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Short communication

Trifluoroacetylation of arylamines using poly-phosphoric acid trimethylsilylester (PPSE)

Simón E. López [a,*], Yelsi Pérez [a], Jelem Restrepo [a], José Salazar [a], Jaime Charris [b]

[a] *Laboratorio de Química Medicinal y Heterociclos, Departamento de Química, Universidad Simón Bolivar, Valle de Sartenejas, Baruta, Caracas 1080-A, Apartado 89000,Venezuela*
[b] *Laboratorio de Síntesis Orgánica, Facultad de Farmacia, Universidad Central de Venezuela, Caracas, Venezuela*

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Abstract

A new, simple and useful procedure is described for the trifluoroacetylation of arylamines using trifluoroacetic acid and poly-phosphoric acid trimethylsilylester (PPSE) as the condensation agent.
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Keywords: Trifluoroacetylation; Trifluoroacetic acid; PPSE

1. Introduction

Trifluoroacetylation of amines, a common procedure for this functional group protection [1], has been achieved by different methodologies which include a variety of reagents and conditions such as trifluoroacetic anhydride [2], *S*-ethyl trifluorothioacetate [3], *N*-(trifluoroacetyl)imidazol [4], ethyl trifluoroacetate [5–7], trifluoroacetyl-triflate [8,9], 2-[(trifluoroacetyl)-oxy]pyridine (TFAP) [10], trifluoroacetyl benzotriazole [11], *N*-(trifluoroacetyl)succinimide [12], $TiO(CF_3COO)_2$ [13], and sodium trifluoroacetate [14]. Other agents are the *S*-dodecyl trifluorothioacetate [15] and *N*-methylbis (trifluoroacetamide) named as MBTFA [16], useful for the GC–MS determination of aminoacids and biological active amines, respectively. Recently, we have described a direct microwave promoted trifluoroacetylation of anilines with trifluoroacetic acid [17]. By other hand, poly-phosphoric acid trimethylsilylester (PPSE, Fig. 1), a stable, viscous and colorless liquid firstly prepared by Imamoto in 1981 [18], has been used to promote several different reactions such as dehydration of amides into nitriles [19], conversion of alcohols into iodides [20], aldol condensations [21], Beckmann rearrangements [22], Pummerer rearrangements [23], Meyer–Schuster rearrangements [24], cyclodehydrations leading to heterocycles [25], and Friedel–Crafts acylations with carboxylic acids under strenuous [26] or mild reaction conditions [27]. As seen above, most of those reactions implicate a key dehydration step made possible by the action of PPSE. In view of our interest in the development of new methodologies for the trifluoroacetylation of functional groups and the synthesis of trifluoromethyl substituted heterocycles, we now decided to explore the trifluoroacetylation of arylamines using trifluoroacetic acid and PPSE as the condensation agent.

2. Results and discussion

The direct trifluoroacetylation of arylamines **1a–g** using trifluoroacetic acid and PPSE is depicted on Scheme 1. In order to optimize the methodology, we decided to study how changes on the preparation of the condensating agent, solvent and temperature affect the trifluoroacetylation of *p*-toluidine **1a** (Table 1). Temperature seems to be critical for this reaction; expecting higher yields at a prolonged time we decided to extend reaction times up to 19 h (entry 5), however, lower yields were obtained, which means the condensating agent is somehow affected at high temperatures and long reaction times.

The methodology was thus applied to other anilines (Table 2) obtaining good yields but observing the reaction seemed to be also affected by the esteric effect, cause *orto*-substituted anilines gave lower yields. Encourage by those results and that on the successful use of PPSE for the

* Corresponding author. Tel.: +58 212 9063986; fax: +58 212 9063961.
E-mail address: slopez@usb.ve (S.E. López).

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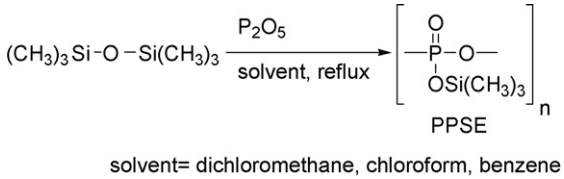
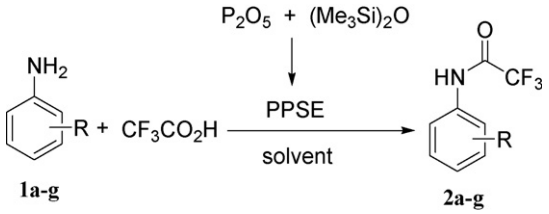


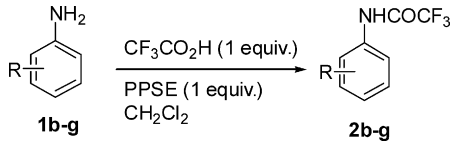
Fig. 1. Preparation of poly-phosphoric acid trimethylsilylester (PPSE).



Scheme 1.

construction of heterocycles [18(c)], we also made an exploration for the preparation of a 3-trifuoromethylated benzothiadiazine (Scheme 2). The 2-amino-5-bromo-benzenesulfonamide **1h**, was reacted with trifluoroacetic acid and 5 equiv. of PPSE giving a mixture of the expected trifluoromethyl heterocycle **3** and the uncyclic precursor trifluoroacetylated benzenesulfonamide **2h** in an almost 6:4 ratio, respectively. This result was promising when compared with a microwave attempted reaction using the same benzenesulfonamide and 1 equiv. of tryfluoroacetic acid. Because good yields were obtained from our reported procedure for the microwave promoted trifluoroacetylation on *orto*-substituted anilines [17], it was reasonable to try the same methodology for **1h**; however, only the starting material was detected using similar reaction conditions. It means, despite the yields of trifluoroacetylation are lower than those described for the microwave reaction, the PPSE promoted trifluoroacetylation of arylamines should also be applied for the synthesis of trifluoromethyl heterocycles. Although the mechanism of this reaction is not clear in detail, it has been postulated that an amide or maybe a silylated amide derivative can be assumed as the intermediate of this reaction, previous to the heterocyclization step for the preparation of some 3-alkyl and 3-aryl *2H*-1,2,4-benzothiadiazine 1,1-dioxides [30]. The developed procedure represents a new, simple and useful alternative for the trifluoroacetylation of arylamines and even for the direct preparation of a 3-trifluoromethyl-benzothiadiazine, a methodology which will be improved for the preparation of other trifluorometyl-substituted heterocycles.

Table 2
Trifluoroacetylation of arylamines using PPSE and trifluoroacetic acid



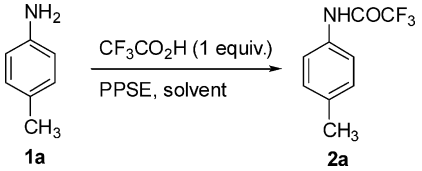
Compound	Melting point (°C)	R	Yield (%)
2b	120–121 (Lit. 123–124) [28]	4-Cl	74
2c	110–111 (Lit. 113–115) [28]	4-OMe	62
2d	122–123 (Lit. 124–126) [29]	4-Br	83[a]
2e	40–41 (Lit. 40–41) [17]	2-Cl	20
2f	92–94	2,4-$(Me)_2$	21
2g	61–62 (Lit. 62–64) [28]	3-Me	73

[a] 5 equiv. of PPSE were needed, reaction time was prolonged up to 12 h.

3. Experimental

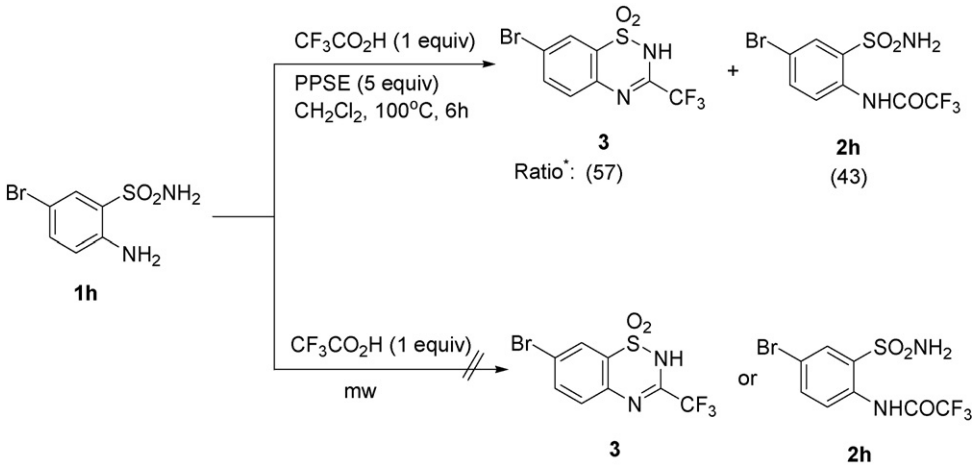
Melting points were determined in a Fischer–Johns micro hot-stage apparatus and are uncorrected. NMR spectra were obtained on a JEOL Eclipse Plus spectrometer in deuterated chloroform or hexadeuterated dimethylsulfoxide, operating at 400 MHz (^{1}H, internal standard TMS) and 376 MHz (^{19}F, internal standard $CFCl_3$); δ values in ppm relative to the internal standard are given.

Table 1
Optimization conditions for the trifluoroacetylation of p-toluidine **1a**



Entry	P_2O_5 (equiv.)	$(Me_3Si)_2O$ (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	10	10	Benzene	120	1	53
2	10	10	Dichloromethane	60	1	16
3	5	5	Dichloromethane	120	6	51
4	5	5	Dichloromethane	120	19	42
5	1	1	Dichloromethane	120	19	18
6	1	1	Dichloromethane	100	5	68[a]
7	1	1	Dichloromethane	80	3	61
8	1	1	Dichloromethane	80	3	40[b]

[a] Pyridine (1 equiv.) was added to the reaction mixture.
[b] mp 107–108 °C (Lit. 109.5–111) [28].



Scheme 2. (*)Determined by ^{1}H NMR, the mixture couldn't be separated by column chromatography, although it was effectively separated by fractional crystallisation from EtOH–H_2O.

The IR spectra were recorded as potassium bromide discs using a Shimadzu CW/IR 470 spectrometer. Mass spectra (GC–MS) were recorded using a gas chromathograph Hewlet Packard 5890 Serie I coupled to a mass detector (EI, 60 eV) Hewlet Packard 5917 A. Microanalyses of new synthesized compounds were performed by Atlantic Microlab Inc. (Norcross, GA, USA); results fell in the range of ±0.4% of the required theoretical values. Silica gel plates ALUGRAM® SIL G/UV254 (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. The 5-bromo-2-amino-benzenesulfonamide **1h** was prepared according to the literature procedure [31]. Microwave irradiation was made with a Goldstar Microwave conventional oven, model MA-690M (600W, 2450 MHz).

3.1. Experimental procedures

3.1.1. General procedure for the preparation of polyphosphoric acid trimethylsilylester (PPSE) in solution

A mixture of phosphorus pentoxide (2.83 g; 20 mmol), hexamethyldisiloxane (4 mL; 20 mmol) and dichloromethane (20 mL) or benzene (20 mL) is refluxed at 80 °C under an argon atmosphere for 2 h, until the solution is clear. Solvent was removed under vacuo and the resulting yellowish liquid was diluted with dicholoromethane (20 mL) or benzene (20 mL). The volatile solution was used for the condensation step with trifluoroacetic acid, and could be stored in a refrigerator for at least 2 weeks without a considerable decrease in its condensation properties.

3.1.2. General procedure for the preparation of N-(phenyl-substituted)-2,2,2-trifluoro-acetamides ***2a–g*** *using trifluoroacetic acid and PPSE as the condensating agent. optimized methodology*

To a solution of PPSE (2 mL, prepared as above) was added trifluoroacetic acid (2 mmol) and the solution heated at 120 °C for 2 h, then allowed to stand until room temperature was reached. The corresponding aniline (2 mmol) was added as a dicloromethane solution (1 mL) dropped with a syringe at room temperature. After addition was completed the reaction mixture was heated at 100 °C for 5 h. The resulting solution was allowed to stand at room temperature, ice cold water was added, the organic layer extracted three times with dichloromethane (3 × 3 mL), dried over anhydrous sodium sulphate and evaporated to give the indicated trifluoroacetamides, which were recrystallised from ethanol-water.

*3.1.2.1. N-(2,4-dimethylphenyl)-2,2,2-trifluoroacetamide (**2f**).* 0.09 g (21% yield), beige solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71(bs, 1H, NH), 7.55 (d, 1H, *J* = 7.0 Hz, H-arom), 7.05 (m, 2H, H-arom), 2.31 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). IR (KBr, cm^{-1}): 3400, 1762, 1549. MS (EI): *m/z* 217 (M^+). Anal Calcd for $C_{10}H_{10}F_3NO$; C, 55.30; H, 4.64; N, 6.45. Found: C, 55.23; H, 4.69; N, 6.40.

*3.1.2.2. N-(3-methylphenyl)-2,2,2-trifluoroacetamide (**2g**).* 0.3 g (73% yield), white crystals, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (bs, 1H, NH), 7.30 (m, 3H, H-arom), 7.04 (d, 1H, *J* = 7.4 Hz, H-arom), 2.35 (s, 3H, CH_3). IR (KBr, cm^{-1}): 3312, 1769, 1654. MS (EI): *m/z* 203 (M^+). Anal Calcd for $C_9H_8F_3NO$; C, 53.21; H, 3.97; N, 6.89. Found: C, 53.32; H, 3.94; N, 6.91.

3.1.3. Preliminary procedure for the preparation of 7-bromo-3-trifluoromethyl-2H-1,2,4-benzothiadiazine-1,1-dioxide ***3*** *using PPSE*

To a solution of PPSE (10 mL, prepared as above) was added trifluoroacetic acid (2 mmol) and the solution heated at 120 °C for 2 h, then allowed to stand until room temperature was reached. 5-bromo-2-aminobenzenesulfonamide **1h** (0.5 g; 2 mmol) crystals were added at room temperature. After addition was completed, the reaction mixture was heated at 100 °C for 6 h. The resulting mixture was allowed to stand at room temperature, ice cold water was added, the organic layer extracted three times with dichloromethane (3 × 5 mL), dried over anhydrous sodium sulphate and evaporated to give a

violet-like coloured solid (0.42 g). A 57:43 ratio mixture of both 7-bromo-3-trifluoromethyl-2*H*-1,2,4-benzothiadiazine-1,1-dioxide **3** and *2-trifluoroacetamido-5-bromo-benzenesulfonamide* **2h** was detected by ^{1}H NMR analysis. Compounds were separated by fractional crystallisation from EtOH–H_2O, cause they couldn't be separated by column chromatography.

*3.1.3.1. 2-Trifluoroacetamido-5-bromo-benzenesulfonamide (**2h**).* 0.18 g (26% yield), white crystals, mp 159–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.21 (bs, 1H, NH), 8.33 (d, 1H, J = 8.8.Hz, 3-H), 8.12 (d, 1H, J = 8.2 Hz, 6-H), 7.76 (dd, 1H, J = 2.2 Hz, J = 8.8 Hz, 4-H), 5.06 (bs, 2H, SO_2NH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ −75.88 (s, 3F, CF_3). IR (KBr, cm^{-1}): 3330, 1760, 1654, 1320, 1175. Anal Calcd for $C_8H_6BrF_3N_2O_3S$; C, 27.68; H, 1.74; N, 8.07. Found: C, 27.74; H, 1.72; N, 8.10.

*3.1.3.2. 7-Bromo-3-trifluoromethyl-2H-1,2,4-benzothiadiazine-1,1-dioxide (**3**).* 0.24 g (37% yield), grey crystals, mp 230–232 °C. ^{1}H NMR (400 MHz, DMSO d_6): δ 12.06 (bs, 1H, SO_2NH), 8.07 (bs, 1H, NH), 7.99 (d, 1H, J = 2.2 Hz, H-arom), 7.88.(dd, 1H, J = 2.2 Hz, J = 8.8 Hz, H-arom), 7.47 (d, 1H, J = 8.8. Hz, H-arom). ^{19}F NMR (376 MHz, DMSO d_6): δ −70.52 (s, 3F, CF_3). IR (KBr, cm^{-1}): 3380, 1625, 1304, 1162. Anal Calcd for $C_8H_4BrF_3N_2O_2S$; C, 29.20; H, 1.23; N, 8.51. Found: C, 29.87; H, 1.25; N, 8.48.

*3.1.4. Attempted microwave condensation of **1h** with trifluoroacetic acid*

A mixture of the benzenesulfonamide **1h** (1 mmol) and trifluoroacetic acid (1 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 four stages, 15 seg each (50% of the MW power) to complete 60 seg. The resulting liquid was cooled at room temperature, which then solidified, ice-cooled water was added, and the solid filtrated and washed several times with water. The ^{1}H NMR and ^{19}F NMR (DMSO d_6) analysis revealed only starting material. Additional MW heating begun the decomposition of the starting material.

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