COMMUNICATION

Synthesis of *N*-CF₃ hydrazines through radical trifluoromethylation of azodicarboxylates

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We report here the synthesis of a novel family of *N*-CF₃ hydrazines from a direct way involving the available and cheap Langlois reagent (CF₃SO₂Na). These derivatives have shown very high stability whatever the conditions used and are excellent precursors for building previously inaccessible *N*-CF₃ functionalized compounds, such as substituted hydrazides, hydrazine-amino-acids, hydrazones, *N*-aziridines and pyrazoles.

The large presence of fluorinated groups on organic compounds provides wide applications in various fields such as pharmaceuticals, agrochemicals, and materials.¹ For bioactive molecules, fluorinated substituents are often sought to improve their physico-chemical properties (e.g., high lipophilicity, pK_a decrease, conformation modification) as well as their metabolic stability. More recently, there has been renewed interest in the synthesis of heteroatom-related structures such as R_f-O, R_f-S² and R_f-N groups, although the latter are still limited.^{2a,3} Indeed, while the synthesis of R₁,R₂-*N*-CF₃ compounds and building blocks increases,^{3,4} the preparation of *N*-CF₃ hydrazines is currently very restricted. Hydrazines⁵ are important motifs for the synthesis of functionalized *N*-heterocyclic compounds⁶ and for their numerous applications in many fields of synthetic chemistry (e.g. pharmaceuticals,⁷ or peptides⁸). Consequently, there is a very strong demand for the design of new hydrazine units. Thus, an efficient and easy approach to *N*-CF₃ hydrazines will be of great interest to build new families of compounds hitherto inaccessible. In this line, we previously reported the nucleophilic trifluoromethylation only on *tert*-butylazodicarboxylate **2b** with the Ruppert-Prakash reagent in a moderate yield (30%) (Scheme 1a).⁹ On the other hand, the group of Schoenebeck described recently the synthesis of aryl *N*-CF₃ hydrazines from *N*-CF₃ carbamoyl fluorides and applied this methodology to access various derivatives (Scheme 1b).¹⁰ Considering the very few reported methodologies to reach *N*-

CF₃ hydrazines and our interest to develop new fluorinated building-blocks, we designed ready-to-use substituted unsymmetrical *N*-CF₃ hydrazines. In recent years, the bench-stable and commercially available Langlois reagent (sodium triflinate, CF₃SO₂Na, **1**) has gained increasing interest as a benign source of CF₃-radicals.¹¹ Therefore, we describe here an efficient radical *N*-trifluoromethylation of azodicarboxylates having different protecting groups to access a wide variety of *N*-CF₃ hydrazines (Scheme 1c).

Scheme 1. Principal access to *N*-CF₃ hydrazine derivatives

We initially undertook the addition of the oxidant TBHP (70% in water, 1.5 equiv.) on the solution of sodium triflinate **1** (1.5 equiv.) and diisopropyl azodicarboxylate **2a** (1 equiv.), in acetonitrile at 0 °C. After addition of the oxidant, and complete disappearance of the yellow color characteristic of the presence of **2a**, the ¹⁹F NMR of the crude revealed two compounds. The first corresponded to the *N*-trifluoromethylsulfonylated compound **4a** (-72 ppm)¹² and the second to the *N*-CF₃ hydrazide **3a** (-60 ppm) in a ratio 90/10 respectively. These conditions mainly favored the addition of triflinate rather than that of the less nucleophilic trifluoromethyl radical. The presence of catalysts such as CuI, Cu(ClO₄) promoted the nucleophilic addition at the expense of radical reaction affording exclusively the compound **4a**. To promote the radical trifluoromethylation, we thought to reverse the addition of the reagents. The triflinate **1** was added to the solution of diazene **2a** and TBHP. The expected *N*-CF₃ compound **3a** was mostly obtained. Under these conditions, the decomposition of the triflinate **1** into the CF₃ radical was preferred (Scheme 2).

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Scheme 2. Preliminary conditions

Subsequently the reaction was optimized with different solvents and oxidants. According to the different conditions listed in the table 1, the DMSO was the best solvent. The main compound **3a** was obtained in 45% after purification. The excess of the trifluoromethyl triflate and TBHP (3 and 5 equiv.) did not enhance the yield. No improvement was observed with $\text{K}_2\text{S}_2\text{O}_8$ as oxidant which required 90 °C with slow addition of trifluoromethyl triflate **1**.

Table 1. Trifluoromethylation of azodicarboxylate **2a**

Entry	T °C	Solvent	Oxidant (1.5)	3a/4a (ratio)	3a (%)
1	rt	MeCN	TBHP	90/10	34 ^[a]
2	rt	DCM/H ₂ O	TBHP	80/20	— ^[a]
3	rt	DMSO	TBHP	93/7	45
4	rt	DMSO/MeOH	TBHP	88/12	37
5	50	DMSO/H ₂ O	$\text{K}_2\text{S}_2\text{O}_8$	53/47	—
6	90	DMSO/H ₂ O	$\text{K}_2\text{S}_2\text{O}_8$	90/10	38

^a Presence of side products and one with two CF_3 groups (compound **C**).

When reactions were carried out in acetonitrile or dichloromethane, the presence of side products was observed. One of these compounds **C** was isolated (14%) and characterized, and corresponded to the bis *N*- and *O*-trifluoromethylation of the azodicarboxylate. The formation of this compound could be explained by the following mechanism (Scheme 3). First the CF_3 radical added on the diazene to give the *N*- CF_3 hydrazide radical **A**. The latter led to the expected product **3** after hydrogen atom transfer (HAT). Also, the intermediate **A** could isomerize into the intermediate **B** to react with the CF_3 radical to afford the compound **C**.

Scheme 3. Proposed mechanism

The presence of the hydrazine ($\text{iPrO}_2\text{CNH-NHCO}_2\text{iPr}$) which can be recovered (15-20%), was also observed at the end of the

reaction and could be due to radical chain and H-bond abstraction pathways. Attempts to trap the nitrogen radical of **A** have been undertaken. Unfortunately, whatever the scavenger used (hydroquinone, alkanes, alcohols for example), no improvement was observed. Optimized conditions have been performed with other commercially available azodicarboxylate derivatives such as *t*Bu **2b**, Et **2c**, Bn **2d** (Scheme 4). The *N*- CF_3 hydrazides **3b** and **3c** were obtained in 57 and 48% yields, respectively. The structure of **3b** was determined by X-ray crystallographic analysis.¹³ From **2d**, yield was low and led to a mixture of side products. The reaction was then extended to unsymmetric azodicarboxylates to get access to dissymmetric and free *N*- CF_3 hydrazides. The addition of the trifluoromethyl triflate **1** was performed on a series of Boc-protected azodicarboxylates **2e-h** with esters, ketones and phenyl groups. Reactions led to a mixture of inseparable regioisomers **3e/3'e** and **3f/3'f** isolated in moderate yield, 46% (60/40) and 41% (50/50), respectively. Hydrazides **3g/3'g** and **3h/3'h** were obtained in 29% (23/77) and 32% (22/78). Concerning the diazenes with carboxamides, complete decomposition was observed from the 1,1'-(azodicarbonyl)-dipiperidine and no reaction occurred from the *tert*-butyl-2-(methyl(phenyl)carbamoyl) diazene-1-carboxylate and the *tert*-butyl-2-(phenylcarbamoyl) diazene-1-carboxylate (Scheme 4).

^a Presence of the $\text{CF}_3\text{SO}_2\text{NZ}'\text{-NZ}$ **4**, < 10%

Scheme 4. Trifluoromethylation of azodicarboxylates

Hydrazines are often used to build peptidomimetics and induce conformations in peptides.⁷ We therefore set out to combine the *N*-CF₃ hydrazine with an amino acid. To access the diazenes **7-8**, which has never been reported before, we first prepared the hydrazine Boc amino-acids **5-6** by coupling the *tert*-butylcarbazate with the alanine.¹⁴ Then the hydrazides **5-6** were treated under classical conditions with NBS and pyridine in dichloromethane at 0 °C or at -78 °C.¹⁵ Unfortunately, the diazene could not be isolated due to its instability. A one pot sequential reaction was then undertaken in DMSO as solvent. After total conversion of the hydrazides **5-6** into diazene with NBS and pyridine (30 min. at room temperature), the TBHP was added and then the aqueous solution of the triflate **1**. Thanks to these new conditions, the *N*-CF₃ hydrazides **9-9'** and **10-10'** could be obtained in 51 and 26% yield in two steps with a ratio of 48/52 and 40/60, respectively (Scheme 5). Interestingly each regioisomers could be easily separated on silica gel. It should be noted that at the end of the reaction the starting hydrazines **5-6** are present and can be recovered after purification (15-27%).

Scheme 5. *N*-trifluoromethylation of aminoacid-diazenes

Another main challenge was to obtain free and deprotected *N*-CF₃ hydrazine building-blocks. Accordingly, we attempted the deprotection of the compound **3b** with HCl (4 N in dioxane). Thankfully CF₃NHNH₂.HCl **11** was obtained and could be characterized (see S.I.) but is too unstable to be stored for several days even at low temperature. A one-pot approach was thus carried out to trap directly **11** in the medium with 1,3-diones to give the corresponding *N*-CF₃ pyrazoles **12** (scheme 6). To date, there are very few methods for accessing *N*-CF₃ pyrazoles. The first involves the use of CF₂Br₂, a known ozone-depleting reagent, followed by fluorination.^{2,3} The second involves the electrophilic *N*-trifluoromethylation of pyrazoles with Togni's reagent.¹⁶ Thus our new approach is an excellent alternative to the synthesis of *N*-CF₃ pyrazoles. In addition, studies have shown that the *N*-CF₃ pyrazoles have excellent stability in aqueous media, improved metabolic stability, and higher lipophilicity.¹⁷

Scheme 6. Synthesis of *N*-CF₃ pyrazoles

Then deprotection of the unsymmetrical *N*-CF₃ hydrazides (as a mixture of regioisomers) was carried out with HCl (4 N in dioxane) overnight (Scheme 7). The Boc group could be removed to afford the clean and stable corresponding *N*-CF₃

hydrazides **13-20**. From the hydrazides **3f/3'f**, only the hydrazide **13** which sublimes slowly at room temperature, could be recovered at the end of the reaction with a not optimized yield of 38%. Unfortunately, the compound **14** is too volatile to be isolated, although detected in fluorine NMR at -60 ppm (see S.I.). The products **3g/3'g** afforded the hydrazides **15** and **16** in good yield (73%), easily separated on silica gel. In the case of the aminoacid-hydrazides **9/9'** and **10/10'**, each molecule has been treated independently to lead pure hydrazides **17**, **18** and as chlorhydrate salts **19**, **20**, respectively. Chiral HPLC analysis of the hydrazines **17**, **18** showed no racemisation of the stereocenter of the amino acid following three reactions carried out from **6** (see S.I.). We unambiguously determined the structure of molecules **18**, **19** thanks to the achievement of their X-ray analyses.¹⁸ By comparing the different X-ray analyses of compounds **3b**, **18** and **19**, the N-N-CF₃ length bond was observed in a range of 1.381-1.413 Å showing an interesting influence of the CF₃ group, while in the nonfluorinated derivatives, the length is around 1.454 Å.¹⁹ For the compound **19**, interactions with hydrogen were also observed between F...H-N (d 2.292 Å, ∠ 72.42°) and F...H-C of the methyl group (d 2.433 Å, ∠ 152.06°). In addition, it is important to note that these new H-N(CF₃)-NHCOR units have so far been unexplored (Scheme 7).

a The hydrazine **14** was too volatile to be isolated.

Scheme 7. Deprotection under acidic conditions

The *N*-debenzylation of the hydrazides **3g/3'g** was also carried out in the presence of Pd/C under atmosphere of H₂. The *N*-CF₃ hydrazide **21** was isolated in a moderate yield of 38% due to its sublimation. The product **22** was detected in the ¹⁹F NMR of the crude but is too volatile to obtain pure (Scheme 8).

Scheme 8. Hydrogenolysis of **3g/3'g**.

The potential of certain *N*-CF₃ hydrazides has been studied in some reactions to elaborate for the first-time inaccessible compounds. To illustrate their reactivity, we carried out some reactions on the *N*-CF₃ hydrazides **15** and **16** (Scheme 9). First

the hydrazide **15** could be oxidized into diazene **23** after treatment with NBS and pyridine in DCM in quantitative yield. Then, C–H amination was carried out between the *N*-CF₃-azocarboxylate **23** and the *N*-dimethylaniline in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)²⁰ to afford the corresponding hydrazine **24** with excellent regioselectivity and good yield (71% in 2 steps). Interestingly, from the hydrazide **16**, the benzyl (*N*-trifluoromethyl) carbamate **25** was obtained after treatment with sodium nitrite and HCl in dichloromethane, which is a stable form of the trifluoromethylamine. The benzyl hydrazide **27** was isolated after reduction of the corresponding hydrazone **26** formed from the benzaldehyde and **16**. The aziridination reaction²¹ could be realized easily in the presence of (diacetoxyiodo)benzene and the methyl *trans*-4-(trifluoromethyl)cinnamate to afford the *N*-CF₃ aminoaziridine **28** in excellent yield (83%). According to the reactions involved, it was observed that the different *N*-CF₃ hydrazines exhibited a very high chemical stability.

Scheme 9. Reactivity of the 1-*N*-CF₃ hydrazides **15** and **16**.

In conclusion, we developed a new pathway to *N*-CF₃ hydrazides prepared by the addition of the CF₃ radical generated *in situ* from sodium triflinate on symmetric and unsymmetric azodicarboxylates. This reaction could also be carried out on diazenes comprising amino acids to afford regioisomers of *N*-CF₃-hydrazide peptidomimetics. The *N*-CF₃ products with removable protecting groups could generate RCO-*N*(CF₃)-NH₂ and H-*N*(CF₃)-NHCOR hydrazines. We believe that these hydrazines will find applications in the synthesis of new compounds such as the discovery of drugs by improving pharmacokinetics but also in the fields of agrochemistry and materials.

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Conflicts of interest

There are no conflicts to declare.

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