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In situ generated CF₃CHN₂ with 3-ylideneoxindoles to access CF₃-containing pyrazolo[1,5-*c*]quinazolines derivatives†

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Toward a selective and facile method for the synthesis of CF₃-containing pyrazolo[1,5-*c*]quinazolines, we developed a [3 + 2] cycloaddition/1,3-H shift/rearrangement/dehydrogenation cascade involving *in situ* generated CF₃CHN₂ 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(sp²)-CF₃ 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(sp²)-CF₃ bond.⁶ Trifluoromethyl free radicals serve as active species in radical trifluoromethylation.⁷

Alternatively, other routes based on the chemical conversions of CF₃-containing building blocks,⁸ especially trifluorodiazaoethane (CF₃CHN₂),⁹ have emerged as a valuable reagent for introducing trifluoromethyl groups into heterocyclic compounds. CF₃CHN₂ readily participates in [2 + 1]-, [3 + 2]-, and [3 + 3]-cycloaddition reactions as a trifluoromethyl-containing dipole, thereby creating new approaches to synthesize CF₃-containing heterocycles.¹⁰ This impressive work

stemmed from a study by the group of Xiao and Lu,¹¹ who reported a [3 + 2] cycloaddition/ring contraction sequence of 3-ylideneoxindoles 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 CF₃-substituted 3,3'-cyclopropyl spirooxindoles.

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 10A inhibitors,¹³ benzodiazepine/adenosine receptors,¹⁴ and AMPA receptors (Fig. 1).¹⁵ Accordingly, considerable efforts have been undertaken to develop efficient synthetic strategies for these

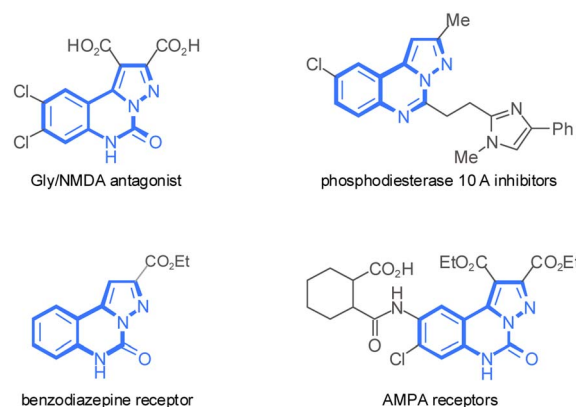


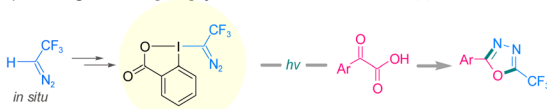
Fig. 1 Some biologically active compounds with a pyrazolo[1,5-*c*]quinazoline core.

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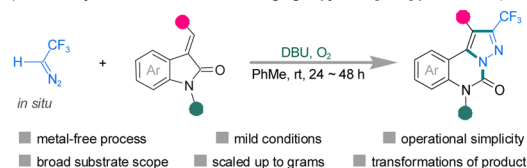
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A) Visible-light-induced [3 + 2] cycloaddition for construction of 1,3,4-oxadiazoles¹⁷B) Rh-catalyzed [2 + 1 + 2] cycloadditions for synthesis of imidazo[1,5-a] N-heterocycles¹⁸

C) DBU-catalyzed cascade reaction for forging of pyrazolo[1,5-c]quinazolines (this work)



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

fascinating bioactive molecules.¹⁶ 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-*c*]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_3CHN_2 for the synthesis of 5- CF_3 -1,3,4-oxadiazoles (Scheme 1A).¹⁷ Recently, a novel sulfonium salt derived from *in situ* generated CF_3CHN_2 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_3CHN_2 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_3CHN_2 to efficiently form pyrazolo[1,5-*c*]quinazoline containing a CF_3 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^a

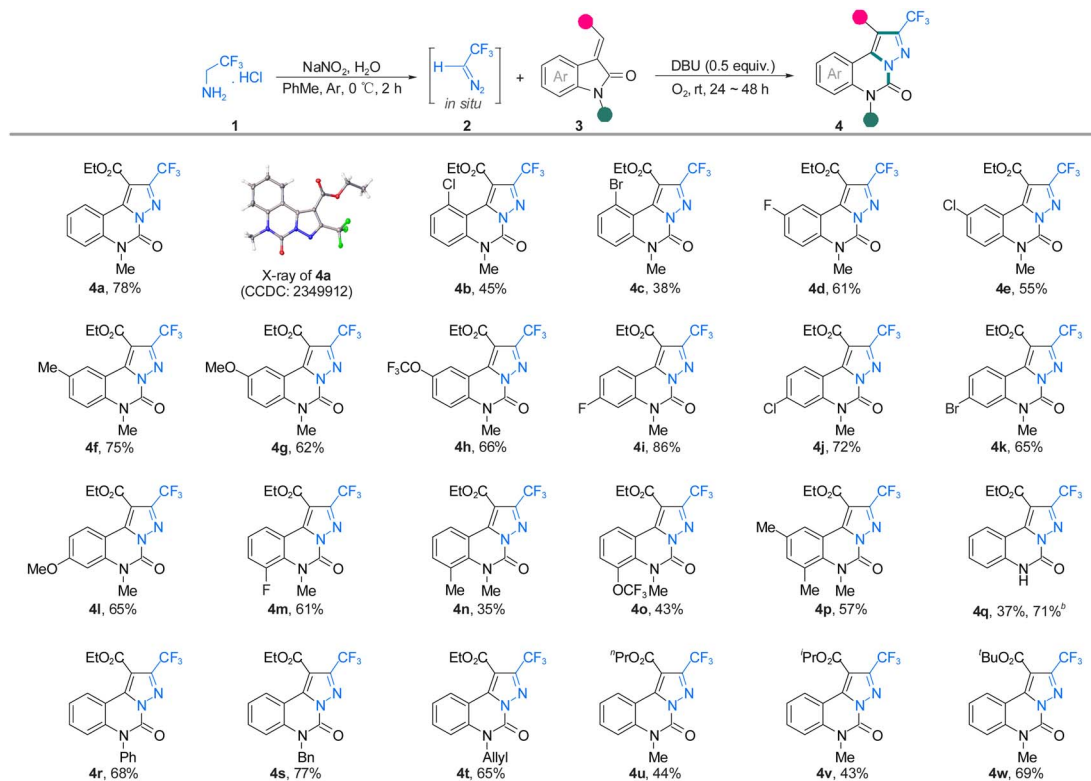
Entry	Solvent	Temperature	Base (x equiv.)	Yield ^b (%)
1 ^c	Et_2O	r.t.	DBU (0.5)	40
2 ^c	1,4-Dioxane	r.t.	DBU (0.5)	N.R.
3 ^c	THF	r.t.	DBU (0.5)	N.R.
4 ^c	DCM	r.t.	DBU (0.5)	33
5	PhMe	r.t.	DBU (0.5)	78
6 ^d	PhMe	r.t.	DBU (0.5)	39
7 ^e	PhMe	r.t.	DBU (0.5)	55
8 ^f	PhMe	r.t.	DBU (0.5)	68
9	PhMe	r.t.	Cs_2CO_3 (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.	^t 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

^a Standard conditions: performed with $\text{CF}_3\text{CH}_2\text{NH}_2 \cdot \text{HCl}$ (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 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_2 atmosphere (balloon) for 48 h. ^b Isolated yields based on 3a are given. ^c The reaction was performed for 120 h. ^d The reaction was performed in 3 mL of dry solvent. ^e The reaction was performed in 10 mL dry solvent. ^f 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_2CO_3 , K_2CO_3 , Et_3N , NaOH, and ^tBuOK (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: $\text{CF}_3\text{CH}_2\text{NH}_2 \cdot \text{HCl}$ (203.25 mg, 1.5 mmol, 6.0 equiv.), NaNO_2 (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_2SO_4 , 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 O_2 atmosphere (balloon) for 48 h.

With the optimized reaction conditions in hand, the scope and generality concerning CF_3CHN_2 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

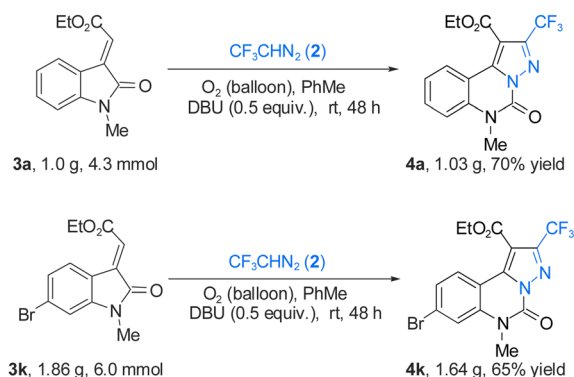




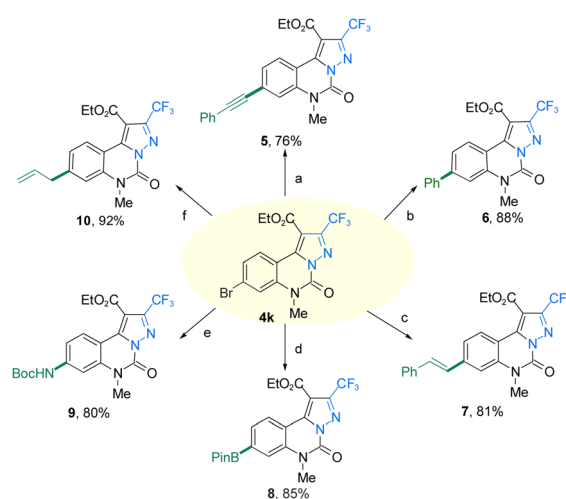
Scheme 2 Substrate scope^a. ^aCH₃CH₂NH₂·HCl (1.5 mmol), NaNO₂ (1.65 mmol) 3-acyldioxindole (0.25 mmol), DBU (0.125 mmol) were stored in PhMe (5 mL) at room temperature under an O₂ atmosphere (balloon) for 48 h. ^bThe substrate for this reaction is ethyl (*E*)-2-(2-oxoindolin-3-ylidene) acetate instead of *tert*-butyl (*E*)-2-(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 (ⁱPr, ^tPr, or ^tBu) 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(PPh₃)₂Cl₂, CuI, Et₃N, phenylacetylene, DMF, Ar, 60 °C, and 24 h. (b) PhB(OH)₂, Cs₂CO₃, Pd(OAc)₂, ^tBuPAD₂, DCE, Ar, 80 °C, and 12 h. (c) Styrene, Pd(PPh₃)₄, PPh₃, Et₃N, DMF, Ar, 140 °C, and 8 h. (d) Pd(OAc)₂, PCy₃, (BPin)₂, KOAc, PhMe, Ar, 70 °C, and 2 h. (e) Pd₂(dba)₃, XPhos, CsCO₃, NH₂Boc, PhMe, Ar, 110 °C, and 12 h. (f) Pd(PPh₃)₄, allyltributylstannane, DMF, Ar, 90 °C, and 1 h.



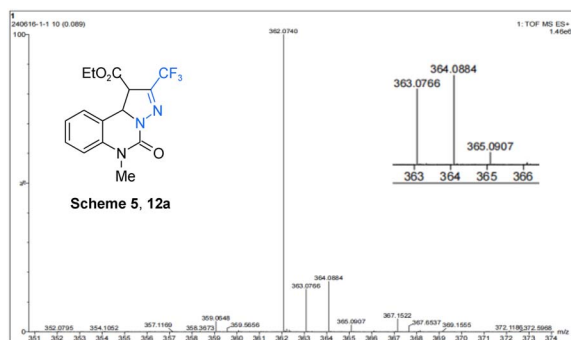
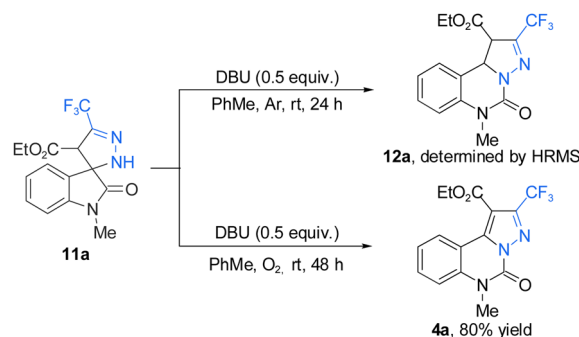


Fig. 2 HRMS of intermediate 12a.

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

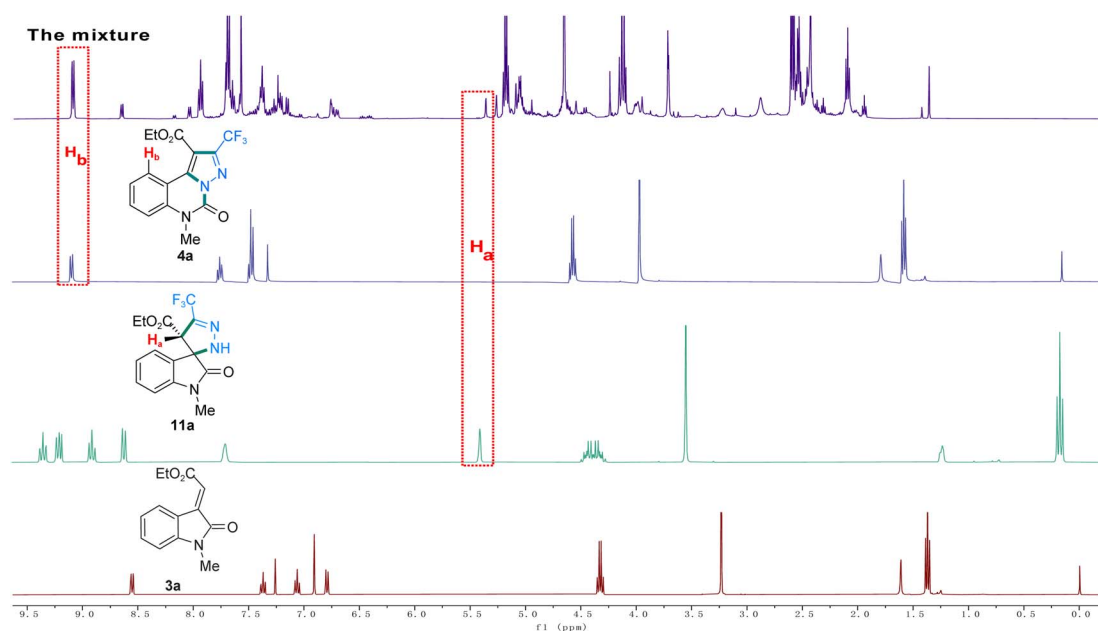
To acquire more information on the mechanism of this cascade reaction, the presence of an intermediate in the reaction liquid under argon was detected by HRMS (Fig. 2), and the template reaction was monitored by ¹H NMR. By monitoring the reaction mixture for 12 h, the reaction raw material **3a**, and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

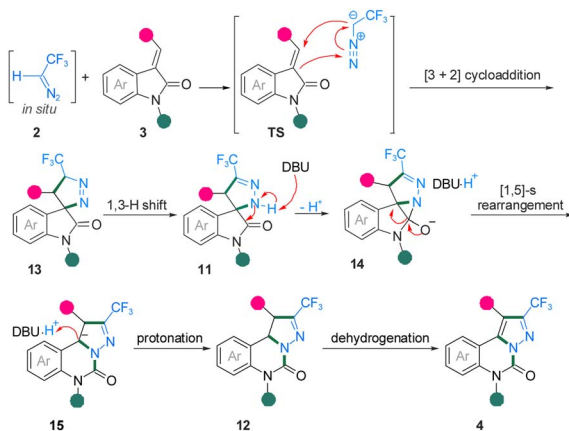


Scheme 5 Control experiments.

characteristic peak appeared in ¹H NMR of the mixture (Fig. 3). By monitoring ¹H 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 CF₃CHN₂ 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 by ring-opening and [1,5]-σ rearrangement to obtain

Fig. 3 ¹H 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*-generated CF_3CHN_2 , carried out in PhMe under Ar atmosphere, to deliver CF_3 -containing 3,3'-cyclopropyl spirooxindole derivatives.¹¹ 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_2 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_3 -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_3CHN_2 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_3CHN_2 is underway in our laboratory.²¹

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. ^1H , ^{19}F , and ^{13}C NMR spectra were measured on a 400, 376, and 100 MHz spectrometer, respectively. CDCl_3 was used as a solvent. ^{19}F chemical shifts were given as δ in ppm downfield from CFCl_3 . 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 $\text{CF}_3\text{CH}_2\text{NH}_2 \cdot \text{HCl}$ (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.

Acknowledgements

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