Chemo- and regio-divergent access to fluorinated 1-alkyl and 1-acyl triazenes from alkynyl triazenes†

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The 1,1,2,2-tetrafluoroethylene unit is prevalent in bioactive molecules and functional materials. Despite being in principle a straightforward strategy to access this motif, the direct tetrafluorination of alkynes involves very hazardous or inconvenient reagents. Therefore, safer and convenient alternatives are sought after. We developed a mild and operationally simple perfluorination method converting 1-alkynyl triazenes into 1,1,2,2-tetrafluoro alkyl triazenes, employing cheap and readily accessible reagents. Moreover, a judicious tuning of the reaction conditions enables access to α-difluoro triazeny ketones. Complementary, electrophilic fluorination of alkynyl triazenes gives rise to the regioisomeric α-difluoro acyl triazenes. These three chemo- and regio-divergent protocols enable access to elusive fluorinated 1-alkyl and 1-acyl triazenes, thus expanding the chemical space for these unusual entities. Furthermore, several reaction intermediates and side products revealed insights on the reaction pathways that may be useful for further fluorination chemistry of alkynes.

Introduction

The incorporation of fluorine atoms or fluoroalkyl groups in organic molecules can alter various physical and chemical properties such as metabolic stabilities, lipophilicities, electron distributions, acid–base equilibria and pharmacological activities.1 These unique characteristics render fluoride-containing functionalities highly appreciated in the design and development of pharmaceuticals, agrochemical candidates and materials.2 As a consequence, the introductions or formations of fluorinated moieties have been a topic of intensive investigations.3 With respect to the fluoroalkyl functionality, 1,1,2,2-tetrafluoroethylene and difluoromethylene moieties are frequently encountered in bioactive molecules and advanced materials (Fig. 1).3 Well-established approaches allow for the transfer of difluoromethylene and (CF2)ₙ (n > 2) groups.4–6 In contrast, the chemistry of isolated 1,1,2,3-tetrafluoroethylene (–CF₂CF₂–) units is less common. It remains underdeveloped compared to the structurally similar but widely-employed trifluoromethyl (–CF₃) and perfluoroethyl (–C₃F₇) groups. To date, there is only a handful of methods for the constructions of tetrafluoroethylene linkages, namely addition reactions across tetrafluoroethenes,7 the use of halotetrafluorokane as a CF₂CF₂ transfer group,8 exhaustive deoxyfluorination of 1,2-diketones using organosulfur reagents9 and lastly, direct fluorinations of internal alkynes.10 Among them, direct fluorinations of alkynes might be the most straightforward and attractive strategy, due to the prompt accessibility and prevalence of carbon–carbon triple bonds in organic molecules (Scheme 1a). However, the number of reports on this seemingly simple procedure is very limited. Moreover, the reported procedures primarily involve harsh conditions using hazardous or inconvenient reagents, such as fluorine gas,10e hydrofluoric acid,10b xenon difluoride,10d and iodine monofluoride or bromine monofluoride.10e Additions of fluoride across different activated alkynes have been investigated.11 Most transformation resulted either in the transfer of a single fluoride or yielding fluoro alkenes. Therefore, a mild and practical fluorination procedure of alkynes would be a very valuable addition to a chemist’s toolbox for the expedient synthesis of 1,1,2,2-tetrafluoroethylene units.

The triazene group12 is a highly useful functionality in a broad variety of molecules having applications in anticancer therapy,13 materials,14 total synthesis15 and solid phase synthesis.16 Triazenes with alkyl or acyl substituents at their N3 atom have been widely studied in medicinal chemistry and organic synthesis (Scheme 1b). Specifically, 3,3-dialkyl triazenes are among the most commonly synthesized triazene compounds due to their easy access via the corresponding dialkyl amines. Moreover, 3-methyl-substituted triazeny units are essential for cytotoxicity and tumor inhibitory activities in anti-cancer drugs such as dacarbazine1b and temozolomide.14e 3-Acyl triazenes have been reported in numerous bioactive compounds,17 as synthetic precursors for aminal radicals,18 acylating agents19 and chemo-dosimeters for cyanide.20 In
contrast, there are much less reports dealing with the synthesis and use of 1-alkyl\textsuperscript{14} and 1-acyl triazenes.\textsuperscript{24} Therefore, a rapid and modular access to 1-alkyl and 1-acyl triazenes would open up opportunities for investigations of their underexposed chemical and biological properties. Over the past years, the use of 1-alkynyl triazenes in organic synthesis has been receiving a growing interest.\textsuperscript{3,2,2,4} Leverageing on their ynamide-like reactivity profile,\textsuperscript{25} we herein report three sets of convenient protocols that allow the fully chemo- and regio-divergent formations of tetrafluoro-alkyl triazenes, difluoro-alkyl triazenes and difluoro acyl triazenes from 1-alkynyl triazenes (Scheme 1c). Such fluorinated 1-alkyl and 1-acyl triazenes expand the chemical space for medicinal chemistry studies involving triazene molecules. Furthermore, these transformations provide potentially useful mechanistic insights for related chemistry with other alkynes.

**Results and discussion**

We initiated our perfluorination studies by exposing 1-naphthyl-substituted alkynyl triazene 1a to various electrophilic halogen sources and fluorides (Table 1). Reaction of 1a with HF-py and 1,3-diiodo-1,3-diiodo hydantoin (DIH) caused a strong decomposition of the starting material. However, formation of tetrafluoro alkyl triazene 2a in 7% yield was observed as well (entry 1). We postulated that formation of 2a arises from a double iodofluorination of 1a followed by a subsequent substitution of the two iodides by fluoride anions. Such formation of a tetrafluoroethyl unit from an alkynyl triazene is not reported and encouraged us to further optimize the transformation. Switching from HF-py to AgF as fluoride source significantly improved the yield of 2a to 38% while as well giving small amounts of α-difluoro triazynyl ketone 3a and 1,2-diketone 4a (entry 2). Both compounds possibly arise from a displacement of the iodides by a water molecule from remaining residual traces of water in the solvent. A screening of electrophilic halogen sources X\textsuperscript{y} did not provide an improvement in yield or selectivity, but additionally gave iodofluoro alkynyl triazene 5a, α-difluoro acyl triazene 6a and diiodo alkynyl triazene 7a (entries 3–5). In most instances, these products were present only in trace amounts. The use of I\textsubscript{2} increased the yield of 5a, while IBr produced more compound 3a (entries 4 and 5).

With DIH as best electrophilic source X\textsuperscript{y}, we proceeded to screen other fluorides. Tetrabutylammonium fluoride (TBAF) and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) favored clearly the formation of 2a (entries 6 and 7), while CsF caused substrate decomposition (entry 8). Gratifyingly, the use of DAST delivered desired product 2a in 92% yield (entry 9). Decreasing the amount of DIH to 1.2 equivalents did not result in a major drop in yield, indicating that both iodine atoms on the hydantoin are consumed in the transformation. The amount of DAST was lowered to four equivalents without compromising the yield and selectivity for 2a (entry 10). However, any further decrease had a negative impact on the product selectivity. Interestingly, the absence of light is essential for selective and efficient formation of 2a (entry 11). Next, we investigated the possibility of shifting the equilibrium towards α-difluoro triazynyl ketone 3a formation. Since only two fluorine atoms are incorporated in 3a, reducing the amount of DAST would be a logical step. The optimal stoichiometry was indeed found to be two equivalents of DAST, giving 3a in 83% yield (entry 12).

The observation of α-difluoro acyl triazene 6 prompted us to investigate its selective formation from 1. Due to the electronic properties and reactivity profile of alkynyl triazenes analogous to that of ynamides,\textsuperscript{25,26} we envisioned that an electrophilic fluorination might lead to 6 (Table 2). To investigate the selective formation of 6b, we initially exposed alkynyl triazene 1b to

**Scheme 1** Fluorinative transformations of alkynes and 1-alkynyl triazenes.
With the optimized three selective conditions (A, B and C), the substrate scope for the perfluorination and regio-divergent oxyfluorinations of 1-alkynyl triazenes was investigated (Table 3). The perfluorination condition A reliably delivered 1,1,2,2-tetrafluorinated alkyl triazenes 2b–2g with electron-rich and electron-poor aryl groups substituents R in good to excellent yields (entries 2–7). The same substrate set underwent both regioselective oxyfluorinations delivering α-difluoro triazynyl ketones 3b–3g (condition B) and α-difluoro acyl triazenes 6b–6g (condition C) with moderate to excellent yields. The structures of 2a and 6e were unambiguously confirmed by X-ray crystallographic analyses (see ESI†). Noteworthy, the transformations also accommodate electron-rich heterocyclic substrates. Subjecting thienyl-substituted alkyne triazene 1h to conditions A and B, a concomitant iodination at 2-position of the thiophene by DIH occurred forming 2h and 3h (entry 8). Condition C delivered expected thienyl product 6h. A piperidinyl group on the R of N3 (1i) was also well accepted (entry 9). Alkyl groups like cyclopropyl (1j), cyclopentyl (1k), tert-butyl (1l) and methoxymethyl (1m) all consistently afforded acyl triazenes 6j–6m in moderate to good yields (entries 10–13) under condition C. These substrates did not provide fluorinated products 2 and 3 under the conditions A or B, with the products being mono iodo acyl triazole 10 (entry 10).

Acyl triazenes are behaving as activated carboxylic acid derivatives and could be synthetically leveraged as such. Indeed, exposure of naphthyl-substituted product 6a to BF3·OEt2 in methanol smoothly provided corresponding methyl ester 11a (Scheme 2). Notably, Lewis-acid activation in

Table 1  Optimization of the formation of fluorinated alkyl triazenes

| Entry | X* | F* | % Conv. | 2a [%] | 3a [%] | 4a [%] | 5a [%] |
|-------|----|----|---------|--------|--------|--------|--------|
| 1     | DIH| HF | 69      | 7      | —      | —      | —      |
| 2     | DIH| AgF | 100 | 38     | 4      | 4      | —      |
| 3     | NIS| AgF | 100 | 30     | 15     | 9      | <2     |
| 4*    | I2 | AgF | 100 | 26     | 15     | 14     | <2     |
| 5     | IBr| AgF | 100 | 8      | 30     | 17     | <2     |
| 6     | DIH| TRAF | 100 | 0      | 0      | <2     | 44     |
| 7     | DIH| TASF | 100 | 0      | 0      | <2     | 31     |
| 8     | DIH| CsF | 100 | 0      | 0      | <2     | —      |
| 9     | DIH| DAST | 100 | 92     | 0      | 0      | —      |
| 10    | DIH| DAST | 100 | 87     | 0      | 6      | —      |
| 11*   | DIH| DAST | 100 | 43     | 31     | 10     | —      |
| 12*   | DIH| DAST | 100 | 0      | 83     | 16     | —      |

*Conditions: 0.10 mmol 1a, 2.5 equiv. X*, 10.0 equiv. F*, 0.1 M in CHCl3, 23 °C for 2 h in the dark. Conversion and yields determined by 1H-NMR with an internal standard. 11% NMR yield of 6a. 1.2 equiv. DIH, 4.0 equiv. DAST. With ambient light. 1.2 equiv. DIH, 2.0 equiv. DAST.

Table 2  Optimization of the formation of α-difluoro acyl triazene 6b

| Entry | F* | Additive (equiv.) | 6b [%] | 8b [%] | 9b [%] |
|-------|----|------------------|--------|--------|--------|
| 1     | Selectfluor | H2O (3) | 0      | 0      | 1      |
| 2     | Selectfluor | H2O (3) | 44     | 38     | 2      |
| 3     | Selectfluor | H2O (3) | 43     | 40     | 3      |
| 4    | NFSI | H2O (3) | 37     | 5      | —      |
| 5     | 10 | H2O (3) | 0      | 0      | 6      |
| 6     | Selectfluor | — | 0      | 0      | 7      |
| 7     | Selectfluor | 2 M NaOH (3) | 45     | 36     | 9      |
| 8     | Selectfluor | (Bu4NOH)·3H2O (3) | 60     | 12     | 11     |
| 9     | Selectfluor | (Me4N)OH·5H2O (3) | 83     | 9      | 12     |
| 10   | Selectfluor | (Me4N)OH·5H2O (2.5) | 85%    | 6      | 13     |
| 11   | Selectfluor | (Me4N)OH·5H2O (1.5) | 66     | 7      | 14     |
| 12   | Selectfluor | (Me4N)OH in MeOH (2.5) | <5     | 0      | 15     |

*Conditions: 0.1 mmol 1b, F*, additive, in 0.4 mL MeCN at 0 °C for 2 h; conversion and yields determined by 1H-NMR with an internal standard. 23 °C. 3.0 equiv. Selectfluor. Reaction was conducted in the dark. Isolated yield.

2.5 equivalents of Selectfluor as an electrophilic fluorine source (F*) and water as an additive (entry 1). Full decomposition of starting material 1b occurred at room temperature. Reasoning that Selectfluor might act as an activator cleaving the triazene group, milder conditions were tested. Indeed, conducting the reaction at a lower temperature of 0 °C provided a mixture of acyl triazene 6b, mono fluoro acyl triazene 8b and the hydrated side product 9b (entry 2). An increased amount of Selectfluor did not improve the outcome (entry 3). Other electrophilic fluorine sources such as N-fluorobenzenesulfinimide (NFSI) or N-fluoropyridinium salt 10 resulted in inferior yields (entries 4 and 5). Notably, the presence of water was found to be essential for the formation of product 6 (entry 6). To suppress 8b formation, which possibly results from the competition of H+ with F*, we turned to more basic additives. Aqueous sodium hydroxide gave no improvement (entry 7). To our delight, a major improvement occurred with alkylammonium hydroxide hydrates, significantly increasing both yield and selectivity for 6b (entries 8–11). The optimal stoichiometry of the superior tetramethylammonium hydroxide was found to be 2.5 equivalents (entry 10), providing 6b in 85% yield. Finally, a methanolic solution of the hydroxide salt majorly caused decomposition, suggesting that methanol is not able to substitute water as a nucleophile (entry 12).
### Table 3 Scope for the different selective perfluorination and oxyfluorinations of alkynyl triazenes

| Entry | 1       | 2 (Condition A) | 3 (Condition B) | 6 (Condition C) |
|-------|---------|-----------------|-----------------|-----------------|
| 1     | 1a      | 1a (87 %)       | 1a (92 %)       | 1a (86 %)       |
| 2     | 1b      | 2b (82 %)       | 1b (89 %)       | 1b (85 %)       |
| 3     | 1c      | 2c (80 %)       | 3c (86 %)       | 6c (90 %)       |
| 4     | 1d      | 2d (93 %)       | 3d (47 %)       | 6d (64 %)       |
| 5     | 1e      | 2e (90 %)       | 3e (83 %)       | 6e (83 %)       |
| 6     | 1f      | 2f (56 %)       | 3f (64 %)       | 6f (77 %)       |
| 7     | 1g      | 2g (77 %)       | 3g (67 %)       | 6g (80 %)       |
| 8     | 1h      | 2h (53 %)       | 3h (33 %)       | 6h (59 %)       |
| 9     | 1i      | 2i (78 %)       | 3i (80 %)       | 6i (79 %)       |
| 10    | 1j      | 10j (54 %)      |                 | 6j (89 %)       |
| 11    | 1k      |                 |                 |                 |
| 12    | 1l      |                 |                 |                 |
| 13    | 1m      |                 |                 | 6m (39 %)       |

*a* Condition A: 0.1 mmol 1, 0.12 mmol DIH, 0.4 mmol DAST, 0.1 M in CHCl₃ at 23 °C for 2 h in the dark.

*b* Condition B: 0.1 mmol 1, 0.12 mmol DIH, 0.2 mmol DAST, 0.1 M in CHCl₃ at 23 °C for 2 h in the dark.

*c* Condition C: 0.1 mmol 1, 0.25 mmol Selectfluor, 0.25 mmol [Me₄N]OH・5H₂O, 0.25 M in MeCN at 0 °C for 2 h under ambient light.

*d* With 5.0 equiv. DAST.

*e* With 0.3 equiv. DAST.

*f* With 10.0 equiv. DAST.

*g* For 5 h.

*h* With 2.4 equiv. DIH.
a suitable acceptor environment such as mesitylene as a solvent initiated a clean Friedel–Crafts acylation leading to ketone 12b with an excellent yield. Attempts to replace the triazene moiety of compounds 2 and 3 by other nucleophiles largely failed, supporting their unusual electronic nature (see as well Scheme 3).

The detection and isolation of fluoro iodo alkene 5a as well as diiodo alkene 7a during the optimization study raised questions regarding their roles in the reaction. To shed some light on the mechanism, we studied the behavior of these species. When compound 5a was subjected to the standard condition of generating 2a, productive full conversion was observed leading to 2a in 79% and trace amount of 3a (Scheme 3a). This result suggests that 5a acts as intermediate species during the conversion of 1-alkynyl triazene 1a to either 2a or 3a. Moreover, product 2a can be formed exposing 3a to DAST only (Scheme 3b). This corroborates the observations that excess DAST shifts the ratio towards formation of 2a over 3a. Next, we tested the formation of diiodo alkene 7a. By combining substrate 1a with 0.6 equivalents of DIH and 1.2 equivalents of tetrabutylammonium iodide, diiodo alkene 7a was formed in 92% yield (Scheme 3c). No product at all was observed in the absence of the iodide source, proving that iodide anions are required for formation of 7a. Isolated 7a was subsequently subjected to the fluorination condition with excess DIH. Even after prolonged reaction times, no fluorinated product was observed and the starting material was fully recovered (Scheme 3d). This result is evident that 7a is not part of the productive reaction pathway. During the course of our functionalization attempts of products 2a and 3a, we found that hydrolysis products 6a and 4a were formed under strongly acidic conditions (Scheme 3e). This observation may be explained by \( \alpha \)-oxydefluorinations of these \( \alpha \)-difluoro triazenes, which appear analogous to \( \alpha \)-difluoro amino derivatives. \( \alpha \)-Oxydefluorinations of \( \alpha \)-difluoro amino derivatives under acidic conditions into amides are well-reported phenomena.\(^{28}\) Noteworthy, these fluorinated triazenes display a much higher stability compared to acid-lability of normal 1-alkyl triazenes.\(^{29}\)

Taking these studies into account, we propose a plausible pathway for the formations of fluorinated products 2, 3 and 6 (Scheme 4). The first iodofluorination of 1-alkynyl triazene 1 by an electrophilic iodonium source and a fluoride anion leads to fluoro iodo alkynyl triazene 5, which is stable enough for isolation. A second iodofluorination could deliver transient diiodo difluoro intermediate 13. It is a rather unstable species depending on the conditions rapidly collapsing into either 2 or 3. When excess fluoride anions are present, the two iodides on 13 get displaced by fluorides furnishing tetrafluorinated alkyl triazene 2. In a low-fluoride environment, the iodides are instead substituted by the oxygen atom of a molecule of water from residual moisture traces present in the solvent. In combination with an electrophilic iodonium source, the liberated iodides could react with 1 to yield diiodo alkene 7, a side product that does not react further under the conditions. Essentially, the formation of 7 leads to a dead end compromising the yield of 2 and 3. Lastly, the \( \alpha \)-oxydefluorinations of 2 and 3 accounts for the observations of 6 and 4 respectively.

**Conclusions**

In summary, we have developed a mild and operationally simple tetrafluorination procedure of alkynyl triazenes employing cheap and readily accessible reagents. The
transformation provides access to alkyl triazenes containing the valuable 1,1,2,2-tetrafluoro ethylene motif. Moreover, a judicious tuning of the reaction conditions promotes an oxydifluorination pathway leading to the selective formation of α-difluoro triazene ketones. Complementary, an electrophilic fluorination of the alkynyl triazenes using Selectfluor enables access to α-difluoro acyl triazenes, which can be subsequently elaborated into α-difluoro esters or α-difluoro ketones. These three distinct fluorinative transformations represent a valuable addition to a chemist’s toolbox for the expedient synthesis of the 1,1,2,2-tetrafluoroethylene and the α-difluoro carbonyl motifs.

Author contributions

JFT and NC conceived, designed and directed the project. JFT conducted the experiments. CTB synthesized the alkynyl triazenes. All authors discussed the results and wrote the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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