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Communication

Lewis base catalyzed ring-expansion of isatin with 2,2,2-trifluorodiazoethane (CF_3CHN_2): An efficient route to 3-hydroxy-4-(trifluoromethyl)quinolinones

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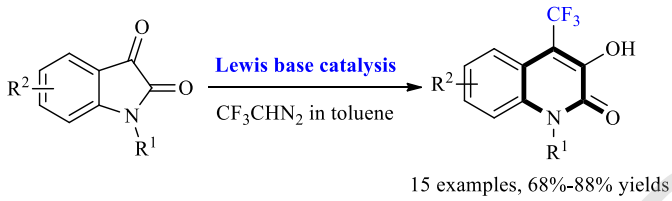
Graphical Abstract



ABSTRACT
A Lewis base catalyzed ring expansion of isatin with 2,2,2-trifluorodiazoethane (CF_3CHN_2) is developed. It is characterized that the merge of tetramethylethylenediamine and CF_3CHN_2 generates reactive triazene intermediates, which construct substituted 3-hydroxy-4-(trifluoromethyl)quinolinones with high efficiency. Synthetic application of the procedure is broadened by 3-trifluormethylpyrazole fused 3-hydroxy-4-(trifluoromethyl) quinolinone synthesis.

Keywords: Ring-expansion, Lewis base, Heterocycle, Quinolinones, Triazene

Quinolinone derivatives have received a great deal of interest in medicinal, bioorganic, and industrial chemistry due to as key privileged scaffolds widely existed in many important biologically active molecules, agrochemicals and pharmaceuticals (Fig. 1) [1]. Trifluoromethyl (CF_3)-containing quinolinone represents as one of the attractive heterocycles because embedding CF_3 moiety could extraordinarily affect their physiochemical, biological, and pharmacological properties [2]. Therefore, the development of new protocols to construct such heterocycles persists as an important goal in medicinal and organic chemistry. Known methods for the synthesis of 4-trifluoromethyl quinolinones involve the condensation of anilines with ethyl 4,4,4-trifluoroacetoacetate [3]. However, these methods suffer from prefunctionalized starting materials and poor regioselectivities. In this context, the development of the efficient methodologies for the synthesis of trifluoromethylated quinolinones is highly desirable in synthetic and medicinal chemistry.

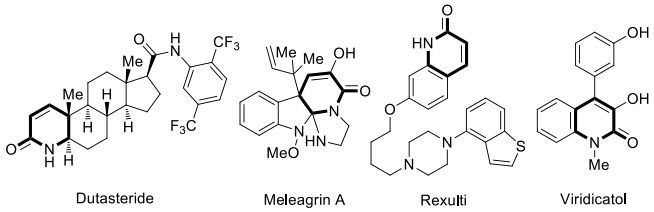
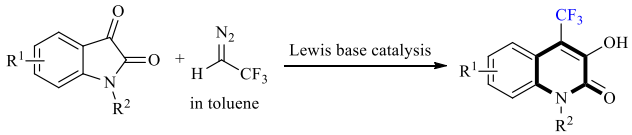


Fig. 1. Selected bioactive molecules containing quinolinone scaffold.

Recently, 2,2,2-trifluorodiazoethane (CF_3CHN_2) has emerged as an attractive fluorine-containing building block based on its different reactivities such as metal carbene precursors, 1,3-dipoles, C-nucleophiles/electrophiles and N-terminal electrophiles [4]. Compelling works have been reported according to these roles, especially ring formation protocols by [2+1] cycloaddition and [3+2] cycloaddition. Since the pioneering work for trifluoromethyl cyclopropanes and cyclopropenes synthesis *via* [2+1] cycloaddition by Carreira group [5], more methods by various catalytic strategy (Fe [4c, 5, 6], Cu [7], Rh [4c, 8], Ru [9], Co [4d], and myoglobin12 [10]) for trifluoromethylated three-membered rings symmetric and asymmetric synthesis have been promoted [5]. Also, versatile protocols for trifluoromethylated five-membered heterocycles synthesis, such as pyrazoles, pyrazolines, 1,2,3-triazoles, and tetrazoles, was established by [3+2] cycloaddition [4j, 11]. Despite huge advances in the trifluoromethylated three- and five- membered ring synthesis, to some extent, these transformations are confined to the cycloaddition reactions. The trifluoromethylated six-membered heterocycles formation via ring expansion using CF_3CHN_2 as a CF_3 synthon still remains rarely exploited.

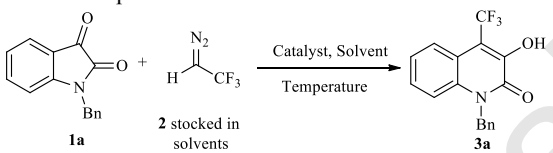


Scheme 1. Lewis base catalyzed ring expansion reactions.

Reported work indicated that the quinolinone ring could be assemble by ring expansion reaction of isatin with diazomethane and Eistert ring expansion of isatin with ethyl diazocetate [12-14]. We have reported the combination of CF_3CHN_2 with Lewis base could make sense in organic synthesis and medicinal chemistry *via* triazene intermediates formation [16]. Herein, as part of our ongoing research, we demonstrate an efficient and facile ring expansion of isatin with CF_3CHN_2 catalyzed by Lewis base to assemble 3-hydroxy-4-(trifluoromethyl) quinolinones with high efficiency (Scheme 1).

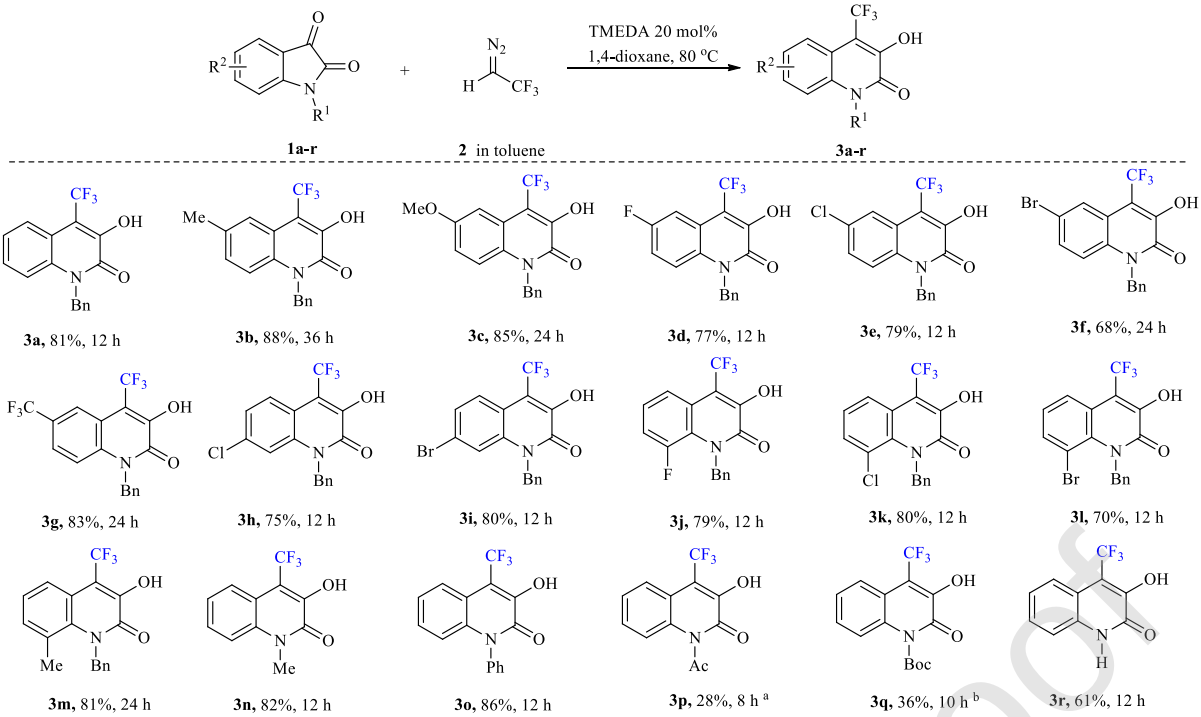
The plan study began with an evaluation of Lewis base in the model reactions of isatin **1a** with CF_3CHN_2 **2** in toluene at 60 °C. Notably, the reaction proceeded smoothly and yielded the desired ring expansion product in moderate yield with Dabco as the catalyst (Table 1, entry 1). Next, we evaluated different Lewis bases (entries 2–7). Interestingly, we found that the TMEDA afforded an efficient reaction (64%) (entry 7). To improve the yield of 3a, various stock solvents of CF_3CHN_2 were examined to indicate that toluene was still essential for the high efficiency of this ring expansion protocol (entry 8-10). Further optimization of this transformation revealed that the external solvent 1,4-dioxane could significantly enhance the reaction efficiency (entry 11 and 13-15). Attempts to increase the yield of 3a were carried out with different reaction temperatures. Notably, this reaction afforded the trifluoromethylated quinolinone heterocycle with excellent yield at 80 °C (entry 12).

Table 1
Condition optimization.[a]



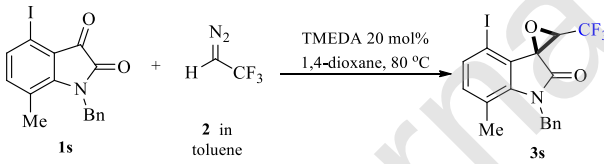
Entry	**2** in solvent	Base	Solvent (0.4 mL)	T (°C)	Yield (%)[b]
1	Toluene	Dabco	--	60	59
2	Toluene	DMAP	--	60	44
3	Toluene	Et_3N	--	60	46
4	Toluene	DIPEA	--	60	54
5	Toluene	DBU	--	60	37
6	Toluene	TMG	--	60	31
7	Toluene	TMEDA	--	60	64
8	THF	TMEDA	--	60	57
9	1,4-Dioxane	TMEDA	--	60	61
10	MeCN	TMEDA	--	60	49
11	Toluene	TMEDA	1,4-Dioxane	60	70
12	Toluene	TMEDA	1,4-Dioxane	80	81
13	Toluene	TMEDA	THF	80	43
14	Toluene	TMEDA	DCE	80	56
15	Toluene	TMEDA	MeCN	80	23

[a] Reaction conditions: isatin **1a** (0.3 mmol, 1.0 equiv.) and CF_3CHN_2 **2** (1.2 mmol, 4 equiv., 1.5 mol/L in stocked solvent), 20 mol% base (0.06 mmol, 0.2 equiv.), 12 h.
[b] Isolated yields after flash chromatography.



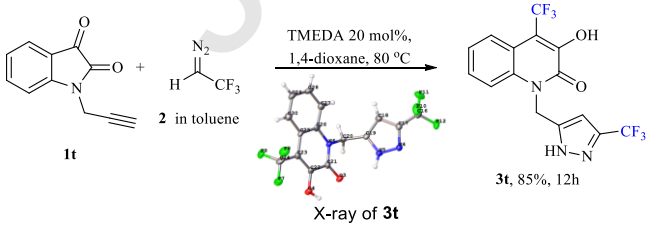
Scheme 2. Scope of substrates. Reaction conditions: **1** (0.3 mmol, 1.0 equiv.) and CF_3CHN_2 (1.2 mmol, 4 equiv., 1.5 mol/L in toluene), 20 mol% TMEDA (0.06 mmol, 0.2 equiv.), 1,4-dioxane (0.4 mL), 80 °C, 12-36 h. [a] produced **3r** with 31% yield. [b] produced **3r** with 37% yield.

With the optimized conditions in hand, we attempted to explore the generality of this ring expansion protocol to construct a range of substituted 3-hydroxy-4-(trifluoromethyl) quinolinones. As indicated in Scheme 2, a number of substituted isatins **1** were suitable for this transformation. Various substrates with both electron-rich (**1b**, **1c**) and electron-deficient (**1d-f**) substituents at 5-position of isatin scaffold were tolerated, yielding the corresponding quinolinones in very good to excellent yields. The trifluoromethoxy substrates **1g** formed the desired product in excellent yield under the standard conditions, thus affording an efficient route to multiple trifluoromethylated compound. Notably, the halogen substituted substrates at different positions were all suitable for the transformation with high efficiency (**3h-l**). Furthermore, this Lewis base-catalyzed ring expansion reaction was extended by variation of the *N*-substituent R^1 of the isatin **1**, resulting in the construction of the corresponding trifluoromethylated products **3n**, **3o** in excellent yields (R^1 = Me, Ph) and **3p**, **3q** in poor yields (R^1 = Ac, Boc). Also, unprotected isatin was also suitable for this transformation and assembled **3r** with high efficiency. However, the iodine incorporated poly-substituted at 4,7-position of isatin could be employed for this protocol without forming the ring-expansion product but affording the spiro-epoxyoxindole product **3s** in 46% yield and leaving an additional iodine group for further transformation.



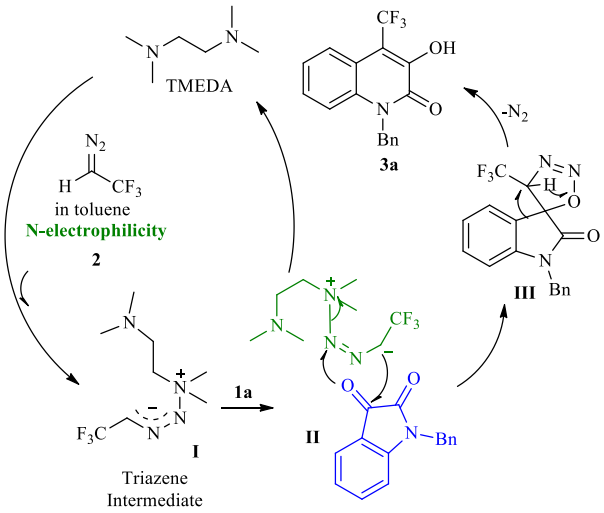
Scheme 3. CF_3-containing spiro-epoxyoxindole synthesis.

To further show the generality of the ring expansion procedure, we performed the reaction of alkyne protected isatin **1t** with CF_3CHN_2 in toluene under the standard conditions. This Lewis base catalytical strategy unlocked new routes for the straightforward and efficient assembly of 3-trifluormethylpyrazole fused 3-hydroxy-4-(trifluoromethyl) quinolinone (Scheme 4). The configurations of compounds **3t** was structurally confirmed by X-ray diffraction analysis and the supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC No. 1886034).



Scheme 4. 3-Trifluormethylpyrazole fused quinolinone synthesis.

A postulated mechanism for this Lewis base catalysis *via* the triazene intermediate is proposed based on our previous work and literature precedents (Scheme 5) [15]. Firstly, triazene intermediate **I** is generated from the N-electrophilicity of CF_3CHN_2 with TMEDA. Then, this intermediate undergoes the 3+2 cycloaddition with isatin **1a** to regenerate catalyst and afford spiroheterocycle intermediate **III**. The subsequent ring expansion step takes place to generate the final product **3a** with loss of nitrogen gas at high temperature.



Scheme 5. Proposed mechanism for ring expansion reactions.

In conclusion, we have developed a Lewis base catalyzed ring expansion of isatins with CF_3CHN_2 *via* triazene formation procedure to synthesize a series of 3-hydroxy-4-(trifluoromethyl) quinolinones in very good to excellent yields. Notably, this ring expansion strategy also allows the synthesis of the 3-trifluormethylpyrazole fused 3-hydroxy-4-(trifluoromethyl) quinolinone. Further applications of Lewis base catalysis with CF_3CHN_2 for the synthesis of related heterocycles will be reported in due course.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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