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New synthesis of trifluorinated amines from 1-bromopropargylic amines in superacid

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Abstract—Treatment of 1-bromopropargylic amines affords the corresponding 1,1,1-trifluoro in one step in HF–SbF_5 medium. 1-Bromo-1,1-difluoro or 2-bromo-1,1,1-trifluoro derivatives could also be prepared, depending on the reaction conditions.

1. Introduction

Considerable attention has been given to fluorinated organic compounds due to their potential use in medicinal and agricultural chemistry.[1] Interest in these fluorinated substances is continuously increasing because introduction of one or more fluorine atoms[2] may significantly modify the chemical, physical, and biological properties of such substances. These modifications are associated with increased stability and lipophilicity, while the steric distortion, compared to the parent compound, is relatively small. Among these fluorinated compounds, trifluorinated ones play an important role, in particular in the design of bioactive products. Nevertheless, despite this growing interest, methods to synthesize such products are still scarce and new methodologies are required. We would like to report a novel access to trifluorinated compounds from 1-bromopropargylic amines **1**–**4** in one step.

2. Reaction of compounds 1–4 in HF–SbF_5

2.1. Starting materials

Amine derivatives **1**, **4** were prepared as indicated in Scheme 1 using Hofmeister[3,4] and Jeon's conditions,[5] respectively. In the piperidine and isoquinoline series, direct alkylation[6] with 1,3-dibromopropyne afforded the corresponding bromopropargylic amines **2** and **3** in moderate yields (41% and 36%, respectively).

These bromopropargylic amine derivatives were then submitted to acidic conditions. Preliminary experiments were performed using HF alone (0 °C, 5 h). In all cases, starting material was recovered. The use of more acidic conditions (HF–SbF_5) was then considered.

2.2. Results

In the present study, the reactions were carried out in HF–SbF_5[7] at low temperature (−40 °C to −60 °C). Starting materials (2 mmol) were fully transformed within 2–15 min of reaction time. In some cases, subsequent treatment with HF–pyridine 70/30 (v/v 1 mL) was required (entries 2, 4, and 5, Table 1) at −78 °C. Then, the resulting mixture was quenched with iced water (150 mL) and sodium carbonate (80 g). After extraction with dichloromethane and usual work-up, the products were isolated by column chromatography over SiO_2.

The results are summarized in Table 1. In HF–SbF_5 alone, **1** yielded a *gem*-bromodifluorinated compound **1a**[8] as major product (entry 1, Table 1) and only minor amounts of the trifluoro derivative **1b** (ratio **1a**/**1b** 11/1, entry 1, Table 2). Addition of a more nucleophilic fluorinating agent (HF–pyridine) allowed total bromide–fluoride exchange to give trifluorinated

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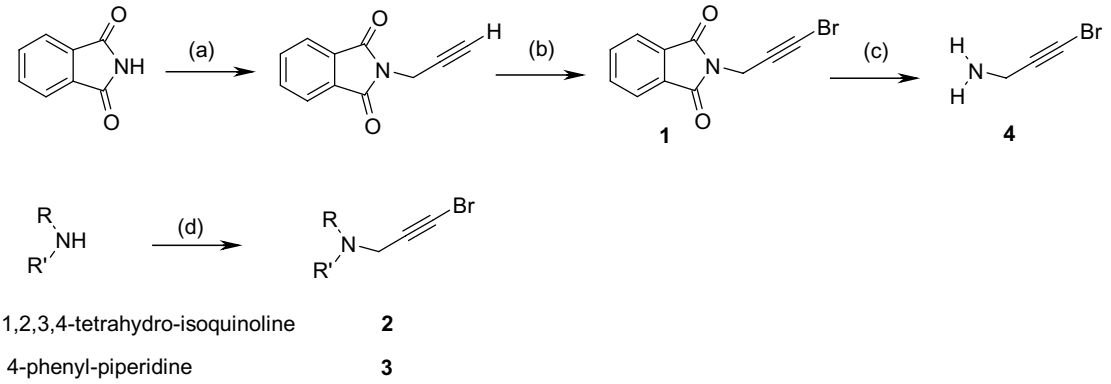


Scheme 1. Synthesis of 1-bromoalkynes **1**–**4**. Reagents and conditions: (a) K_2CO_3, propargyl bromide, crown ether 18-C-6, benzene, (b) NBS, $AgNO_3$, acetone, (c) (i) $H_2N–NH_2$, MeOH; (ii) HCl/MeOH, (d) 1,3-dibromopropyne, NaH, THF.

Table 1. Reactivity of 1-bromopropargylic amine derivatives in HF–SbF_5

Entry	Compound	HF–SbF_5		HF–pyridine	Temperature (°C)	Products (yield %)
		Molar ratio	Time (min)			
1	**1**	15/1	10		−60	**1a**/**1b** (77)
2	**1**	7/1	10	12 h	−40	**1b** (88)
3	**2**	7/1	5	2 h	−40	**2b** (60)[a]
4	**3**	7/1	15		−40	**3b** (96)[a]
5	**4**	7/1	2	2 h	−60	**4a** (27)[b] + **4b** (16)[b]

[a] Isolated after hydrogenolysis.
[b] Separated after acylation.[9]

Table 2. Ratio of fluoro compounds in HF–SbF_5

Entry	Compound	Time (min)	CF_2Br/CF_3
1	Phthalimide **1**	10	11/1
2	Isoquinoline **2**	5	1/1
3	Piperidine **3**	1	3/1
4	Primary amine **4**	2	4/1

product **1b**[10] in good yield (entry 2, Table 1). Double addition of HF followed by bromide–fluoride exchange was also observed for amines **2** and **3**, albeit at different rates (Fig. 1).

Since bromodifluoro and trifluoro compounds turned out to be inseparable by chromatography, ^{19}F NMR was used to determine their ratio at different reaction times (Table 2). Starting from isoquinoline **2**, a mixture of CF_2Br/CF_3 derivatives was observed after 5 min at −40 °C (entry 2, Table 2). Complete exchange to afford **2b** required the use of HF–pyridine (entry 3, Table 1). Addition of HF to piperidine **3** as well as halide exchange was faster leading to **3b** in high yield in HF–SbF_5 alone (entry 4, Table 1 and entry 3, Table 2). In both cases, partial aromatic ring bromination (vide infra) was also observed and the reaction mixture was treated with H_2–Pd/C before separation.

Particular behavior was observed for primary amine **4**. In addition to the expected CF_2Br/CF_3 derivatives (entry 4, Table 2) or CF_3 product (**4b**[12] after HF–pyridine treatment), a 1,2-dibromo-1,1-difluoro derivative **4a**[11] (entry 5, Table 1) was also formed. Halide exchange was not observed in the case of **4a** at −60 °C after 2 h.

2.3. Reaction mechanism

Taking into account these data, the postulated mechanism is outlined in Scheme 2. In HF–SbF_5, amines are *N*-protonated (in the case of **2** and **3**, aromatic rings are also protonated). Further protonation gives a vinylic carbenium ion **B**, trapped by a complex fluoride ion (SbF_6^-, $Sb_2F_{11}^-$, ...) to afford a bromofluoro intermediate **C**. Starting from the latter, two mechanisms can be considered. The first one (reaction pathway a) implies a protonation of the bromofluoroalkene **C** to afford **D** which is trapped by a fluoride ion to give ion **E**, precursor of the bromodifluoro compound. At this stage, **E** may also undergo protonation followed by elimination of HBr to yield ion **F** which can react as previously described to afford the trifluorinated compounds **1b**–**4b** (entries 2–5, Table 1). This exchange is observed in HF–SbF_5 alone but generally necessitates a more fluorinating reagent (HF–pyridine) to reach completion. An analogous exchange has been previously observed in electrophilic trifluoromethylation of substituted anilines, indolines, oxindoles, and indoles in superacid.[13,14]

The unexpected formation of the 2-bromoderivative **4a** (entry 5, Table 1) can be explained following pathway b (Scheme 2). The bromofluoro alkene **C** can react with electrophilic bromine to give cyclic bromonium ion **G**[15]

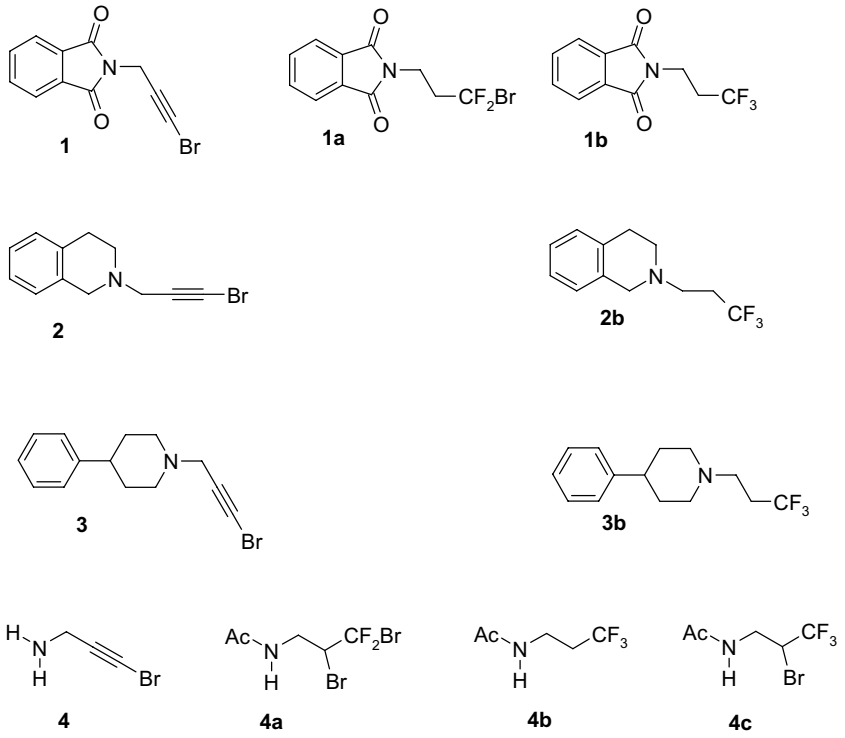
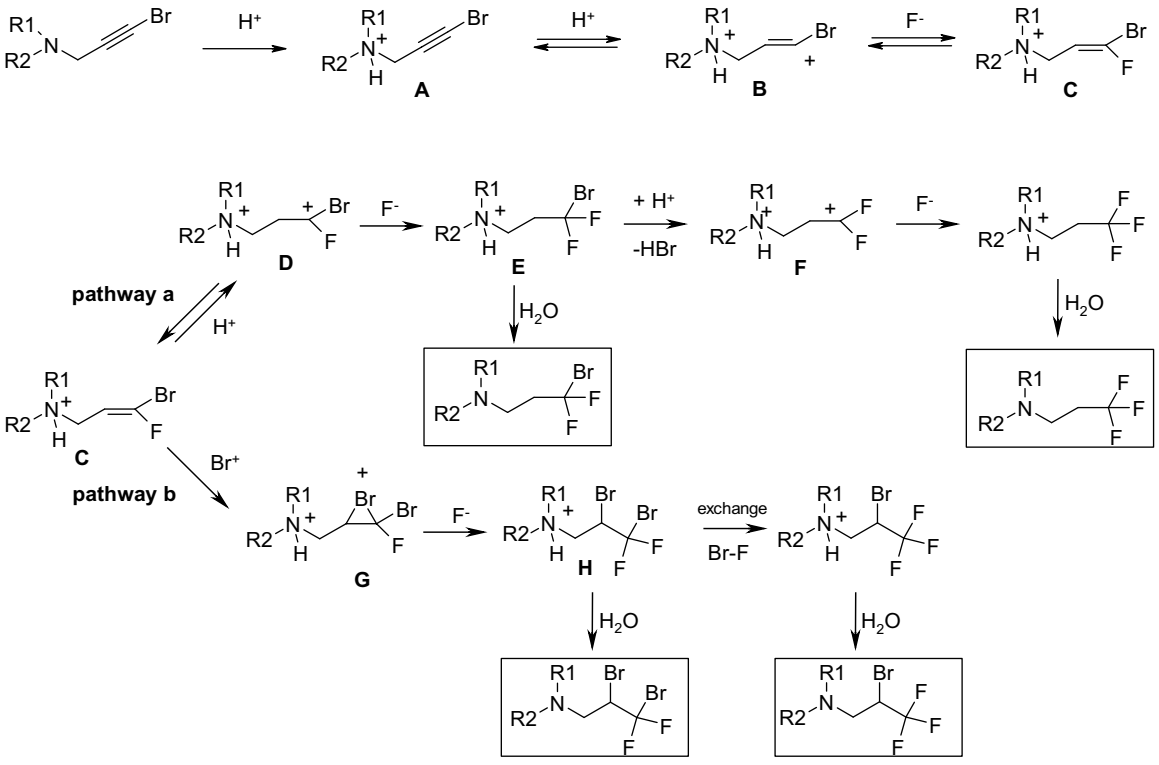


Figure 1. Starting materials and fluorinated amines.



Scheme 2. Proposed mechanism for the formation of fluorinated compounds.

which adds a fluoride ion to afford **H**, precursor of **4a** (Table 1, entry 5). Electrophilic bromine 'Br^{+}' results from the oxidation of HBr (generated in situ, pathway a), a process which has been previously observed in *meta*-bromination of phenols[16] and *gem*-difluoration of bromoamines in superacid.[9]

Table 3. Reactivity of **1–4** in HF–SbF_5 with **NBS** (20 h)

Entries	Compound	Conditions[a]	$CHBrCF_3/CF_3$
1	Phthalimide **1**	10 min/−50 °C	2/1
2	Piperidine **2**	15 min/−40 °C	1/4
3	Isoquinoline **3**	5 min/−40 °C	1/4
4	Amine **4**	2 min/−50 °C	49/1

[a] Followed by treatment with HF–pyridine.

3. Reaction of compounds 1–4 in HF–SbF_5 with NBS

To confirm the mechanism for the formation of compound **4a**, derivatives **1–4** were treated with the electrophilic bromide donor NBS in superacid medium. Under these conditions, bromination of the aromatic substrate is also expected and as a consequence an excess of NBS (3 or 4 equiv) was used to perform this study.

In all cases, subsequent treatment with HF–pyridine was carried out for 20 h to complete bromine–fluorine exchange. ^{19}F NMR was then used to determine the ratio of 2-bromo-1,1,1-trifluoro and 1,1,1-trifluoro compounds (Table 3). Almost selective bromination was only observed for primary amine **4** (**4c**,[17] 27%), while trifluoro compounds were still the major ones for amines **2** and **3** (entries 2, 3, Table 3).

These results can be accounted for by considering the equilibrium between N-protonated form **C** and diprotonated ion **D**. The reaction course may be governed by the relative stability of these two entities, depending on the amine substitution (Scheme 2).

In case of amines **2** and **3**, electron-donating effects of alkyl substituents stabilize ion **C**. Easy protonation occurs to give ion **D**, a precursor of trifluoroderivatives (Scheme 2).

In contrast, N-protonated form **C** in free amine appears destabilized. In this case, protonation is disfavored and irreversible addition of electrophilic bromide 'Br^+' occurs leading to cyclic bromonium ion **G**, a precursor of α-bromotrifluoro products (Scheme 2). For amide series, an equilibrium between these two pathways is observed in favor of predominant addition of electrophilic bromide (entry 1, Table 3).

4. Conclusion

In HF–SbF_5, the reaction of 1-bromopropargylic amines affords trifluorinated amine derivatives in good yields. 1-Bromodifluoroamines or 2-bromo-1,1,1-trifluoro products could also be isolated depending on the reaction conditions and amine substitution. Further modification of these compounds may be of interest for the synthesis of fluorinated bioactive compounds. Nucleophilic[18,19] and radical induced[20] substitution of bromine have been described in the literature on bromo-difluoro or trifluoro derivatives. Such applications[21] as well as studies of other haloalkynes are underway in our laboratory.

Acknowledgments

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7. The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangement in place.
8. Compound **1a**: ^1H NMR (300 MHz, $CDCl_3$, TMS as internal standard): δ 7.91–7.84 (m, 2H, H-4, and H-7), 7.78–7.72 (m, 2H, H-5, and H-6), 4.00 (t, $J = 7.0$ Hz, 2H, H-1′), 2.83 (m, 2H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (C-1 and C-3), 134.2 (C-5 and C-6), 131.8 (C-3a and C-7a), 123.5 (C-4 and C-7), 120.2 (t, $^1J_{CF} = 305$ Hz, C-3′), 42.1 (t, $^2J_{CF} = 22$ Hz, C-2′), 32.8 (t, $^3J_{CF} = 4.2$ Hz, C-1′). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −45.9 (t, $J = 11.3$ Hz). HRMS ($C_{11}H_8NO_2F_2{}^{79}Br$): Calcd 302.97065, Found 302.9701.
9. (a) Specific work-up was used in the case of volatile amine **4**: compounds **4a** and **4b** were isolated after acylation was carried out by treatment of the aqueous phase with acetic anhydride (4 mL, 3 h; then additional 2 mL for 24 h) and extraction as usual; (b) Moine, A.; Thibaudeau, S.; Martin, A.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2002**, *43*, 4119–4122.
10. Compound **1b**: ^1H NMR (300 MHz, $CDCl_3$, TMS as internal standard): δ 7.90–7.85 (m, 2H, H-4, and H-7), 7.78–7.74 (m, 2H, H-5, and H-6), 3.97 (t, $J = 7.2$ Hz, 2H, H-1′), 2.63–2.48 (m, 2H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (C-1 and C-3), 134.2 (C-5 and C-6), 131.8 (C-3a and C-7a), 125.7 (q, $^1J_{CF} = 277$ Hz, C-3′), 123.5 (C-4 and C-7), 32.3 (q, $^2J_{CF} = 29$ Hz, C-2′), 31.2 (q, $^3J_{CF} = 4.1$ Hz, C-1′). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −66.9 (t, $J = 8.5$ Hz). HRMS ($C_{11}H_8NO_2F_3$): Calcd 243.05071, Found 243.0495.
11. Compound **4a**: ^1H NMR (300 MHz, $CDCl_3$, TMS as internal standard): δ 6.32 (sl, 1H, H-1), 4.53–4.46 (m, 1H, H-2′), 4.18–4.10 (m, 1H, H-1′), 3.44–3.34 (m, 1H, H-1′), 1.98 (s, 3H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0 (C-2), 119.6 (t, $^1J_{CF} = 307$ Hz, C-3′), 54.5 (t, $^2J_{CF} = 23$ Hz, C-2′), 42.9 (C-1′), 23.3 (C-3). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −47.0 (dd, $J = 164$ Hz, $J = 5.6$ Hz), −52.4 (dd, $J = 164$ Hz, $J = 11$ Hz). HRMS ($C_3H_3F_2{}^{79}Br{}^{81}Br$: [M−•$NHCOCH_3$]+): Calcd 236.85491, Found 236.8558.
12. Compound **4b**: ^1H NMR (300 MHz, $CDCl_3$, TMS as internal standard): δ 5.81 (sl, 1H, H-1), 3.43 (m, 2H, H-1′), 2.36–2.10 (m, 2H, H-2′), 1.92 (s, 3H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7 (C-2), 126.8 (q, $^1J_{CF} = 277$ Hz, C-3′), 34.0 (q, $^2J_{CF} = 28$ Hz, C-2′), 33,4 (q, $^3J_{CF} = 4.4$ Hz, C-1′), 23.5 (C-3). ^{19}F NMR (external standard C_6F_6

($\delta F = -162.90$), $CDCl_3$): δ −66.3 (t, $J = 9.9$ Hz). HRMS ($C_5H_8NOF_3$): Calcd 155.05580, Found 155.0563.

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17. Compound **4c**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS as internal standard): δ 6.29 (sl, 1H, H-1), 4.50–4.35 (m, 1H, H-2′), 4.05–3.97 (m, 1H, H-1′), 3.60–3.47 (m, 1H, H-1′), 1.98 (s, 3H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0 (C-2), 123.7 (q, $^1J_{CF} = 278$ Hz, C-3′), 45.7 (q, $^2J_{CF} = 31$ Hz, C-2′), 41.1 (C-1′), 23.5 (C-3). ^{19}F NMR (external standard C_6F_6 ($\delta F = -162.90$), $CDCl_3$): δ −72.0 (d, $J = 8.5$ Hz). HRMS ($C_5H_7NOF_3{}^{79}Br$): Calcd 232.96631, Found 232.9680.
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21. As an example, substitution of **1a** using allyltributyltin and a catalytic amount of AIBN affords the corresponding allyldifluoro compound in good yield (93%).