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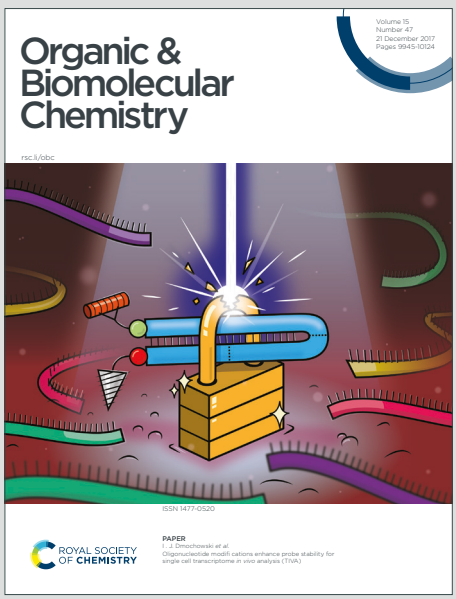

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ARTICLE

$FeCl_3$-catalyzed oxidative decarboxylation of aryl/ heteroaryl acetic acids: preparation of selected API impurities

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There is an ever-increasing demand for impurities required for profiling as regulatory agencies seek information during registration. Herein, we report $FeCl_3$-catalyzed oxidative decarboxylation of aryl-, and heteroaryl acetic acids to corresponding carbonyl compounds. A variety of useful aldehydes and ketones were prepared in a simple one-pot transformation by employing environmentally benign, low cost, and readily available iron salt. The utility of this method has been demonstrated by preparing five valuable API impurities including a multi-gram scale synthesis of ketorolac impurity B for the first time.

Introduction

Impurity profiling is an important and essential activity in modern drug development in order to ensure the quality of active pharmaceutical ingredients (APIs) and ultimately the safety of patients. As per the guidelines published by the International Conference on Harmonization (ICH), all impurities presence (at a level of ~0.10% or more) have to be identified and characterized.[1] Regulatory agencies emphasize on impurity profile during the registration of drugs. These impurities may creep in during the process development or formulation stages, or upon storage of APIs/formulated medicines.[2] As per regulatory requirements, and to take drugs into the markets for necessary approvals, there is a need for impurity profiling. The preparation of impurities of drugs has received significant attention owing to their remarkable properties and of medicinal interest. Therefore, demand for API impurities synthesis is continuously increasing for the purpose of profiling.[3] Although, most of the identified impurities of APIs are commercially available, they are very expensive– as they are prepared in multiple synthetic steps or prepared in very poor yields through forced degradation of marketed APIs. To overcome these issues, we were interested in synthesizing API impurities of selected important marketed drugs with ketone/aldehyde functionality, resulting from corresponding aryl acetic acid moiety containing drugs (Figure 1). For this purpose, we wanted to utilize a direct oxidative decarboxylation, to prepare carbonyl compounds, starting from carboxylic acids, which has not been documented extensively.[4-6] This method is particularly interesting as many active pharmaceutical ingredients in particular with aryl or heteroaryl acetic acids undergo such transformation to generate corresponding impurities. Although, in this context, several strategies were developed, they are not directly represented a good compromise in API impurity synthesis, and there are a few earlier studies reported in the literature for the decarboxylation of carboxylic acids to aldehydes and ketones by photoredox method which required an expensive Ruthenium catalyst and special reaction setup.[4b]

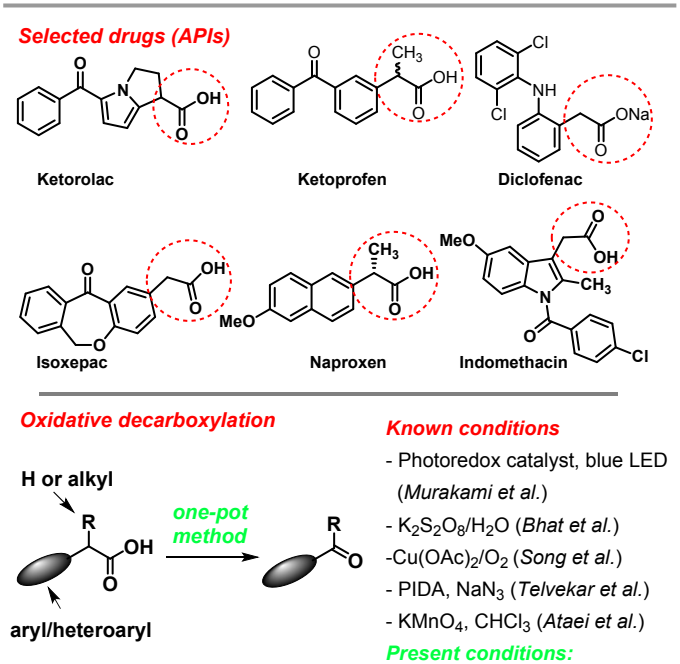

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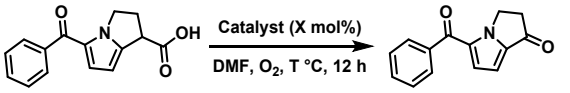
Figure 1. Structures of selected APIs with aryl acetic moieties and known methods for oxidative decarboxylation

In an elegant study, $K_2S_2O_8$ was used to catalyze decarboxylation process in a viable aqueous medium.[4c] On the other hand, $Cu(OAc)_2/O_2$ combined system was demonstrated at elevated temperatures with limited substrate scope to drug molecules.[5a,b] In an early study, decarboxylation of arylacetic acids were achieved using diacetoxyiodobenzene/NaN_3,[5c] $KMnO_4$.[6a] A similar type of Mn/$NaIO_4$ catalyzed reactions were reported limiting to features of this transformation.[7] Developing new and effective methods for the oxidative decarboxylation, particularly, in the context of API impurities, it is very interesting and expected to attract attention of broad scientific community. In view of developing particularly sustainable catalytic manifolds based on 3d metals,[8] iron-catalyzed transformations[9] stand out because of iron's high earth abundance, affordability, and low toxicity.[10]

Results and discussion



Ketorolac API (1) **Ketorolac impurity B (2)**

entry	Catalyst (10 mol%)/ solvent	Temp (°C)	Yield (%)[b]
1	PIDA, NaN_3/ACN	rt	no product
2	$KMnO_4$/DCM	rt	no product
3	$K_2S_2O_8/H_2O$	90	no product
4	$Cu(OAc)_2$/DMSO/O_2	120	11
5	$Cu(OTf)_2$/DMF/ O_2	110	trace
6	$CuBr_2$/DMF/ O_2	110	Trace
7	$CuSO_4$/DMF/ O_2	110	~5
8	Cu_2O/DMF/ O_2	110	19
9	$FeCl_3$/DMF/ O_2	110	74
10	$FeCl_3$/DMF/ O_2	110	77[c]
11	$FeCl_3$/DMSO/ O_2	110	57
12	$FeCl_3$/NMP/ O_2	110	34
13	$FeCl_3$/DMF/air	110	13
14	$FeSO_4$/DMF/ O_2	110	21
15	$FeCl_3$/DMF/N_2	110	no product
16	$FeCl_3/H_2O$	110	no product

[a]Reaction conditions: In all cases, reactions were carried out using **1** (1mmol), catalyst (10 mol%), solvent (2 mL) under respective atmosphere, [b]isolated yield, [c]reaction performed with 20 mol% of catalyst, DMF = *N,N*-dimethylformamide, DMSO = Dimethyl sulfoxide, NMP = *N*-Methyl-2-pyrrolidone.

Scheme 1. Optimization of the oxidative decarboxylation[a]

These unique features have sparked intense interest, leading to great advances in the field of iron-catalyzed C–H functionalization. Herein, we disclose a $FeCl_3$-catalyzed oxidative decarboxylation of various arylacetic acids to aldehydes / ketones using O_2 as a terminal oxidant.

Initially, our focus was to prepare the much needed ketorolac impurity B (**2**)[11] since Gu and co-workers' first report of photo induced protocol to synthesize ketorolac impurity B in which a mixture of products were isolated, and seem to be lack of practicality to reproduce the compounds which dates back to 1988, no considerable research has been focused on the synthesis this privileged API impurities till date.[11c] Seeking to address these challenges, and practical drawbacks, we have used ketorolac API to prepare **2** through a possible oxidative decarboxylation method. However, the well-known methods[4-6] that we have attempted did not produce the desired product (**Scheme 1**, entry 1,2). An attempt to perform the reaction in aqueous medium in the presence of $K_2S_2O_8$ did not afford the decarboxylative product, instead a heap of insoluble material was recovered (**Scheme 1**, entry 3). The possible reason could be these methods effectively work for aromatic systems, where as our substrate is heteroaromatic system. To address these apparent challenges, we wanted to explore a different set of protocols, in particular, by employing readily accessible copper and iron salts for the required oxidative decarboxylation. Our initial findings arose to realize that the conversion of ketorolac drug **1** when 10 mol% of $Cu(OAc)_2$ were mixed in DMSO under O_2 atmosphere at 120 °C. While the color of substrate **1** was an off-white solid, a pale yellow color appeared simultaneously upon heating. As anticipated, oxidative decarboxylative product **2** was obtained in 11% isolated yield (**Scheme 1**, entry 4). An increase in the amount of catalyst (20 mol%) and use of other Cu salts such as $Cu(OTf)_2$, $CuBr_2$ or $CuSO_4$ did not improve yields (**Scheme 1**, entries 5-7). However, Cu_2O gave slight improvement (19%) of expected product (**Scheme 1**, entry 8). To overcome these apparent drawbacks and inefficiency of above screened catalysts, we turned our attention to iron salts – as iron metal is most abundant, inexpensive, less toxic and environmentally benign.[12] Although, iron catalysis is underexplored, compared to precious metals, past decade saw a rise in a number of publications in the pursuit of sustainability.[13] Delightfully, the desired product 2 was smoothly obtained in 74% yield with 10 mol% of $FeCl_3$ (**Scheme 1**, entry 9). Increasing the amount of $FeCl_3$ (20 mol%) resulted only in slightly improved yield of the desired product (Scheme 1, entry 10). Variation of solvents (DMSO, NMP) did not help in improving the outcome of the product (**Scheme 1**, entry 11, 12). When the reaction carried out under an air atmosphere also significantly decreased the yield (**Scheme 1**, entry 13). Use of other Fe salt also yielded the desired product in unsatisfactory yield (**Scheme 1**, entry 14). Finally, the reaction carried out under nitrogen atmosphere, and in water proved the necessity of organic solvent and oxygen atmosphere for the present study (**Scheme 1**, entry 15, 16). It was noteworthy that the use of 10 mol% of $FeCl_3$ was

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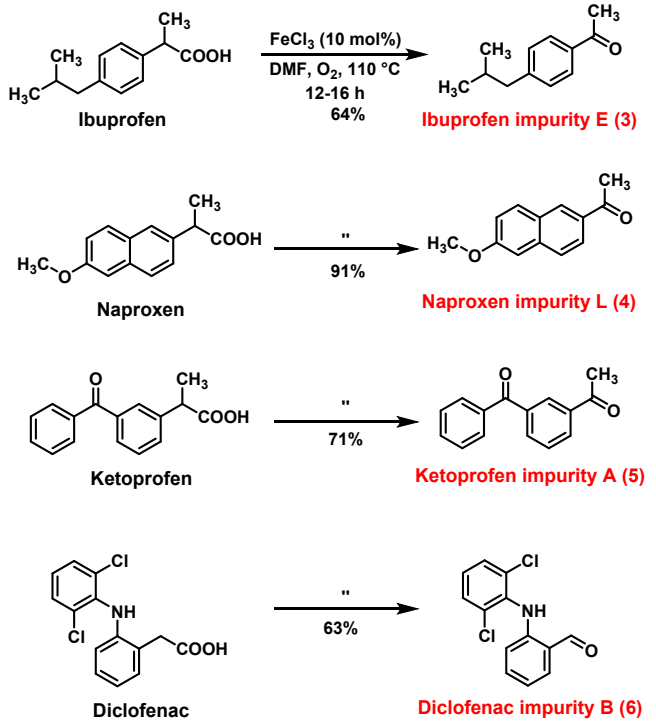
found to be optimal, and this reaction proceeded more smoothly with 74% yield (Scheme 1, entry9). The identity of ketorolac impurity B (**2**) structure was determined using spectral data and also further confirmed with the help of single crystal X-ray structure (**Scheme 2**).

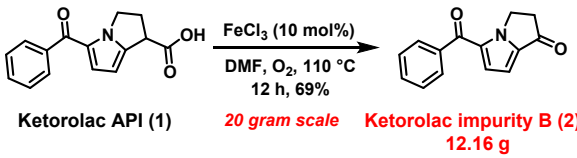
Having finalized optimized conditions for the desired transformation using ketorolac API, we focused our attention on other drug molecules, to explore the scope of the reaction and also to have ready access to the corresponding API impurities. As shown in **Scheme. 2**, four popular APIs such as ibuprofen, naproxen, ketoprofen and diclofenac sodium were chosen to access their corresponding impurities. All the four APIs with aryl/heteroaryl acetic acid moieties smoothly converted into their corresponding impurities under optimized reaction conditions. We observed the best isolated yield in the case of naproxen (**Scheme 2**). To demonstrate the efficacy of the present method and also to generate sufficient required quantities of the impurity **2**, a multi-gram scale reaction on ketorolac **1** was carried out successfully and obtained the desired ketorolac impurity B, **2** as a bright orange color solid in good yields (**Scheme 2**; actual pictures of API and synthesized impurity **2** are shown in graphical abstract).[14]

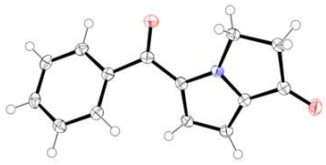
Although, $FeCl_3$-catalyzed decarboxylation followed by cyclization to access quinazolinones, quinazolinesvia via *in situ* generated carbonyl compounds from the corresponding arylacetic acids was documented, however, this approach is limiting in isolation of carbonyl compounds,[15] and there is no documented method to prepare carbonyl compounds from arylacetic acids by employing $FeCl_3$. Therefore, we were interested to understand the generality of the present method with a variety of substrates, in particular, substituted aryl acetic acids to access carbonyl compounds. As expected, the indomethacin drug yielded the respective aldehyde in good yield (**Scheme 3**;**7**). Also, a different α-methyl aryl acetic acids resulted in the corresponding methyl ketones (**8**-**11**). We also investigated the same reaction conditions with diphenyl acetic acid and indane-1-carboxylic acid and obtained the desired products **12** and **13** in good yields, respectively (**Scheme 3**). To increase scope of the method, various phenylacetic acids bearing both electron-withdrawing and electron-donating substituents on the aromatic ring were successfully converted into their aldehydes under identical conditions (**Scheme 3; 14**-**22**). Naphthyl, biphenylacetic acids also underwent smooth conversion to give the desired products in good yields (**Scheme 3; 23**-**25**). Ultimately, heteroaromatics were also successfully converted in to their respective carbonyl compounds under the adopted reaction conditions in good yields (**Scheme 3; 26**,**27**). Having synthesized a series of aldehydes, ketones, we turned our attention to examine the reactivity of benzylic position of ketorolac derivative **28**. Compound **28** was subjected to optimized identical conditions and realized that only the compound **2** (ketorolac impurity B) was obtained in good yields. These results proved that the current optimized conditions are good enough to catalyze both decarboxylation and oxidation of active methylene group such as double benzylic without assistance of any oxidants[16] other than oxygen (**Scheme 3**).

As documented in literature on related transformations,[4b,5, 15,16] the present reaction mechanism of $FeCl_3$-catalyzed aerobic oxidative functionalization is expected to go through a radical pathway. The arylacetic acid **1** in the presence of Fe forms benzylic radical **A**, which is readily trapped by molecular oxygen and generates peroxide radical **B**. Subsequently, an intramolecular abstraction of hydrogen atom from carboxyl group of **B** forms intermediate **C**, which upon releasing CO_2 and OH radical eventually forms the final product. During the present study, we also observed, that the 10 mol% of $FeCl_3$ is capable enough to catalyze oxidative decarboxylation followed by benzylic oxidation[15e-h] of **28** to yield **2** (**Scheme 4**). Recent available reports notified the necessity of *tert*-butyl hydroperoxides, aqueous HCl in $FeCl_3$ catalyzed benzylic carbon degradation reaction into carbonyl compounds.[15c,16] The present protocol with the use of 10 mol% $FeCl_3$ avoided the use of such hydroperoxides, and acidic medium conditions to benzylic carbon oxidation and successfully catalyze both decarboxylation, and oxidation of benzylic carbon in a single operation.



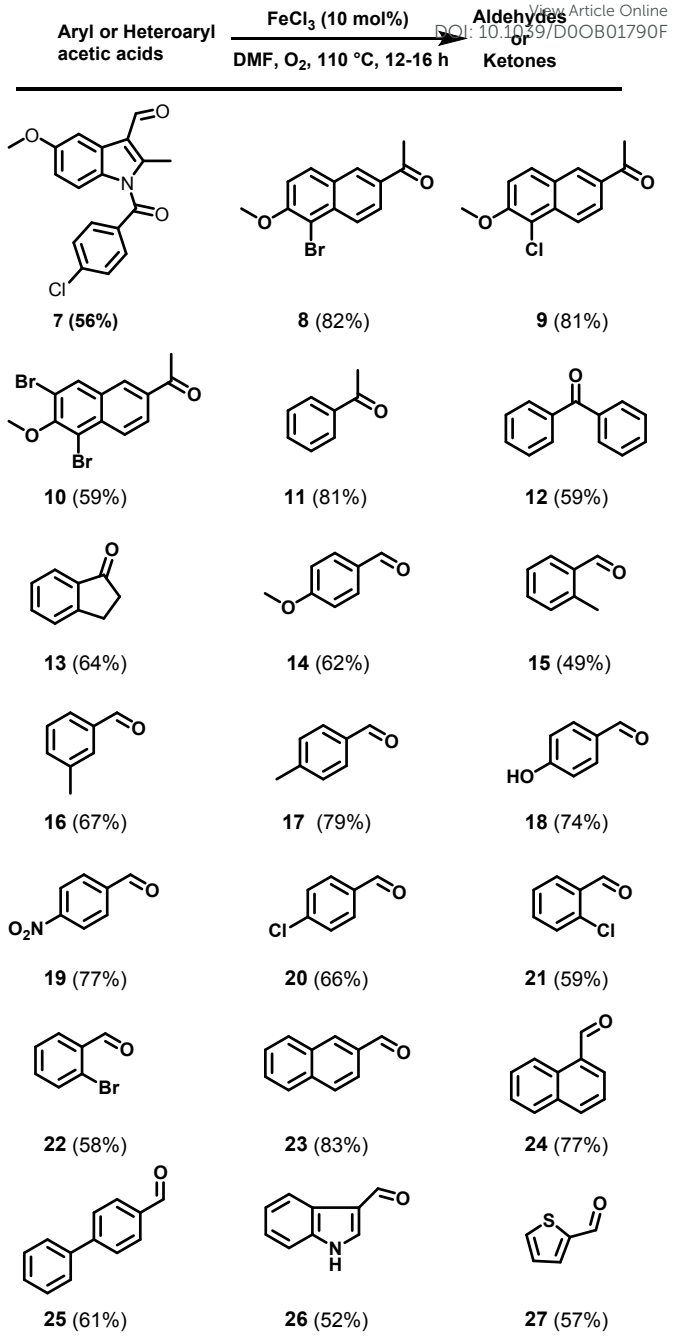
Gram-scale synthesis





ORTEP of **2** (CCDC#1961334)

Scheme 2. Synthesis of API impurities[a,b]



[a] Only products from the reaction are shown here.
[b]Reaction conditions: Arylacetic acid (0.8mmol), catalyst (10 mol%) solvent (2 mL)

Scheme 3. Substrate scope of oxidative decarboxylation[ab]

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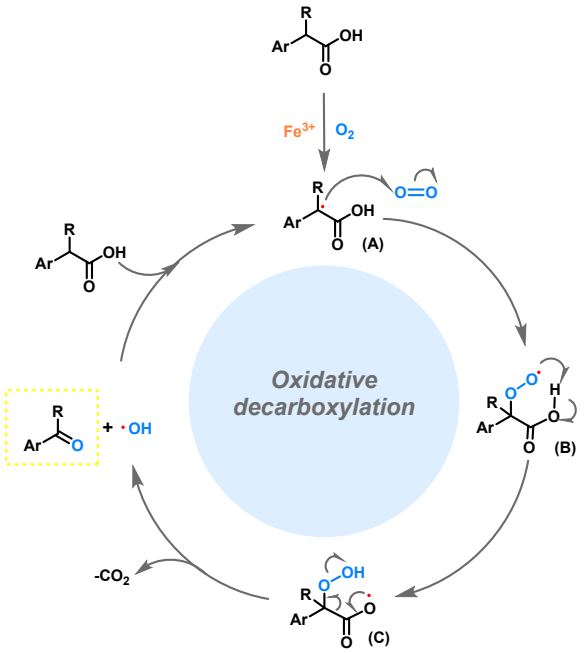
Conclusions

In summary, we have utilized $FeCl_3/O_2$ system to catalyse the transformation (oxidative decarboxylation) of arylacetic acids and drug molecules with same functional moiety to obtain corresponding carbonyl compounds. The highlight of the present disclosure is to provide access to important API impurities of popular drugs and a multi-gram scale synthesis of ketorolac impurity **B** for the first time. Excellent functional group tolerance was observed during the course of the reaction to furnish aldehydes and ketones in good yields. The present method could be applied for the synthesis of other medicinally important compounds. In addition, it will expand the scope and utility of decarboxylation in organic synthesis as well.



Scheme 4. Plausible mechanism for oxidative decarboxylation

Experimental section

General information

All reactions were carried out in oven-dried glassware under a positive pressure of oxygen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials and solvents were obtained from commercial suppliers and used as received without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), 2,4-DNP solution or Iodine adsorbed on silica gel followed by heating with a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Melting points (mp) were determined using a Bruker capillary melting point apparatus and are uncorrected. Deuterated solvents for NMR spectroscopic analyses were used as received. All ^1H, ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz or 500 MHz spectrometer. Coupling constants were measured in Hertz. Chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: br s = road singlet, br d = broad doublet, s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, q = quartet, m = multiplet. HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, QExactive). Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

General procedure for the synthesis of API impurities & carbonyl compounds.

In an 100 mL oven-dried flask containing a magnetic stirring bar were added carboxylic acids (1.0 equiv) in anhydrous DMF (60 mL), $FeCl_3$ (10 mol%) in sequence under O_2 atmosphere. The reaction mixture was heated at 110 °C in an oil bath for 12 h. Then, the reaction mixture was cooled to room temperature, filtered through celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 5:1 to 3:1) to give the pure products **2-27.**

Experimental data for API impurities and carbonyl compounds

5-Benzoyl-2,3-dihydro-1H-pyrrolizin-1-one (2). According to the general procedure, in an 10 mL oven-dried flask containing a magnetic stirring bar were added ketorolac **1** (0.200 g, 0.78 mmol) in anhydrous DMF (1.5 mL), $FeCl_3$ (0.012 g, 10 mol%) in sequence under O_2 atmosphere. The reaction mixture was heated at 110 °C in an oil bath and the completion of the reaction was monitored by TLC (12 h). After fully consumption of the starting material, the reaction mixture was cooled to room temperature, filtered through celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 5:1 to 3:1) to give the pure product **2** as a blood red solid. Mp: 136-138 °C. Yield: 0.131 g, 74%. IR (neat) 3214, 2934, 2810, 2369, 1718, 1711, 1272, 1168, 955, 872 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 6.8, 4.7 Hz, 2H), 7.55 (td, *J* = 7.0, 2.6 Hz, 1H), 7.49 – 7.41 (m, 2H), 6.93 (t, *J* = 4.4 Hz, 1H), 6.75 – 6.58 (m, 1H), 4.67 (dd, *J* = 11.3, 5.8 Hz, 2H), 3.07 (dd, *J* = 11.3, 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 186.1, 138.2, 137.2, 132.6, 131.7, 129.1, 128.6, 124.5, 106.6, 44.6, 39.0. HRMS (ESI)$^+$*m/z*: $[M + H]^+$Calcd for $C_{14}H_{12}NO_2$ 226.0868; Found 226.0869.

Gram scale synthesis of compound 2. According to the general procedure, in an 500 mL oven-dried flask containing a magnetic stirring bar were added ketorolac **1** (20 g, 78.32 mmol) in anhydrous DMF (250 mL), $FeCl_3$ (1.26 g, 10 mol%) in sequence under O_2 atmosphere. The reaction mixture was heated at 110 °C in an oil bath and the completion of the reaction was monitored by TLC (12 h). After fully consumption of the starting material, the reaction mixture was cooled to room temperature, filtered through celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 5:1 to 3:1) to give the pure product **2** as a blood red solid. Yield: 12.16g, 69%.

4. Crystal data for compound 2. The product was recrystallized using EtOAc and pet ether. $C_{14}H_{11}NO_2$, M = 225.24, crystal size 0.43 × 0.34 × 0.3 mm, monoclinic, space group P 21/c, with *a* = 10.1140(5) Å, *b* = 10.3178(5) Å, *c* = 10.5034(5) Å, α = 90°, β = 102.09°, γ = 90°, *V* = 1071.76(9) Å^3; *T* = 105 K, R_1 = 0.0309, wR_2 = 0.0765 on observed data, *Z* = 4, D_{calcd} = 1.396 g cm^{-3}, *F*(000) = 472.0, absorption coefficient = 0.094 mm^{-1}, *l* = 0.71073 Å, 1781 reflections were collected on a Bruker APEX-II CCD single-crystal diffractometer, 1891 observed reflections [(I >2σ(I)]. The largest difference peak and hole was 0.219 and –0.175 eÅ^{-3}, respectively. The structure was solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL-97 software (CCDC 1961334).

1-(4-Isobutylphenyl)ethan-1-one (3).[5a] It was synthesized from *RS*)-2-(4-(2-Methylpropyl)phenyl)propanoic acid by following an analogous procedure described for **2**. Thick yellow oil. Yield: 0.109 g, 64%. IR (neat) 2924, 2361, 2102, 1684, 1461, 1267, 1177, 958, 849 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 2.52 (d, *J* = 7.1 Hz, 2H), 1.89 (dt, *J* = 13.1, 6.7 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 147.5, 134.9, 129.2, 128.3, 45.3, 30.0, 26.4, 22.3.

1-(6-Methoxynaphthalen-2-yl)ethan-1-one (4).[17] It was synthesized from (+)-(*S*)-2-(6-Methoxynaphthalen-2-yl)propanoic acid by following an analogous procedure described for **2**. White solid. Mp: 147-149 °C. Yield: 0.159 g, 91%. IR (neat) 3344, 2964, 1673, 1463, 1266, 1056, 1014, 966 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.01 (d, *J* = 1.6 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.20 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 3.94 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 159.4, 137.2, 132.7, 131.0, 130.1, 128.0, 127.1, 124.7, 119.9, 105.5, 55.4, 26.5.

1-(3-Benzoylphenyl)ethan-1-one (5).[4b] It was synthesized from (*RS*)-2-(3-benzoylphenyl)propanoic acid by following an analogous procedure described for **2**. White solid. Mp: 87-89 °C. Yield: 0.125 g, 71%. IR (neat) 3063, 1657, 1594, 1424, 1357, 1290, 1235, 1145, 960 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.58 (q, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 196.0, 138.1, 137.2, 137.0, 134.4, 133.0, 131.9, 130.1, 129.8, 128.8, 128.6, 26.7.

2-((2,6-dichlorophenyl)amino)benzaldehyde (6).[18] It was synthesized from sodium 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate by following an analogous procedure described for **2**. (Reaction carried out with 0.100 g scale). Yellow solid. Mp: 139-141 °C. Yield: 0.056 g, 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 9.79 (s, 1H), 7.62 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.38 – 7.31 (m, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 147.0, 136.1, 135.3, 134.6, 134.4, 128.8, 127.7, 119.3, 117.7, 113.3.

1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-carbaldehyde (7).[4b] It was synthesized from 2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid by following an analogous procedure described for **2**. (Reaction carried out with 0.100 g scale). Thick greenish oil. Yield: 0.051 g, 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.80 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 6.72 (s, 2H), 3.86 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 168.3, 157.3, 148.7, 141.0, 132.1, 131.8, 130.7, 129.6, 127.0, 118.4, 114.3, 113.9, 103.3, 55.8, 12.7.

1-(5-Bromo-6-methoxynaphthalen-2-yl)ethan-1-one (8). It was synthesized from 2-(5-bromo-6-methoxynaphthalen-2-yl)propanoic acid by following an analogous procedure described for **2.**Colorless solid. Mp: 164-166 °C. Yield: 0.148 g, 82%. IR (neat) 2926, 1663, 1616, 1466, 1348, 1273, 1239, 1053, 942 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 1.6 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 8.06 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 9.1 Hz, 1H), 4.04 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 155.4, 135.9, 132.9, 130.8, 130.4, 128.6, 126.7, 125.8, 114.0, 108.5, 56.8, 26.5. HRMS (ESI)$^+$*m/z*: [M + H]$^+$Calcd for $C_{13}H_{12}BrO_2$279.0021; Found 279.0017.

1-(5-Chloro-6-methoxynaphthalen-2-yl)ethan-1-one (9). It was synthesized from 2-(5-chloro-6-methoxynaphthalen-2-yl)propanoic acid by following an analogous procedure described for **2.** Colorless solid. Mp: 164-166 °C. Yield: 0.148 g, 82%. IR (neat) 2931, 1670, 1621, 1476, 1353, 1276, 1249, 1062, 884 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.4 Hz, 1H), 8.24 (d, *J* = 9.0 Hz, 1H), 8.09 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 4.06 (s, 3H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 154.7, 134.2, 133.1, 130.4, 129.9, 128.4, 125.6, 124.1, 117.0, 114.2, 56.9, 26.7. HRMS (ESI)$^+$*m/z*: [M + H]$^+$ Calcd for $C_{13}H_{13}ClO_2$235.0526; Found 235.0526.

1-(5,7-dibromo-6-methoxynaphthalen-2-yl)ethan-1-one (10). It was synthesized from 2-(5,7-dibromo-6-methoxynaphthalen-2-yl)propanoic acid by following an analogous procedure described for **2.** Mp: 151-153 °C. Yield: 0.055 g, 59%. IR (neat) 2918, 1711, 1621, 1459, 1328, 1251, 1219, 1027, 928 cm^{-1}. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 1.6 Hz, 1H), 6.83 (dd, *J* = 8.9, 1.7 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 6.16 – 5.94 (m, 1H), 2.81 (s,3H), 1.46 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 197.6, 155.7, 135.4, 133.0, 130.8, 130.4, 128.6, 126.6, 125.8, 114.0, 108.4, 57.0, 26.7. HRMS (ESI)$^+$*m/z*: [M + H]$^+$Calcd for $C_{13}H_{11}Br_2O_2$356.9126; Found 356.9130.

Phenylethanone (11).[5c] It was synthesized from 2-Phenylpropionic acidby following an analogous procedure described for **2.**Thick pale yellow oil. Yield: 0.117 g, 73%. IR (neat) 1680, 1592, 1445, 1358, 1259, 1179, 1078, 1022, 954 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 5.1, 2.6 Hz, 2H), 7.55 (dd, *J* = 8.5, 4.4 Hz, 1H), 7.45 (dd, *J* = 12.4, 5.7 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 137.1, 133.1, 128.6, 128.3, 26.3.

Diphenylmethanone (12).[4c] It was synthesized from 2,2-diphenylacetic acid by following an analogous procedure described for **2**. Pale brown solid. Mp: 53-55 °C. Yield: 0.139 g, 81%. IR (neat) 1656, 1597, 1446, 1312, 1272, 1175, 1151, 1074, 918, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.0 Hz, 2H), 7.64 – 7.55 (m, 1H), 7.54 – 7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 137.6, 132.4, 130.1, 128.1.

2,3-dihydro-1H-inden-1-one (13).[19] It was synthesized from 2,3-dihydro-1H-indene-1-carboxylic acid by following an analogous procedure described for 2. Colorless solid. Mp: 40-42 °C. Yield: 0.079 g, 49%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.7 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 3.16 – 2.97 (m, 2H), 2.71 – 2.53 (m, 2H); 13C NMR (100MHz, $CDCl_3$) δ 206.9, 155.1, 137.0, 134.5, 127.2, 126.7, 123.5, 36.1, 25.7.

4-Methoxybenzaldehyde (14).[5c] It was synthesized from 4-Methoxyphenylacetic acid by following an analogous procedure described for **2**. Thick yellow oil. Yield: 0.101 g, 62%. ^1H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.86 (d, *J* = 11.3 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 164.8, 132.2, 130.0, 114.1, 55.7.

2-Methylbenzaldehyde (15).[4c]It was synthesized from *o*-Tolylacetic acid by following an analogous procedure described for **2**. Pale yellow oil. Yield: 0.103 g, 64%. ^1H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.50 (q, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 6.7 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 140.6, 134.1, 133.6, 132.1, 131.8, 126.3, 19.6.

3-Methylbenzaldehyde (16).[4c] It was synthesized from *m*-Tolylacetic acid by following an analogous procedure described for **2**. Pale yellow oil. Yield: 0.107 g, 67%. IR (neat) 2727, 1695, 1592, 1246, 1149, 778 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.68 (s, 2H), 7.42 (s, 2H), 2.42 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 138.9, 136.5, 135.4, 130.1, 128.9, 127.3, 21.2.

4-Methylbenzaldehyde (17).[4c] It was synthesized from *p*-Tolyl acetic acid by following an analogous procedure described for **2**. Thick oil. Yield; 0.127 g, 79%.IR (neat) 2824, 2733, 1691, 1603, 1387, 1301, 1209, 1167, 845 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.93 (d, *J* = 2.0 Hz, 1H), 7.74 (s, 2H), 7.29 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 192.0, 145.5, 134.2, 129.4, 21.8.

4-Hydroxybenzaldehyde (18).[4c] It was synthesized from 4-Hydroxyphenylacetic acid by following an analogous procedure described for **2.**Dark brown powder. Mp: 117-119 °C. Yield: 0.119 g, 74%. IR (neat) 3212, 1676, 1610, 1515, 1461, 1294, 1166, 830 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.79 (s, 1H), 7.76 (d, *J* = 11.2 Hz, 2H), 6.94 (d, *J* = 11.1 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 191.1, 163.7, 132.6, 129.0, 116.1.

4-Nitrobenzaldehyde (19). [4c] It was synthesized from 4-Nitro phenylacetic acid by following an analogous procedure described for **2.**Dark yellowish powder. Mp: 107-109 °C. Yield: 0.129 g, 77%. IR (neat) 2850, 1708, 1605, 1532, 1350, 1199, 1104, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 190.2, 150.7, 139.5, 130.1, 124.1.

4-Chlorobenzaldehyde (20).[4c] It was synthesized from 4-chloro phenylacetic acid by following an analogous procedure described for **2.** Yellowish thick oil. Yield: 0.053 g, 64%. IR (neat) 2931, 2874, 1716, 1483, 1451, 1412, 1226, 1009, 949 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.82 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.7, 160.0, 128.8, 125.2, 112.6.

2-Chlorobenzaldehyde (21).[4c] It was synthesized from 2-chloro phenylacetic acid by following an analogous procedure described for **2.**Pale brownish thick oil. Yield: 0.048 g, 59%. ^1H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.90 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.52 (td, *J* = 7.7, 1.1 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 137.9, 135.1, 132.4, 130.6, 129.34, 127.3.

2-Bromobenzaldehyde (22).[4c] It was synthesized from 2-Bromo phenylacetic acid by following an analogous procedure described for 2. Thick colorless oil. Yield: 0.101 g, 58%. IR (neat) 2865, 1691, 1585, 1437, 1392, 1262, 1195, 1032, 821 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.91 – 7.85 (m, 1H), 7.63 – 7.58 (m, 1H), 7.45 – 7.37 (m, 2H); 13C NMR (125MHz, $CDCl_3$) δ 191.8, 135.4, 133.9, 133.4, 129.8, 128.0, 127.1.

2-Naphthaldehyde (23).[1] It was synthesized from 2-Naphthaleneacetic acid by following an analogous procedure described for **2.** Thick colorless oil. Yield: 0.140 g, 83%. IR (neat) 3057, 2822, 1685, 1625, 1464, 1347, 1263, 1164, 1117, 860 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.29 (s, 1H), 8.00 – 7.84 (m, 4H), 7.59 (dt, *J* = 15.1, 7.1 Hz, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 192.4, 136.5, 134.7, 134.8, 132.7, 129.6, 129.2, 128.0, 126.9, 122.8.

1-Naphthaldehyde (24).[5a] It was synthesized from 1-Naphthaleneacetic acid by following an analogous procedure described for **2**. Thick colorless oil. Yield: 0.129 g, 77%. IR (neat) 1740, 1515, 1214, 1058, 964 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 9.24 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.86 (dd, *J* = 12.5, 8.0 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.53 (dd, *J* = 12.0, 7.7 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 193.8, 136.8, 135.3, 133.7, 131.4, 130.5, 129.1, 128.5, 127.0, 124.9.

[1,1'-biphenyl]-4-carbaldehyde (25).[20] It was synthesized from 4-Biphenylacetic acid by following an analogous procedure described for **2**. Thick colorless oil. Yield: 0.105 g, 61%. IR (neat) 2911, 2852, 1687, 1366, 831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.62 – 7.56 (m, 2H), 7.48 – 7.35 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 191.9, 147.2, 139.7, 135.3, 130.3, 129.1, 128.5, 127.7, 127.4.

1H-indole-3-carbaldehyde (26).[21] It was synthesized from Indole-3-acetic acid by following an analogous procedure described for **2**. Dark brown solid. Mp: 201-203 °C. Yield: 0.086g, 52%. IR (neat) 3435, 3203, 2966, 2934, 2878, 1644, 1453, 1216, 1055, 966 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 12.19 (s, 1H), 9.98 (s, 1H), 8.32 (d, *J* = 3.1 Hz, 1H), 8.15 (dd, *J* = 5.7, 2.6 Hz, 1H), 7.56 (dd, *J* = 6.0, 2.5 Hz, 1H), 7.39 – 7.14 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.0, 138.5, 137.1, 124.2, 123.5, 122.2, 120.9, 118.2, 112.5.

Thiophene-2-carbaldehyde (27).[4c] It was synthesized from 2-Thiopheneacetic acid by following an analogous procedure described for **2**. Thick greenish oil. Yield: 0.090g, 57%. IR (neat) 3097, 2826, 1654, 1516, 1415, 1208, 1043, 855 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, *J* = 1.2 Hz, 1H), 7.68 (dd, *J* = 10.1, 4.5 Hz, 2H), 7.11 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 144.0, 136.7, 135.3, 128.3.

Conflicts of interest

There are no conflicts to declare.

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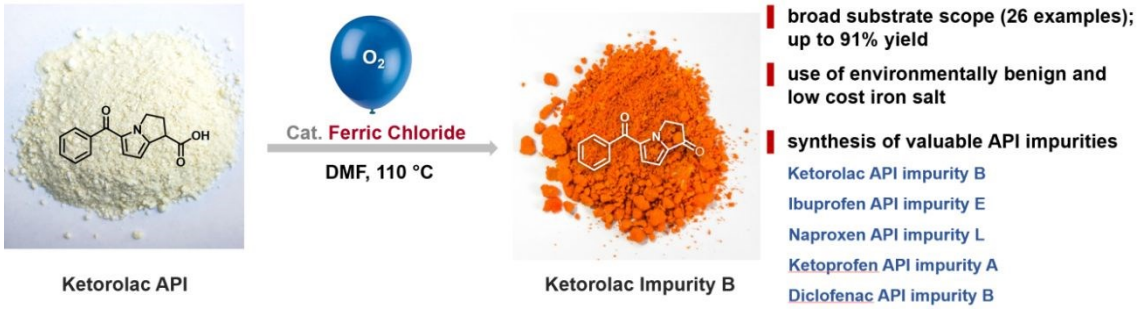

Graphical abstract

Impurities are unwanted chemical substances that arise during synthesis of APIs and remains with them. These impurities may affect the properties of drugs in human body. Impurity profiling is an important protocol in the process of drug registration. An Iron catalyzed oxidative decarboxylation method is used to synthesize of five important impurities and extended for other substrates. This one-pot, environmentally benign protocol is practically easy and successful for gram-scale synthesis of ketorolac impurity for the first time.