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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 triazenyl 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 fluorine-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).[4] Well-established approaches allow for the transfer of difluoromethylene and $(CF_2)_n$ ($n > 2$) groups.[3a,5] In contrast, the chemistry of isolated 1,1,2,2-tetrafluoroethylene ($-CF_2CF_2-$) units[6] is less common. It remains underdeveloped compared to the structurally similar but widely-employed trifluoromethyl ($-CF_3$) and perfluoroethyl ($-C_2F_5$) 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 halotetrafluoroalkane as a CF_2CF_2 transfer group,[8] exhaustive deoxyfluorination of 1,2-diketones using organosulfur reagents[9] 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,[10a] hydrogen fluoride,[10b] xenon difluoride[10d] and iodine monofluoride or bromine monofluoride.[10c] 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 group[12] is a highly useful functionality in a broad variety of molecules having applications in anticancer therapy,[13] materials,[14] total synthesis[15] 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 triazenyl units are essential for cytotoxicity and tumor inhibitory activities in anti-cancer drugs such as dacarbazine[13b] and temozolomide.[13c] 3-Acyl triazenes have been reported in numerous bioactive compounds,[17] as synthetic precursors for aminyl radicals,[18] acylating agents[19] and chemo-dosimeters for cyanide.[20] In

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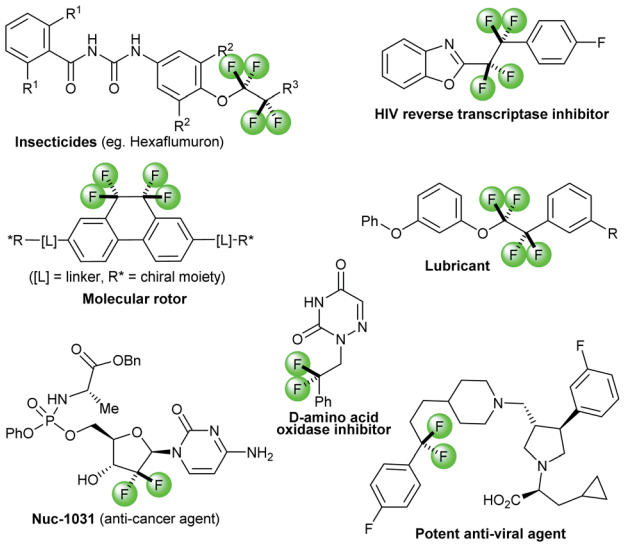
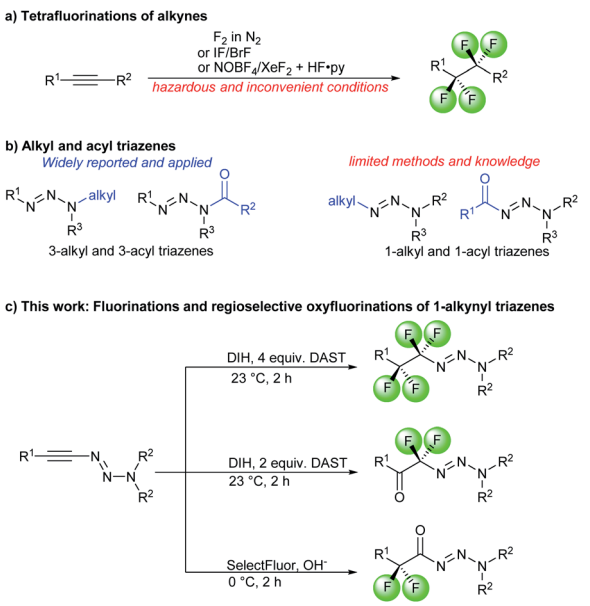


Fig. 1 Selected examples of functional molecules containing 1,1,2,2-tetrafluoroethylene and difluoromethylene linkages.



Scheme 1 Fluorinative transformations of alkynes and 1-alkynyl triazenes.

contrast, there are much less reports dealing with the synthesis and use of 1-alkyl[21] and 1-acyl triazenes.[22] Therefore, a rapid and modular access to 1-alkyl and 1-acyl triazenes would open up opportunities for investigations of their underexplored chemical and biological properties. Over the past years, the use of 1-alkynyl triazenes in organic synthesis has been receiving a growing interest.[12a,23,24] Leveraging on their ynamide-like reactivity profile,[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 α-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.

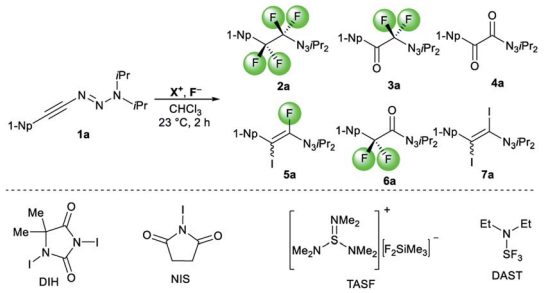
Results and discussion

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 5,5-dimethyl-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 tetrafluoroethylene 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 triazenyl 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 $\mathbf{X}^+$ did not provide an improvement in yield or selectivity, but additionally gave iodofluoro alkenyl triazene **5a**, α-difluoro acyl triazene **6a** and diiodo alkenyl triazene **7a** (entries 3–5). In most instances, these products were present only in trace amounts. The use of I_2 increased the yield of **5a**, while IBr produced more compound **3a** (entries 4 and 5).

With DIH as best electrophilic source $\mathbf{X}^+$, 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 triazenyl 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,[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

Table 1 Optimization of the formation of fluorinated alkyl triazenes[a]

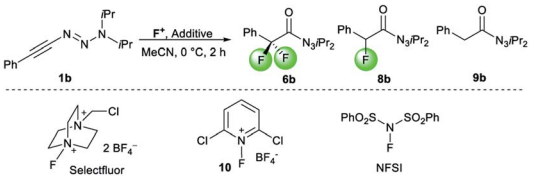


Entry	X^+	F^-	% Conv.[b]	2a [%]	3a [%]	4a [%]	5a [%]
1	DIH	HF·py	69	7	—	—	—
2	DIH	AgF	100	38	4	4	—
3	NIS	AgF	100	30	15	9	<2
4[c]	I_2	AgF	100	26	15	14	<2
5	IBr	AgF	100	8	30	17	<2
6	DIH	TBAF	100	0	0	<2	44
7	DIH	TASF	100	0	0	<2	31
8	DIH	CsF	100	0	0	<2	—
9	**DIH**	**DAST**	**100**	**92**	**0**	**0**	**—**
10[d]	DIH	DAST	100	87	0	6	—
11[d,e]	DIH	DAST	100	43	31	10	—
12[f]	**DIH**	**DAST**	**100**	**0**	**83**	**16**	**—**

[a] Conditions: 0.10 mmol **1a**, 2.5 equiv. X^+, 10.0 equiv. F^-, 0.1 M in $CHCl_3$, 23 °C for 2 h in the dark. [b] Conversion and yields determined by ^{1}H-NMR with an internal standard. [c] 11% NMR yield of **6a**. [d] 1.2 equiv. DIH, 4.0 equiv. DAST. [e] With ambient light. [f] 1.2 equiv. DIH, 2.0 equiv. DAST.

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*-fluorobenzenesulfonimide (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 2 Optimization of the formation of α-difluoro acyl triazene **6b**[a]



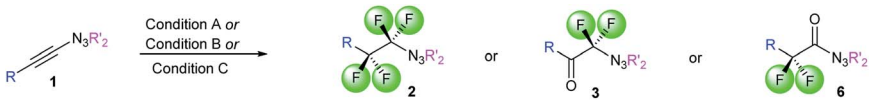
Entry	F^+	Additive (equiv.)	6b [%]	8b [%]	9b [%]
1[b]	Selectfluor	H_2O (3)	0	0	1
2	Selectfluor	H_2O (3)	44	38	2
3[c]	Selectfluor	H_2O (3)	43	40	3
4[d]	NFSI	H_2O (3)	0	37	5
5	10	H_2O (3)	0	0	6
6	Selectfluor	—	0	0	7
7	Selectfluor	2 M NaOH (3)	45	36	9
8	Selectfluor	$(Bu_4NOH)\cdot 30H_2O$ (3)	60	12	11
9	Selectfluor	$(Me_4N)OH\cdot 5H_2O$ (3)	83	9	12
10	**Selectfluor**	**$(Me_4N)OH\cdot 5H_2O$ (2.5)**	**85**[e]	**6**	**13**
11	Selectfluor	$(Me_4N)OH\cdot 5H_2O$ (1.5)	66	7	14
12	Selectfluor	$(Me_4N)OH$ in MeOH (2.5)	<5	0	15

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

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 perfluorinative 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 triazenyl 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†).[27] Noteworthy, the transformations also accommodate electron-rich heterocyclic substrates. Subjecting thienyl-substituted alkynyl 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 triazene **10** (entry 10).

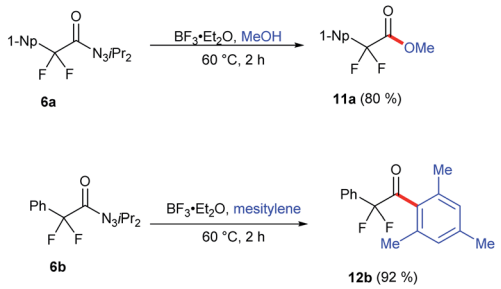
Acyl triazenes are behaving as activated carboxylic acid derivatives[21a] and could be synthetically leveraged as such. Indeed, exposure of naphthyl-substituted product **6a** to $BF_3\cdot OEt_2$ in methanol smoothly provided corresponding methyl ester **11a** (Scheme 2). Notably, Lewis-acid activation in

Table 3 Scope for the different selective perfluorination and oxyfluorinations of alkynyl triazenes[a]



Entry	1	2 (Condition A)[a]	3 (Condition B)[b]	6 (Condition C)[c]
1	**1a**	**2a** (87 %)	**3a** (92 %)	**6a** (86 %)
2	**1b**	**2b** (82 %)	**3b** (89 %)	**6b** (85 %)
3	**1c**	**2c**[d] (80 %)	**3c** (86 %)	**6c** (90 %)
4	**1d**	**2d** (93 %)	**3d**[e] (47 %)	**6d** (64 %)
5	**1e**	**2e** (90 %)	**3e** (93 %)	**6e** (83 %)
6	**1f**	**2f**[f] (56 %)	**3f**[g] (64 %)	**6f** (77 %)
7	**1g**	**2g** (77 %)	**3g**[g] (67 %)	**6g** (80 %)
8	**1h**	**2h**[h] (53 %)	**3h**[h] (33 %)	**6h** (59 %)
9	**1i**	**2i** (78 %)	**3i** (80 %)	**6i** (79 %)
10	**1j**	**10j** (54 %)		**6j** (89 %)
11	**1k**			**6k** (84 %)
12	**1l**			**6l** (63 %)
13	**1m**			**6m** (39 %)

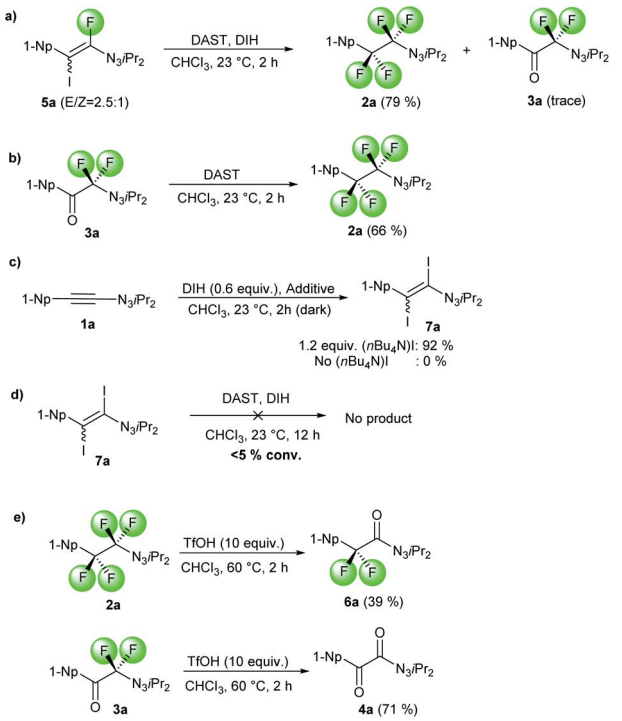
[a] Condition A: 0.1 mmol **1**, 0.12 mmol DIH, 0.4 mmol DAST, 0.1 M in $CHCl_3$ at 23 °C for 2 h in the dark. [b] Condition B: 0.1 mmol **1**, 0.12 mmol DIH, 0.2 mmol DAST, 0.1 M in $CHCl_3$ at 23 °C for 2 h in the dark. [c] Condition C: 0.1 mmol **1**, 0.25 mmol Selectfluor, 0.25 mmol $(Me_4N)OH\cdot 5H_2O$, 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.



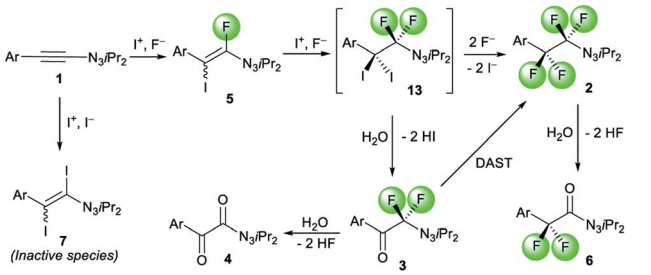
Scheme 2 Functionalization of acyl triazene **6a**.

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



Scheme 3 Reactivity and mechanistic studies.



Scheme 4 Suggested pathway map of the formation of fluorinated products and intermediates.

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 evidence 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 α-oxydefluorinations of these α-difluoro triazenes, which appear analogous to α-difluoro amino derivatives. α-Oxydefluorinations of α-difluoro amino derivatives under acidic conditions into amides are well-reported phenomena.[28] Noteworthy, theses 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 iodine source and a fluoride anion leads to fluoro iodo alkenyl 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 iodine 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 α-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 triazenyl 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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