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$FeCl_3$-Mediated Synthesis of 2-(Trifluoromethyl)quinazolin-4(3*H*)-ones from Isatins and Trifluoroacetimidoyl Chlorides

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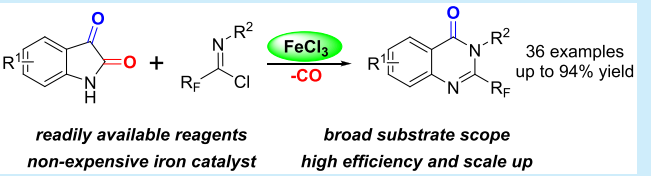
ABSTRACT: An $FeCl_3$-mediated cascade coupling/decarbonylative annulation reaction for the efficient construction of 2-(trifluoromethyl)quinazolin-4(3*H*)-ones has been developed. This transformation employs readily available isatins and trifluoroacetimidoyl chlorides as the starting materials, providing a facile and practical route to diverse biologically relevant quinazolin-4(3*H*)-one derivatives. A plausible reaction pathway has been proposed based on the mechanistic observations.



Quinazolin-4(3*H*)-ones are one class of highly privileged structural motifs that widely exist in natural products and biologically active pharmaceuticals (Figure 1).[1] They possess a variety of useful biological activities, including anticancer, antiviral, anticonvulsant, anti-inflammatory, antifungal, and antimalarial activities.[2] Therefore, except for the traditional synthetic strategies involving 2-aminobenzamide and its derivatives, tremendous impressive methods have been developed for the construction of functionalized quinazolin-4(3*H*)-ones.[3]

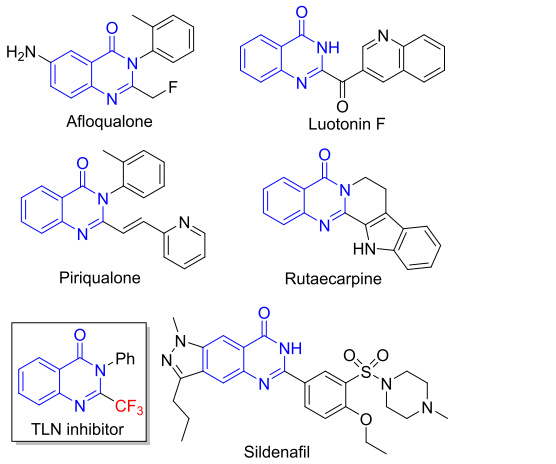
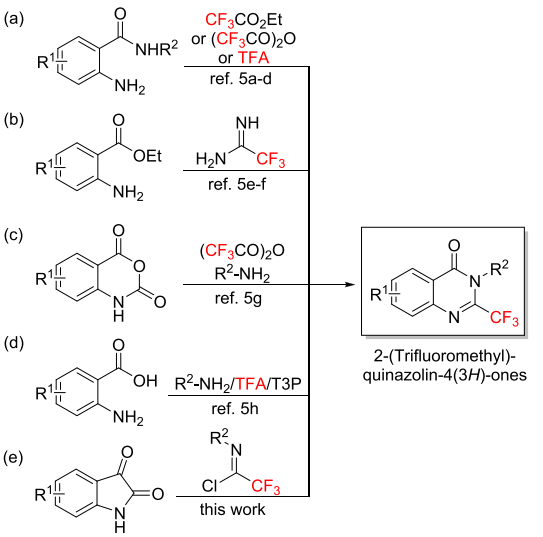


Figure 1. Selected examples of biologically active quinazolin-4(3*H*)-ones.

Because of the unique properties of fluorine atoms, the substituents involving fluorine or trifluoromethyl could greatly improve the physicochemical and pharmacological properties of heterocyclic molecules.[4] Nevertheless, among the vast literature regarding the synthesis of quinazolin-4(3*H*)-ones, the reported approaches for the efficient assembly of 2-trifluoromethyl substituted quinazolin-4(3*H*)-ones are rather limited.[5] For instance, anthranilic amides were applied as versatile substrates to react with ethyl trifluoroacetate, trifluoroacetic anhydride, or TFA under different conditions for producing 2-trifluoromethylquinazolin-4(3*H*)-ones (Scheme 1a).[5a−d] Another synthetic pathway is the annulation of anthranilic esters with unstable

Scheme 1. Synthesis of 2-Trifluoromethylquinazolin-4(3*H*)-ones Derivatives



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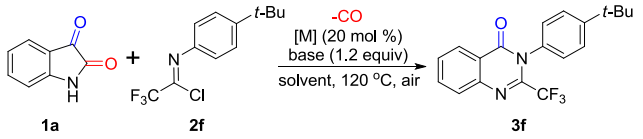
trifluoroacetamidine (Scheme 1b).[5e,f] The reaction of isatoic anhydride with trifluoroacetic anhydride and the subsequent displacement with amines could afford the target molecules, which was reported by Bergman and co-workers (Scheme 1c).[5g] Recently, the Tortoioli group described a one-pot approach for the synthesis of 2-trifluoromethylquinazolin-4(3*H*)-ones through a T3P (*n*-propanephosphonic anhydride)-promoted cascade reaction of anthranilic acids and amines by using TFA as the trifluoromethyl source (Scheme 1d).[5h] Furthermore, the cyclization of nitrile derivatives with trifluoroacetic anhydride also provided another access to 2-trifluoromethylquinazolin-4(3*H*)-ones.[5i] The transformation of isatins into 2-trifluoromethylquinazolin-4(3*H*)-ones was reported, which involved multistep conversion.[6] Despite an impressive advance made in the field, most of the existing methods generally require harsh reaction conditions, not readily accessible reagents, poor yields, or narrow substrate scope. Consequently, the exploration of more general and efficient strategies for the preparation of 2-trifluoromethylquinazolin-4(3*H*)-ones from readily available starting materials is still highly desirable.

Isatins have been widely applied as versatile building blocks for the construction of a variety of *N*-heterocycles.[7] Among various isatin-based reactions, ring-expansions and decarboxylative couplings of isatins offer facile and direct routes to build structurally diverse heterocyclic compounds. For instance, Wu and co-workers developed a series of *tert*-butyl hydroperoxide (TBHP)-promoted oxidative cyclization reactions of isatins for the synthesis of quinazolin-4(3*H*)-ones and tryptanthrins,[8] 12*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-12-ones,[9] and 3-carboxylate-4-quinolone derivatives,[10] respectively. Huang and Yin described a copper-catalyzed domino reaction of isatins and 2-bromopyridines to enable the formation of 11*H*-pyrido[2,1-*b*]-quinazolin-11-ones.[11] Encouraged by the seminal works involving isatins and our ongoing research on the heterocyclic synthesis,[12] we herein report a $FeCl_3$-mediated cascade coupling/decarbonylative annulation of readily available isatins with trifluoroacetimidoyl chlorides to lead to 2-(trifluoromethyl)quinazolin-4(3*H*)-ones (Scheme 1e). Notably, the trifluoroacetimidoyl chlorides are easily prepared and have been extensively employed as a kind of important trifluoromethyl-containing synthon.[13]

Initially, the isatin **1a** and *N*-(4-(*tert*-butyl)phenyl)-2,2,2-trifluoroacetimidoyl chloride **2f** were chosen as model substrates to optimize the reaction conditions. The reaction of **1a** and **2f** was carried out in the presence of 1.2 equiv of NaH and 4 Å MS in DMF at 40 °C for 10 h, then at an elevated temperature of 120 °C for another 20 h. Gratifyingly, the cascade decarboxylative cyclization reaction proceeded smoothly to give the desired product **3f** in 19% yield in the absence of any metal catalysts (Table 1, entry 1). Considering the important promotive effect of metals, CuCl (20 mol %) was used as a catalyst to be added into the reaction and the yield was greatly increased to 64% (Table 1, entry 2). Stimulated by the positive result, different copper salts and other transition metals (nickel and iron) were surveyed in the transformation. The observations revealed that $FeCl_3$ was the best catalyst to improve the reaction's efficiency and the product **3f** could be delivered in up to 92% isolated yield (Table 1, entries 3−10). The screening of other bases was next performed, including $NaHCO_3$, Na_2CO_3, Cs_2CO_3, and NEt_3, which showed inferior reactivity compared with NaH (Table 1, entries 11−14). Further investigation of the solvent effect using different solvents indicated that DMF was the optimal candidate (Table 1, entries 15−19). Lowering the temperature had a

Table 1. Optimization of Reaction Conditions[a]



entry	[M] (mol %)	base (equiv)	solvent (mL)	yield[b] (%)
1		NaH	DMF	19
2	CuCl	NaH	DMF	64
3	CuBr	NaH	DMF	52
4	CuI	NaH	DMF	64
5	$Cu(OAc)_2$	NaH	DMF	32
6	$CuCl_2$	NaH	DMF	59
7	$Ni(OTf)_2$	NaH	DMF	55
8	$FeCl_2$	NaH	DMF	88
9	$Fe(OTf)_3$	NaH	DMF	78
10	**$FeCl_3$**	**NaH**	**DMF**	**98 (92)**[c]
11	$FeCl_3$	$NaHCO_3$	DMF	39
12	$FeCl_3$	Na_2CO_3	DMF	32
13	$FeCl_3$	Cs_2CO_3	DMF	24
14	$FeCl_3$	NEt_3	DMF	67
15	$FeCl_3$	NaH	THF	42
16	$FeCl_3$	NaH	CH_3CN	22
17	$FeCl_3$	NaH	toluene	23
18	$FeCl_3$	NaH	Dioxane	38
19	$FeCl_3$	NaH	DMSO	73
20	$FeCl_3$	NaH	DMF	65[d]
21	$FeCl_3$	NaH	DMF	91[e]
22	$FeCl_3$	NaH	DMF	43[f]

[a]Reaction conditions: **1a** (0.20 mmol), **2f** (0.24 mmol), [M] (20 mol %), base (1.2 equiv), and 4 Å MS (50 mg) in solvent (2.0 mL) at 40 °C for 10 h, then at 120 °C for another 20 h. [b]Yields determined by GC analysis using dodecane as an internal standard. [c]Isolated yield. [d]90 °C. [e]130 °C. [f]The reaction was performed under N_2 atmosphere.

detrimental influence on the reaction and elevating the reaction temperature to 130 °C resulted in a slight decrease of the yield (Table 1, entries 20−21). Performing the reaction under inert atmosphere could give the product **3f** in 43% yield (Table 1, entry 22). It is reasonable that the reaction at 40 °C for 10 h could be beneficial for the initial coupling of isatin and trifluoroacetimidoyl chloride, and the subsequent reaction at elevated temperature could facilitate the decarbonylative cyclization process.

With the establishment of the optimized reaction conditions, the generality and limitation of the present transformation was studied with respect to a series of fluorinated imidoyl chlorides (Scheme 2). The reaction exhibited broad substrate scope, as verified that numerous *N*-aryl-trifluoroacetimidoyl chlorides bearing electron-donating or -withdrawing groups reacted smoothly with isatins to give the corresponding 2-(trifluoromethyl)quinazolin-4(3*H*)-one products in good to excellent yields (**3a**−**3r**). The electronic effect (**3a**−**3r**) and steric hindrance (**3b**−**3d**, **3o**−**3q**) of the aryl ring exerted a negligible influence on the reaction due to the observed comparable yields of these substrates. The good tolerance of the halogen atom (F, Cl, Br, and I) at different positions on the aryl ring demonstrated good compatibility of the protocol (**3j**−**3m**, **3o**−**3q**). The transformation could be easily scaled up to 1 mmol scale in 71% yield for the product **3f**. The trifluoroacetimidoyl chlorides bearing a naphthalene ring were also applicable to the current reaction to lead to the desired products **3s** and **3t** in 79−84% yields. Noteworthy was that

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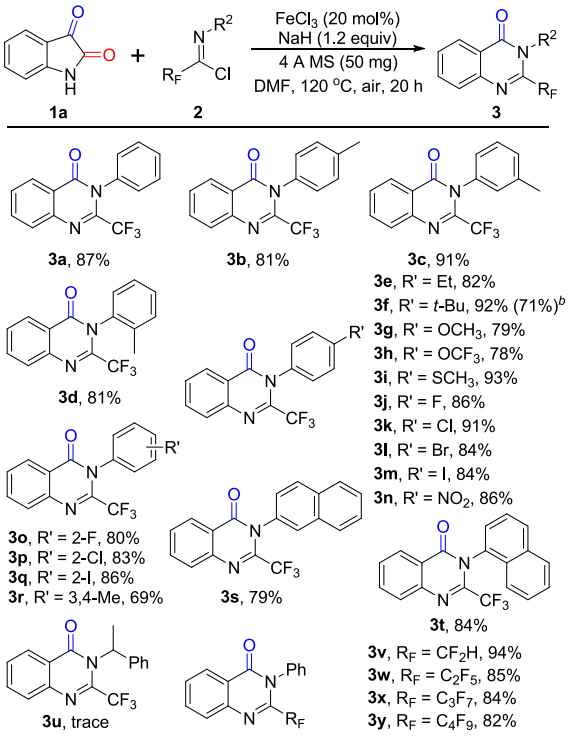
Scheme 2. Scope of Fluorinated Imidoyl Chlorides[a]



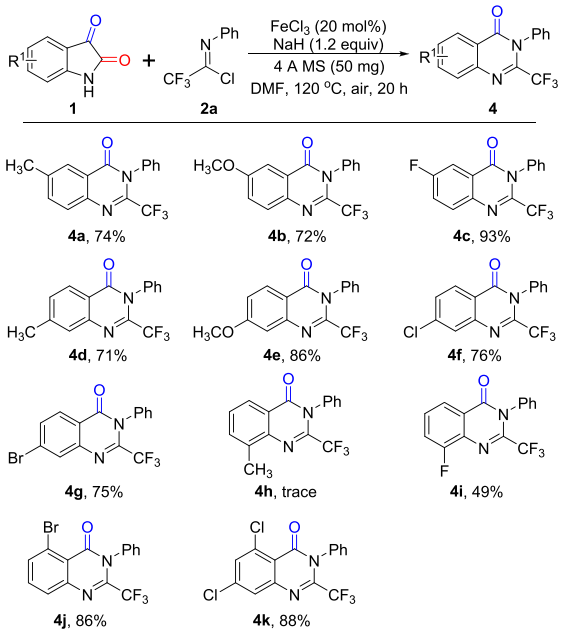
[a]Reaction conditions: 1a (0.2 mmol), 2 (0.24 mmol), $FeCl_3$ (20 mol %), NaH (1.2 equiv), and 4 Å MS (50 mg) in DMF (2.0 mL) at 40 °C for 10 h, then at 120 °C for another 20 h, isolated yields. [b]The reaction was performed on 1 mmol scale.

trifluoroacetimidoyl chloride derived from aliphatic amine was not suitable for the transformation and only a trace of product **3u** was detected. Furthermore, several other fluorinated imidoyl chlorides were applied as viable substrates to furnish the various fluoroalkyl-substituted quinazolin-4(3*H*)-ones with high efficiency (**3v**−**3y**). The exact structure of the obtained product **3p** was further confirmed by single X-ray diffraction analysis (CCDC: 2010044).[14]

The scope of the protocol was further extended by the employment of a library of isatins (Scheme 3). Diverse isatins bearing different substituents smoothly participated in the decarboxylative annulation reactions to deliver the corresponding products in moderate to excellent yields (**4a**−**4g**, **4i**−**4k**). The substitutions located at 4-, 5-, 6-, and 7- positions of isatins could be all tolerant, displaying the good generality of the reaction. It was worth mentioning that steric hindrance of the substituents located at the 7-position of isatins had a great effect on the transformation due to the observed inferior yield of product **4i** and no reactivity of 7-methylindoline-2,3-dione. Notably, the halogen atom at different positions survived the reaction, offering the synthetic handle for further modification.

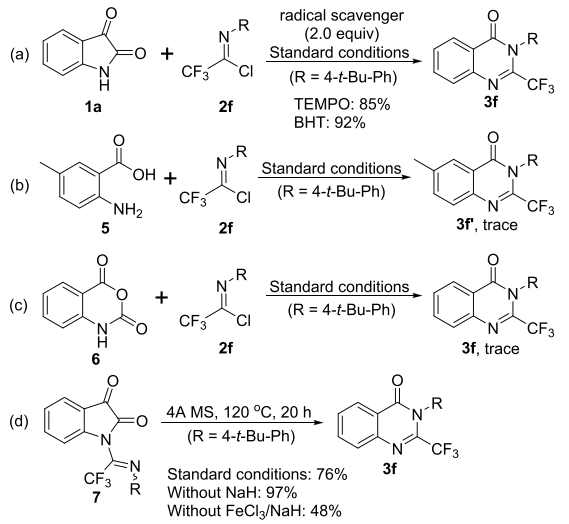
The reaction mechanism was investigated by performing several control experiments, as outlined in Scheme 4. Initially, the radical trapping experiments were implemented by the addition of 2.0 equiv of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and BHT (2,4-di-*tert*-butyl-4-methylphenol) under the standard conditions, and almost no influence upon the reaction yield was observed, which indicated that the reaction possibly did not undergo a radical pathway (Scheme 4a). The reaction of 2-amino-5-methylbenzoic acid **5** with trifluoroacetimidoyl chloride **2f** under the optimal conditions failed to furnish the

Scheme 3. Scope of Isatins.[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol) $FeCl_3$ (20 mol %), NaH (1.2 equiv), and 4 Å MS (50 mg) in DMF (2.0 mL) at 40 °C for 10 h, then at 120 °C for another 20 h, isolated yields.

Scheme 4. Control Experiments



desired product, suggesting the irreplaceability of isatin in the reaction (Scheme 4b). Furthermore, the 1*H*-benzo[*d*][1,3]-oxazine-2,4-dione **6** was employed as substrate to react with **2f**, and only trace of the target 2-(trifluoromethyl)quinazolin-4(3*H*)-one product **3f** was detected. Therefore, the isatoic anhydride **6** did not act as the intermediate of this reaction, which was usually identified as the key intermediate in oxidant-promoted reactions of isatin (Scheme 4c).[8−10] Finally, the coupling product **7** of isatin **1a** with **2f** was submitted into the standard conditions and the desired product **3f** was obtained in 76% yield. When the reaction was performed without NaH or without $FeCl_3$ and NaH, the product **3f** was delivered in 97% or 48% yield, respectively (Scheme 4d). The above observations demonstrated the intermediacy of compound **7**. In addition, the decarbonylative cyclization step could be enabled by only

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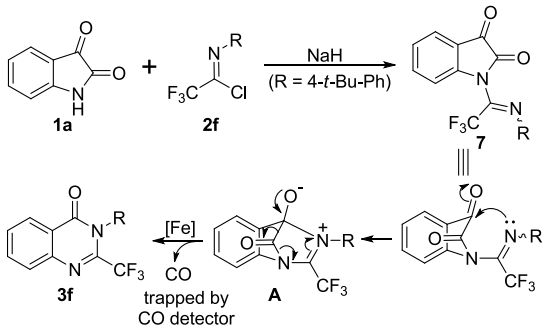
heating and greatly facilitated by $FeCl_3$, whereas the additional NaH inhibited this process (Scheme 4d).

On the basis of the mechanistic observations and precedent literatures,[11,15] we proposed a plausible mechanism for the reaction as depicted in Scheme 5. At first, the coupling of isatin

Scheme 5. Plausible Reaction Mechanism



1a with trifluoroacetimidoyl chloride **2f** in the presence of NaH gave the compound **7**. Subsequently, the intramolecular nucleophilic attack of amidine nitrogen atom to ketone could lead to a tricyclic zwitterionic intermediate **A**. Finally, the decarbonylative process of intermediate **A** in the presence or absence of $FeCl_3$ occurred to enable the formation of 2-(trifluoromethyl)quinazolin-4(3*H*)-one **3f** with the extrusion of carbon monoxide,[11,15] which was successfully trapped by CO detector. The reaction proceeded smoothly in the absence of water or strong oxidant, so the decarbonylative process with the release of carbon dioxide was presumably not involved in the reaction,[8−11] which was further verified by the result of the control experiment as shown in Scheme 4c.

In conclusion, an $FeCl_3$-mediated cascade coupling/decarbonylative annulation reaction of isatin with fluorinated imidoyl chlorides has been disclosed, providing a straightforward and efficient approach for the assembly of pharmaceutically valuable quinazolin-4(3*H*)-one derivatives. The transformation has several notable features, including readily available reagents, nonexpensive iron catalyst, broad substrate scope, high efficiency, and easy scalability. A reasonable reaction mechanism has been proposed according to the preliminary mechanistic studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01927.

General comments, general procedure, optimization details, analytic data, and NMR spectra PDF)

Accession Codes

CCDC 2010044 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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