introduction

Trifluoroacetylation has become a common and useful procedure for the protection of amines [1]. There are a number of reagents and methods for the trifluoroacetylation of amines, these include the use of trifluoroacetic anhydride, [2] *S*-ethyl trifluorothioacetate [3], ethyl trifluoroacetate [4–6], *N*-(trifluoroacetyl)imidazole [7], 2-[(trifluoroacetyl)-oxy]pyridine (TFAP) [8], trifluoroacetyl triflate [9,10], trifluoroacetyl benzotriazole [11], *N*-(trifluoroacetyl)succinimide [12], $TiO(CF_3COO)_2$ [13], and sodium trifluoroacetate [20]. However, many of them suffered from disadvantages, such as the low boiling point, volatility and corrosive nature of the widely employed trifluoroacetic anhydride, the moisture sensitivity of *N*-(trifluoroacetyl)imidazole or the bad smelling by-product ethanodiol generated from the reaction with *S*-ethyl trifluoroacetate. Recently, a convenient method has been developed for the selective 4-dimethylamino-pyridine-catalyzed trifluoroacetylation of anilines with ethyl trifluoroacetate [6], but an important limitation of this methodology arises from its longer reaction times, which are around 24 h.

During the course of our investigation toward the synthesis of novel fluorinated heterocyclic compounds [14], we needed to prepare some trifluoroacetylated anilides. In view of the usefulness of microwave irradiation as a tool for organic synthesis [15], we decided to explore the direct trifluoroacetylation of anilines with trifluoroacetic acid under microwave irradiation. A report on the preparation of amides from a microwave-mediated reaction between aliphatic amines and aromatic or aliphatic acids has appeared [16].

2. Results and discussion

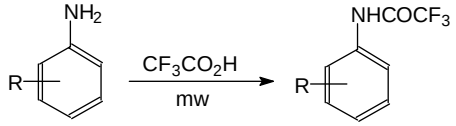
The direct microwave-mediated reaction of substituted anilines **1a–j** with trifluoroacetic acid is depicted on Scheme 1. In order to examine the scope of this methodology, we employed a variety of electron-withdrawal and electron-donating groups in different positions of the aniline aromatic ring (Table 1). Standard conditions were established varying the reaction time and the microwave power source (Table 1). It is worth mentioning that all the trifluoroacetanilides **2a–j** obtained are stable at high temperature and therefore the dielectric heating has not caused any decomposition problem. The reaction was carry out without solvent, with an equal molar amount of the corresponding aniline and trifluoroacetic acid, and thus proceeds through the aniline trifluoroacetate salt. The reaction was very clean and no by-products were detected. The workup procedure involves only a simple filtration of the precipitated anilide followed by washing with water. All the products were obtained in high yields and purity, as indicated by NMR analysis. Also, the ^{19}F NMR data for all synthesized compounds are reported.

* Corresponding author. Tel.: +58-2-129063986; fax: +58-2-129063961.
E-mail address: jsalazar@usb.ve (J. Salazar).

0022-1139/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0022-1139(03)00198-2

Table 1

Compound	R	Melting point (°C)	Yield (%)	MW power (Watts)	Irradiation time (s)
2a	H	85–86 (Lit. 87–88) [17]	90	180	30
2b	4–Cl	119–121 (Lit. 123–124) [17]	95	180	30
2c	4–Br	122–123 (Lit. 124–126) [18]	85	180	30
2d	4–F	108–109 (Lit. 110–111) [17]	92	180	30
2e	4–OMe	110–111 (Lit. 113–115) [17]	87	180	30
2f	3–Cl	67–68 (Lit. 66–68) [17]	95	180	30
2g	4–Me	106–107 (Lit. 109.5–111) [17]	92	180	30
2h	2–OMe	47–48 (Lit. 50.0–50.5) [19]	80	300	60
2i	3–OMe	72–73 (Lit. 71–72) [17]	87	180	30
2j	2–Cl	40–41	80	300	60



1 a-j **2 a-j**

Scheme 1.

In conclusion, we have developed a new convenient microwave-promoted trifluoroacetylation of anilines. The simplicity of the procedure, short reaction times, high yields of products and the use of unexpensive, affordable reagents, render this method particularly attractive to organic chemists.

3. Experimental

Melting points were determined in a Thomas–Hoover (UNIMELT) capillary melting point apparatus and are uncorrected. MW irradiation was made with a GoldStar Microwave conventional oven, model MA-690M (600 W, 2450 MHz). NMR spectra were obtained on a JEOL Eclipse Plus spectrometer in deuterated chloroform, operating at 400 MHz (^{1}H, internal standard TMS) and 376 MHz (^{19}F, internal standard $CFCl_3$); δ values in ppm relative to the internal standard are given. The high resolution mass spectra (EI-HRMS) were obtained on a JEOL JMS-AX505WA mass spectrometer. Silica gel plates ALUGRAM® SIL G/UV$_{254}$ (Macherey-Nagel GmbH & Co., Germany) were used for TLC testing. Reagents were obtained from Aldrich (Milwaukee, MI, USA) or Merck (Darmstadt, Germany) and used without further purification.

3.1. General experimental procedures

3.1.1. General procedure for the preparation of N-(phenyl-substituted)-2,2,2-trifluoro-acetamides **2a–j**

A mixture of the corresponding aniline **1a–j** (3.0 mmol) and trifluoroacetic acid (3.0 mmol) in a 25 ml capped conical flask was put into a teflon cylinder container (5 cm diameter × 15 cm height) and microwave irradiated at three stages (10–20 seg each) to complete the indicated time. After been cooled to room temperature, to the resulting mixture was added an amount of ice-water to precipitate the products which were then filtered and washed with cool water. All products were obtained in high purity as indicated by TLC and ^{1}H NMR analysis.

*3.1.1.1. N-phenyl-2,2,2-trifluoro-acetamide (**2a**).* 0.50 g (90% yield), crystals, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.26 (m, 1H, H-arom), 7.39 (t, 2H, $J = 8.8$ Hz, H-arom), 7.56 (d, 2H, $J = 8.0$ Hz, H-arom), 7.95 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.61 (s, 3F, CF_3).

*3.1.1.2. N-(4-chlorophenyl)-2,2,2-trifluoro-acetamide (**2b**).* 0.63 g (95% yield), crystals, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, 2H, $J = 9.1$ Hz, H-arom), 7.53 (d, 2H, $J = 9.1$ Hz, H-arom), 7.90 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.56 (s, 3F, CF_3).

*3.1.1.3. N-(4-bromophenyl)-2,2,2-trifluoro-acetamide (**2c**).* 0.68 g (85% yield), crystals, ^{1}H NMR (400 MHz, $CDCl_3$): 7.47 (d, 2H, $J = 9.1$ Hz, H-arom), 7.51 (d, 2H, $J = 9.1$ Hz, H-arom), 7.94 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.71 (s, 3F, CF_3).

*3.1.1.4. N-(4-fluorophenyl)-2,2,2-trifluoro-acetamide (**2d**).* 0.57 g (92% yield), crystals, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06–7.12 (m, 2H, H-arom), 7.52-7.55 (m, 2H, H-arom), 7.89 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.56 (s, 3F, CF_3), −114.58 (s, 1F, F-arom).

*3.1.1.5. N-(4-methoxyphenyl)-2,2,2-trifluoro-acetamide-(**2e**).* 0.54 g (87% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H, OCH_3), 6.90 (d, 2H, $J = 8.8$ Hz, H-arom), 7.46 (d, 2H, $J = 8.8$ Hz, H-arom), 7.87 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.51 (s, 3F, CF_3).

*3.1.1.6. N-(3-chlorophenyl)-2,2,2-trifluoro-acetamide (**2f**).* 0.63 g (95% yield), crystals, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, 1H, $J = 8.1$ Hz, H-arom), 7.31 (t, 1H, $J = 8.1$ Hz, H-arom), 7.42 (d, 1H, $J = 8.1$ Hz, H-arom), 7.66 (t, 1H, $J = 1.8$ Hz, H-arom), 8.08 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.44 (s, 3F, CF_3).

*3.1.1.7. N-(4-methylphenyl)-2,2,2-trifluoro-acetamide (**2g**).* 0.55 g (92% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 7.18 (d, 1H, $J = 8.4$ Hz, H-arom), 7.43 (d, 1H, $J = 8.4$ Hz, H-arom), 7.92 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −76.15 (s, 3F, CF_3).

*3.1.1.8. N-(2-methoxyphenyl)-2,2,2-trifluoro-acetamide (**2h**).* 0.49 g (80% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H, OCH_3), 6.93 (dd, 1H, $J = 1.1$ Hz, J=8.1 Hz, H-arom), 7.00 (ddd, 1H, $J = 1.1$ Hz, $J = 8.1$ Hz, $J = 8.1$ Hz, H-arom), 7.16 (ddd, 1H, $J = 1.1$ Hz, $J = 8.1$ Hz, $J = 8.1$ Hz, H-arom), 7.23–7.27 (m, 2H, H-arom), 8.30 (dd, 1H, $J = 8.1$ Hz, $J = 8.1$ Hz, H-arom), 8.57 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.71 (s, 3F, CF_3). HRMS: Calcd. for $C_9H_8F_3NO_2$: 219.0507. Found: 218.9746.

*3.1.1.9. N-(3-methoxyphenyl)-2,2,2-trifluoro-acetamide (**2i**).* 0.53 g (87% yield), crystals, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 6.78 (dd, 1H, H-arom, $J = 2.6$ Hz, $J = 8.0$ Hz), 7.04 (dd, 1H, H-arom, $J = 2.6$ Hz, $J = 8.0$ Hz), 7.26–7.30 (m, 2H, H-arom), 7.90 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.66 (s, 3F, CF_3).

*3.1.1.10. N-(2-chlorophenyl)-2,2,2-trifluoro-acetamide(**2j**).* 0.53 g (80% yield), crystals, ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.18 (ddd, 1H, H-arom, $J = 1.4$, $J = 7.7$ Hz), 7.34 (ddd, 1H, H-arom, $J = 1.4$ Hz, $J = 7.7$ Hz), 7.44 (dd, 1H, H-arom, $J = 1.4$ Hz, $J = 7.7$ Hz), 8.31 (dd, 1H, H-arom, $J = 1.4$ Hz, $J = 7.7$ Hz), 8.56 (bs, 1H, NH). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.46 (s, 3F, CF_3). HRMS: Calcd. for $C_8H_5ClF_3NO$: 223.0012. Found: 223.0097.

Acknowledgements

This work was supported in part from a financial aid given by Decanato de Investigaciones (Universidad Simón Bolívar, Caracas) and Unidad de Laboratorios (Universidad Simón Bolívar, Caracas). The authors thank Laboratorio de RMN of the Departamento de Química-Universidad Simón Bolívar (BID-CONICIT, Project QF13) for spectral facilities and Miss Indira Vera for her technical assistance. Also, to Professor Julio Herrera (USB) for his collaboration with HRMS.

References

[1] T.W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, Wiley, New York, 1991, p. 353.
[2] (a) E.J. Broune, S.H. Henry, C.E.M. Tatlow, J.C. Tatlo, J. Chem. Soc. (1952) 4014.;
(b) L.F. Fieser, M. Fieser, Reagents for Organic Synthesis, Wiley, New York, 1967, p. 1221.
[3] E.E. Schallenberg, M. Calvin, J. Am. Chem. Soc. 77 (1955) 2779.
[4] T.J. Curphey, J. Org. Chem. 44 (1979) 2805.
[5] D. Xu, K. Prasad, O. Repic, T.J. Blacklock, Tetrahedron Lett. 36 (1995) 7357.
[6] M. Prashad, B. Hu, O. Repiè, T.J. Blacklock, Tetrahedron Lett. 41 (2000) 9957.
[7] H.A. Staab, G. Wahner, Angew. Chem. 72 (1960) 35.
[8] T. Kaumi, M. Shimada, T. Morita, A. Kitajima, Bull. Chem. Soc. Jpn. 63 (1990) 2252.
[9] T.R. Forbus Jr., J.C. Martin, J. Org. Chem. 44 (1978) 313.
[10] T.R. Forbus Jr., S.L. Taylor, J.C. Martin, J. Org. Chem. 53 (1988) 3108.
[11] A.R. Katritzky, B. Yang, D. Semenzin, J. Org. Chem. 62 (1997) 726.
[12] A.R. Katritzky, B. Yang, G. Qiu, Z. Zhang, Synthesis (1) (1999) 55.
[13] N. Iranpoor, B. Zeynizadeh, J. Chem. Res (S). (1999) 124.
[14] S.E. López, O. Rebollo, J. Salazar, C. Yánez, J.E. Charris, J. Fluorine Chem. 120 (2003) 71.
[15] (a) R.A. Abramovitch, Org. Prep. Proc. Int. 23 (1991) 685;
(b) S. Caddick, Tetrahedron 51 (1995) 10403;
(c) A. Loupy, A. Ptit, J. Hamelin, F. Texier-Boullet, P. Jacqualt, D. Mathe, Synthesis (1998) 1213;
(d) R.S. Varma, Green Chem. (1993) 43;
(e) L. Perreux, A. Loupy, Tetrahedron 57 (2001) 9199;
(f) P. Lidstrom, J. Tierney, J. Wathey, Tetrahedron 57 (2001) 9225;
(g) N.F.K. Kaiser, U. Bremberg, M. Larhed, C. Moberg, A. Halberg, Angew. Chem., Int. Ed. 39 (2000) 3595;
(h) J. Westman, Org. Lett. 3 (2001) 3745;
(i) C.T. Brain, S.A. Brunton, Synlett (2001) 382.
[16] M.P. Vásquez-Tato, Synlett (1993) 506.
[17] C.E. Stauffer, J. Am. Chem. Soc. 94 (1972) 7887.
[18] S.W. Wright, D.L. Hageman, L.D. McClure, J. Org. Chem. 59 (1994) 6095.
[19] M. Pailer, W.J. Hubsch, Monatsch. Chem. 97 (1966) 1541.
[20] Q.-Z. Zhou, Z.-C. Chen, Synth. Commun. 30 (2000) 3189.