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$FeCl_3$-catalyzed tandem condensation/intramolecular nucleophilic addition/C–C bond cleavage: a concise synthesis of 2-substitued quinazolinones from 2-aminobenzamides and 1,3-diketones in aqueous media

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ABSTRACT

A concise approach for the synthesis of 2-substituted quinazolinones using an iron-catalyzed tandem reaction of 2-aminobenzamides with acyclic or cyclic 1,3-diketones via condensation, intramolecular nucleophilic addition, C–C bond cleavage in an aqueous solution of poly(ethylene glycol) under oxidant-free conditions has been developed.

Nitrogen heterocycles have aroused considerable interest because of their presence in many therapeutically and biologically active compounds. In particular, quinazolinones are building blocks for approximately 150 naturally occurring alkaloids and many marketed drugs.[1] Such compounds have a wide range of useful biological and therapeutic activities,[2] such as antimalarial, antihypertensive, antimicrobial, anti-inflammatory, and anticancer activities.

Because of their remarkable importance, many efforts have been made to prepare such compounds from a variety of starting materials, of which 2-aminobenzamides are probably the most typical.[3] In general, the quinazolinones were constructed by the reaction of 2-aminobenzamides with carboxylic acids,[4] carbonyls,[5] β-ketoesters,[6] benzyl alcohol,[5i,7] methylarenes,[8] or carbonylative conditions.[9] Notably, most of the reported synthetic routes require excess amounts of oxidants or bases. Suitable ligands or microwave irradiation conditions are necessary in some cases. Therefore, eco-friendly and practical methods to access valuable 2-substituted quinazolinones are highly desirable. To continue our research interest in iron catalysis[10] and catalytic reactions in green media,[11] we have reported a simple, eco-friendly, and practical iron-catalyzed strategy for synthesis of 2-substituted quinazolinone derivatives through tandem condensation, intramolecular nucleophilic addition, C–C bond cleavage of 2-aminobenzamides, and acyclic or cyclic 1,3-diketones in an aqueous solution of poly (ethylene glycol) under oxidant-free conditions (Scheme 1).

Initially, 2-aminobenzamide (**1a**) and 2,4-pentanedione (**2a**) were used as the model substrates to optimize reaction conditions including iron catalyst, solvents, and catalyst loading. As shown in Table 1, eight iron catalysts (10 mol %) were tested in poly(ethylene glycol) (PEG-400) as the solvent at 100 °C for 24 h (entries 1–8). Iron trichloride hexahydrate ($FeCl_3{\cdot}6H_2O$) provided the desired product **3aA** in highest yield (entry 8), which was superior to the anhydrous counterpart (entry 2). We supposed that water may enhance the reactivity of this transformation, so the reaction was attempted in pure water. However, the yield was not increased due to the poor solubility of the reactants (entry 9). Then, a mixture of PEG-400/H_2O was used as solvent. As expected, the desired product was obtained in higher yield (entries 10–12), and PEG-400/H_2O (1:9) was the optimal choice (entry 12; 80% yield). The yield of **3aA** could be increased from 80% to 91% when the catalyst loading was doubled (entry 13).

Then, a wide range of 1,3-diketones were employed in the reactions with 2-aminobenzamide (**1a**) under the optimized conditions (Table 2). On comparing with **2A**, heptane-3,5-dione (**2B**) gave a lower yield of **3aB** under identical conditions (**3aA**: 91%; **3aB**: 83%). In contrast, the product **3aC** was obtained in moderate yield

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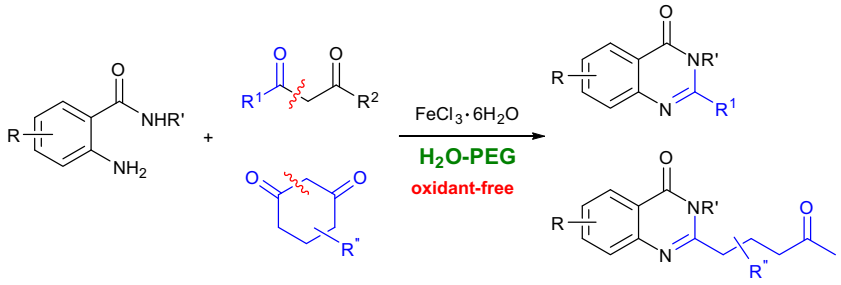
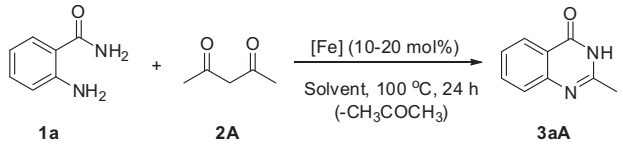


Scheme 1. A green synthesis of 2-substitued quinazolinones.

Table 1
Optimization of the reaction conditions for **3aA**[a]



1a **2A** **3aA**

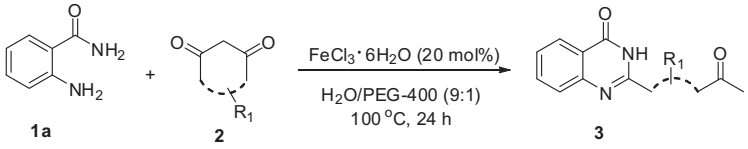
Entry	[Fe] (mol %)	Solvent	Yield[b] (%)
1	$FeCl_2$ (10)	PEG-400	26
2	$FeCl_3$ (10)	PEG-400	42
3	$FeBr_3$ (10)	PEG-400	48
4	$Fe(OAc)_2$ (10)	PEG-400	<5
5	$Fe(OTf)_2$ (10)	PEG-400	50
6	$Fe(BF_4)_2{\cdot}6H_2O$ (10)	PEG-400	32
7	$Fe(ClO_4)_3{\cdot}6H_2O$ (10)	PEG-400	46
8	$FeCl_3{\cdot}6H_2O$ (10)	PEG-400	60
9	$FeCl_3{\cdot}6H_2O$ (10)	H_2O	41
10	$FeCl_3{\cdot}6H_2O$ (10)	PEG-400/H_2O (1:1)	70
11	$FeCl_3{\cdot}6H_2O$ (10)	PEG-400/H_2O (1:4)	74
12	$FeCl_3{\cdot}6H_2O$ (10)	PEG-400/H_2O (1:9)	80
13	$FeCl_3{\cdot}6H_2O$ (20)	PEG-400/H_2O (1:9)	91

[a] *Reaction conditions*: 2-aminobenzamide (**1a**; 0.2 mmol), 2,4-pentanedione (**2A**; 0.3 mmol), solvent (1.0 mL), 100 °C, 24 h.
[b] Isolated yield.

when sterically hindered 2,6-dimethylheptane-3,5-dione (**2C**) was used as the reaction partner (entry 3; **3aC**: 36%). The reaction of amide **1a** and 1,3-diphenylpropane-1,3-dione (**2D**) could take place smoothly to provide the product 2-phenylquinazolin-4(3*H*)-one (**3aD**) (entry 4). Next, we attempted the reactions of **1a** with the unsymmetrical 1,3-diketones, 1-phenylbutane-1,3-dione (**2E**), and 1,1,1-trifluoropentane-2,4-dione (**2F**). Interestingly, the same product **3aA** was observed through selective C–C bond cleavage (entries 5 and 6). It maybe ascribed to the higher reactivity of the acetyl group than benzoyl and trifluoroacetyl groups. Finally, the cyclic 1,3-diketones cyclohexane-1,3-dione (**2G**) and 2-methylcyclohexane-1,3-dione (**2H**) were also subjected to this transformation. The corresponding products (**3aG**) and (**3aH**) were generated in 52% and 68% yields, respectively (entries 7 and 8).

As shown in Scheme 2, to further evaluate the scope of this novel strategy for the synthesis of 2-substituted quinazolinones, various *N*-substituted 2-aminobenzamides **1a**–**k** were examined. For example, the reaction of 2-amino-*N*-methylbenzamide (**1b**) and pentane-2,4-dione (**2A**) gave the desired product 2,3-dimethylquinazolin-4(3*H*)-one (**3bA**) in 84% yield. Notably, *N*-aryl-2-aminobenzamides bearing electron-donating groups (**1d**; 4-Me, **1e**; 2-Me, and **1f**; 4-MeO) or electron-withdrawing groups (**1g**; 3-Cl, **1h**; 4-Cl, and **1i**; 3,4-Cl_2) on the benzene ring also

Table 2
The scope of 1,3-diketones[a]



1a **2** **3**

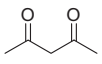
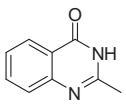
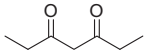
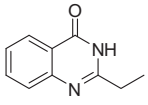
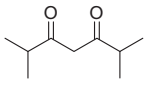
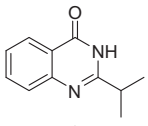
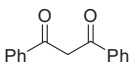
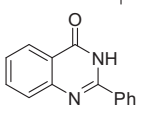
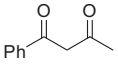
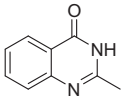
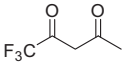
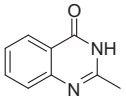
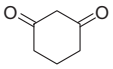
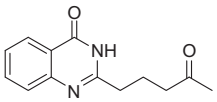
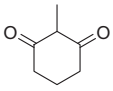
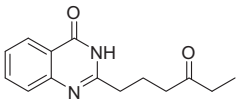
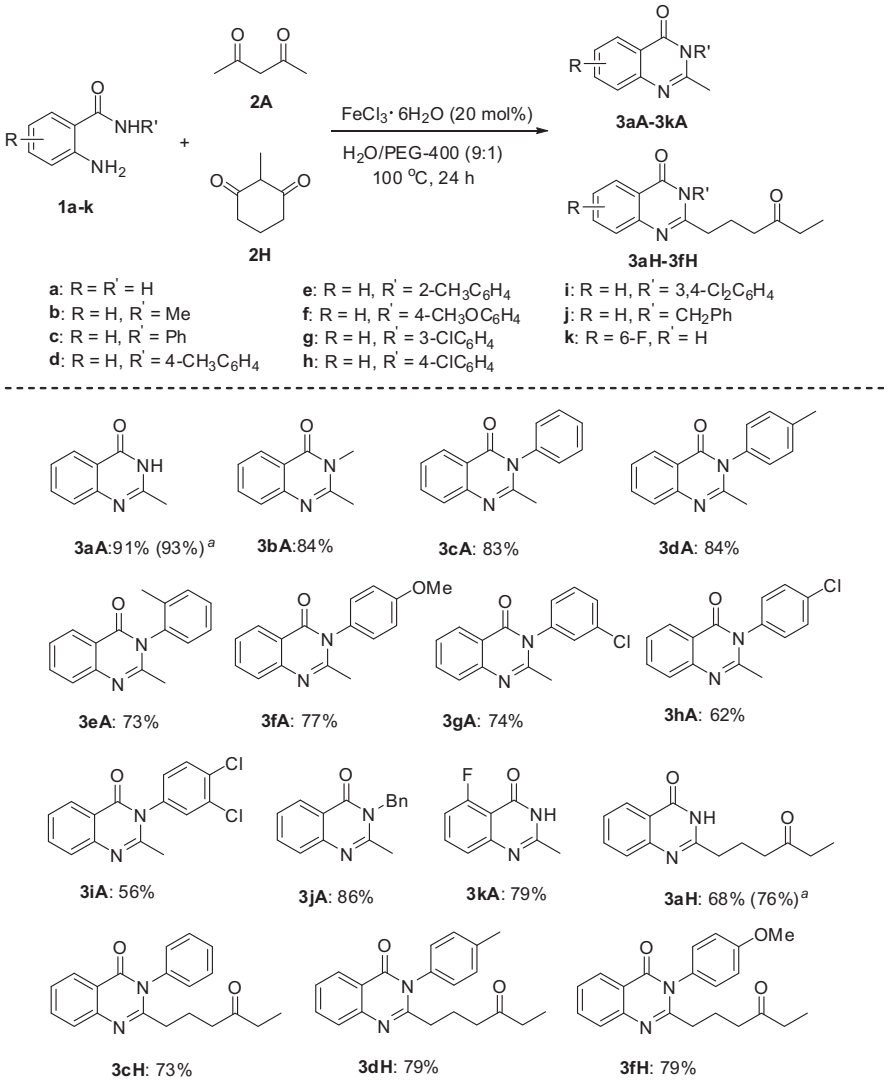
Entry	2		3		Yield[b] (%)
1		**2A**		**3aA**	91
2		**2B**		**3aB**	83
3		**2C**		**3aC**	36
4		**2D**		**3aD**	40

Table 2 (*continued*)

Entry	2		3		Yield[b] (%)
5		**2E**		**3aA**	79
6		**2F**		**3aA**	61
7		**2G**		**3aG**	52
8		**2H**		**3aH**	68

[a] *Reaction conditions*: 2-aminobenzamide (**1a**; 0.2 mmol), 1,3-diketone (**2**, 0.3 mmol), $FeCl_3{\cdot}6H_2O$ (0.04 mmol), PEG-400/H_2O (1.0 mL, 1/9), 100 °C, 24 h.
[b] Isolated yield.



Scheme 2. The scope of 2-aminobenzamides **1**. *Reaction conditions*: 2-aminobenzamide (**1**; 0.2 mmol), 1, 3-diketones (**2A** or **2H**; 0.3 mmol), $FeCl_3{\cdot}6H_2O$ (0.04 mmol), PEG-400/H_2O (1.0 mL, 1/9), 100 °C, 24 h, isolated yield. [a]Gram scale reaction: 2-aminobenzamide (**1a**; 10 mmol), 1,3-diketone (**2A** or **2H**; 12 mmol), $FeCl_3{\cdot}6H_2O$ (2.0 mmol), PEG-400/H_2O (30 mL, 1/9), 100 °C, 24 h, isolated yield.

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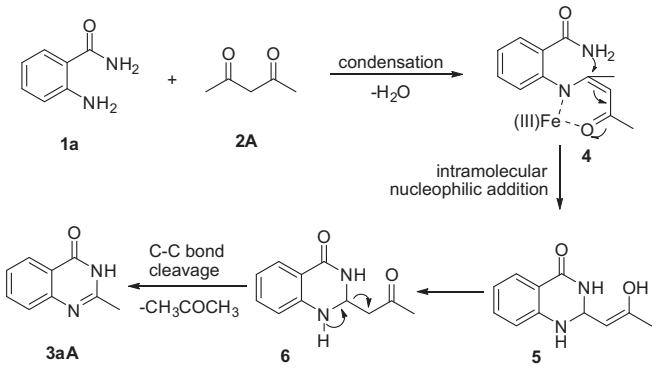

Scheme 3. A proposed catalytic cycle of this reaction.

underwent the transformation to give the corresponding products **3cA**–**3iA** in 56–84% yield. 2-Amino-*N*-benzylbenzamide (**1j**) and 2-amino-6-fluorobenzamide (**1k**) were also subjected to the reaction, and quinazolinones **3jA** and **3kA** were isolated in 86% and 79% yields, respectively. The full atom-economic reaction of amides **1** and acyclic 1,3-diketone (**2H**) provided the corresponding products **3aH**, **3cH**, **3dH**, and **3fH** in 68–79% yields. To demonstrate the scalability of this approach, gram scale syntheses of **3aA** and **3aH** were performed, as shown in Scheme 2 and 93% and 76% isolated yields were obtained, respectively.

Based on the results obtained above and the literature,[12] a proposed catalytic cycle of this reaction is shown in Scheme 3. The formed enamine **4** from 2-aminobenzamide **1a** and pentane-2,4-dione **2A** coordinates with Fe(III) via the nitrogen and oxygen of the enamine. The complexation enhances the intramolecular nucleophilic addition of enone and amide leading to aminal **5**, followed by tautomerization to give intermediate **6**. The C–C bond cleavage reaction would finally occur to generate the desired product **3aA**.

In conclusion, we have developed a concise approach for the synthesis of 2-substituted quinazolinones from readily available 2-aminobenzamides and 1,3-diketones. The process is efficiently catalyzed by non-precious and relatively non-toxic $FeCl_3{\cdot}6H_2O$ via tandem condensation, intramolecular nucleophilic addition, and C–C bond cleavage in aqueous media. Further study focusing on the iron-catalyzed C–C bond cleavage of 1,3-diketones in organic synthesis is underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.094.

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