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## COMMUNICATION

Synthesis of *N*-CF<sub>3</sub> hydrazines through radical trifluoromethylation of azodicarboxylates

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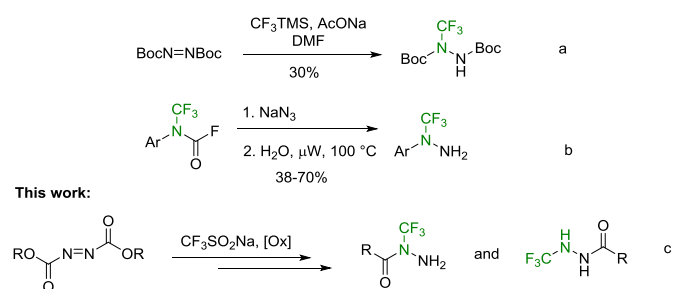
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**We report here the synthesis of a novel family of *N*-CF<sub>3</sub> hydrazines from a direct way involving the available and cheap Langlois reagent (CF<sub>3</sub>SO<sub>2</sub>Na). These derivatives have shown very high stability whatever the conditions used and are excellent precursors for building previously inaccessible *N*-CF<sub>3</sub> 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.<sup>1</sup> For bioactive molecules, fluorinated substituents are often sought to improve their physico-chemical properties (e.g., high lipophilicity, pKa 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 Rf-*O*, Rf-*S*<sup>2</sup> and Rf-*N* groups, although the latter are still limited.<sup>2a,3</sup> Indeed, while the synthesis of R<sub>1</sub>,R<sub>2</sub>-*N*-CF<sub>3</sub> compounds and building blocks increases,<sup>3,4</sup> the preparation of *N*-CF<sub>3</sub> hydrazines is currently very restricted. Hydrazines<sup>5</sup> are important motifs for the synthesis of functionalized *N*-heterocyclic compounds<sup>6</sup> and for their numerous applications in many fields of synthetic chemistry (e.g. pharmaceuticals,<sup>7</sup> or peptides<sup>8</sup>). Consequently, there is a very strong demand for the design of new hydrazine units. Thus, an efficient and easy approach to *N*-CF<sub>3</sub> 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).<sup>9</sup> On the other hand, the group of Schoenebeck described recently the synthesis of aryl *N*-CF<sub>3</sub> hydrazines from *N*-CF<sub>3</sub> carbamoyl fluorides and applied this methodology to access various derivatives (Scheme 1b).<sup>10</sup> Considering the very few reported methodologies to reach *N*-

CF<sub>3</sub> hydrazines and our interest to develop new fluorinated building-blocks, we designed ready-to-use substituted unsymmetrical *N*-CF<sub>3</sub> hydrazines. In recent years, the bench-stable and commercially available Langlois reagent (sodium triflinate, CF<sub>3</sub>SO<sub>2</sub>Na, **1**) has gained increasing interest as a benign source of CF<sub>3</sub>-radicals.<sup>11</sup> Therefore, we describe here an efficient radical *N*-trifluoromethylation of azodicarboxylates having different protecting groups to access a wide variety of *N*-CF<sub>3</sub> hydrazines (Scheme 1c).



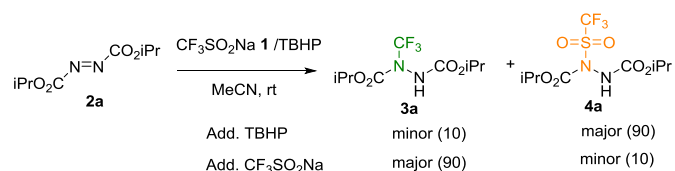
**Scheme 1.** Principal access to *N*-CF<sub>3</sub> hydrazine derivatives

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 <sup>19</sup>F NMR of the crude revealed two compounds. The first corresponded to the *N*-trifluoromethylsulfonylated compound **4a** (-72 ppm)<sup>12</sup> and the second to the *N*-CF<sub>3</sub> 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(ClO<sub>4</sub>) 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*-CF<sub>3</sub> compound **3a** was mostly obtained. Under these conditions, the decomposition of the triflinate **1** into the CF<sub>3</sub> radical was preferred (Scheme 2).

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**Scheme 2.** Preliminary conditions

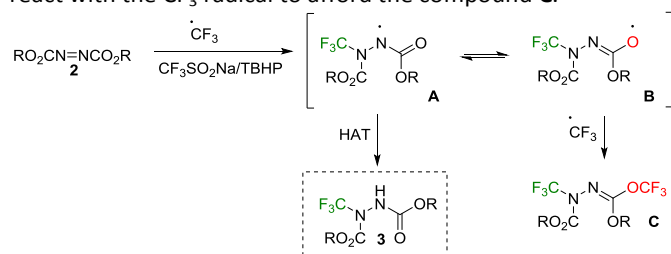
Subsequently the reaction was optimized with different solvents and oxidants. According to the different conditions listed in the table 1, the DMSO was the best solvent. The main compound **3a** was obtained in 45% after purification. The excess of the triflinate and TBHP (3 and 5 equiv.) did not enhance the yield. No improvement was observed with K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> as oxidant which required 90 °C with slow addition of triflinate **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 <sup>[a]</sup> |
| 2     | rt   | DCM/H <sub>2</sub> O  | TBHP   | 80/20         | - <sup>[a]</sup>  |
| 3     | rt   | <b>DMSO</b>           | <b>TBHP</b>                                  | <b>93/7</b>   | <b>45</b>         |
| 4     | rt   | DMSO/MeOH             | TBHP   | 88/12         | 37                |
| 5     | 50   | DMSO/H <sub>2</sub> O | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> | 53/47         | -                 |
| 6     | 90   | DMSO/H <sub>2</sub> O | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> | 90/10         | 38                |

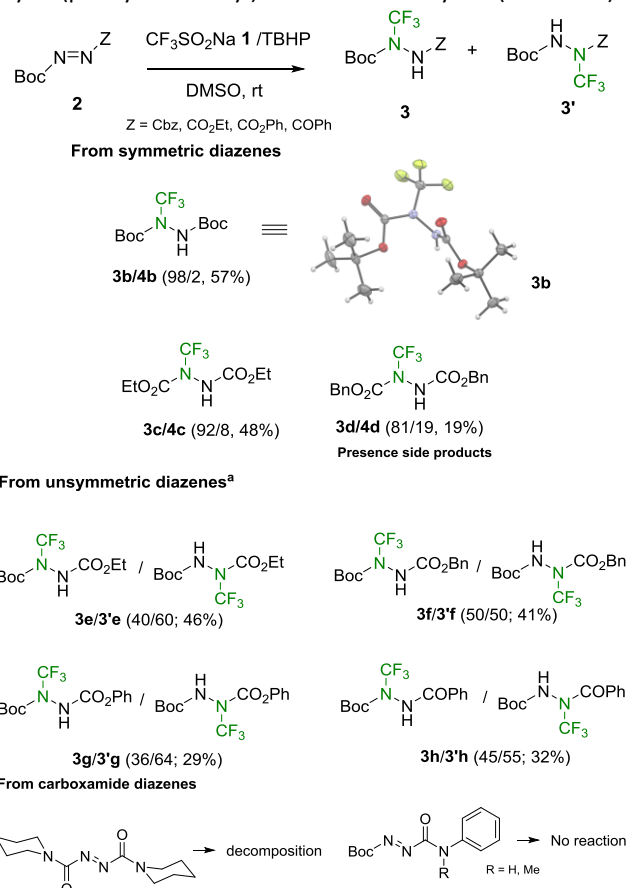
<sup>a</sup> Presence of side products and one with two CF<sub>3</sub> groups (compound **C**).

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<sub>3</sub> radical added on the diazene to give the *N*-CF<sub>3</sub> 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<sub>3</sub> radical to afford the compound **C**.

**Scheme 3.** Proposed mechanism

The presence of the hydrazine (iPrO<sub>2</sub>CNH-NHCO<sub>2</sub>iPr) which can be recovered (15-20%), was also observed at the end of the

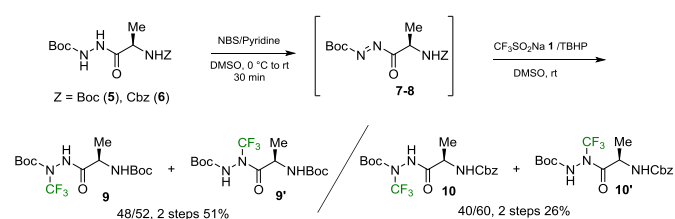
reaction and could be due to radical chain and H-bond abstraction pathways. Attempts to trap the nitrogen radical of **A** have been undertaken. Unfortunately, whatever the scavenger used (hydroquinone, alkanes, alcohols for example), no improvement was observed. Optimized conditions have been performed with other commercially available azodicarboxylate derivatives such as *t*Bu **2b**, Et **2c**, Bn **2d** (Scheme 4). The *N*-CF<sub>3</sub> hydrazides **3b** and **3c** were obtained in 57 and 48% yields, respectively. The structure of **3b** was determined by X-ray crystallographic analysis.<sup>13</sup> 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<sub>3</sub> hydrazides. The addition of the triflinate **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).



<sup>a</sup> Presence of the CF<sub>3</sub>SO<sub>2</sub>NZ'-NZ **4**, < 10%

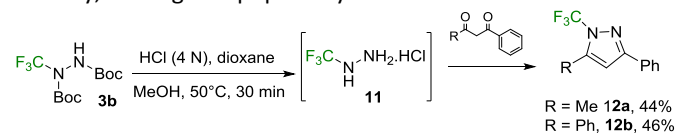
**Scheme 4.** Trifluoromethylation of azodicarboxylates

Hydrazines are often used to build peptidomimetics and induce conformations in peptides.<sup>7</sup> We therefore set out to combine the *N*-CF<sub>3</sub> 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.<sup>14</sup> Then the hydrazides **5-6** were treated under classical conditions with NBS and pyridine in dichloromethane at 0 °C or at -78 °C.<sup>15</sup> 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 triflinate **1**. Thanks to these new conditions, the *N*-CF<sub>3</sub> 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

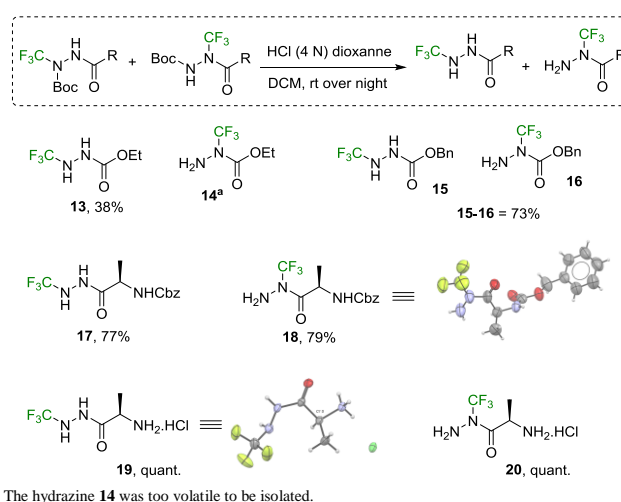
Another main challenge was to obtain free and deprotected *N*-CF<sub>3</sub> hydrazine building-blocks. Accordingly, we attempted the deprotection of the compound **3b** with HCl (4 N in dioxane). Thankfully CF<sub>3</sub>NHNH<sub>2</sub>.HCl **11** was obtained and could be characterized (see S.I.) 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*-CF<sub>3</sub> pyrazoles **12** (scheme 6). To date, there are very few methods for accessing *N*-CF<sub>3</sub> pyrazoles. The first involves the use of CF<sub>2</sub>Br<sub>2</sub>, a known ozone-depleting reagent, followed by fluorination.<sup>2,3</sup> The second involves the electrophilic *N*-trifluoromethylation of pyrazoles with Togni's reagent.<sup>16</sup> Thus our new approach is an excellent alternative to the synthesis of *N*-CF<sub>3</sub> pyrazoles. In addition, studies have shown that the *N*-CF<sub>3</sub> pyrazoles have excellent stability in aqueous media, improved metabolic stability, and higher lipophilicity.<sup>17</sup>



**Scheme 6.** Synthesis of *N*-CF<sub>3</sub> pyrazoles

Then deprotection of the unsymmetrical *N*-CF<sub>3</sub> 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*-CF<sub>3</sub>

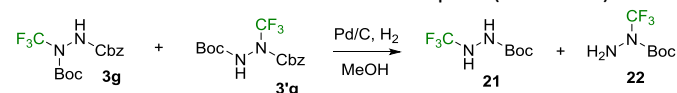
hydrazides **13-20**. From the hydrazides **3f/3'f**, only the hydrazide **13** which sublimes slowly at room temperature, could be recovered at the end of the reaction with a not optimized yield of 38%. Unfortunately, the compound **14** is too volatile to be isolated, although detected in fluorine 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.<sup>18</sup> By comparing the different X-ray analyses of compounds **3b**, **18** and **19**, the *N*-*N*-CF<sub>3</sub> length bond was observed in a range of 1.381-1.413 Å showing an interesting influence of the CF<sub>3</sub> group, while in the nonfluorinated derivatives, the length is around 1.454 Å.<sup>19</sup> 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(CF<sub>3</sub>)-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

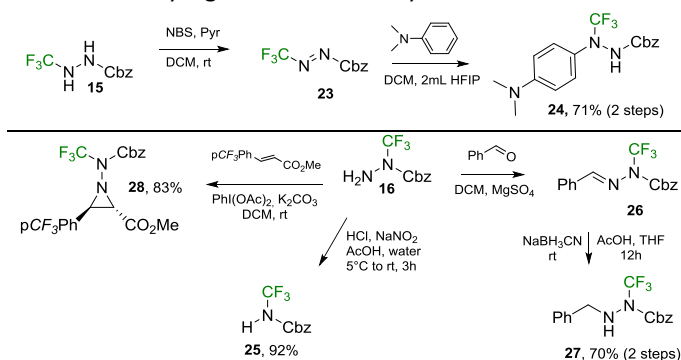
The *N*-debenzylation of the hydrazides **3g/3'g** was also carried out in the presence of Pd/C under atmosphere of H<sub>2</sub>. The *N*-CF<sub>3</sub> hydrazide **21** was isolated in a moderate yield of 38% due to its sublimation. The product **22** was detected in the <sup>19</sup>F NMR of the crude but is too volatile to obtain pure (Scheme 8).



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

The potential of certain *N*-CF<sub>3</sub> 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*-CF<sub>3</sub> 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*-CF<sub>3</sub>-azocarboxylate **23** and the *N*-dimethylaniline in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)<sup>20</sup> 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 reaction<sup>21</sup> could be realized easily in the presence of (diacetoxy)iodobenzene and the methyl *trans*-4-(trifluoromethyl)cinnamate to afford the *N*-CF<sub>3</sub> aminoaziridine **28** in excellent yield (83%). According to the reactions involved, it was observed that the different *N*-CF<sub>3</sub> hydrazines exhibited a very high chemical stability.



**Scheme 9.** Reactivity of the 1-*N*-CF<sub>3</sub> hydrazides **15** and **16**.

In conclusion, we developed a new pathway to *N*-CF<sub>3</sub> hydrazides prepared by the addition of the CF<sub>3</sub> 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*-CF<sub>3</sub>-hydrazide peptidomimetics. The *N*-CF<sub>3</sub> products with removable protecting groups could generate RCO-*N*(CF<sub>3</sub>)-NH<sub>2</sub> and H-*N*(CF<sub>3</sub>)-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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