Synthesis of trifluoromethylated 2H-azirines through Togni reagent-mediated trifluoromethylation followed by PhIO-mediated azirination

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Abstract
The reaction of enamine compounds with the Togni reagent in the presence of CuI afforded β-trifluoromethylated enamine intermediates, which were converted directly to biologically interesting trifluoromethylated 2H-azirines by an iodosobenzene (PhIO)-mediated intramolecular azirination in a one-pot process.

Introduction
The trifluoromethyl group is a striking structural motif, which can be widely found in the fields of pharmaceutical and agrochemical sciences. The introduction of this functional group in drug molecules can enhance their chemical and metabolic stability, improve their lipophilicity and bioavailability, and increase protein-binding affinity [1-6]. In this regard, the CF₃ group has been introduced into many pharmaceutical agents [7-16]. For example, fluoxetine hydrochloride (Figure 1, A) [4,9,10] (Prozac®, an antidepressant and a selective serotonin reuptake inhibitor for the treatment of major depressive disorders, obsessive–compulsive disorders, etc.), teriflunomide (Figure 1, B) [11-13] (Aubagio®, the active metabolite of leflunomide for the treatment of multiple sclerosis), and pleconaril (Figure 1, C) [14-16] (an antiviral drug), all possess this privileged substituent. Although many useful synthetic methods [17-21] have been established for introducing the CF₃
group into various organic molecules, the further development of novel routes for the selective trifluoromethylation is of continuing interest for synthetic and medicinal chemists.

Togni reagents, including 1-(trifluoromethyl)-1,2-benziodoxol-3(1H)-one (1) and trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (1'), are effective and efficient hypervalent iodine reagents for trifluoromethylation reactions of a variety of substrates [22,23]. These reagents have found wide applications in the area of organofluorine chemistry, synthetic method development as well as medicinal chemistry [24-40]. For example, the Togni reagents have been successfully applied to introduce the CF$_3$ group into pharmaceutical agents such as the fluoxetine derivative D (Figure 1), the mefloquine derivative E [41] and compound F [42] – a potential anti-HIV drug bearing a NCF$_3$ moiety.

$2H$-Azirines are a class of highly strained and reactive molecules containing a C–N double bond. The exclusive framework can be found in some natural products [43-47], which were shown to possess antibiotic activities [43,44]. Furthermore, compounds with this structural motif are also useful building blocks for the synthesis of functionalized amino derivatives and N-containing heterocyclic derivatives [48-51]. Thus, this class of compounds has gained considerable attention from synthetic chemists and many useful synthetic approaches [52-55] have been developed for accessing this exclusive class of heterocycles. In our previous works, we have realized the application of hypervalent iodine reagents for the construction of the $2H$-azirine skeleton starting from enamines 2 via intramolecular oxidative cyclization (Scheme 1) [56,57]. When the R$^2$ substituent is alkyl or aryl, the corresponding substrates 2 were converted to a series of alkylated or arylated $2H$-azirines 3 in the presence of phenyliodine diacetate (PIDA) in 1,2-dichloro-
ethane (DCE) [56]. Alternatively, the treatment of β-unsaturated enamine substrates \((2, R^2 = H)\) with PhIO in 2,2,2-trifluoroethanol (TFE) afforded 2-trifluoroethoxy-2H-azirines 4 [57]. The latter process involves an intermolecular oxidative trifluoroethoxylation and the subsequent oxidative intramolecular azirination. In continuation of our interest in the construction of the 2H-azirine skeleton bearing versatile substituents, we herein report that the biologically interesting CF\(_3\) group can be incorporated into the privileged 2H-azirine framework through the Togni reagent 1-mediated trifluoromethylation followed by PhIO-mediated azirination in a one-pot process.

**Results and Discussion**

It is well documented that Togni reagents can realize the direct trifluoromethylation of alkenes [58-60] and electron-rich enamides [61]. Inspired by this, we envisaged that Togni reagent 1 could also enable the introduction of a CF\(_3\) group to the β-position of enamine substrates, and the so-obtained trifluoromethylated enamines could undergo a hypervalent iodine-mediated intramolecular azirination to give the corresponding trifluoromethylated 2H-azirines [56,57]. To test this conversion, the readily available enamine 5a was used as a model substrate. The treatment of 5a with Togni reagent 1 in the presence of Cul in N,N-dimethylformamide (DMF) [62] at room temperature for two hours afforded the β-trifluoromethylated enamine 6a in a 23% yield. Subjecting enamine 6a to PhIO in 1,2-dichloroethane (DCE) for 12 hours at room temperature led to the formation of the desired β-trifluoromethylated 2H-azirine 7a in a yield of 60% (Scheme 2).

In order to make the synthesis of β-trifluoromethylated 2H-azirine more concise and convenient, we were keen to probe whether the two-step synthesis could be combined into a one-pot process. For this purpose, we first carried out the reaction of Togni reagent 1 and 5a in the presence of Cul in DMF at room temperature, followed by an addition of PhIO. However, only trace amounts of the expected product 7a were obtained (Table 1, entry 1). We next screened various solvents to

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**Table 1: Optimization of reaction conditions.**

| Entry | Catalyst | Oxidant | Solvent | Temp. (°C) | Yield (%) |
|-------|----------|---------|---------|------------|-----------|
| 1     | Cul      | PhIO    | DMF     | rt         | trace     |
| 2     | Cul      | PhIO    | CH\(_3\)CN | rt   | 13        |
| 3     | Cul      | PhIO    | DCE     | rt         | 24        |
| 4     | Cul      | PhIO    | toluene | rt         | 12        |
| 5     | Cul      | PhIO    | DCE     | 40         | 35        |
| 6     | Cul      | PhIO    | DCE     | 60         | 55        |
| 7     | Cul      | PhIO    | DCE     | reflux     | 48        |
| 8     | CuCl     | PhIO    | DCE     | 60         | 49        |
| 9     | CuBr     | PhIO    | DCE     | 60         | 50        |
| 10    | CuOAc    | PhIO    | DCE     | 60         | 38        |
| 11    | Cul      | PIDA    | DCE     | 60         | 46        |
| 12    | Cul      | PIFA    | DCE     | 60         | 30        |

\(\text{a}\)Reaction conditions: Togni reagent 1 (1.2 mmol), 5a (1.0 mmol), catalyst (0.2 mmol), oxidant (1.5 mmol) in solvent (10 mL) unless otherwise stated.

\(\text{b}\)The oxidant was added to the reaction mixture after the substrate 5a was completely consumed (TLC analysis).\(\text{c}\)isolated yield.
increase the reaction outcome (Table 1, entries 1–4). Judging by the yield of the desired product, it was concluded that DCE was the best solvent (Table 1, entry 3). By increasing the reaction temperature from rt to 60 °C, the yields significantly increased to 55% (Table 1, entries 3, 5 and 6). However, an attempt to improve the product yield by operating the reaction at a higher temperature was unsuccessful (Table 1, entry 7). Replacing the catalyst CuI with other commonly used copper catalysts including CuCl, CuBr and CuOAc led to a decreased yield in each case (Table 1, entries 8–10). In addition, the other commonly employed hypervalent iodine(III) reagents, namely, PIDA and phenyliodine bis(trifluoroacetate) (PIFA) were tested, but the results indicated that they were ineffective to further improve the yields (Table 1, entries 11 and 12).

With the optimized conditions in hand, we next explored the substrate scope for this newly established one-pot oxidative trifluoromethylation and azirination reaction. As shown in Scheme 3, a variety of substrates bearing halogen substituents at the ortho, meta and para-positions of the phenyl ring in the substrates were converted to the expected 2H-azirines 7b–e in 45–65% one-pot yield. Notably, the substrate having a trifluoromethyl group at the meta-position in the phenyl ring also afforded the desired 2H-azirine product 7f bearing two CF₃ sub-

**Scheme 3:** Togni reagent/PhIO-mediated one-pot synthesis of β-trifluoromethyl 2H-azirines. Reaction conditions: 1 (1.2 mmol), 5 (1.0 mmol), CuI (0.2 mmol), PhIO (1.5 mmol) in DCE (10 mL) unless otherwise stated. PhIO was added to the reaction mixture after the substrate 5 was completely consumed (TLC analysis). Yields refer to isolated yields.
stituents in a satisfactory one-pot yield. Various enamine sub-
strates with electron-donating groups (p-Me, o-Me and 3,4-di-
O Me) in the aryl ring, also reacted efficiently under the con-
tions of the one-pot process to afford the corresponding prod-
ucts 7g–i in a yield of 40–67%. Furthermore, when replacing
the methoxycarbonyl group in 5a with a cyano or N-methyl-N-
phenylformyl group, the corresponding substrates 5j and 5k
were converted to the desired products 7j and 7k in a yield of
49% and 57%, respectively. The methoxy group in the ester
moiety could also be replaced by the n-butoxy group, with the
desired product 7l being isolated in a yield of 62%. In addition,
this method was also applicable to substrates bearing naphthyl
or thienyl groups at R substitution to give the desired products
7m and 7n in a yield of 43% and 45%, respectively. However,
the method was not applicable to the substrate bearing an alkyl
group, as the reaction of 5o, even at lower temperatures
(−20 °C, 0 °C, 20 °C and 40 °C) gave a complex mixture after
adding PhIO.

To gain further insights into the reaction mechanism, 2,2,6,6-
tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical
scavenger, was introduced to the model reaction (Scheme 4)
following the method previously reported in the literature [63].
It was found that the trifluoromethylation was hampered and the
TEMPO-CF₃ adduct 8 was formed as a major product based on
the analysis of its $^{19}\text{F}$ NMR (δ −55.67).

The above results from the experiment provided supportive evi-
dence that the CF₃ radical was likely involved as a reactive
species in the reaction process. Based on this and previous
reports [62-68], a possible reaction pathway has been proposed
and is outlined in Scheme 5. Initially, CuI catalytically acti-
vates the Togni reagent 1, leading to the formation of the CF₃-
containing radical intermediate 9. Decomposition of the inter-
mediate 9 produces (2-iodobenzoyloxy)copper(II) iodide (10)
[65,66] with the simultaneous release of a CF₃ radical. Then,
the reaction of enamine 5a with the CF₃ radical affords the car-
bon-centered radical 11. Next, the reaction of 10 and 11, possibly through an electron-transfer process, along with the conversion of intermediate 10 to 2-iodobenzoic acid enables the conversion of intermediate 11 to 6a (possibly tautomerized from its imine isomer) [69]. Finally, the β-trifluoromethylated enamine 6a undergoes intramolecular azirination affording the corresponding β-trifluoromethylated 2H-azirine via a known pathway [56,57].

Conclusion
In summary, we have reported an efficient hypervalent iodine-mediated trifluoromethylation and azirination process. In this transformation, the introduction of the CF3 group to the β-position of enamines followed by the intramolecular azirination was realized in a one-pot process, providing a general and straightforward access to biologically interesting trifluoromethylated 2H-azirine compounds. This method features mild reaction conditions, a simple operation, and metal-free characteristics. The presence of both, the biologically interesting CF3 group and the 2H-azirine skeleton in the products obtained might making them interesting for further applications in biological studies.

Supporting Information
Supporting Information File 1
Synthetic details and characterization data.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-123-S1.pdf]

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