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Fe-Catalyzed Cascade Reaction: C-H Activation and Cyclization in Efficiently Coumarin Synthesis

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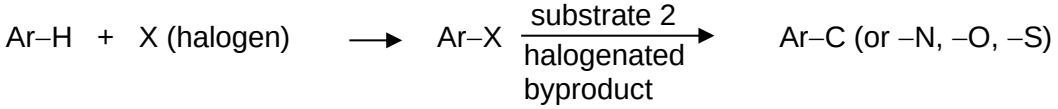
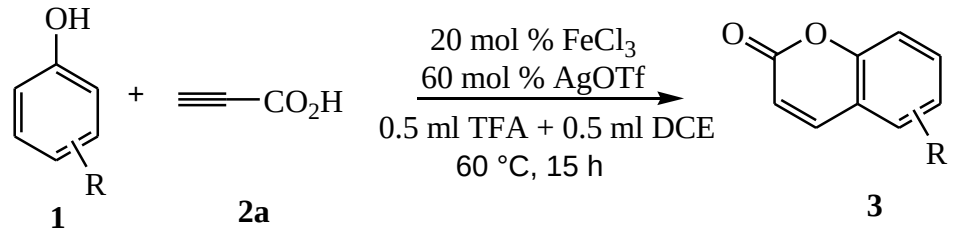
Extended Abstract

In general, the C–H bonds are omnipresent in organic/medicinal compounds in pharmaceutical fields, and the C–H bond is usually characterized as low reactive, because the bond dissociation energy of C–H bond is usually very large, e.g. 105 and 110 kcal/mol in CH_4 and C_6H_6. Therefore, direct functionalization of C–H bond is challenging and conventionally, it requires the pre-functionalization using halogenated compounds producing the halogenated byproducts as shown in Scheme 1.



Scheme 1. C–H bond functionalization in conventional method.

In the conventional strategy for direct C-H activation and cyclization in organic synthesis, the metallic systems of precious metals: Pd, Pt, Au, Ru, Ag etc. and La-series metals are usually used, and the main issues are high cost and toxicity for the contamination of these metals with products [1-3]. Still now, little attention has been paid to the nontoxic iron as a catalyst in such fields, although Fe-systems are very cheap in cost and environmentally benign compared to conventional transition metal catalysts. On the other hand, Coumarin and its derivatives occur widely in nature and most of them show biological activities: antioxidant, analgesic, anti-inflammatory and antimutagenic and so play a great role in medicine fields [4]. To date, many reactions for coumarin synthesis have been reported in [4], including various named reactions such as the Perkin, Knoevenagel and Pechmann reactions using transition-metal catalysts [2,3]. Therefore, Targeting for a greener, nontoxic and cheaper methodology for coumarin synthesis, we developed a Fe-catalytic system, in-situ $Fe(OTf)_3$ (OTf = triflate ion) formed instantly in order to avoid moisture contact which can destroy it and it showed C-H activation and cyclization between propynoic acid: R-C≡-CO_2H (R = H, alkyl) and different phenols at a time, and these results afforded 33-95% coumarins (about 20 scopes for different coumarins) under the optimized conditions shown in Scheme 2.



Scheme 2. Fe-catalyzed C-H activation and cyclization between propynoic acid and phenols in mixture of trifluoroacetic acid (TFA) and dichloroethane (DCE).

To understand the efficiency of Fe(III)-catalyzed coumarin synthesis, these results was compared with those from the previous palladium- and platinum-catalyzed reaction of **2a** with **1** in trifluoroacetic acid, and the comparative results revealed that this Fe-catalyzed reaction explored better yields of coumarins than those found in palladium- and platinum-catalyzed reactions [3,5]. Different substitute screening revealed lower activity yielding low yield in case of terminal methyl substituent in propynoic acid, $H_3C\text{-}C{\equiv}C\text{-}CO_2H$ (**2b)** compared to that of **2a**, due to the absence of more acidic terminal H. In the case of different phenols, the role of electronic and inductive effects was observed in such catalytic cascade reactions.

Experimentally, the $Fe(OTf)_3$ was formed in-situ by the reaction between Ag(OTf) and $FeCl_3$ in the mixed solvent of TFA and DCE and characterized by UV-Vis spectroscopy. The individual product was identified by NMR and quantified after purification by column chromatography.

In conclusion, this methodology of Fe(III)-catalyzed coumarin synthesis is expected to have a high degree of different medicinal coumarin derivatives, because it is a highly efficient and environmentally friendly economical nontoxic process and hopefully it would play a great role in the sectors of medicine/pharmaceuticals as well as chemistry/catalysis.

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