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Bromination/desilicobromination of silylated monofluoroalkenes using tetrabutylammonium tribromide under microwave conditions

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ABSTRACT

New conditions for the bromination/desilicobromination of silylated monofluoroalkenes using tetrabutylammonium tribromide under microwave conditions are presented. The reaction is fast (20 min) and provide, after the desilicobromination step, the bromofluoroalkene where the replacement of the silyl group is done with retention of configuration with little or no stereochemical erosion. Isomeric enrichment is even observed in one case. Optimization of the reactions conditions and applications to various substrates are reported.

1. Introduction

We recently reported a 5-step sequence for the stereoselective synthesis of tetrasubstituted monofluoroalkenes (**4**) starting from commercially available 2,2,2-trifluoro-1-iodoethane (Fig. 1) [1,2]. One of the key steps of the sequence was the bromination/desilicobromination reaction (**2** → **3**) where the silyl group was replaced by a bromine atom with retention of configuration and a simultaneous isomeric enrichment [1].

Recognizing the importance of the monofluoroalkene motif [3] in medicinal chemistry [4,5], we decided to apply this sequence for the synthesis of fluorinated analogues of bioactive compounds. In that sense, we needed access to compound **6a** that was going to be used as a versatile and key intermediate for our syntheses. Bromination/desilicobromination of **5a** to produce **6a** had been performed previously with success (Fig. 2) [1].

Unfortunately, problems at the bromination step were sometime encountered while repeating this transformation forcing us to investigate novel and more reliable conditions. Herein, we report the use of tetrabutylammonium tribromide (n-Bu_4NBr_3) under microwave conditions for the bromination of silylated monofluoroalkenes. The reaction is fast (20 min) and provide, after the desilicobromination step, the bromofluoroalkene where the replacement of the silyl group is done with retention of configuration with little or no stereochemical erosion. Isomeric enrichment is even observed in one case.

2. Results and discussion

Bromination/desilicobromination of silylated monofluoroalkene **5a** under the original conditions [1,6] gave full conversion with the major product being the desired bromofluoroalkene **6a** (55% isolated yield) along with an unidentified side-product (ca. 31% estimated by ^{19}F NMR of the crude product) (Table 1, entry 1). In addition, no isomeric enrichment was observed. The results varied slightly using different bottles of bromine but in all cases, the side-product was present in significant amounts and the Z/E ratio of the bromofluoroalkene was moderate. Slight variations of the original conditions were also explored. For instance, adding a base (K_2CO_3) in the bromination step led to a cleaner reaction (i.e. side-product free) although the isolated yield was low and the Z/E was nearly identical to the starting silylated alkene (entry 2). Alternatively, using tetrabutylammonium fluoride (TBAF) as the base in the desilicobromination step [7] led to complete decomposition (entry 3). Based on those results, we decided to screen for other reaction conditions that would not rely on using bromine. Directly replacing Br_2 by n-Bu_4NBr_3, a reagent reported as an alternative to Br_2 for various bromination reactions [8], led to no reaction (entry 4). Performing the bromination under microwave heating under solvent-free condition gave a low conversion with an excellent selectivity (entry 5). Since no side-product was detected and the Z/E ratio for the bromofluoroalkene was excellent

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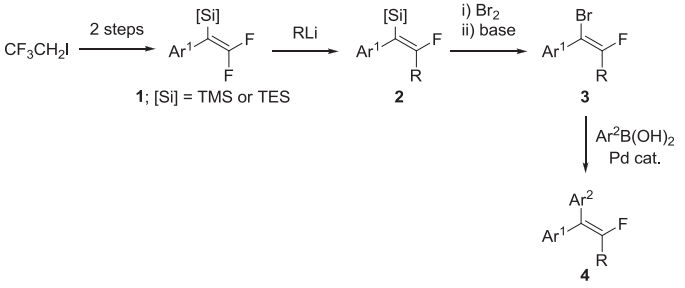


Fig. 1. Synthetic approach to tetrasubstituted monofluoroalkenes.

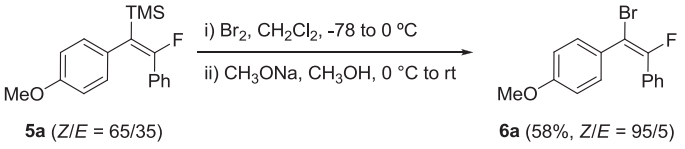
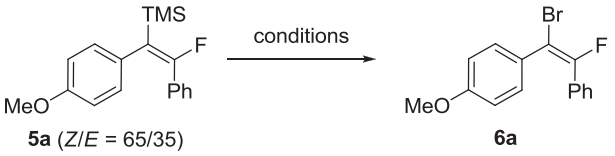


Fig. 2. Bromination/desilicobromination of silylated monofluoroalkene **5a**.

$(Z/E > 97/3)$, further optimization was undertaken and selected results are shown in Table 2.

Under solvent-free conditions, heating for 10 min the reaction mixture in the microwave either at 80 or 125 °C provided low conversion (<5%). Running the reaction at 150 °C completely shuts down the reaction. We hypothesized that adding a solvent would help the reaction to proceed however still no reaction was observed using CH_3CN at 160 °C. Fortunately, running the reaction at 100 °C in water provided a promising 48% conversion with only one isomer present in the crude mixture as detected by ^{19}F NMR analysis. A slight improvement was obtained when using CH_3OH, a preferred solvent according to Pfizer solvent selection guide [9] (entry 6) and further optimization were performed using that solvent. Initially, the effect of reaction time was then evaluated and the best conversions were observed when the reaction was allowed to run for 15 min (compared to 10 and 25 min). Increasing the amount of n-Bu_4NBr_3 from 1 to 1.4 equivalents led to full conversion (entry 9). It is worth noting that in all cases, ^{19}F NMR analysis of the crude product showed a $Z/E > 97/3$ for **6a** indicating an isomeric enrichment similarly to what had been observed with the original conditions [1]. Finally, some fine-tuning of the reaction

Table 1
Initial screening.



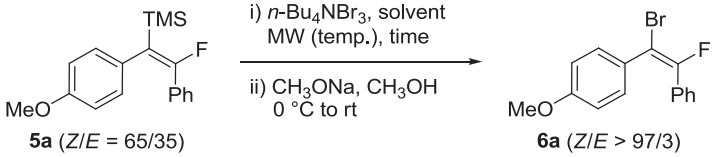
Entry	Conditions	Results
1	(i) Br_2, CH_2Cl_2, −78 °C to rt (ii) CH_3ONa, CH_3OH, 0 °C to rt	55% yield[a] (Z/E = 63/37)[b]
2	(i) Br_2, K_2CO_3, CH_2Cl_2, −78 °C to rt (ii) CH_3ONa, CH_3OH, 0 °C to rt	46% yield (Z/E = 71/29)[b]
3	(i) Br_2, CH_2Cl_2, −78 °C to rt (ii) TBAF, THF, 0 °C to rt	Decomposition[c,d]
4	(i) n-Bu_4NBr_3, CH_2Cl_2, 50 °C (ii) CH_3ONa, CH_3OH, 0 °C to rt	No reaction[c]
5	(i) n-Bu_4NBr_3, MW, 100 °C, 2 min (ii) CH_3ONa, CH_3OH, 0 °C to rt	2% conv.[c] ($Z/E > 97/3$)[c]

[a] The crude product was contaminated by ca. 31%, as estimated by ^{19}F NMR, of an unidentified side-product.
[b] Determined by ^{19}F NMR analysis of the isolated product after purification by flash chromatography.
[c] Determined by ^{19}F and/or ^{1}H NMR analysis of the crude mixture.
[d] Absence of ^{19}F NMR signals in the crude mixture.

conditions was performed (results not shown) and led to the use of 1.5 equiv. of n-Bu_4NBr_3 with heating at 80 °C for 20 min. These conditions provided cleaner crude products with fewer impurities and were used for the examination of other substrates (Table 3).

Performing the bromination/desilicobromination using the optimized conditions on **5a**, the bromofluoroalkene **6a** was isolated in 60% yield with a $Z/E > 97/3$ (entry 1). Using silylated monofluoroalkene **5b** bearing a 2-(*tert*-butyldimethylsilyloxy)ethoxy side-chain gave the alcohol **6b** in 84% yield with a slight stereochemical erosion (entry 2). The deprotection of the silylated alcohol under those conditions indicates a limitation in term of functional group tolerance. Finally, silylated monofluoroalkene bearing different 2-(dialkylamino)ethoxy side-chain were submitted to the bromination/desilicobromination reaction. The desired bromofluoroalkenes were isolated in low to moderate yield with little or no stereochemical erosion (entries 3–5). In all these cases, complete separation by flash chromatography of the desired products from n-Bu_4NBr_3 related residues (various tetrabutylammonium salts as

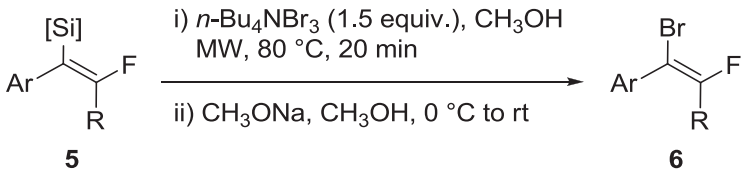
Table 2
Optimization of the bromination/desilicobromination using n-Bu_4NBr_3.



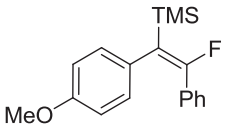
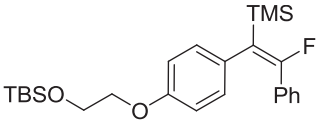
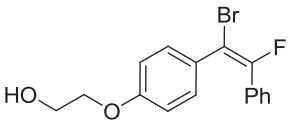
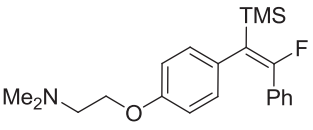
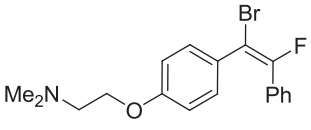
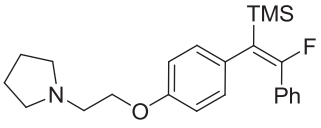
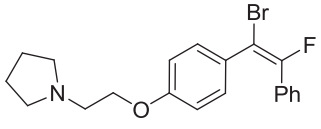
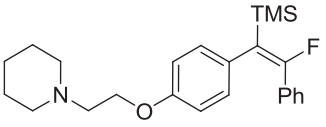
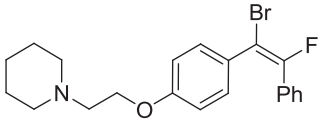
Entry	Solvent	Temp. (°C)	Time (min)	n-Bu_4NBr_3 equiv.	Conv. (%)[a]
1	–	80	10	1	3
2	–	125	10	1	5
3	–	150	10	1	0
4	CH_3CN	160	10	1	0
5	H_2O	100	10	1	48
6	CH_3OH	80	10	1	51
7	CH_3OH	80	15	1	70
8	CH_3OH	80	25	1	63
9	CH_3OH	80	15	1.4	100

[a] Determined by ^{19}F and/or ^{1}H NMR analysis of the crude mixture.

Table 3
Selected bromination/desilicobromination of silylated monofluoroalkenes using *n*-Bu_4NBr_3.



5 **6**

Entry	Substrate	Product	Yield (%)[a]	*Z*/*E*[b]
1	 **5a** (*Z*/*E* = 65/35)	**6a**	60	>97/3
2	 **5b** (*Z*/*E* = 97/3)	 **6b**	84	85/15
3	 **5c** (*Z*/*E* = 95/5)	 **6c**	35	>97/3
4	 **5d** (*Z*/*E* > 97/3)	 **6d**	25	>97/3
5	 **5e** (*Z*/*E* = 96/4)	 **6e**	39	88/12

[a] Isolated yield.
[b] Determined by ^{19}F and/or ^{1}H NMR analysis of the crude mixture.

detected by ^{1}H NMR) proved to be somewhat challenging due to similar polarities and partly explains the low isolated yields since the crude ^{19}F NMR showed mostly the desired product.

In conclusion, we have reported the use of tetrabutylammonium tribromide under microwave conditions for the bromination of silylated monofluoroalkenes. The reaction is fast, reliable and provides, after the elimination of the silyl group under basic condition, the bromofluoroalkene where the replacement of the silyl group is done with retention of configuration with little or no stereochemical erosion. Isomeric enrichment is even observed in one case. The bromofluoroalkenes generated will be used for the synthesis of fluorinated bioactive compounds and these results will be reported in due course.

3. Experimental

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. ^{1}H, ^{13}C and ^{19}F spectra were recorded on a VARIAN Inova 400 MHz or a BRUKER Avance 300 MHz in $CDCl_3$ at ambient temperature using tetramethylsilane (^{1}H NMR) or residual $CHCl_3$ (^{1}H and ^{13}C NMR) as the internal standard, or $CFCl_3$ (^{19}F NMR) as the external standard. Infrared spectra were recorded on a Bomem FT-IR MB-Series or a Thermo Scientific Nicolet 380 FT-IR spectrometer. High-resolution mass spectra were obtained on a LC/MS-TOF Agilent 6210 using electrospray ionization (ESI). Reactions performed under microwave heating were conducted in a Biotage® Initiator using a sealed vessel.

3.1. General procedure for the bromination/desilicobromination reaction

To a stirred solution of the silylated compounds (1 mmol) in MeOH (9 mL) was added *n*-Bu_4NBr_3 (1.5 mmol). The mixture was heated for 20 min at 80 °C under microwave irradiation. After cooling the reaction mixture back to rt, it was treated with 1.5 M solution of CH_3ONa in CH_3OH (4 mmol) at 0 °C, stirred for 30 min at this temperature and allowed to warm to rt over 1 h. Water was

added and the layers were separated. The aqueous layer was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The crude material was purified by flash chromatography to give the desired product.

*3.1.1. (Z)-1-(1-bromo-2-fluoro-2-phenylvinyl)-4-methoxybenzene (**6a**)*

Following the general procedure on a 0.375 mmol scale of **5a**, the desired product (69 mg, 60%, $Z/E > 95/5$) was isolated as a yellow oil by flash chromatography using 1% Et_2O/petroleum ether. The spectroscopic data were in agreement with the literature [1].

*3.1.2. (Z)-2-(4-(1-bromo-2-fluoro-2-phenylvinyl)phenoxy)ethanol (**6b**)*

Following the general procedure on a 0.135 mmol scale of **5b**, the desired product (38 mg, 84%, Z/E = 85/15) was isolated as white crystals by flash chromatography using 15% EtOAc/hexanes. IR (neat) ν = 3375, 2933, 2875, 1604, 1507, 1488, 1289, 1247, 1066, 913, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.8 Hz), 7.22 (m, 3H), 6.79 (m, 4H), 4.03 (m, 4H), 3.94 (m, 4H), 2.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 154.8 (d, J_{C-F} = 250 Hz), 131.9 (d, J_{C-F} = 3 Hz), 129.5, 128.4, 128.1 (d, J_{C-F} = 5 Hz), 114.8, 114.2, 113.3, 104.2 (d, J_{C-F} = 30 Hz), 69.4, 61.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.3 (s, 1F); HRMS-ESI calcd for $C_{16}H_{15}BrFO_2$ $[M+H]^+$ 337.0236, found 337.0234.

*3.1.3. (Z)-2-(4-(1-bromo-2-fluoro-2-phenylvinyl)phenoxy)-N,N-dimethylethanamine (**6c**)*

Following the general procedure on a 0.22 mmol scale of **5c**, the desired product (20.1 mg, 25%, $Z/E > 95/5$) was isolated as a yellow oil by flash chromatography using 2% MeOH/CH_2Cl_2. IR (neat) ν = 2943, 2820, 2771, 1603, 1508, 1248, 1174, 1032, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 7.20 (d, 2H, J = 4.2 Hz), 6.83 (d, 2H, J = 8.7 Hz), 4.05 (t, 2H, J = 5.6 Hz), 2.73 (t, 2H, J = 5.7 Hz), 2.33 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 158.6 (d, J_{C-F} = 245 Hz), 131.6 (d, J_{C-F} = 3 Hz), 130.8, 129.9, 129.8, 129.4, 127.9 (d, J_{C-F} = 5 Hz), 114.8, 114.0, 65.1, 57.7, 50.3, 45.2, 29.7, 21.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −85.7 (s, 1F); HRMS-ESI calcd for $C_{18}H_{20}BrFNO$ $[M+H]^+$ 364.0707, found 364.0713.

*3.1.4. (Z)-1-(2-(4-(1-bromo-2-fluoro-2-phenylvinyl)phenoxy)ethyl)pyrrolidine (**6d**)*

Following the general procedure on a 0.16 mmol scale of **5d**, the desired product (13.5 mg, 35%, $Z/E > 95/5$) was isolated as a yellow-orange oil by flash chromatography using 2% MeOH/CH_2Cl_2. IR (neat) ν = 2924, 2851, 1603, 1508, 1249, 1227, 1174, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 7H), 6.83 (d, 2H, J = 8.6 Hz), 4.11 (t, 2H, J = 5.8 Hz), 2.92 (t, 2H, J = 5.7 Hz), 2.65 (m, 4H), 1.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 158.9, 154.8 (d, J_{C-F} = 250 Hz), 131.9 (d, J_{C-F} = 3 Hz), 129.5, 128.3, 128.1 (d, J_{C-F} = 5 Hz), 114.9, 114.4, 54.8, 34.4, 32.2, 25.2, 23.6, 22.9, 14.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −85.6 (s, 1F); HRMS-ESI calcd for $C_{20}H_{22}BrFNO$ $[M+H]^+$ 390.0863, found 390.0877.

*3.1.5. (Z)-1-(2-(4-(1-bromo-2-fluoro-2-phenylvinyl)phenoxy)ethyl)piperidine (**6e**)*

Following the general procedure on a 0.97 mmol scale of **5e**, the desired product (118 mg, 39%, Z/E = 88/12) was isolated as a brown oil by flash chromatography using 2% MeOH/CH_2Cl_2. IR (neat) ν = 2933, 1603, 1508, 1247, 1174, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 7H), 6.81 (d, 2H, J = 8.7 Hz, 4.11 (t, 2H, J = 5.9 Hz), 2.80 (t, 2H, J = 6.0 Hz) 2.53 (m, 4H), 1.63 (m, 4H), 1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 154.7 (d, J_{C-F} = 249 Hz), 131.8 (d, J_{C-F} = 3 Hz), 131.0, 129.3, 129.1, 129.0, 128.3, 128.1 (d, J_{C-F} = 5 Hz), 159.4, 115.0, 114.3, 66.1, 58.0, 55.2, 26.0, 24.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −84.6 (s, 1F); HRMS-ESI calcd for $C_{21}H_{23}BrFNO$ $[M+H]^+$ 407.1033, found 407.1033.

Acknowledgments

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