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# In situ generated CF<sub>3</sub>CHN<sub>2</sub> with 3-ylideneoxindoles to access CF<sub>3</sub>-containing pyrazolo[1,5-c] quinazolines derivatives†

Ming-Cheng Hu,<sup>a</sup> Hai-Tao Zhou,<sup>a</sup> Yu-Chen Fang,<sup>a</sup> Li-Ren Zhang,<sup>a</sup> Bao-Dong Cui,<sup>ab</sup> Yong-Zheng Chen \*\* and Mei Bai \*\* \*\* and Mei Bai \*\* \*\* \*\*

Toward a selective and facile method for the synthesis of CF<sub>3</sub>-containing pyrazolo[1,5-c]quinazolines, we developed a [3 + 2] cycloaddition/1,3-H shift/rearrangement/dehydrogenation cascade involving in situ generated CF<sub>3</sub>CHN<sub>2</sub> and 3-ylideneoxindoles with DBU as a base. The reaction is distinguished by its mild conditions, metal-free process, operational simplicity, and broad functional group tolerance, thus presenting a convenient protocol for the construction of pyrazolo[1,5-c]quinazolines that are of interest in medicinal chemistry.

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### Introduction

The trifluoromethyl group, which can be regarded as a classical group in drugs and drug candidates, was introduced to modulate physicochemical properties and increase the binding affinity of molecules. For instance, the drugs Prozac, Celebrex and Januvia are all active agents.1 Therefore, the introduction of the trifluoromethyl group is of great interest in various areas of organic and medicinal chemistry.2 In particular, direct trifluoromethylation plays a pivotal part in organic chemistry. Numerous methods have been demonstrated to be able to promote C(sp<sup>2</sup>)-CF<sub>3</sub> bond formation, including nucleophilic trifluoromethylation,3 electrophilic trifluoromethylation,4 and radical trifluoromethylation.5 In recent years, radical trifluoromethylation has been explored as a powerful tool for the construction of the C(sp<sup>2</sup>)-CF<sub>3</sub> bond.<sup>6</sup> Trifluoromethyl free radicals serve as active species in radical trifluoromethylation.<sup>7</sup>

Alternatively, other routes based on the chemical conversions of CF<sub>3</sub>-containing building blocks, especially trifluorodiazoethane (CF3CHN2),9 have emerged as a valuable reagent for introducing trifluoromethyl groups into heterocyclic compounds.  $CF_3CHN_2$  readily participates in [2 + 1]-, [3 + 2]-, and [3 + 3]-cycloaddition reactions as a trifluoromethylcontaining dipole, thereby creating new approaches to synthesize CF<sub>3</sub>-containing heterocycles. 10 This impressive work

Owing to the significant biological activities of both quinazoline and pyrazole derivatives, pyrazolo[1,5-c]quinazolines formed by N-fusing quinazolines with pyrazoles have occupied an important position in drug design. Examples of the biological activities of pyrazolo[1,5-c]quinazolines include Gly/NMDA antagonists,12 phosphodiesterase inhibitors,13 10A benzodiazepine/adenosine receptors,14 and AMPA receptors (Fig. 1).15 Accordingly, considerable efforts have been undertaken to develop efficient synthetic strategies for these

benzodiazepine receptor

Fig. 1 Some biologically active compounds with a pyrazolo[1,5-c] quinazoline core.

AMPA receptors

stemmed from a study by the group of Xiao and Lu,11 who reported a [3 + 2] cycloaddition/ring contraction sequence of 3ylideneoxindoles with in situ generated CF3CHN2 without a transition-metal catalyst. Initial [3 + 2] cycloaddition occurred smoothly to give corresponding cycloadducts, and the subsequent ring contraction reaction worked very well in refluxing PhMe to afford the final CF<sub>3</sub>-substituted 3,3'-cyclopropyl spirooxindoles.

<sup>&</sup>lt;sup>a</sup>Key Laboratory of Biocatalysis & Chiral Drug Synthesis of Guizhou Province, School of Pharmacy, Zunyi Medical University, Zunyi 563000, China

<sup>&</sup>lt;sup>b</sup>Key Laboratory of Basic Pharmacology of Ministry of Education, Joint International Research Laboratory of Ethnomedicine of Ministry of Education, Zunyi Medical University, Zunyi 563000, China

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metal-free process

Scheme 1 Applications of *in situ* generated  $CF_3CHN_2$  in the construction of  $CF_3$ -containing N-heterocycles.

operational simplicity

mild conditions

fascinating bioactive molecules. However, some involved multistep synthesis, harsh reaction conditions, lower yields, or poor chemoselectivity. Therefore, the development of readily available and easily accessible pyrazolo[1,5- $\epsilon$ ]quinazolines is exciting and practically useful.

In 2021, we reported a visible-light-induced [3 + 2] cycloaddition of α-ketoacids with a hypervalent iodine(III) reagent derived from in situ generated CF<sub>3</sub>CHN<sub>2</sub> for the synthesis of 5-CF<sub>3</sub>-1,3,4-oxadiazoles (Scheme 1A).<sup>17</sup> Recently, a novel sulfonium salt derived from in situ generated CF3CHN2 was prepared by our group, and it was applied in Rh-catalyzed [2 + 1 + 2]cycloadditions to afford imidazo[1,5-a] N-heterocycles (Scheme 1B).18 As part of our continuing interests in organic fluorine chemistry,19 as well as our recent progress in cycloadditions for the synthesis of N-heterocycles from in situ generated CF<sub>3</sub>CHN<sub>2</sub> and its derivatives,  $^{17-19}$  we further applied a [3 + 2] cycloaddition/ 1,3-H shift/rearrangement/dehydrogenation cascade process starting from easily available 3-ylideneoxindoles and CF<sub>3</sub>CHN<sub>2</sub> to efficiently form pyrazole[1,5-c]quinazoline containing a CF<sub>3</sub> group. Herein, we wish to report our preliminary studies on this subject (Scheme 1C).

#### Results and discussion

We commenced our investigation by screening reaction parameters for the coupling between *in situ* generated  $CF_3CHN_2$  (2) and 3-ylideneoxindole 3a (Table 1). Using DBU as a base, a coupling occurred, and the desired  $CF_3$ -containing pyrazole [1,5-c]quinazoline product 4a was isolated in 40% yield in the presence of  $Et_2O$  (Table 1, entry 1). Switching the solvent to DCM slightly decreased the yield (Table 1, entry 4). Different solvents were also investigated; however, this led to no desired reaction (Table 1, entries 2 and 3). The reaction time is significantly prolonged when utilizing alternative solvents, such as  $Et_2O$  and DCM, which require a duration of 120 h. Interestingly, employing PhMe as the reaction solvent enables the completion of the entire reaction within a span of 48 h. PhMe was found to

Table 1 Investigation of reaction conditions<sup>a</sup>

Entry	Solvent	Temperature	Base (x equiv.)	Yield <sup>b</sup> (%)
1 <sup>c</sup>	Et <sub>2</sub> O	r.t.	DBU (0.5)	40
$2^c$	1,4-Dioxane	r.t.	DBU (0.5)	N.R.
$3^c$	THF	r.t.	DBU (0.5)	N.R.
$4^c$	DCM	r.t.	DBU (0.5)	33
5	PhMe	r.t.	DBU (0.5)	78
$6^d$	PhMe	r.t.	DBU (0.5)	39
$7^e$	PhMe	r.t.	DBU (0.5)	55
$8^f$	PhMe	r.t.	DBU (0.5)	68
9	PhMe	r.t.	$Cs_2CO_3$ (0.5)	N.R.
10	PhMe	r.t.	$K_2CO_3(0.5)$	N.R.
11	PhMe	r.t.	$Et_3N(0.5)$	N.R.
12	PhMe	r.t.	NaOH (0.5)	N.R.
13	PhMe	r.t.	<sup>t</sup> BuOK (0.5)	N.R.
14	PhMe	r.t.	DBN (0.5)	50
15	PhMe	r.t.	DBU (0.25)	60
16	PhMe	r.t.	DBU (0.75)	60
17	PhMe	r.t.	DBU (1.0)	50
18	PhMe	−10 °C	DBU (0.5)	66
19	PhMe	0 °C	DBU (0.5)	59
20	PhMe	40 °C	DBU (0.5)	46
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<sup>a</sup> Standard conditions: performed with CF<sub>3</sub>CH<sub>2</sub>NH<sub>2</sub>·HCl (1.5 mmol, 6.0 equiv.), NaNO<sub>2</sub> (1.65 mmol, 6.6 equiv.) 0.2 mL H<sub>2</sub>O at 0 °C for 2 h. The mixture was dried, and later 3a (0.25 mmol, 1.0 equiv.), DBU (0.5 equiv.) and 5 mL of drying solvent were added at room temperature under an O<sub>2</sub> atmosphere (balloon) for 48 h. <sup>b</sup> Isolated yields based on 3a are given. <sup>c</sup> The reaction was performed for 120 h. <sup>d</sup> The reaction was performed in 3 mL of dry solvent. <sup>e</sup> The reaction was performed in 10 mL dry solvent. <sup>f</sup> The reaction was performed in 15 mL dry solvent.

be superior to the others, and product 4a was obtained in 78% yield within the optimal reaction time (48 h) (Table 1, entry 5). We also screened the bases required for the reaction and found that Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Et<sub>3</sub>N, NaOH, and <sup>t</sup>BuOK (Table 1, entries 9-13) could not perform the expected reaction. Only DBN provides the required product 4a in 50% yield (Table 1, entry 14). Screening with base loading showed that 0.5 equiv. was better than other methods, with a yield of 78% (Table 1, entries 15-17 vs. entry 5). The effect of temperature was also examined, and all resulted in slightly reduced yields, and room temperature was confirmed to be the best one (Table 1, entries 18-20 vs. entry 5). Therefore, the optimal reaction conditions were summarized: CF<sub>3</sub>CH<sub>2</sub>NH<sub>2</sub>·HCl (203.25 mg, 1.5 mmol, 6.0 equiv.), NaNO<sub>2</sub> (115.5 mg, 1.65 mmol, 6.6 equiv.) and  $H_2O$  (0.2 mL) were stirred in 5.0 mL of PhMe at 0 °C for 2 h in a 100 mL double-necking bottle under Ar. After drying Na<sub>2</sub>SO<sub>4</sub>, 3a (57.6 mg, 0.25 mmol, 1.0 equiv.) and DBU (0.5 equiv.) were added, and the reaction mixture was stirred at room temperature under an O2 atmosphere (balloon) for 48 h.

With the optimized reaction conditions in hand, the scope and generality concerning CF<sub>3</sub>CHN<sub>2</sub> were next examined in the coupling of compound 4 (Scheme 2). The introduction of fluorine, chlorine, and bromine substituents at different positions of 3-ylideneoxindole was tolerated under mild conditions, and

Scheme 2 Substrate scope<sup>a</sup>.  ${}^{a}CH_{3}CH_{2}NH_{2} \cdot HCl$  (1.5 mmol), NaNO<sub>2</sub> (1.65 mmol) 3-acyldioxoindole (0.25 mmol), DBU (0.125 mmol) were stored in PhMe (5 mL) at room temperature under an O<sub>2</sub> atmosphere (balloon) for 48 h.  ${}^{b}The$  substrate for this reaction is ethyl (*E*)-2-(2-oxoindolin-3-ylidene) acetate instead of tert-butyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate.

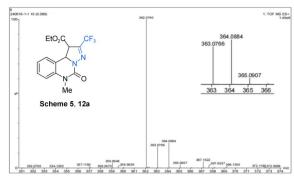
the products were isolated in 35–86% yield (4a–w). The reaction was also compatible with disubstituted ethyl (*E*)-2-(1,5,7-trimethyl-2-oxoindolin-3-ylidene) acetate that contains an electron-donating substituent on the phenyl ring, affording 4p in 57% yields. Steric hindrance seems to play an important factor in affecting the results, with 3-ylideneoxindole bearing different protecting groups (Ph, Bn, and allyl) on nitrogen reacting quite well with 2, giving 4r, 4s, and 4t in moderate yields. In contrast, the addition of a Boc-protecting group to 3-ylideneoxindole results in the removal of the Boc-protecting group in 37% yield (4q), and the same product can be obtained without any group on nitrogen, but the yield is relatively

high (71%). The 3-ylideneoxindoles bearing variation of the ester moiety ( $^n$ Pr,  $^i$ Pr, or  $^t$ Bu) could also undergo this [3 + 2] cycloaddition/1,3-H shift/rearrangement/dehydrogenation cascade process, though leading to the corresponding

Scheme 3 Gram-scale reactions.

Scheme 4 Transformation of 4k. (a)  $Pd(PPh_3)_2Cl_2$ , Cul,  $Et_3N$ , phenylacetylene, DMF, Ar, 60 °C, and 24 h. (b)  $PhB(OH)_2$ ,  $Cs_2CO_3$ ,  $Pd(OAc)_2$ ,  $PBUPAd_2$ , DCE, Ar, 80 °C, and 12 h. (c) Styrene,  $Pd(PPh_3)_4$ ,  $PPh_3$ ,  $Et_3N$ , DMF, Ar, 140 °C, and 8 h. (d)  $Pd(OAc)_2$ ,  $PCy_3$ ,

EtO<sub>2</sub>C



Scheme 5 Control experiments. Fig. 2 HRMS of intermediate 12a.

products in moderate yields (4u-w). The structure of product 4a was also unambiguously confirmed by single-crystal X-ray analysis.

To demonstrate the high efficiency of the reaction, 4a and 4k were scaled up under optimized conditions. As shown in Scheme 3, the final yield of 4a is 1.02 g with a 70% yield. The yield of 4k was 65% to 1.64 g. At the same time, the practicability of the reaction is further analyzed. The resulting product 4k could be further transformed to 5 in 76% yield, 6 in 88% yield, 7 in 81% yield, 8 in 85% yield, 9 in 80% yield, and 10 in 92% yield through transition-metal-catalyzed Sonogashira coupling, Suzuki-Miyaura coupling, Heck coupling, Miyaura borylation, Ullmann-Ma amination and Stille coupling, respectively (Scheme 4).20

To acquire more information on the mechanism of this cascade reaction, the presence of an intermediate in the reaction liquid under argon was detected by HRMS (Fig. 2), and the template reaction was monitored by <sup>1</sup>H NMR. By monitoring the reaction mixture for 12 h, the reaction raw material 3a, and the reaction intermediate 11a, it was found that the corresponding

DBU (0.5 equiv.) PhMe, Ar, rt, 24 h Me 12a, determined by HRMS EtO<sub>2</sub>C DBU (0.5 equiv.) PhMe, O<sub>2</sub>, rt, 48 h Me 4a, 80% yield

characteristic peak appeared in <sup>1</sup>H NMR of the mixture (Fig. 3). By monitoring <sup>1</sup>H NMR of the mixed solution 12 h after the reaction, we found that substrate 3a was completely consumed, and the characteristic peaks of intermediate product 11a and product 4a appeared. To investigate the reaction mechanism based on the key intermediates 13a, 11a, and 12a, three control experiments were explored. However, it is troublesome to obtain the intermediate 13a owing to its scarcity, but the presence of 11a can be detected by 1H NMR. Notably, 11a can transform to intermediate 12a under the Ar atmosphere, and 4a has been realized from 11a in 80% yield under the O2 atmosphere (Scheme 5). These results indicate that 11a, 12a, and 13a are possible intermediates for the formation of 4a.

Based on the above results and our previous reports, 19c we postulate a plausible mechanism, which is depicted in Scheme 6. In situ generated  $CF_3CHN_2$  with 3-ylideneoxindoles via [3 + 2] cycloaddition forms intermediate 13, followed by a 1,3-H shift process to yield the intermediate 11. Intermediate 11 is deprotonated and closed by DBU to obtain intermediate 14, followed ring-opening and  $[1,5]-\sigma$  rearrangement to obtain

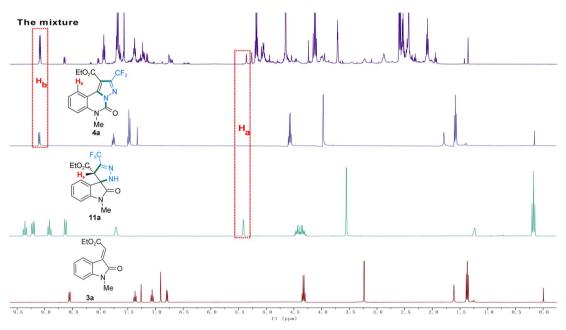
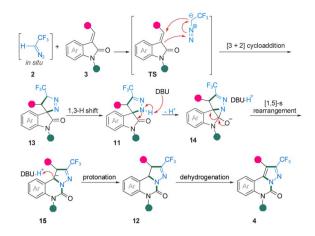


Fig. 3 <sup>1</sup>H NMR determination of the possible intermediates.



Scheme 6 Proposed reaction mechanism.

intermediate 15. Intermediate 12 is obtained by protonation of intermediate 15. Finally, intermediate 12 is dehydrogenated in the presence of oxygen to obtain compound 4. In particular, due to the conjugated system of compound 4, the dehydrogenation step might be a driving force for the transformation of intermediate 11 into fused heterocycles 4.

Xiao and Lu's group have developed the example of a sequential [3 + 2] cycloaddition/ring contraction reaction of 3-ylideneoxindoles with *in situ-g*enerated CF<sub>3</sub>CHN<sub>2</sub>, carried out in PhMe under Ar atmosphere, to deliver CF<sub>3</sub>-containing 3,3'-cyclopropyl spirooxindole derivatives.<sup>11</sup> In contrast, our synthetic strategy opens the route to pyrazolo[1,5-c]quinazolines by a 1,3-dipolar cycloaddition in the presence of DBU in PhMe under the O<sub>2</sub> atmosphere. The desired spirooxindole 4 was afforded in moderate to 86% yields. The reaction proceeded under mild conditions with broad moderate to well yields. The mild reaction conditions, broad substrate scope, and simple and convenient handling make this method of accessing functionalized CF<sub>3</sub>-containing N-heterocycle practical and fascinating.

### Conclusions

An atom-economical protocol of valuable and versatile pyrazolo [1,5-c]quinazolines has been achieved by a sequential [3 + 2] cycloaddition/1,3-H shift/rearrangement/dehydrogenation process, proceeding in moderate to good yields at room temperature. The reaction proceeded under mild conditions with good functional group tolerance, which also constructed pyrazolo[1,5-c]quinazolines from easily accessible 3-ylideneoxindoles and CF<sub>3</sub>CHN<sub>2</sub> without the need for multistep parallel synthesis. Efforts toward expanding this methodology to a broader 3-ylideneoxindole scope are currently underway. Further research on this topic with *in situ* generated CF<sub>3</sub>CHN<sub>2</sub> is underway in our laboratory.<sup>21</sup>

# **Experimental section**

#### General experimental information

Unless otherwise specified, all commercially available reagents are utilized without further purification. Silica gel column chromatography (300–400 mesh) is employed.  $^{1}$ H,  $^{19}$ F, and  $^{13}$ C NMR spectra were measured on a 400, 376, and 100 MHz spectrometer, respectively. CDCl<sub>3</sub> was used as a solvent.  $^{19}$ F chemical shifts were given as  $\delta$  in ppm downfield from CFCl<sub>3</sub>. High-resolution mass spectra HRMS measurements were obtained on a TOF analyzer.

The preparation of 3-ylideneoxindoles was conducted following the previously reported method.

#### Representative procedure for the synthesis of compound 4a

A 50 mL flask with a stir bar was charged with  $CF_3CH_2NH_2 \cdot HCl$  (1.5 mmol, 6.0 equiv.),  $NaNO_2$  (1.65 mmol, 6.6 equiv.), 0.2 mL  $H_2O$  at 0 °C for 2 h. The mixture was then dried, then 3a (0.25 mmol, 1.0 equiv.), DBU (0.5 equiv.) and 5 mL of the drying solvent were added at room temperature under an  $O_2$  atmosphere (balloon) for 48 h (as monitored by TLC). Finally, the mixture was concentrated under reduced pressure and then purified by silica gel flash column chromatography (using a solvent system of petroleum ether/ethyl acetate = 10:1) to obtain the target compound 4a (65.9 mg, yield 78%).

### Data availability

The data supporting this article have been included as part of the ESI.†

### Conflicts of interest

There are no conflicts of interest to declare.

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