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ORIGINAL PAPER

Iron-catalyzed cascade synthesis of nitrogen polycycles from alkynoic acids and functionalized amines

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Abstract

Catalysis by first-row transition metals is of increasing interest in the context of the scarcity of chemical resources. For instance, iron is promising due to its abundance, low toxicity and unique electronic features. Here we synthesized quinazoline alkaloids from alkynoic acids and functionalized amines in the presence of iron dibromide and pyridine in toluene or, alternatively, in a solventless reaction system. We studied iron sources, reaction media and the effect of additives. Results show 39–99% yields and regioselective preparation of nitrogen- and oxygen-containing scaffolds. This is the first example of a cascade process involving alkynoic acids catalyzed by iron. Fe is more abundant, cheaper and less toxic than other Au, Cu and Ru catalysts previously reported for similar transformations.

Keywords Nitrogen heterocycles · Oxygen heterocycles · Alkynoic acids · Iron catalysts · Cascade reactions · Amines

Introduction

Catalysis is one of the pillars of green chemistry. Indeed, one of the main strategies for the minimization of the amount of unwanted by-products is the replacement of stoichiometric chemical procedures by efficient catalytic protocols (Anastas and Warner 1998). Precious metals are prevalent in catalysis, but the decreasing availability of these inherently scarce metals has led to mining and refining of lower-grade metal ores, costly operations that require a large amount of resources and that cause soil erosion and pollution of groundwater, surface water and soil. On this basis, implementation of increasingly sustainable processes has latterly spurred the search for more available and less toxic metal catalysts (Ludwig and Schindler 2017).

Iron is one of the most abundant metals in earth and an essential element for many living organisms (Expert 2012; Crichton 2016). It has been known for long that iron can promote several organic transformations, but its catalytic role akin to that of some precious late transition metals remained unrevealed until recently. In addition to the wide range of oxidation states that iron can adopt (from −2 to +5), this convenient metal has the ability to transfer one or two electrons to a substrate, thus enabling not only radical reactions but also processes based on oxidative addition and reductive elimination steps (Rana et al. 2021; Casnati et al. 2020; DaBell and Thomas 2020; Zhang et al. 2020; Guđmundsson and Bäckvall 2020; Piontek et al. 2018; Wei and Darcel 2019; Bauer and Knölker 2015; Bolm et al. 2014). In this regard, the activation of carbon–carbon triple bond of alkynes by iron Lewis acids, or even low-valent iron complexes, can promote several annulation, cycloisomerization (enyne derivatives and allenols) and other cyclization processes leading to the formation of several heterocycles such as benzo- and dihydrofurans, coumarines, quinolines, oxathiines, dibenzoxepines, benzocarbazoles and cyclobutane-fused pyrrolidines, *inter alia* (Gay et al. 2010; Mantovani et al. 2014; Wang et al. 2011; Sonehara et al. 2017; Yao et al. 2012, Sivaraman and Perumal 2014; Teske and Plietker 2016; Fürstner et al. 2008; Gudmundsson et al. 2018, Kramm et al. 2018; Boominathan et al. 2015; Sreedevi et al. 2010).

A number of polyheterocycles have been synthesized by a versatile cascade process between alkynoic acids and functionalized amines. It has been proposed that a

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metal-catalyzed cycloisomerization of the alkynoic acid followed by a nucleophilic attack by the amine on the resulting lactone generates a ketoamide intermediate that upon intramolecular condensation and subsequent reaction with the additional nucleophilic center provides complex polycyclic compounds structurally related to several alkaloids with COX-1 and COX-2 inhibiting and bronchodilatory activities such as Vasicine, Mackinazoline, Batracyclin and Tryptanthrine (Kshirsagar 2015; Nepali et al 2012). Gold catalysts have been predominantly used for this purpose (Yang et al. 2007; Cadierno 2020; Zhou et al. 2010a, b, 2011; Feng et al. 2010, 2012; Ji et al. 2013; Li et al. 2013; Qiao et al. 2019; Jia et al. 2019; Patil et al. 2010, 2012, 2013) though copper-catalyzed (Naidu and Reddy 2016) and ruthenium-catalyzed (Zheng et al. 2020) methodologies have been also reported. However, to the best of our knowledge, there is no example of the use of iron in such transformations that provide a direct access to potentially pharmacologically active compounds. Indeed, no cascade cycloisomerization/ketoamide formation/double intramolecular cyclocondensation has been described for iron catalysts so far. Following our research on iron-promoted hydroamidations and on other metal-catalyzed tandem processes involving alkynes (Herrero et al. 2012; Moure et al. 2014) we envisioned that iron salts could promote such a domino process, thus procuring a more sustainable alternative to the use of precious metals (Fig. 1). Herein we wish to report our results on the iron-catalyzed cascade reaction between alkynoic acids and functionalized amines.

Experimental

General. Commercially available reagents were used throughout without purification unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) at 20 °C. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ ($\delta = 7.26$ for 1H and $\delta = 77.00$ for ^{13}C). Coupling constants, J, are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC (thin-layer chromatography) was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM).

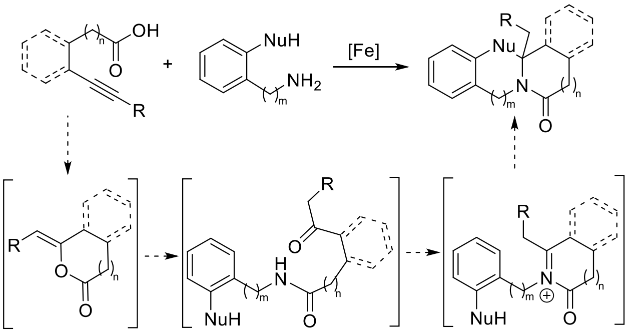


Fig. 1 Synthesis to nitrogen heterocycles based on an iron-catalyzed reaction between alkynoic acids and functionalized amines. Initial hypothesis

General Procedure A: A screw-capped tube was charged with amine (0.50 mmol), alkynoic acid (0.75 mmol), $FeBr_2$ (0.05 mmol), pyridine (0.20 mmol) and toluene (1 mL). The reaction mixture was heated to 150 °C for 24 h and allowed to cool to room temperature. The resulting mixture was purified by silica gel flash column chromatography to afford the corresponding compound.

General Procedure B: A screw-capped tube was charged with amine (0.50 mmol), alkynoic acid (0.75 mmol), $FeBr_2$ (0.05 mmol) and pyridine (0.20 mmol). The reaction mixture was heated to 100 °C for 24 h and allowed to cool to room temperature. The resulting mixture was purified by silica gel flash column chromatography to afford the corresponding compound (see Supplementary Material section for further details).

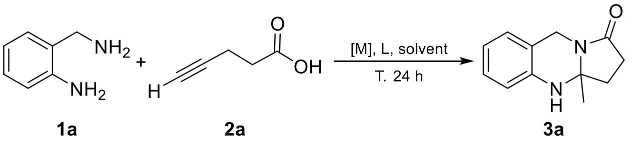
Results and discussion

Optimization of reaction conditions

2-Aminobenzylamine **1a** and 4-pentynoic acid **2a** were chosen as model substrates for the optimization of reaction conditions. After a number of initial experiments, we observed that indoloquinazolinone **3a** was obtained with moderate to good yields after heating the substrates in the presence of iron(III) chloride hexahydrate and pyridine in different solvents (Table 1, entries 1–4). The best results were achieved using toluene and ethanol as reaction media (entries 1–2). We resolved to use toluene as solvent for the following assays in order to avoid the possible competition with ethanol if less nucleophilic amine derivatives were used. Other organic and inorganic bases (Na_2CO_3, Cs_2CO_3, DMAP) were also assayed but provided significantly inferior results.

The role of the catalyst seemed critical since the heterocycle was obtained in low yield in the absence of any metal source (entry 9). The formation of product **3a** under the latter conditions could be explained by considering a thermally induced partial cycloisomerization of the acid. Regarding the catalyst system, $FeBr_2$ provided the best results (entries 5–7) probably due to its superior carbophilia. In fact, aluminum trichloride, a more acidic Lewis acid, turned out to be not a suitable metal source (entry 8). Unfortunately, the decrease of the catalyst loading reduced considerably the reaction yield (entry 15 vs 11 and 16 vs 12).

Table 1 Iron-catalyzed reaction between 2-aminobenzylamine **1a** and 4-pentinoic acid **2a**. Optimization of reaction conditions



Entry[a]	[*M*] (mol%)	*L* (mol%)	Solvent (mL/mmol)	*T* (°C)	Yield (%)[b]
1	$FeCl_3$ $6H_2O$ (10 mol%)	Pyr (40 mol%)	PhMe (4 mL/mmol)	150	74
2	$FeCl_3$ $6H_2O$ (10 mol%)	Pyr (40 mol%)	EtOH (4 mL/mmol)	150	76
3	$FeCl_3$ $6H_2O$ (10 mol%)	Pyr (40 mol%)	DCE (4 mL/mmol)	100	65
4	$FeCl_3$ $6H_2O$ (10 mol%)	Pyr (40 mol%)	H_2O (4 mL/mmol)	150	35
5	$FeBr_2$ (10 mol%)	Pyr (40 mol%)	PhMe (4 mL/mmol)	150	89
6	$FeBr_2$ (10 mol%)	Pyr (40 mol%)	EtOH (4 mL/mmol)	150	82
7	$FeBr_2$ (10 mol%)	–	PhMe (4 mL/mmol)	150	81
8	$AlCl_3$ (10 mol%)	Pyr (40 mol%)	PhMe (4 mL/mmol)	150	37
9	–	–	PhMe (4 mL/mmol)	150	20
10	$FeBr_2$ (10 mol%)	Pyr (40 mol%)	PhMe (8 mL/mmol)	150	41
11	$FeBr_2$ (10 mol%)	Pyr (40 mol%)	PhMe (2 mL/mmol)	150	97
12	$FeBr_2$ (10 mol%)	Pyr (40 mol%)	–	100	86
13	$FeBr_2$ (10 mol%)	–	PhMe (2 mL/mmol)	150	87
14[c]	$FeBr_2$ (10 mol%)	–	–	100	80
15	$FeBr_2$ (4 mol%)	Pyr (40 mol%)	PhMe (2 mL/mmol)	150	78
16[c]	$FeBr_2$ (4 mol%)	Pyr (40 mol%)	–	100	35

[a] Reaction conditions: **1a**, **2a** (1.5 equiv.), catalyst (4–10 mol%), L (0–40 mol%), solvent (0–4 ml), T, 24 h

[b] Yield of isolated product

[c] The reaction was heated at 100 °C for 48 h. DCE: 1,2-Dichloroethane. Pyr: Pyridine

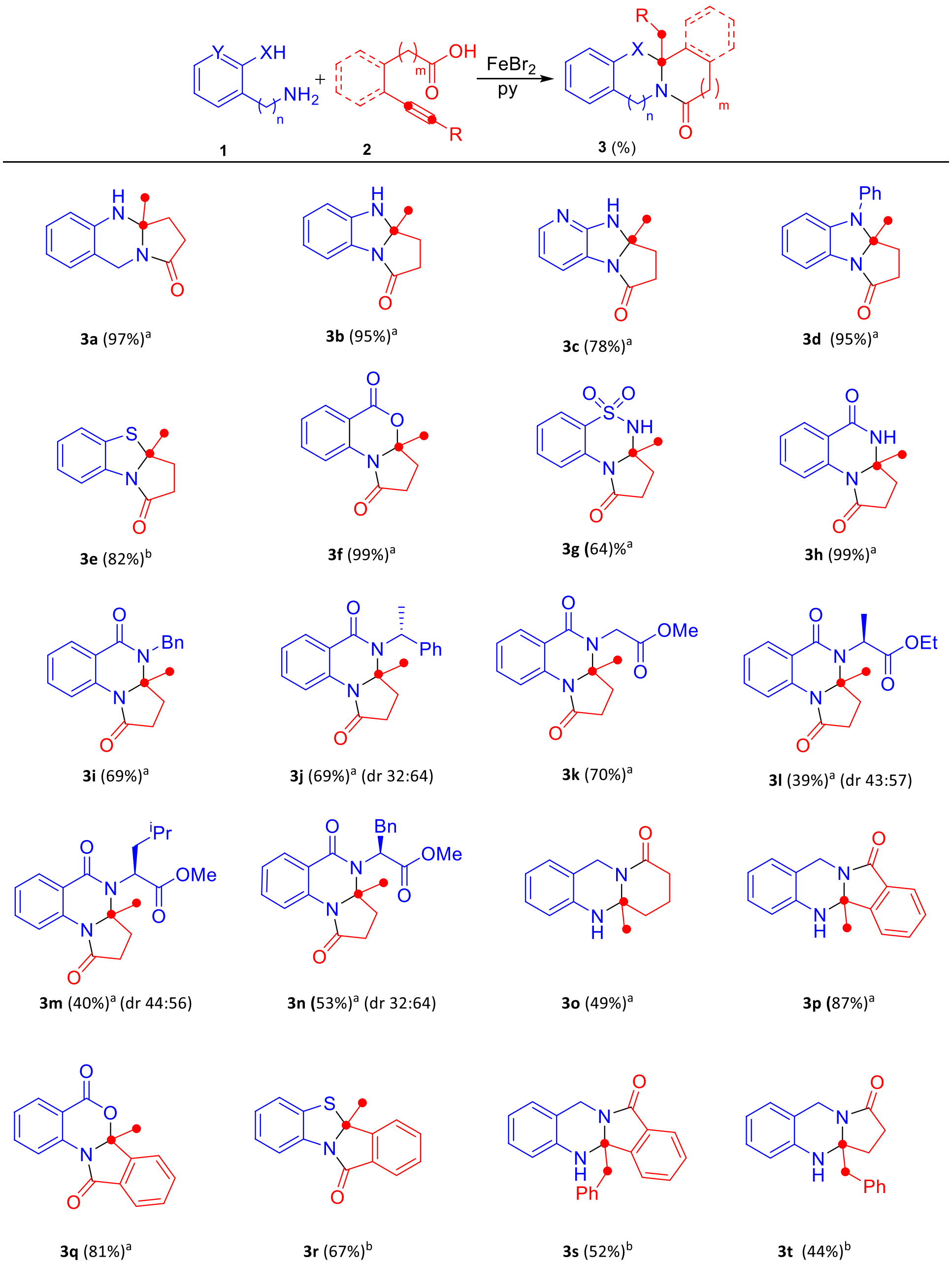
Besides, a catalytic amount of pyridine had a slightly positive effect (entry 7 vs 5, 13 vs 11 and 14 vs 12), and a more important variable was the concentration of the reaction mixture (entries 10–12). Higher concentrations resulted in better results (entry 11) and interestingly, **3a** was also isolated in good yields when reactants were heated in the absence of solvent at a much lower temperature (100 °C, entry 12). Therefore we chose $FeBr_2$ (10 mol%) and pyridine (40 mol%) in toluene at 150 °C or, alternatively, at 100 °C with no solvent as the optimized conditions to explore the scope of the reaction.

Substrate

Different diamines **1** were initially reacted with 4-pentynoic acid **2a**. To our delight, in all cases target pyrrolidinone-fused compounds **3a-n** were selectively obtained in moderate to excellent yields (Fig. 2). The nucleophilicity of the functional groups of substrates **1** was the key to rationalizing the obtained structure. As expected, the more nucleophilic functional group would be responsible for the opening of the furanone generated by cycloisomerization of 4-pentynoic acid, being the *N*-acyliminium ion intermediate attacked by the second nucleophile. In the case of 2-amino substituted anilines, the difference in nucleophilicity between both amino groups plays a pivotal role in the outcome of the reaction. In fact, an excellent yield for the tricycle was obtained from *N*-fenil-1,2-diaminobenzene **1d**, whereas 1,2-diaminobenzene **1b** provided a complex mixture of products from which heterocycle **3b** was isolated in moderate yield. In this case, the similar reaction rate of both amino groups might result in reaction with two furanone units leading to a diamide intermediate that could not evolve to the product. In this regard, it should be pointed out the completely regioselective access to pyrroloimidazopyridinone **3c** from 2,3-diaminepyridine **1c**, thus proving not only our hypothesis above but also that the presence of a pyridine ring in the dinucleophile did not hinder the progress of the reaction. Another interesting feature of the reaction from *N*-phenyl-1,2-diaminobenzene **1d** is the fact that secondary amines can participate in the reaction as long as they are weaker nucleophiles than the primary amine moiety so that a secondary amide intermediate, unable to evolve to the final product, is not formed.

Other *o*-funcionalized aniline derivatives also reacted with 4-pentynoic acid to provide selectively polycycles

Fig. 2 Reaction of alkynoic acids with 2-substituted anilines. Isolated yields are shown in parentheses. [a]Reaction conditions: **1**, **2** (2 equiv.), $FeBr_2$ (10 mol%), pyridine (40 mol%), toluene (2 mL/mmol), 150 °C, 24 h. [b]Reaction conditions: **1**, **2** (2 equiv.), $FeBr_2$ (10 mol%), pyridine (40 mol%), 100 °C, 24 h



3a (97%)[a] **3b** (95%)[a] **3c** (78%)[a] **3d** (95%)[a]

3e (82%)[b] **3f** (99%)[a] **3g** (64)%[a] **3h** (99%)[a]

3i (69%)[a] **3j** (69%)[a] (dr 32:64) **3k** (70%)[a] **3l** (39%)[a] (dr 43:57)

3m (40%)[a] (dr 44:56) **3n** (53%)[a] (dr 32:64) **3o** (49%)[a] **3p** (87%)[a]

3q (81%)[a] **3r** (67%)[b] **3s** (52%)[b] **3t** (44%)[b]

3e–3h with excellent yields. Except for thiadiazine **3e**, better results were observed when the reaction was carried out in toluene at 150 °C. Following the same trend as with diamines, the aminolysis of the alkylidene lactone took place initially, being the carboxamide, carboxi, sulfonamide or mercapto group responsible for the second nucleophilic attack. Besides, reaction with *N*-substituted amides provided tetrahydropyrroloquinazoline-1,5-diones **3i-3n** although in lower yields, especially in the case of bulky substituents on the amide nitrogen.

The optimized conditions were then applied to other alkynoic acids. Pyridoquinazolinone **3o** was obtained from 2-aminobenzylamine and 5-hexynoic acid but in lower yield than pyrroloquinazolinone **3a**, seemingly due to the more difficult cycloisomerization of 5-hexynoic acid (Bunce and Nammalwar 2011). In contrast, better results were obtained from 2-ethynilbenzoic acid, which was supposed to react via formation of 3-methyleneisobenzofuran-1(3*H*)-one, thus providing tetracycles **3p–3r**. The methodology also allowed us to prepare selectively quinazolines **3s** and **3t** from non-terminal alkynes 2-phenylethynyl benzoic acid and 5-phenyl-4-pentynoic acid respectively. However, neat heating at 100 °C was required to achieve moderate yields of these two benzylated derivatives. In addition to the spectroscopic analysis data, X-ray crystallographic analysis of derivatives **3g** and **3p** confirmed the assigned structure and therefore underpinned the proposed regioselectivity.

As mentioned before, the related cascade reactions described in the literature have been carried out using Au(I) (often Au(I)-Ag(I)), Cu(II) and Ru(II) catalysts. In addition to the higher cost of these precious and semiprecious metal catalyst systems (4–25 times as much as $FeBr_2$/py/PhMe), the extensive mining of natural resources for the extraction of the aforementioned scarce metals should not be ignored. Iron is the 5th most abundant element found on Earth crust, and in contrast to gold, copper or ruthenium, iron compounds and salts exhibit low toxicity or are practically harmless (Egorova and Ananikov 2017). Although pyridine is used in our protocol, only a catalytic amount (40 mol%) is required to get selectively target tri- and tetracyclic products **3a–t**. Moreover, except for pyrido[2,1-*b*]quinazolin-9-one **3o**, comparable and even superior yields were obtained for polyheterocycles **3a–b**, **3f**, **3h** and **3o–q** in comparison with previously reported procedures (see Table S1 for a comparative analysis).

Mechanistic studies

With the aim of gathering information about the mechanism of the reaction catalyzed by $FeBr_2$, furanone **4** was reacted with *o*-aminobenzylamine (Fig. 3a). The reaction in the presence of the iron salt provided tricycle **3a** in very good yield, hence supporting our hypothesis on the participation of an enol lactone intermediate as a result of an initial cycloisomerization step. The significantly lower yield obtained in the absence of $FeBr_2$/pyridine pointed to the assistance of the metal catalyst in the subsequent steps. Conversely, a basic reaction environment (Cs_2CO_3) hinders the progress of the reaction, probably by preventing dehydration and formation of the key *N*-acyliminium intermediate **III** (Fig. 3d). We also confirmed that the combination of $FeBr_2$ and pyridine was able to cause the cycloisomerization of 4-pentynoic acid, since isomeric furanone **5** was isolated when 4-pentynoic acid was heated with $FeBr_2$/pyridine in the absence of the dinucleophile (Fig. 3b).

The formation of 5-phenylmethylaminopyrrolidinone **8** and the dimeric compound **9** from the reaction between 4-pentynoic acid and benzyl amine (Fig. 3c) is consistent with the intermediacy of an *N*-acyliminium intermediate (Fig. 3c). Indeed, the above compounds **8–9** can be easily rationalized as products from the addition of benzylamine and the enamide in equilibrium with the *N*-acyliminium ion, respectively, to the said iminium intermediate (Figure S1 and Figure S2). Finally, isolation of *N*-phenyl-4-propynamide **7** was expectable considering the high temperature and the presence of a Lewis acid in the reaction media. Nevertheless, it should be pointed out that no amide derivative was detected when *ortho*-functionalized anilines or benzylamines were employed in these reactions.

On the basis of the results from the performed assays we propose that, like in other metal-catalyzed domino processes from alkynoic acids, the reaction would be initiated by the coordination of iron catalyst to the triple bond, thus

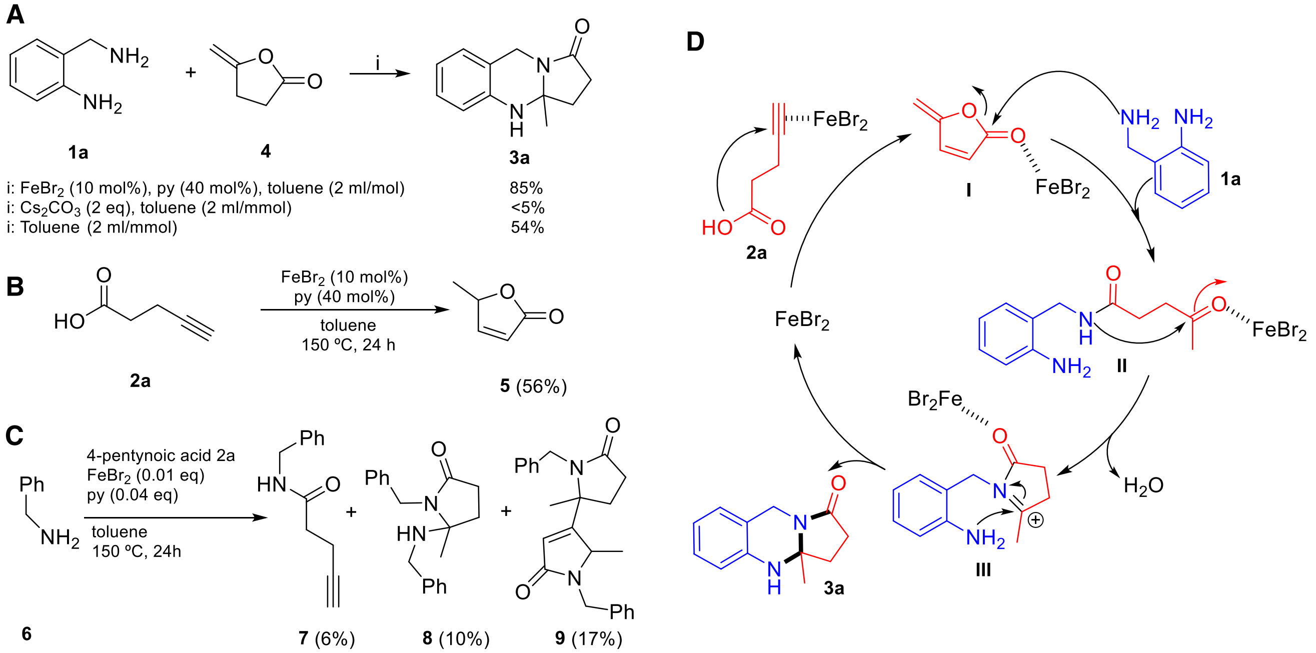


Fig. 3 Complementary experiments performed to clarify the mechanism of $FeBr_2$-catalyzed reaction of alkynoic acids and substituted amines (**a**–**c**) and proposed reaction mechanism (**d**)

facilitating the cycloisomerization of the acid to furanone intermediate **I**, which would generate ketoamide **II** by aminolysis with **1a**. The activation of the ketone function at **II** by the iron salt would trigger the formation of highly reactive *N*-acyliminium ion **III**, which would undergo an intramolecular addition of the amine moiety to give pyrroloquinazolinone **3a** (Fig. 3d).

Conclusion

We have developed a new catalytic system based on iron(II) bromide for the high-yielding synthesis of nitrogen, oxygen and sulfur heterocycles from alkynoic acids and functionalized amines. Considering the comparable yields obtained, the natural abundance of iron sources and the environmental concern over the exploitation of natural resources, we conclude that such an inexpensive, accessible and low-toxicity metal salt as iron(II) bromide offers a viable and more sustainable alternative to the previously reported catalytic systems, based on precious or semiprecious metals. With regard to the reaction mechanism, a number of experiments involving reaction with plausible intermediates or in the absence of the functionalized amine shed light on the role of the catalyst system. Thus, the reported one-step methodology probably takes place through a cycloisomerization/nucleophilic addition/cyclodehydration cascade where the iron catalyst is involved not only in the initial cycloisomerization step but is essential for achieving good results in this straightforward access to pyrrolo and isoindolo-fused heterocycles.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10311-022-01477-y.

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Author contributions MTH, RS and GU contributed to searching and collating of the relevant literature and the proofreading of the document. Investigation, experimental and analysis were carried out by JD, EA, AS and YR. MTH and RS conceptualized and supervised the study and wrote the body of the article. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials Supporting information for characterization of synthesized compounds is provided including NMR data.

Declarations

Conflict of interests Authors declare no competing financial interest.

Consent for publication All the authors have seen and approved the final version of the manuscript.

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