Journal Pre-proofs

HFIP-Mediated Strategy towards β-Oxo Amides and Subsequent Friedel-Craft Type Cyclization to 2-Quinolinones using Recyclable Catalyst

Arup K. Kabi, Raghuram Gujjarappa, Nagaraju Vodnala, Dhananjaya Kaldhi, Ujjawal Tyagi, Kalisadhan Mukherjee, Chandi C. Malakar

Please cite this article as: Kabi, A.K., Gujjarappa, R., Vodnala, N., Kaldhi, D., Tyagi, U., Mukherjee, K., Malakar, C.C., HFIP-Mediated Strategy towards β-Oxo Amides and Subsequent Friedel-Craft Type Cyclization to 2-Quinolinones using Recyclable Catalyst, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet. 2020.152535

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Tetrahedron Letters

HFIP-Mediated Strategy towards β-Oxo Amides and Subsequent Friedel-Craft Type Cyclization to 2-Quinolinones using Recyclable Catalyst

Arup K. Kabi,[a] Raghuram Gujjarappa,[a] Nagaraju Vodnala,[a] Dhananjaya Kaldhi,[a] Ujjawal Tyagi,[a] Kalisadhan Mukherjee,[b] Chandi C. Malakar*[a]

[a] Department of Chemistry, National Institute of Technology Manipur, Langol, Imphal - 795004, Manipur, India.
[b] Department of Science, School of Technology, Pandit Deendayal Petroleum University, Raisan, Gandhinagar, Gujarat - 382007, India.

ARTICLE INFO

ABSTRACT

A simple and cost-effective 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)-mediated protocol for the synthesis of β-oxo amides has been described by using amines and β-keto esters as substrates. The reaction conditions were found to be highly efficient towards the cleavage of C-O bond and consequent formation of the products in excellent yields and selectivity. The obtained β-oxo amides were further transformed in to the synthetically useful 2-quinolinones *via* intramolecular Friedel-Craft type cyclization of aromatic ring using ferrites as a recyclable catalyst. A spectrum of substrates bearing broad range of functional groups were well tolerated under the reaction conditions. The proposed mechanistic pathways were substantially verified by literature and mass-spectroscopic evidences.

Introduction

Oxo amides are well known as significant building blocks in organic synthesis and are used for the formation of varieties of biologically important scaffolds.[1] The existence of several reactive sites in one molecule spreads their application in numerous strategies towards the synthesis of pharmaceuticals, proteins, natural products and synthetic polymers.[2-4] The impressive properties of acetoacetamides, such as stability, high polarity and functional-group tolerance witnessed them as most interesting functional groups in all regions of organic chemistry.[4] Apart from their immense recognition as bioactive compounds, an enormous number of heterocyclic moieties having distinct pharmacological and biological activities[4b-4c,4f,4k] were synthesized involving various bond-forming transformations[4a,4d,4e,4h,4i,5-6] using substituted β-keto amides (Figure 1). These *N*-heterocyclic scaffolds include pyrazoles, 3-isoxazolols, pyrazolones, furans, diazepines, indanones, *N*-hydroxyindoles, β- lactams and 2-quinolinones.[5-6] In particular, 2-quinolinone is a prevalent structural motif in several natural products and synthetic pharmaceuticals with an immense spectrum of biological activities including antibiotic, anticancer, antiviral and antihypersensitivity (Figure 1).[7] The substituted 2-quinolinones are also adequate fluorescent markers for amino acids, peptides, amino carbohydrates and amino polysaccharides.[8] Therefore, the synthesis of a wide varieties of such multi-functionalized molecules through evolution of a new domino reaction could be the key addition to existing synthetic access for these scaffolds.[9]

During the past years a broad spectrum of novel and simple strategies have been developed for the preparation of *N*-substituted β-keto amides.[4,10-14] The well-known synthetic protocols for their synthesis includes acylation of amide enolates or their synthetic equivalents.[10] The two component reaction of amines with β-keto acids or their synthetic analogues such as β-ketoesters, β-ketothioesters, ketene dimer and acylketenes violate the green chemistry ideologies.[11-13] In addition, few other notable contributions towards this purpose include the utilization of diketenes or diketene-acetone adducts,[4b] diazonium salts,[12a] isoxazolium salts[14] at higher temperature (Scheme 1). Recently, silver salt[4g] and basic ionic liquid[10] catalyzed protocols were also reported for the synthesis of these molecules (Scheme 1).
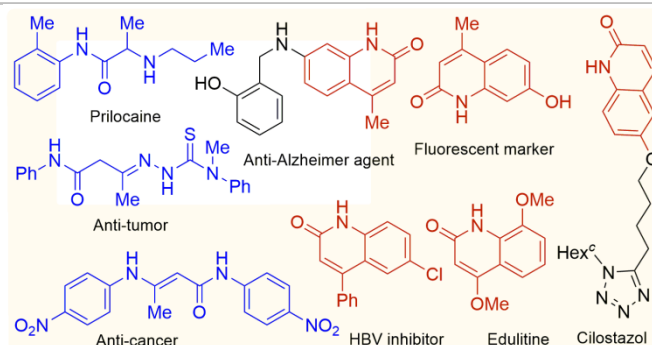

Figure 1. Medicinal importance of amides and quinolinones scaffolds.

Although, these protocols found suitable and useful; however, the disadvantages such as formation of stoichiometric amounts of objectionable by-products, high

temp[...] starting materials and poor substrate scope were not clearly resolved.[4,10-14] Therefore, the development of surrogate and efficient approaches still remains attractive and acceptable.
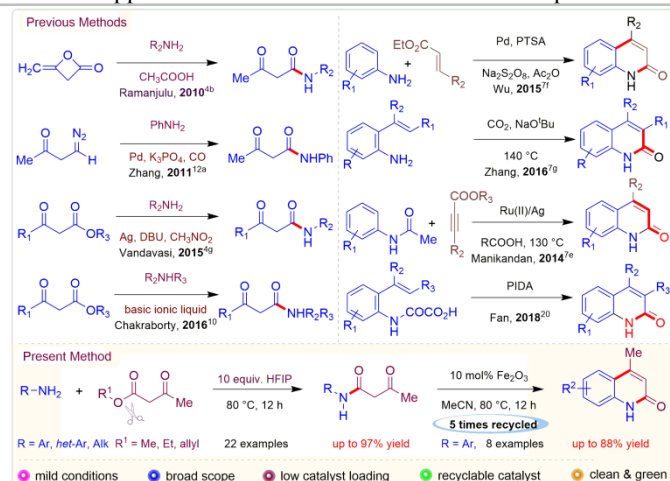
Scheme 1. Approaches towards the synthesis of β-oxo amides and 2-quinolinones.

In view of this, during our continuous efforts towards development of novel methods, we were successful in exploring HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) as a suitable reagent for the synthesis of substituted β-keto amides from amines and β-ketoesters as simple substrates. On the other hand, HFIP which is usually known as solvent and in limited cases, it was revealed that it can act as reducing agent to attain a broad range of chemical conversions.[15] The hydrogen bonding features of HFIP to assist substrates to undergo chemical transformations, makes it adaptable organic solvent in synthetic organic chemistry as well as in biochemistry.[16]

Similarly, the preparation of 2-quinolinone scaffolds has been acknowledged with significant attention in medicinal chemistry and drug discovery. As an outcome, numerous synthetic approaches were described in the literature for the synthesis of 2-quinolinone derivatives.[17] The conventional approaches towards 2-quinolinone derivatives were described using strong acid-mediated intramolecular cyclization of β-keto amides (Knorr synthesis)[6a] and base-mediated intramolecular aldol condensation of 2-aminophenyl substituted carbonyl compounds (Fried-lander synthesis).[18] Similarly, 2-quinolinones were efficiently synthesized *via* Pd-catalyzed reaction conditions using hazardous carbon monoxide as carbonyl source.[19] In another protocol, the acrylate derivatives were used as carbonyl source under highly acidic reaction conditions.[7e-f] Recently, a green methodology was reported by utilizing CO_2 as the carbonyl source for the lactamization of 2-vinylaniline under transition-metal-free environment.[7g] Even though this methodology deals with CO_2 fixation, it suffers from drawbacks such as high reaction temperature (140 °C) and a huge excess of strong base (4.5 equiv.). Very recently, intramolecular Heck-type decarboxylative reaction was reported using iodine (III)-mediated reaction conditions (Scheme 1).[20]

Although, all of these reported methods found enormous applicability in synthetic organic chemistry, they suffer from disadvantages such as toxic reagents, non-availability of starting materials and high loading of base, which limits their utility in industrial scales. To meet the expectations of industries, it is important to formulate a robust and cost-effective protocol. In this context, iron-oxides can be which are already known for their catalytic activity to achieve several organic transformations.[21] Moreover, low cost and environmental friendly iron catalyst arrives auspicious for industrial-scale synthesis and further research could fascinate on operationally simple and cost-effective methods. In this perspective, we report the synthesis of 2-quinolinone derivatives from β-keto amides by using ferrites as recyclable catalyst. The competent β-keto amides were prepared from amines and ketoesters under HFIP-mediated reaction conditions.

Having the intension to establish an efficient procedure towards the synthesis of β-keto amides, which are known to be the key precursors for various bioactive molecules,[22] we started experimental proceedings by choosing readily available aniline (**1a**) and ethyl acetoacetate (**2a**) as model substrates (Table 1). To begin with, the reaction of aniline (**1a**) and ethyl acetoacetate (**2a**) was carried out in the presence of TEMPO as organocatalyst and KO*t*Bu as a base in DMSO at 100 °C for 16 hours to obtain the desired product **3aa** in 15% yield (Table 1, Entry 1). In order to improve the yield of product **3aa**, we have screened different organocatalysts such as thiourea, niacin, 3-nitropyridine and *L*-proline, and Cs_2CO_3 as a mild base (Table 1, Entry 2-6). Surprisingly, all of the screened reagents contributed to deliver moderate yields of the product **3aa** and the maximum yield (46%) of product **3aa** was noticed in case of 30 mol% niacin and 3 equiv. of Cs_2CO_3 in DMSO at 120 °C for 24 hours (Entry 6). Based on our recent findings and literature report, we have shown that HFIP can play a very significant role in the catalytic transformations.[15] Hence, we have desired to employ HFIP as reagent in place of organocatalysts for establishing the suitable method towards the formation of β-keto amide **3aa**. The reaction of substrates **1a** and **2a** was carried out in the presence of 1 equiv. of HFIP and 3 equiv. of Cs_2CO_3 in MeCN at 80 °C for 20 hours (Entry 7). Interestingly, the reaction conditions gave an improved yield of 68% for the product **3aa**, which proves the efficacies of these reaction conditions. The reaction yields were further increased to 72% and 78%, when the reactions were carried out in presence of 3 equiv. and 5 equiv. of HFIP respectively (Entries 8-9). To evaluate the role of HFIP and base to obtain the expected product **3aa**, a reaction between **1a** and **2a** was carried out in the presence of 5 equiv. of HFIP and 3 equiv. of Cs_2CO_3 separately (Table 1, Entries 10-11). To our surprise, the reaction conditions gave an awful result of 17% product yield in absence of HFIP (Entry 10) and an exceptional result of 85% yield of product **3aa** in absence of Cs_2CO_3 (Entry 11). To further justify the role of solvent, a reaction was carried out under neat conditions to obtain **3aa** with an identical yield of 87% (Entry 12). It was obvious from the previous results that the reaction can be accomplished in absence of base and solvent. Next, to investigate the amount of HFIP required for this transformation, a reaction of **1a** and **2a** was performed using 3 equiv. and 10 equiv. of HFIP separately (Entries 13-14). It was evident from the obtained results that 10 equiv. of HFIP drastically increases the yield of **3aa** to 97% (Entry 14), whereas 3 equiv. of HFIP gave 81% yield of the product **3aa** (Entry 13). Next, we intended to assess the effect of reaction temperature and reaction time (Entries 15-18). However, none of the performed reactions resulted in the better yield of product **3aa**. Finally, to clarify the role of fluorinated alcohol, we have carried out the reaction of **1a** and **2a** in presence of 10 equiv. of TFE (2,2,2-Trifluoroethanol) at 80 °C for 12 hours, which lead to the formation of β-keto amide **3aa** only in 45% yield (Entry 19). After executing an extensive screening of the reaction conditions using aniline (**1a**) and ethyl acetoacetate (**2a**) as model substrates, we realized the maximum yield of
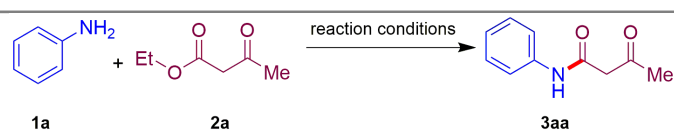
produ[...]ell presence of 10 equiv. of HFIP at 80 °C for 12 hours (Table 1, Entry 14).

tolerated to contribute for the formation of β-keto amides **3ga-qa** in 52-81% yields, although the yield of the products were slightly less than the substrates embedded with electron-donating groups.

Table 1. Initial optimization for the synthesis of β-keto amide **3aa**.[a]

| Entry	Catalyst/Reagent (Equiv.)	Base (Equiv.)	Reaction conditions	3aa % yield[b]
1	TEMPO (0.1)	KO^{t}Bu (2.5)	DMSO, 100 °C, 16 h	15
2	Thiourea (0.1)	Cs$_2$CO$_3$ (3.0)	DMSO, 100 °C, 16 h	19
3	Niacin (0.1)	Cs$_2$CO$_3$ (3.0)	DMSO, 100 °C, 16 h	38
4	3-nitropyridine (0.1)	Cs$_2$CO$_3$ (3.0)	DMSO, 120 °C, 16 h	34
5	*L*-proline (0.3)	Cs$_2$CO$_3$ (3.0)	DMSO, 100 °C, 16 h	40
6	Niacin (0.3)	Cs$_2$CO$_3$ (3.0)	DMSO, 100 °C, 24 h	46
7	HFIP (1)	Cs$_2$CO$_3$ (3.0)	MeCN , 80 °C, 20 h	68[c]
8	HFIP (3)	Cs$_2$CO$_3$ (3.0)	MeCN , 80 °C, 20 h	72[c]
9	HFIP (5)	Cs$_2$CO$_3$ (3.0)	MeCN , 80 °C, 20 h	78[c]
10	-	Cs$_2$CO$_3$ (3.0)	MeCN , 80 °C, 12 h	17[c]
11	HFIP (5)	-	MeCN , 80 °C, 12 h	85[c]
12	HFIP (5)	-	80 °C, 16 h	87[c,d]
13	HFIP (3)	-	80 °C, 12 h	81[c,d]
14	**HFIP (10)**	**-**	**80 °C, 12 h**	**97[c,d]**
15	HFIP (10)	-	100 °C, 12 h	95[c,d]
16	HFIP (10)	-	50 °C, 12 h	71[c,d]
17	HFIP (10)	-	80 °C, 16 h	96[c,d]
18	HFIP (10)	-	80 °C, 8 h	85[c,d]
19	TFE (10)	-	80 °C, 12 h	45[c,d]

[a] Unless otherwise indicated all reactions were carried out with 1 mmol of 1**a** and 1.2 mmol of **2a** in 1 mL solvent in a vial.

[b] Isolated yields.

[c] Reactions were carried out in sealed vial.

[d] Reactions were carried out under neat conditions.

After having the best optimized reaction conditions for the synthesis of β-keto amides **3**, we explored the scope of this transformation by employing wide range of amines **1a-v** and β-oxo esters **2a-c** (Scheme 2). It was realized that the anilines with electron-donating groups (EDGs) such as Me, *i*Pr, OMe were excellently tolerated under the established conditions to give β-keto amides **3aa-fa** in 78-97% yields. On the other hand, the electron-withdrawing groups (EWGs) such
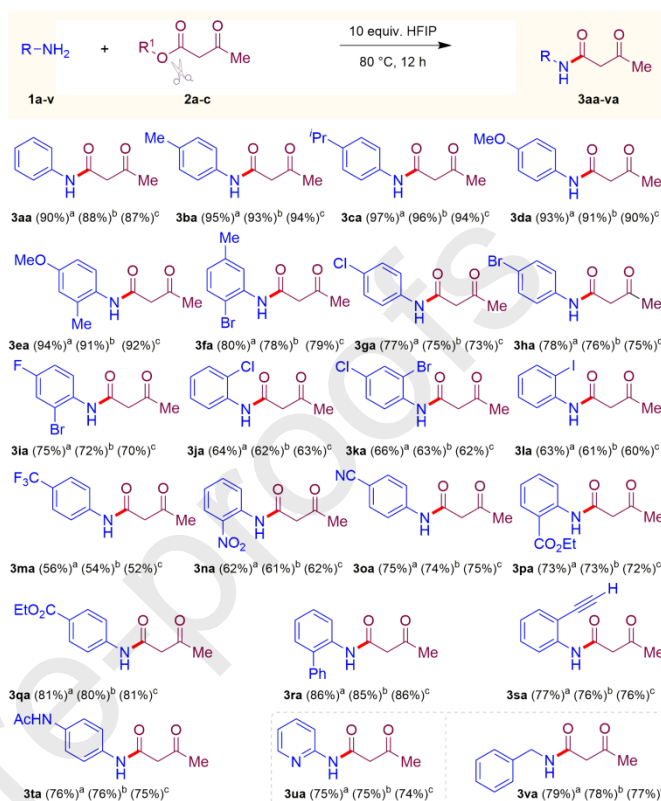
Scheme 2. Synthesis of β-keto amide derivatives using various amines and β-keto esters.

[a] Reaction yields of β-keto amides **3** using ethyl acetoacetate (**2a**).

[b] Reaction yields of β-keto amides **3** using methyl acetoacetate (**2b**).

[c] Reaction yields of β-keto amides **3** using allyl acetoacetate (**2c**).

Under these reaction conditions, functional groups such as phenyl, alkynyl and amidyl on the aromatic ring were successfully participated to obtain the corresponding β-keto amides **3ra-ta** in 75-86% yields. Surprisingly, the transformation was also accomplished successfully with *hetero*-aromatic amines and aliphatic amines under the developed reaction conditions to deliver corresponding β-keto amides **3ua-va** in 74-79% yields.

After establishing the comprehensive synthesis of β-keto amides, we desired to extend the current protocol towards the synthesis of biologically and medicinally important *N*-heterocycles. With reference to this objective, it is noteworthy to state that according to the previous report when the active methylene group is locked with the alkyl substituents, the intramolecular C-H alkenylation of the aromatic ring resulted the product with exo-cyclic double bond.[6b] In the same report, it was also observed that if the mono-functional group was installed on the active methylene group, the corresponding intramolecular C-H alkenylation annulation did not lead in the formation of the corresponding product with endo-cyclic double bond. In contrary of the previous report, we attempted to devise the catalytic system towards the installation of endo-cyclic double bond in the Friedel-Craft type cyclization process.

Table 2. Initial optimization for the synthesis of 2-quinolinones **4aa**.[a]

| Entry	Reagent/Catalyst (mol%)	Reaction conditions	4aa % yield[b]
1	HFIP (1000)	80 °C, 12 h	NR
2	Fe$_2$O$_3$ (50)	MeCN, 80 °C, 12 h	85
3	**Fe$_2$O$_3$ (10)**	**MeCN, 80 °C, 12 h**	**88**
4	Fe$_2$O$_3$ (10)	DMA, 80 °C, 12 h	53
5	Fe$_2$O$_3$ (10)	DMSO, 80 °C, 12 h	61
6	Fe$_2$O$_3$ (10)	Dioxane, 80 °C, 12 h	58
7	Fe$_2$O$_3$ (10)	MeCN, 100 °C, 12 h	86[c]
8	Fe$_2$O$_3$ (10)	MeCN, 60 °C, 12 h	65
9	Fe$_2$O$_3$ (10)	MeCN, 80 °C, 8 h	61
10	Fe$_2$O$_3$ (10)	MeCN, 80 °C, 16 h	81
11	Fe$_2$O$_3$ (20)	MeCN, 80 °C, 12 h	85
12	Fe$_2$O$_3$ (5)	MeCN, 80 °C, 12 h	74

[a] Unless otherwise mentioned, all reactions were carried out with 1 mmol of **3aa** in 1 mL solvent in a vial.
[b] Isolated yields.
[c] Reactions were carried out in sealed vial.

In pursuing this objective, we initiated our activities by carrying out the reaction of β-keto amide **3aa** under the developed reaction conditions in presence of HFIP (Table 2, Entry 1). To our disappointment, we end up with unreacted starting materials. In order to synthesize the valuable heterocyclic moiety, further optimization studies were performed with transition metal catalysts. Thus, the reaction of β-keto amide **3aa** was carried out in presence of 50 mol% of recyclable Fe$_2$O$_3$–nanoparticle[23] as catalyst and in this case it was observed that the yield of **4aa** was increased to 85% (Table 2, Entry 2). Afterwards, reducing the catalyst loading to 10 mol%, the reaction yield was not hampered, rather the reaction provided an astonishing isolated yield of 88% for the product **4aa** (Table 2, Entry 3). Next, we have examined different solvents like DMA, DMSO, dioxane to illustrate the solvent effect on reaction parameters (Table 2, Entries 4-6). Finally, to maximize the chemical yield of product **4aa**, the reaction was performed under different temperatures, catalyst loading and for different time durations (Entries 7-12). However, none of these reaction conditions showed better efficacies towards the further enhancement of the yield for 2-quinolinone **4aa**. After carrying out considerable amounts of screening of reaction conditions using β-keto amide **3aa** as model substrate, we have considered 10 mol% of Fe$_2$O$_3$ in MeCN as solvent at 80 °C for 12 hours as the optimum conditions for affording the compound **4aa** (Table 2, Entry 3) *via* intramolecular Friedel-Craft type cyclization of the arene moiety.

the preparation of 2-quinolinones **4aa**, the scope of this transformation was explored by taking various β-keto amides **3aa-ea**, **ga-ha**, **ra** embedded with both electron-donating and electron-withdrawing groups (Scheme 3). The reaction of β-keto amides **3aa-ea** bearing electron-rich functional groups such as Me, ^{i}Pr and OMe were well tolerated under the developed reaction conditions to deliver the desired 2-quinolinones **4aa-ea** in 83-88% yields. Similarly, electron-withdrawing functional groups such as Cl and Br also holds good to contribute for the preparation of 2-quinolinones **4fa-ga** in 70-74% yields. The β-keto amide **3ra** bearing a phenyl functional group was found suitable to afford the corresponding 2-quinolinone **4ha** in 78% yield.
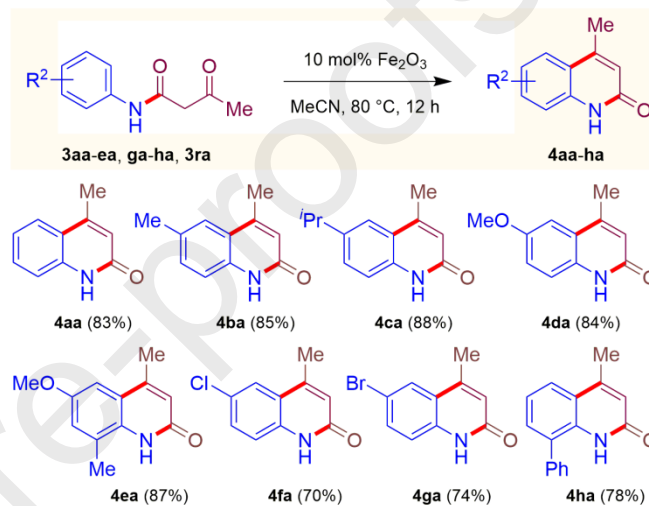
**Scheme 3.** Synthesis of 2-quinolinone derivatives using various β-keto amides.

Having successfully established the ferrite-catalyzed tandem cyclization reaction for the synthesis of 2-quinolinones, we were fascinated to verify the recyclability of the catalyst to enhance its advantages and wide applications.[24] Interestingly, the catalytic system was consistent with the formation of product **4aa** without losing its catalytic activity significantly even after 5th catalytic cycle (Figure 2).
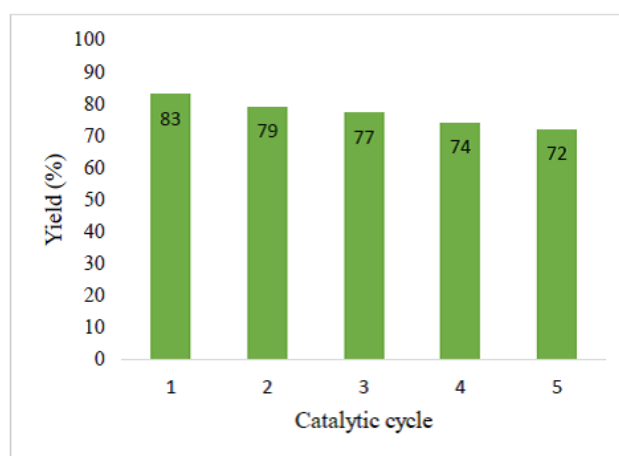
Figure 2. Recyclability test of Fe$_2$O$_3$-catalyzed synthesis of **4aa**.

After, the successful evolution and execution of the described methods for the synthesis of a wide range of β-keto amides as well as 2-quinolinones, we attempted to inspect the plausible mechanistic pathways for the developed protocol. In pursuit of establishing a plausible

have carried out the reaction of aniline (**1a**) ([M]$^+$ = 93.1, [M+H]$^+$ = 94.1) and ethyl acetoacetate (**2a**) under the developed reaction conditions and course of the reaction was monitored and examined by gas chromatography-mass spectrometry (GC-MS) after an equal interval of 3 hours. The mass-spectroscopic data revealed that the mechanism could proceed *via* the formation of intermediates **A** ([M]$^+$ = 205.3, [M+H]$^+$ = 206.3), **D** ([M]$^+$ = 159.3, [M+H]$^+$ = 160.4) to achieve the desired product **3aa** ([M]$^+$ = 177.2) (details of mass spectra are given in Figure 4, SI). Next, we focused on establishing plausible reaction mechanism for the formation of 2-quinolinones by taking acetoacetanilide (**3aa**) ([M]$^+$ = 177.2) as model substrate under the standard reaction conditions. The course of the reaction was supervised and investigated using gas chromatography-mass spectrometry (GC-MS) after an equal interval of 3 hours. According to the obtained GC-MS data, no clear indications of any intermediates were observed except for the desired product **4aa** ([M]$^+$ = 159.2, [M+H]$^+$ = 160.4) (details of mass spectra are given in Figure 5, SI).
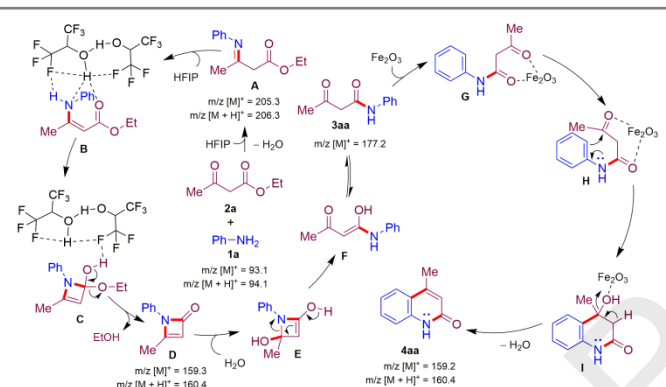
Scheme 4. Plausible reaction mechanism towards the synthesis of β-keto amides and 2-quinolinones.

Having all the possible information from the above experiments and literature reports,[4g,5b] we attempted to propose a plausible reaction mechanism for two distinct chemical transformations (Scheme 4). According to proposed reaction mechanism for the formation of β-keto amides **3**, the intermediate **A** ([M]$^+$ = 205.3, [M+H]$^+$ = 206.3) can be resulted from the condensation of **1a** ([M]$^+$ = 93.1, [M+H]$^+$ = 94.1) and **2a**. Next, the intermediate **A** may undergo hydrogen bonding interaction with HFIP resulting in an intermediate of type **B**. The intermediate **B** can undergo intramolecular cyclization in the presence of HFIP to give intermediate **C**, which upon subsequent elimination of ethanol may lead to the formation of a 4-membered β-lactam **D** ([M]$^+$ = 159.3, [M+H]$^+$ = 160.4). The intermediate **D** further undergoes nucleophilic attack by H$_2$O and subsequent ring opening to yield the enol intermediate **F**, which tautomerizes to deliver the desired product **3aa** ([M]$^+$ = 177.2).

With regard to the intramolecular Friedel-Craft type cyclization of the compound **3aa**, we assume that the catalyst Fe$_2$O$_3$ acting as a Lewis acid by weak bonding interactions with carbonyl groups to result in an intermediate **G**. The Lewis acid properties of Fe$_2$O$_3$ induces carbonyl group of ketone to undergo cyclization with aromatic ring to acquire intermediate **I**, which upon dehydration resulted in the formation of product **4aa** ([M]$^+$ = 159.2, [M+H]$^+$ = 160.4).

In conclusion, we have described a facile and experimentally simple strategy for the synthesis of β-keto amide

preparation of various bioactive molecules. The transformation has been accomplished by HFIP-induced C-O bond cleavage and consecutive site-selective C-N bond formation under the reaction conditions. The relatively mild nature of this method tolerates a wide spectrum of functional groups towards contribution of excellent yields for the formation of products. Subsequently, Fe$_2$O$_3$ nanoparticle has been identified as an efficient, stable and recyclable catalyst that allows rapid and easy entry in to medicinally significant 2-quinolinones in a single step *via* intramolecular Friedel-Craft type cyclization approach using β-keto amides in good to excellent yields.

Acknowledgments

Supplementary Material

A detailed supporting information is available which includes the purity and source of the reagents, characterization data for Fe$_2$O$_3$-nanoparticle, copies of GC–MS for investigation of the reaction mechanism, experimental procedures, ^{1}H NMR and ^{13}C NMR of the final products. Supplementary material for this article can be found in online version, at doi……...

References and notes

1. a) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957-4980; b) Couto, I.; Tellitu, I.; Domínguez, E. *J. Org. Chem.* **2010**, *75*, 7954-7957. c) Zhang, Z.; Fang, S.; Liu, Q.; Zhang, G. *J. Org. Chem.* **2012**, *77*, 7665-7670; d) Xia, L.; Lee, Y. R. *Org. Biomol. Chem.* **2013**, *11*, 5254-5263; e) Zhang, Z.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2013**, *15*, 4822-4825; f) Wang, Z.; Bi, X.; Liao, P.; Liu, X.; Dong, D. *Chem. Commun.* **2013**, *49*, 1309-1311; g) Hirai, S.; Asahara, H.; Nishiwaki, N. *Tetrahedron Lett.* **2016**, *57*, 5896-5898; h) Zhao, X.; Liu, T.-X.; Ma, N.; Zhang, G. *J. Org. Chem.* **2017**, *82*, 6125-6132.

2. a) Zhang, R.; Zhang, D.; Liang, Y.; Zhou, G.; Dong, D. *J. Org. Chem.* **2011**, *76*, 2880-2883; b) Knapp, J. M.; Zhu, J. S.; Wood, A. B.; Kurth, M. J. *ACS Comb. Sci.* **2012**, *14*, 85-88; c) Liu, W.; Zhou, P.; Chen, C.; Zhang, Q.; Zhu, Z. *Org. Biomol. Chem.* **2013**, *11*, 542-544; d) Tan, L.; Zhou, P.; Chen, C.; Liu, W. *Beilstein J. Org. Chem.* **2013**, *9*, 2681-2687; e) El-Meligie, S. E. M.; Khalil, N. A.; El-Nassan, H. B.; Ibraheem, A. A. M., *Curr. Org. Chem.* **2019**, *23*, 2005-2015.

3. a) Pattabiraman, V. R.; Bode, J. W. *Nature*, **2011**, *480*, 471-479; b) Allen, C. L.; Williams, J. M. *Chem. Soc. Rev.* **2011**, *40*, 3405-3415; c) Stolze, S. C.; Kaiser, M. *Synthesis*, **2012**, *44*, 1755-1777.

4. a) Xin, X.; Wang, Y.; Kumar, S.; Liu, X.; Lin, Y.; Dong, D. *Org. Biomol. Chem.* **2010**, *8*, 3078-3082; b) Ramanjulu, J. M.; DeMartino, M. P.; Lan, Y.; Marquis, R. *Org. Lett.* **2010**, *12*, 2270-2273; c) Sirisha, K.; Bikshapathi, D.; Achaiah, G.; Reddy, V. M. *Eur. J. Med. Chem.* **2011**, *46*, 1564-1571; d) Sengupta, T.; Gayen, K. S.; Pandit, P.; Maiti, D. K. *Chem. Eur. J.* **2012**, *18*, 1905-1909; e) Bonne, D.; Constantieux, T.; Coquerel, Y.;

Y. R. *RSC Adv.* **2014**, *4*, 36905-36916; g) Vandavasi, J. J. K.; Hsiao, C.-T.; Hu, W.-P.; Boominathan, S. S. K.; Wang, J.-J. *Eur. J. Org. Chem.* **2015**, 3171-3177 and references cited therein; h) Feng, X.; Wang, J.-J.; Xun, Z.; Huang, Z.-B.; Shi, D.-Q. *J. Org. Chem.* **2015**, *80*, 1025-1033; i) Goyal, S.; Patel, J. K.; Ganger, M.; Kumar, K.; Nair, V. A. *RSC Adv.* **2015**, *5*, 3187-3195; j) Ojeda-Porras, A.; Gamba-Sánchez, D. *J. Org. Chem.* **2016**, *81*, 11548-11555; k) Shahraki, O.; Edraki, N.; Khoshneviszadeh, M.; Zargari, F.; Ranjbar, S.; Saso, L.; Firuzi, O.; Miri, R. *Drug Des., Dev. Ther.* **2017**, *11*, 407-418.

5.   a) Štefane, B.; Polanc, S. *Tetrahedron* **2007**, *63*, 10902- 10913 and the references cited therein; b) Sridharan, V.; Ruiz, M.; Menéndez, J. C. *Synthesis*, **2010**, *6*, 1053-1057.

6.   a) Sai, K. K. S.; Gilbert, T. M.; Klumpp, D. A. *J. Org. Chem.* **2007**, *72*, 9761-9764; b) Wang, Y.; Li, W.-Q.; Che, G.; Bi, X.; Liao, P.; Zhang, Q.; Liu, Q. *Chem. Commun.* **2010**, *46*, 6843-6845.

7.   a) Beier, N.; Labitzke, E.; Mederski, W. W. K. R.; Radunz, H.-E.; Rauschenbach-Ruess, K.; Schneider, B. *Heterocycles* **1994**, *39*, 117-131; b) Naik, H. S. B.; Ramesha, M. S.; Swetha, B. V.; Roopa, T. R. *Phosphorus, Sulfur, and Silicon* **2006**, *181*, 533-541; c) Claassen, G.; Brin, E.; Crogan-Grundy, C.; Vaillancourt, M. T.; Zhang, H. Z.; Cai, S. X.; Drewe, J.; Tseng, B.; Kasibhatla, S. *Cancer Lett.* **2009**, *274*, 243-249; d) Nikpour, M.; Sadeghian, H.; Saberi, M. R.; Nick, R. S.; Seyedi, S. M.; Hosseini, A.; Parsaee, H.; Bozorg, A. T. D. *Bioorg. Med. Chem.* **2010**, *18*, 855-862; e) Manikandan, R.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 3568-3571 and the references cited therein; f) Wu, J.; Xiang, S.; Zeng, J.; Leow, M.; Liu, X.-W. *Org. Lett.* **2015**, *17*, 222-225; g) Zhang, Z.; Liao, L.-L.; Yan, S.-S.; Wang, L.; He Y.-Q.; Ye, J.-H.; Li, J.; Zhi, Y.-G.; Yu, D.-G. *Angew. Chem., Int. Ed.* **2016**, *55*, 7068-7072 and the references cited therein; h) Naeem, A.; Badshah, S. L.; Muska, M.; Ahmad, N.; Khan, K. *Molecules* **2016**, *21*, 268-286; i) Jain, S.; Chandra, V.; Jain, P. K.; Pathak, K.; Pathak, D.; Vaidya, A. *Arabian J. Chem.* **2019**, *12*, 4920-4946.

8.   Micotto, T. L.; Brown, A. S.; Wilson, J. N. *Chem. Commun.* **2009**, 7548-7550.

9.   Tietze, L. F. in *Domino Reactions: concepts for efficient organic synthesis*; Wiley-VCH: Weinheim, Germany, **2014** and references cited therein.

10. Chakraborty, A.; Majumdar, S.; Maiti, D. K. *Tetrahedron Lett.* **2016**, *57*, 3298-3302 and references cited therein.

11. a) Ponde, D. E.; Deshpande, V. H.; Bulbule, V. J.; Sudalai, A.; Gajare, A. S. *J. Org. Chem.* **1998**, *63*, 1058-1063; b) Suri, O. P.; Satti, N. K.; Suri, K. A. *Synth. Commun.* **2000**, *30*, 3709-3718; c) Chakraborty, K.; Devakumar, C. *J. Agric. Food Chem.* **2005**, *53*, 5959-5968; d) O'Halloran, N.; James, J. P.; Downey, C. A.; O'Malley, P.; Duff, T.; Bertrand, J. *Heterocycles* **2008**, *75*, 2681-2701; e) Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415-418; f) Perrone, S.; Salomone, A.; Caroli, A.; Falcicchio, A.; Citti, C.; Cannazza, G.; Troisi, L. *Eur. J. Org. Chem.* **2014**, 5932-5938; g) Gama, F. H. S.; de Souza de Souza, R. O. M. A.; Garden, S. J. *RSC Adv.* **2015**, *5*, 70915-70928.

12. a) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, W.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330-4341; b) Sharma, P.; Liu, R.-S. *Chem. Eur. J.* **2015**, *21*, 4590-4594.

13. a) Ancizu, S.; Moreno, E.; Solano, B.; Villar, R.; Burguete, A.; Torres, E.; Pérez-Silanes, S.; Aldana, I.; Monge, A. *Bioorg. Med. Chem.* **2010**, *18*, 2713-2719; b) Huggins, M. T.; Barber, P. S.; Florian, D.; Howton, W. *Synth. Commun.* **2012**, *38*, 4226-4239; c) Jaggavarapu, S. R.; Kamalakaran, A. S.; Jalli, V. P.; Gangisetty, S. K.; Ganesh, M. R.; Gaddamanugu, G. *J. Chem. Sci.* **2014**, *126*, 187-195.

14. DeShong, P.; Cipollina, J. A.; Lowmasted, N. K. *J. Org. Chem.* **1988**, *53*, 1356-1364.

15. a) Liang, S.; Hammond, G. B.; Xu, B. *Chem. Eur. J.* **2017**, *23*, 17850-17861; b) Tang, R.-J.; Milcent, T.; Crousse, B. *Eur. J. Org. Chem.* **2017**, 4753-4757; c) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, *1*, 88; d) Sinha, S. K.; Bhattacharya, T.; Maiti, D. *React. Chem. Eng.* **2019**, *4*, 244-253; e) Gujjarappa, R.; Vodnala, N.; Putta, V.P.R.K.; Reddy, V. G.; Malakar, C. C. *Tetrahedron Lett.* **2020**, *61*, 151588.

16. a) Kushwaha, K.; Pinter, B.; Shehzadi, S. A.; Malakar, C. C.; Velde, C. M. L. V.; de Proft, F.; Tehrani, K. A. *Adv. Synth. Catal.* **2016**, *358*, 41-49; b) Ebule, R.; Liang, S.; Hammond, G. B.; Xu, B. *ACS Catal.* **2017**, *7*, 6798-6801.

17. a) *Research* **2003**, 628-629; b) Glasnov, T. N.; Stadlbauer, W.; Kappe, C. O. *J. Org. Chem.* **2005**, *70*, 3864-3870; c) Nadaraj, V.; Selvi, S. T. *Indian J. Chem.* **2007**, *46B*, 1203-1207; d) Minville, J.; Poulin, J.; Dufresne, C.; Sturino, C. F. *Tetrahedron Lett.* **2008**, *49*, 3677-3681; e) Rajendran, A.; Karthikeyan, C.; Rajathi, K.; Ragupathy, D. *J. Chem. Sci.*, **2012**, *124*, 877-881; f) Reddy, M. S.; Thirupathi, N.; Babu, M. H. *Eur. J. Org. Chem.* **2012**, 5803-5809; g) Bhat, S. I.; Trivedi, D. R. *RSC Adv.* **2014**, *4*, 11300-11304; h) Xia, Y.; Gan, L.; Wang, K.; Li, Z.; Ma, D. *J. Am. Chem. Soc.* **2016**, *138*, 13493-13496; i) Elenich, O. V.; Lytvyn, R. Z.; Skripskaya, O. V.; Lyavinets, O. S.; Pitkovych, Kh. E.; Yagodinets, P. I.; Obushak, M. D. *Russ. J. Org. Chem.* **2016**, *52*, 373-378; j) Luo, L.; Tao, K.; Peng, X.; Hu, C.; Lu, Y.; Wang, H. *RSC Adv.* **2016**, *6*, 104463-104466; k) Xie, L.-Y.; Qu, J.; Peng, S.; Liu, K.-J.; Wang, Z.; Ding, M.-H.; Wang, Y.; Cao, Z.; He, W.-M. *Green Chem.* **2018**, *20*, 760-764; l) Kubica, K. P.; Taciak, P. P.; Czajkowska, A.; Stokfisz-Ignasiak, A.; Wyrebiak, R.; Podsadni, P.; Młynarczuk-Biały, I.; Malejczyk, J.; Mazurek, A. P. *Acta Pol. Pharm.* **2018**, *75*, 891-901; m) Hou, J.; Ee, A.; Feng, W.; Xu, J.-H.; Zhao, Y.; Wu, J. *J. Am. Chem. Soc.* **2018**, *140*, 5257-5263; n) Fan, H.; Wan, Y.; Pan, P.; Cai, W.; Liu, S.; Liu, C.; Zhang, Y. *Chem. Commun.* **2020**, *56*, 86-89.

18. Domínguez-Fernández, F.; López-Sanz, J.; Pérez-Mayoral, E.; Bek, D.; Martín-Aranda, R. M.; López-Peinado, A. J.; Čejka, J. *ChemCatChem* **2009**, *1*, 241-243 and the references cited therein.

19. Ferguson, J.; Zeng, F.; Alwis, N.; Alper, H. *Org. Lett.* **2013**, *15*, 1998-2001.

20. Fan, H.; Pan, P.; Zhang, Y.; Wang, W. *Org. Lett.* **2018**, *20*, 7929-7932 and the references cited therein.

21. a) Mohallem, N. D. S.; Silva, J. B.; Nascimento, G. L. T.; Guimarães, V. L. *Nanocomposites* **2012**, *18*, 457-481, ; b) Joya, M. R.; Barón-Jaimez, J.; Barba-Ortega, J. *J. Phys.: Conf. Ser.* **2013**, *466*, 012004; c) Kharisov, B. I.; Dias, H.V.R.; Kharissova, O. V. *Arabian J. Chem.* **2019**, *12*, 1234-1246.

22. a) Hynes, M. J.; Clarke, E. M. *J. Chem. Soc. Perkin Trans. 2* **1994**, 901-904; b) Chisholm, G.; Kennedy, A. R.; Beaton, L.; Brook, E. *Acta Cryst.* **2002**, *58*, 645-648; c) Lu, B.; Ma, D. *Org. Lett.* **2006**, *8*, 6115-6118; d) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345-5348; e) Li, J.-H.; Zhang, Y.-H.; Song, R.-J.; Xie, Y.-X.; Deng, C.-L.; Liang, Y. *Synthesis* **2007**, *19*, 2957-2966; f) Maiti, A.; Reddy, P. V. N.; Sturdy, M.; Marler, L.; Pegan, S. D.; Mesecar, A. D.; Pezzuto, J. M.; Cushman, M. *J. Med. Chem.* **2009**, *52*, 1873-1884; g) Kumar, B. R. P.; Sankar, G.; Baig, R. B. N.; Chandrashekaran, S. *Eur. J. Med. Chem.* **2009**, *44*, 4192-4198; h) Li, W.; Ma, X.; Fan, W.; Tao, X.; Li, X.; Xie, X.; Zhang, Z. *Org. Lett.* **2011**, *13*, 3876-3879; i) Saudi, M. N. S.; El-Semary, M. M. A.; Elbayaa, R. Y.; Jaeda, M. I.; Eissa, M. M.; Amer, E. I.; Baddour, N. M. *Med. Chem. Res.* **2012**, *21*, 257-267; j) Arjunan, V.; Kalaivani, M.; Senthilkumari, S.; Mohan, S. *Spectrochim. Acta, Part A* **2013**, *115*, 154-174; k) Liu, X.; Xin, X.; Xiang, D.; Liang, Y.; Xin, X.; Li, W.; Dong, D. *RSC Adv.* **2013**, *3*, 1346-1349; l) Liu, X.; Zhang, Q.; Xin, X.; Zhang, R.; Zhang, N.; Liang, Y.; Dong, D. *RSC Adv.* **2014**, *4*, 36234-36240; m) Wilhelm, E. A.; Machado, N. C.; Pedroso, A. B.; Goldani, B. S.; Seus, N.; Moura, S.; Savegnago, L.; Jacob, R. G.; Alves, D. *RSC Adv.* **2014**, *4*, 41437-41445; n) Azzam, R. A.; Mohareb, R. M. *Chem. Pharm. Bull.* **2015**, *63*, 1055-1064.

23. **Preparation of Hematite iron oxide (α-Fe_2O_3) nano-particles:** Hematite iron oxide (α-Fe_2O_3) nano-particles are prepared from iron (III) nitrate precursor through auto-combustion process. The iron (III) nitrate is dissolved first in distilled water followed by the addition of three mole equivalent of solid glycine. Glycine (consists of one –NH_2 and one –COOH group), a simple amino acid plays here dual role as fuel for combustion process as well as chelating agent to make complex with the metal precursor. The prepared solution is heated for 1 h at 100 °C to evaporate the liquid content. The concentrated mass is then heated at 150 °C until the auto-combustion is initiated. The auto-combustion is considered as a thermally induced redox reaction where the glycine and nitrate ion (NO_3^-) play the role of reducing and oxidizing agent respectively. Such auto-combustion process results enormous heat which decomposes the iron (III)-glycine complex followed by the formation of dried Fe_2O_3 particles. Dried particles are calcined further at 600 °C for 2 h to obtain crystalline hematite Fe_2O_3 particles.

24. **Catalyst Recycling:** The catalyst was separated by centrifugation and the solution containing reaction products was taken out for extraction process. The separated catalyst was

further purification or reactivation for the next run.

25. a) Ogura, K.; Sasaki, H.; Seto, S. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 306-313; b) Harries, H. J.; Hughes, R. K.; Smith, T. *J. Inorg. Nucl. Chem.* **1972**, *34*, 1609-1613; c) García, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron* **1994**, *50*, 6935-6940; d) Xinhe, X.; Baokun, Y.; Songjun, L.; Guocheng, L.; Nan, J.; Xianqiang, J.; Kuncheng, C.; Xijie, L.; Yuandong, H.; Hui, Z. CN108341774A, **2018**.

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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
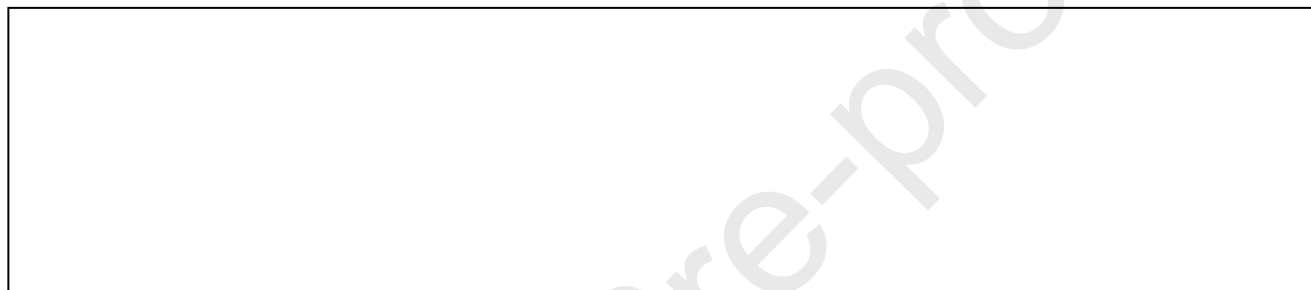
26.
- Regioselective synthesis of β-oxo amides and 2-quinolinones.
- HFIP as a simple and cost-effective reagent.
- Ferrites as a recyclable catalyst.
- Intramolecular Friedel-Craft type cyclization.
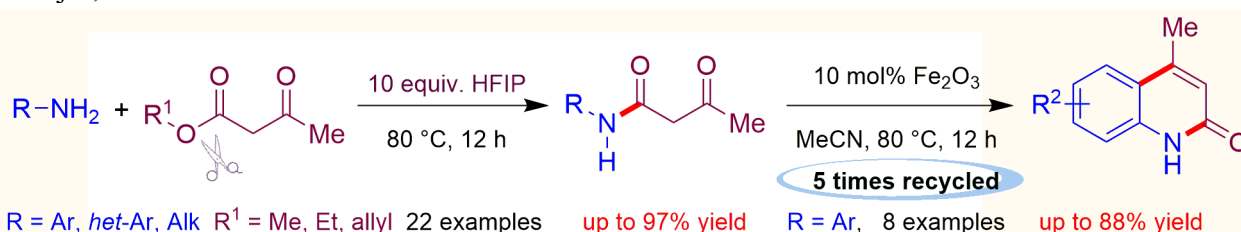- Site-selective C-N and C-C bond formation.

27.
Graphical Abstract

28.

HFIP-Mediated Strategy towards β-Oxo Amides and Subsequent Friedel-Craft Type Cyclization to 2-Quinolinones using Recyclable Catalyst

Leave this area blank for abstract info.

Arup K. Kabi,[a] Raghuram Gujjarappa,[a] Nagaraju Vodnala,[a] Dhananjaya Kaldhi,[a] Ujjawal Tyagi,[a] Kalisadhan Mukherjee,[b] Chandi C. Malakar*[a]

$R-NH_2$ + R^1 ester-dione → 10 equiv. HFIP, 80 °C, 12 h → β-oxo amide → 10 mol% Fe_2O_3, MeCN, 80 °C, 12 h, **5 times recycled** → 2-quinolinone

R = Ar, *het*-Ar, Alk R^1 = Me, Et, allyl   22 examples   up to 97% yield   R = Ar,   8 examples   up to 88% yield

● mild conditions ● broad scope ● low catalyst loading ● recyclable catalyst ● clean & green