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Iron-Based Imidazolium Salt as Dual Lewis Acid and Redox Catalyst for the Aerobic Synthesis of Quinazolines

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A low transition temperature mixture formed with 1-butyl-3-(methoxycarbonylmethyl)imidazolium chloride and iron(III) chloride has proven to be an efficient catalyst for the synthesis of quinazolines following a sequence of condensation-cyclization-oxidation reactions. The protocol is simple and effective for coupling 2-acylanilines and benzylamines to form nitrogen containing heterocycles with moderate to excellent yields (up to 93%), being possible to perform the reaction in preparative scale. The functionalized imidazolium salt is crucial for the activation of the reagents under solvent-free conditions, and the presence of iron in the catalyst mediates the oxidation step with atmospheric oxygen. These features make the presented procedure better, from an environmental point of view, than other processes previously described. For this comparison, different "green" metrics have been used, such as atom economy, stoichiometric factor, reaction mass efficiency, E-factor, and EcoScale.

Introduction

The synthesis of bioactive molecules is one of the main areas of interest of modern organic chemistry, as there is high demand for new drugs to treat a variety of ailments. Due to their extensive presence in naturally occurring compounds, nitrogen-containing heterocycles are especially prominent among privileged scaffolds for drug design.[1] Among them, quinazolines (1,3-diazanaphthalenes or benzo-pyrimidines) are an important family whose interest has drastically increased over the last 50 years.[2] The quinazoline skeleton is naturally present in more than 150 alkaloids, some of which exhibit remarkable bioactivity, such as vasicine, the first quinazoline alkaloid isolated, which acts as an antitussive and bronchodilator.[3] Asperlicin, a strong cholescystokinin antagonist, Febrifugine, an antimalarial, or Luotonin A, which has demonstrated potential against the murine leukaemia P-338 cell line, are other notable examples (Figure 1).[2,4]

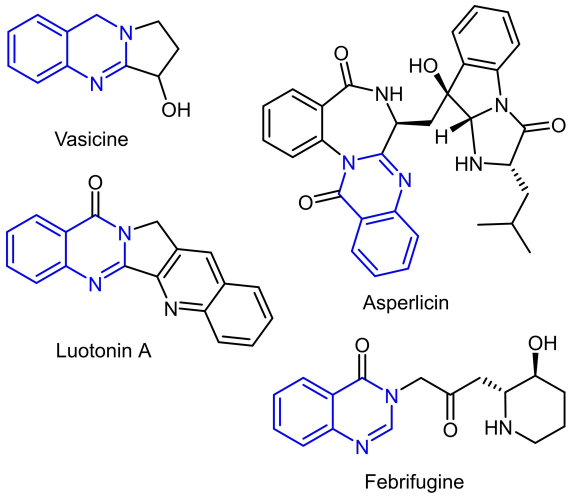

Figure 1. Notable alkaloids containing the quinazoline scaffold.

As revealed by the study of quinazoline-based alkaloids, this heterocycle scaffold is particularly interesting due to its enormously broad scope of possible interactions, which has led to a whole generation of bioactive compounds. As of today, a wide array of quinazolines have found their way into commercial drug formulations, such as antineoplasics (Gefitinib, Erlotinib), antifungals (Albaconazole), antihypertensives (Prazosin), antidiabetics (Linagliptin), diuretics (Fenquizone), anticonvulsants (Methaqualone), anti-inflammatories (Proquazone), cardiotonics (Quazinone), or antivirals (Benzouracil), among others (Figure 2 and Figure 3).[2,5]

Besides these commercialized compounds, there are loads of other active quinazolines in several stages of testing, with new potential applications such as anti-tubercular or antibiotic activities.[6] This has resulted in the development of a plethora of synthetic methodologies for the obtention of this type of compounds. Albeit multistep procedures are usually employed for preparing complex molecules, the construction of the quinazoline core is relatively straightforward, involving the cyclization of two or more synthons and an oxidation step. This way, quinazolines can be obtained from *o*-aminobenzyl alcohols via condensation with nitriles,[7] benzylamines,[8] or aldehydes.[9] Similarly, *o*-aminobenzylamines are common starting materials

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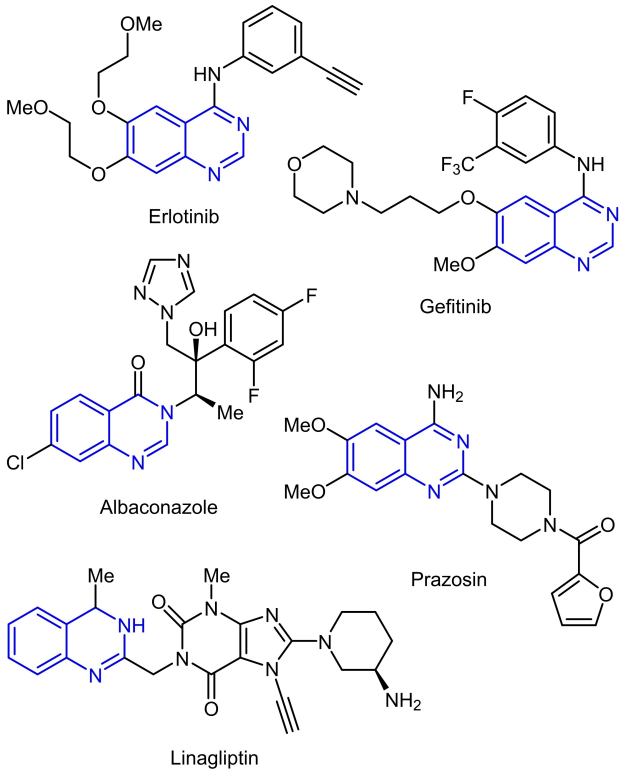


Figure 2. Marketed antineoplasics, antifungal, antihypertensive and antidiabetic having a quinazoline unit.

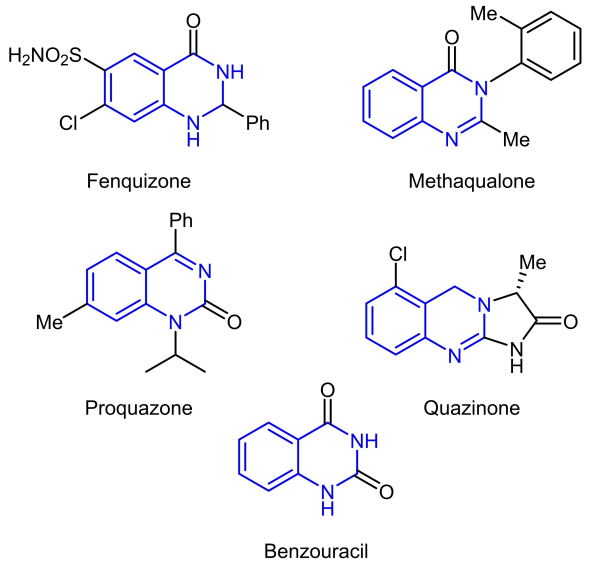
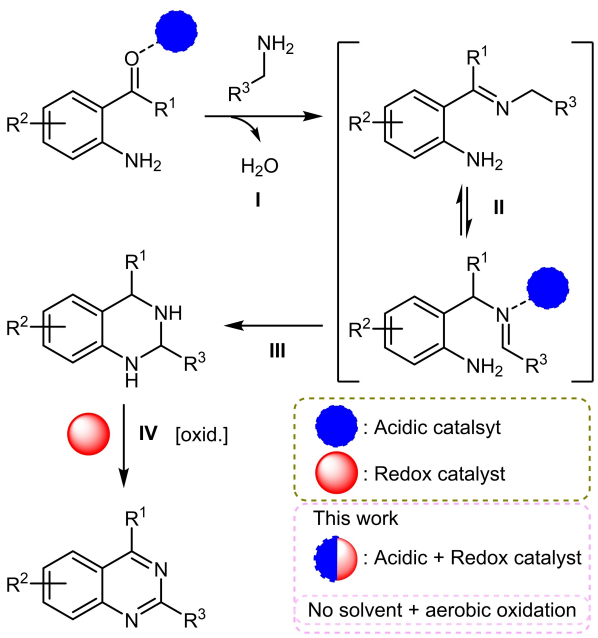


Figure 3. Marketed diuretic, anticonvulsant, anti-inflammatory, cardiotonic and antiviral having a quinazoline unit.

to couple with aldehydes,[9b,10] benzyl alcohols,[7a,10c] benzylamines,[10c] nitriles,[11] or trihalobenzenes.[12] In this sense, Ullman-type condensation between *o*-bromobenzylamines and amides produced the corresponding quinazoline derivatives.[13] Instead of benzylamines, the use of imino compounds, such as amidines,[14] imidates,[15] and oximes,[16] has been explored with success in the preparation of quinazolines. Another interesting strategy involves the use of anthranilic acid derivatives and surrogates thereof, such as anthranilamides,[17] anthranilonitriles,[18] *o*-halobenzonitriles,[19] or isatoic anhydrides,[20] which reacted with different electrophiles leading to the target quinazoline unit. Moreover, *o*-acylanilines have been also employed in combination with benzaldehydes,[21] acyl halides,[22] amides,[23] nitriles,[24] methylarenes,[25] or amines,[17a] to assemble the quinazoline moiety. The latter methodology is reasonably well documented, although most protocols have shortcomings in terms of catalyst selection, the use of external oxidants or hazardous solvents. Therefore, the possibility of improving the sustainability of the procedure with a multifunctional catalyst is of interest to our research group.

Metal catalysts employed include copper nanoparticles,[26] ceric ammonium nitrate (CAN),[27] and the metal-organic framework (Co)-ZIF-67,[28] whereas metal-free protocols involve catalysts such as iodine,[29] 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy (TEMPOL),[30] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[31] and graphite oxide.[32] The oxidant of choice is mostly *tert*-butyl hydroperoxide (TBHP), albeit some methodologies employ oxygen balloons.[29a,30] The use of oxygen is undoubtedly a step forward compared to other protocols in terms of sustainability, but handling pure oxygen requires precautions. Lastly, this type of transformation demands temperatures above 100 °C, so solvents such as acetonitrile, xylene or toluene are commonly used, and in some cases neat conditions have been described, but always with the premise of operating in sealed equipment.[26,29]

The transformation under consideration involves four main steps (Scheme 1). First, an imine is formed by condensation of the benzylamine with the carbonyl of the aniline ring (step **I**, Scheme 1). After an intermediate tautomerization (step **II**,



Scheme 1. Plausible mechanistic pathway for the reaction.

Scheme 1), an intramolecular nucleophilic attack from the aniline-nitrogen to the iminic carbon produces the corresponding tetrahydroquinazoline (step **III**, Scheme 1), which is oxidized to afford the final product (step **IV**, Scheme 1).[29b] To achieve maximum efficiency, as many steps as possible must be promoted, which requires two different types of catalysis working in tandem.

Based on the experience of our research group, improving the sustainability of quinazoline synthesis with the selection of the appropriate catalyst was considered as a working model. Herein, we report a simple methodology for the synthesis of 2- and 2,4-substituted quinazolines from 2-formyl or 2-acylanilines, and benzylamines. An efficient and inexpensive iron(III)-based catalyst can promote both steps of the reaction under solvent-free conditions: (1) condensation-cyclization, and (2) subsequent oxidation using atmospheric air as the terminal oxidant (Scheme 1).

Results and Discussion

Iron-based imidazolium salts (IBIS), which are low transition temperature mixtures (LTTMs) formed by the combination of equimolecular amounts of imidazolium salts and iron halides, can be efficient catalysts. The interaction between the components causes a depression in the melting point of the mixture, resulting in a homogeneous ionic medium which is liquid at room temperature.[33] A wide variety of imidazolium salts are compatible, so the properties of the mixture can be fine-tuned to suit certain applications. Among them, carboxy-functionalized imidazolium salts exhibit Lewis acidic behaviour both by themselves,[34] and in combination with metal salts (such as iron),[35] whereas the presence of an alkyl chain seems to play an important role on the ability of the imidazolium salt to form LTTMs.[36] Perhaps most importantly, IBIS can carry out oxidation procedures under aerobic conditions, eliminating the need for external oxidizers.[35,37] This way, a single catalyst would be able to promote all steps in the reaction with a dual role (i.e. Lewis acid and redox catalysis). Our choice for the imidazolium core bears a carboxy moiety and an alkyl chain (Scheme 2). 1-Butyl-3-(methoxycarbonylmethyl)-imidazolium chloride can be obtained by the substitution of 1-butylimidazole, and subsequently transformed in the corresponding low transition temperature mixture in combination with iron(III) chloride (Scheme 2). The formed iron-based imidazolium salt resulted in a homogeneous mixture with a glass transition temperature of −55.5 °C (Figure 4). The preparation of IBIS is a one-flask two-step process with almost quantitative yields in both steps, and it can be performed in multigram scale. The atom-economy (AE) of both steps is 100% due to the incorporation of all the atoms in the compounds. It is worthy to mention that the latter step can be carried out with iron(III) chloride hexahydrate with the same efficiency, although the hydration water would be released as waste. In terms of environmental impact, the first step presents an environmental factor (E-factor) of 4.7 considering the solvent (diethyl ether) needed for washing the resulting imidazolium chloride. Interestingly, the second step presents an ideal E-factor (0.0), due to the lack of waste. The complete (two-step) process has an E-factor of 2.8, validating the sustainability of the procedure.[38] This may be of significance if catalyst separation is not feasible with low environmental impact.

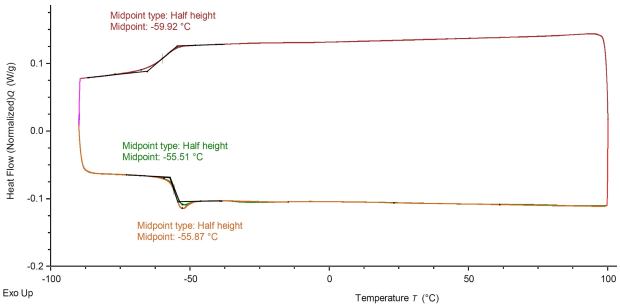
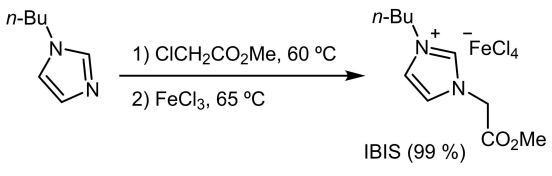


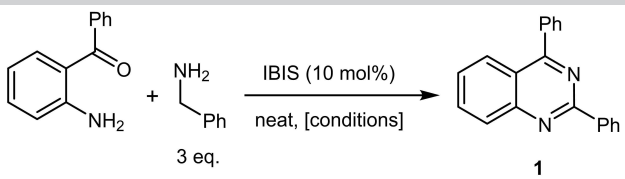
Figure 4. DSC curve for the IBIS.

Next, the synthesis of 2,4-diphenylquinazoline from 2-aminobenzophenone and benzylamine was selected as the model reaction to test the IBIS as dual catalyst, in the absence of any solvent. The initial tests for the optimization are compiled in Table 1. The model reaction, in the presence of 10 mol% of IBIS, was carried out in an open flask giving a conversion of 12% to the expected product after 16 h (Table 1, entry 1), although a significant amount (62%) of the corresponding tetrahydroquinazoline ($m/z = 286$; GC/MS) was observed. Likewise, the reaction under argon atmosphere (Table 1, entry 2) gave similar conversion to the product, so it seems that the catalyst does not complete the oxidation process under these conditions although it promotes the condensation steps



Scheme 2. Formation of the iron-based imidazolium salt as a low transition temperature mixture (molar ratio 1:1).

Table 1. Optimization of the reaction conditions.



Entry	T [°C]	time [h]	Conditions	Conv. [%][a]
1	110	16	Open flask	12
2	110	16	Argon	18
3	110	16	Air flow[b]	41
4	110	24	Air flow[b]	75
5	130	22	Air flow[b]	97

[a] Conversion of 2-aminobenzophenone to product **1**, determined by GC/MS. [b] Set at 50 mL/min.

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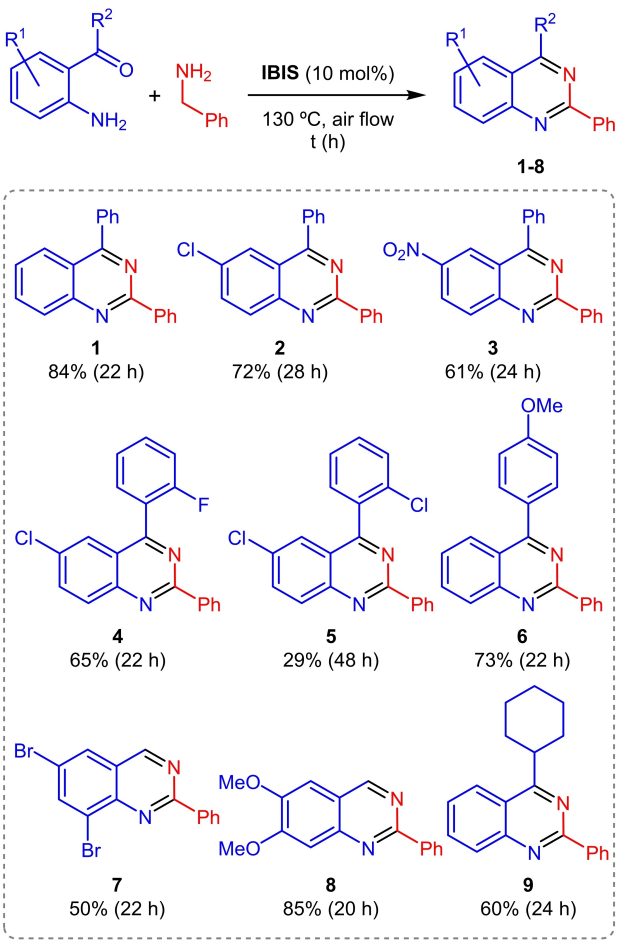
very effectively. The use of a flow of atmospheric air into the open flask facilitated the presence of oxygen over the reaction mixture, resulting in a meaningful improvement in the formation of quinazoline (41% conversion, Table 1, entry 3). Extending the reaction time to 24 h resulted in a conversion to product of 75% (Table 1, entry 4). Finally, increasing the temperature to 130 °C resulted in a quantitative conversion in 22 h (Table 1, entry 5). Thus, the IBIS catalyst promotes, in a very efficient way, the coupling of the starting reagents and in the presence of atmospheric oxygen results in the oxidation of the tetrahydro-intermediate.

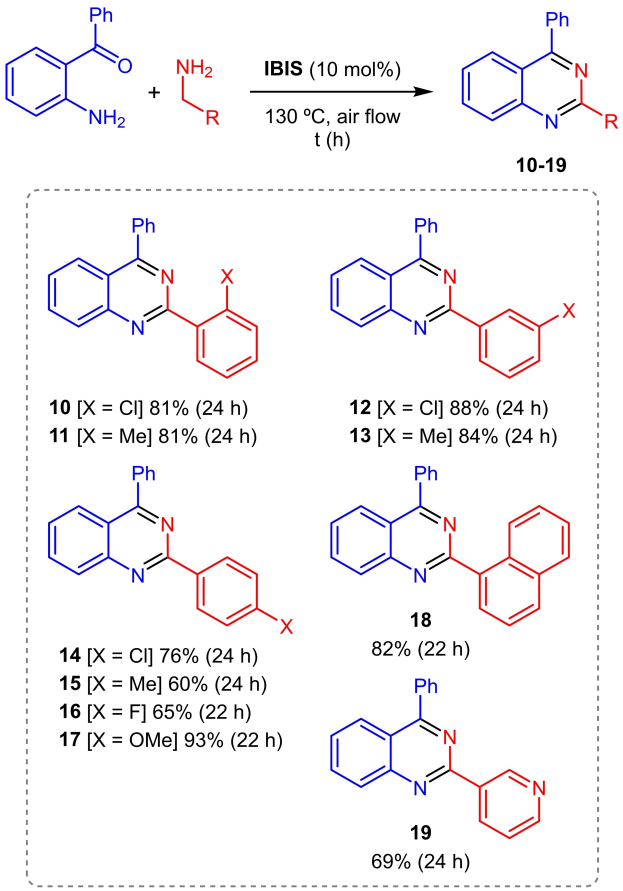
With the optimized conditions established, the scope of this sequence of reactions was explored by combining different 2-aminoaryl ketones with benzylamine forming the products shown in Scheme 3. The reactions were monitored by GC/MS to adjust the reaction times. Overall, the reactions proceeded smoothly, yielding the expected products with moderate to good yields. The 2-aminoaryl ketones bearing electron-withdrawing groups on the aniline ring gave marginally lower yields, compared to the model reaction (compounds **2** and **3**, Scheme 3). The reduced electron density of the reagent should facilitate the first reaction step (i.e. the formation of the imine), while slowing down the next step (i.e. the intramolecular cyclization to form the tetrahydroquinazoline). In these cases, the electron-withdrawing group is in the para-position with respect to the amino group and in the meta with respect to the ketone, so its effect is expected to be greater in the cyclization step, as observed. On the other hand, the reaction seems to be affected by steric factors in the vicinity of the carbonyl. Thus, compound **4** with a fluoro substituent next to the carbonyl could be obtained in 65% yield after 22 h, whereas compound **5**, with a chloro substituent in ortho-position, could only be isolated in 29% yield after 48 h of reaction (Scheme 3). This effect had been observed previously when using imidazolium salts as Lewis acids.[36] Next, the presence of an electron-donating group (such as methoxy) has been considered to evaluate the influence of higher electron density in the initial imine formation. Thus, 2-aminophenyl 4-methoxyphenyl ketone was coupled successfully with benzylamine to form compound **6** with 73% yield (Scheme 3). The reaction was carried out with 2-aminobenzaldehydes giving the corresponding quinazolines **7** and **8** (Scheme 3). The difference in electron-density in the starting aminobenzaldehydes provided better results with the most electron-rich (85% of compound **8**), probably due to a more favored ring-closing step by nucleophilic attack as mentioned before (Scheme 3). Finally, the methodology is applicable to 2-aminoaryl alkyl ketones, leading to the formation of quinazoline **9** with alkyl substitution at the C-4 (Scheme 3).



Scheme 3. Evaluation of 2-aminoaryl ketones for the formation of quinazolines using IBIS as catalyst. Reaction conditions: ketone (0.5 mmol), benzylamine (1.5 mmol), IBIS (0.05 mmol), air flow (50 mL/min), 130 °C. Isolated yield of pure product (in brackets reaction time, h).

To broaden the scope to other amines, 2-aminobenzophenone was reacted in the presence of the dual catalyst with different benzylamines, employing the air flow and solvent-free protocol (Scheme 4). In general terms, the relative position of the substituents on the aromatic ring does not seem to significantly influence the outcome of the reaction, as benzylamines substituted with moderately electron-withdrawing or electron-donating substituents at the 2, 3 and 4 position gave good conversion, being isolated in good yield within a margin of error (Scheme 4). Products **15** and **16**, with substituents in *para*-position, were isolated with lower yields than expected. In contrast, 4-methoxybenzylamine gave compound **17** which was isolated with 93% yield (Scheme 4). Thus, the *para*-substituted benzylamines gave more inconsistency in terms of yields, albeit due to the purification process. In addition, 1-naphthylmethanamine reacted smoothly giving the expected quinazoline **18** with 82% yield. Heteroaromatics substrates, such as 3-picolylamine, proved to be also suitable for this transformation, being compound **19** isolated with 69% yield (Scheme 4).

The protocol described does not use solvent and employs atmospheric air as the final oxidant, these being key features for the improvement of the sustainability of quinazoline synthesis. The main drawback from the environmental point of view is the purification of the final product, although this problem is common to the other procedures described in the literature. Therefore, for a first comparison, the E-factor (environmental factor) referred to the reaction "kernel", excess of reagents and catalyst, and to the reaction solvent have been calculated (Figure 5).[41] According to the literature, method-



Scheme 4. Evaluation of benzylamines for the formation of quinazolines using IBIS as catalyst. Reaction conditions: ketone (0.5 mmol), benzylamine (1.5 mmol), IBIS (0.05 mmol), air flow (50 mL/min), 130 °C. Isolated yield of pure product (in brackets reaction time, h).

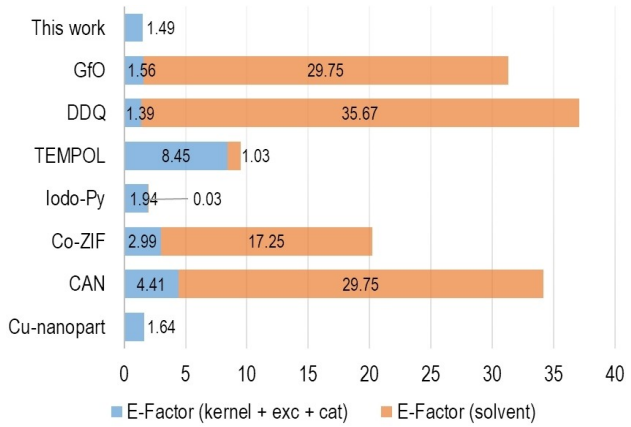


Figure 5. Environmental factors refer to the "kernel", excess of reagents and catalyst of the reaction (blue) and to the solvent (orange): Comparison of the protocol using IBIS and other protocols from the literature, in the preparation of **1**.

ologies with both metal catalysts [such as, Cu-nanoparticles,[26] ceric ammonium nitrate (CAN),[27] and the cobalt-organic framework[28] (Co)-ZIF-67] and metal-free catalysts [such as, iodo-pyridine,[29] 4-hydroxy-2,2,6,6-tetramethylpiperdinyloxy (TEMPOL),[30] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[31] and graphite oxide (GfO)[32]] have been used in the comparison. For the reaction itself without considering the purification process, the use of catalyst IBIS results on an E-factor of 1.49 (kg of waste/kg of product), being the lowest of all similar processes using metallic and non-metallic catalysts (Figure 5). The graph shows that the use of solvent significantly increases the E-factor of the reaction, so the reactions catalyzed with copper nanoparticles, with I_2-pyridine, or with IBIS generate less waste, the last catalyst being better due to the use of atmospheric oxygen as oxidant instead of *tert*-butyl hydroperoxide.

Next, different metrics have been considered to develop understanding on the environmental impact compared to previous methodologies. Thus, atom economy (AE), stoichiometric factor (SF), reaction mass efficiency (RME) and EcoScale have been calculated, in addition to the reaction yield. The AE is, in a balanced chemical reaction, the percentage of the molecular weight of the reactants that ends up in the desired product.[41] The SF is the ratio between the mass of reagents used and the mass of the stoichiometric reagents according to the balanced reaction, giving an idea of the excess reagent consumption.[41] For a single reaction, Curzons defined the RME as the ratio between the mass obtained of the target product and the mass of all reagents employed (expressed as a percentage).[41] The EcoScale, presented by Van Aken, represents an analytic tool to evaluate the quality of an organic synthesis based on yield, cost, safety conditions and ease of work-up/purification.[42] This semi-quantitative scale is a valuable tool to compare different synthesis of the same product, the value being calculated as 100 minus a range of penalty points according to the synthetic procedure. The parameters for different catalytic systems in the preparation of quinazoline **1** are collected in Table 2.

Compared to other metal catalysts, the process described with IBIS presents better parameters in general (Figure 6). Although the yields are comparable in all cases, the use of atmospheric oxygen as oxidant considerably improves the AE, RME and EcoScale values, as the other processes use *tert*-butyl hydroperoxide which generates more residues and can lead to more safety issues. Among the other metal catalysts, copper nanoparticles are more effective allowing the reaction to be carried out with a stoichiometric amount of oxidant and in the absence of solvents. As well, the use of IBIS is clearly better than non-metal catalyzed processes (Figure 7). Again, most of the catalysts require the use of TBHP as the final oxidant, which has an adverse effect on the sustainability of the process. Thus, lower AE, RME and EcoScale values are observed for the use of iodo-pyridine, DDQ and graphite oxide as catalysts. At this point, it is worth mentioning that the protocols described using DDQ,[31] and graphite oxide[32] use a sub-stoichiometric amount of TBHP, not being described what other oxidant is involved in the process to obtain the reported yield, so probably the "green" metrics would be even lower for these catalysts. In addition, the use of TEMPOL as a catalyst is similar to the IBIS

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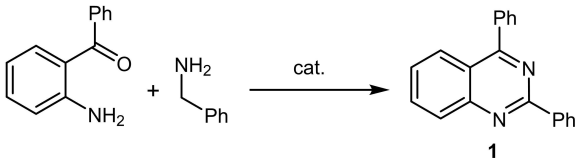
Table 2. Green metrics of differently catalyzed protocols in the preparation of quinazoline **1**.



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Catalyst	Yield [%]	AE [%][a]	SF[a]	RME [%][a]	Eco Scale
IBIS[b]	84	83.9	1.64	43.1	71
Cu-nps[c]	90	58.3	1.63	39.4	61
CAN[d]	93	58.3	3.46	19.2	53
Co-ZIF[e]	89	58.3	2.52	25.3	55
I_2-Py[f]	91	58.3	1.83	35.6	47
TEMPOL[g]	91	83.9	7.11	10.7	70
DDQ[h]	86	58.3	1.47	43.5	51
Gf-Oxide[i]	93	58.3	1.65	40.3	49

[a] AE: Atom Economy (%); SF: Stoichiometric Factor; RME: Reaction Mass Efficiency (Curzons definition, %). [b] Procedure described in this work. [c] Cu-nanoparticles as catalyst (ref. [26]). [d] CAN as catalyst (ref. [27]). [e] Co-based-ZIF as catalyst (ref. [28]). [f] Iodo as catalyst (ref. [29b]). [g] TEMPOL as catalyst (ref. [30]). [h] DDQ as catalyst (ref. [31]). [i] Graphite Oxide as catalyst (ref. [32]).

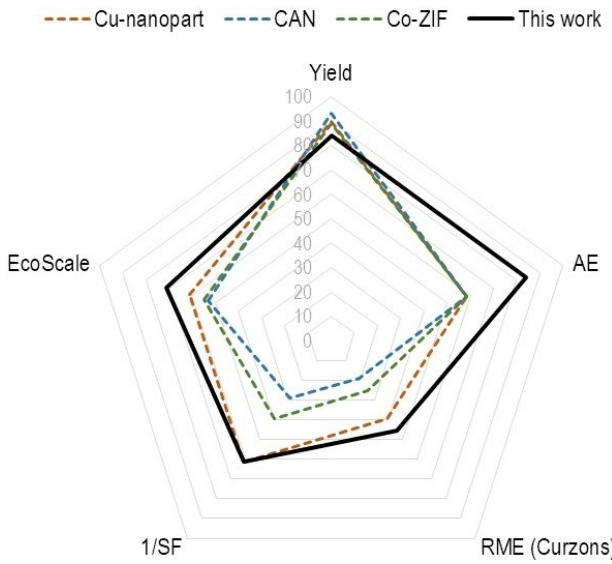

Figure 6. Radial-pentagon diagram with metrics (0–100): Yield, AE, RME (Curzons), 1/SF, and EcoScale. Comparison with metal catalyzed preparations of quinazoline **1**.

catalyst in terms of EcoScale and AE, but the need for an oxygen balloon negatively affects other parameters.

Finally, to demonstrate the robustness of our system, the synthesis of compound **1** was carried out in preparative scale, being possible to isolate it in 69% yield under the same working conditions. The reaction in gram scale allowed the purification by recrystallization (using ethanol) representing a way of reducing the waste of the procedure (E-factor global of 9.8), although the yield decreases to 51%. The setup of the reaction, especially on large scale, can include a collector for

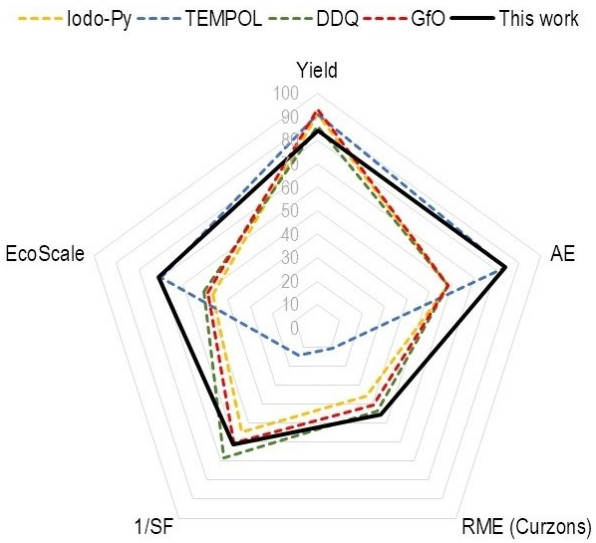

Figure 7. Radial-pentagon diagram with metrics (0–100): Yield, AE, RME (Curzons), 1/SF, and EcoScale. Comparison with metal-free catalyzed preparations of quinazoline **1**.

the outgoing airflow to collect possible products that are discharged into the atmosphere (see Supporting Information).

Conclusion

To conclude, 1-butyl-3-(methoxycarbonylmethyl)-imidazolium chloride and iron(III) chloride have formed a low transition temperature mixture, which resulted in an efficient and robust catalyst in the preparation of different quinazoline derivatives. This novel catalytic protocol promotes a sequence of reactions based on its intrinsic characteristics. Thus, the carboxy-imidazolium salt plays a key role in the activation of the reagents allowing to carry out the reaction in the absence of any solvent. Moreover, the iron in the catalyst allows to employ the atmospheric oxygen for the last oxidation step to form nitrogen containing heterocycles. Therefore, the catalytic system in this study shows remarkable characteristics that make it more sustainable that other previously reported catalysts. Based on different parameters to measure the environmental impact (such as yield, E-factor, atom economy, reaction mass efficiency, stoichiometric factor, and EcoScale), the synthesis of quinazoline mediated by iron-based imidazolium salts is significantly better than other processes based on both metal and non-metal catalysts. The results show an overall superiority in economic and ecological parameters. In addition, the presented catalyst works on a preparative scale, providing access to potentially bioactive compounds in multigram quantities in a more sustainable way.

Experimental Section

Reagents and instruments. All reagents and solvents are commercially available (Alfa-Aesar, Apollo Scientific, Honeywell-Fluka, Fluorochem, Sigma-Aldrich, TCI) and were used without further purification. Flash silica for column chromatography was purchased from Silicycle (Silica Flash P60 230–400 mesh). Melting points were determined with a Reichert Thermovar microscope and are expressed as uncorrected values. Low-resolution mass spectra were recorded on an Agilent 5973 Network mass spectrometer equipped with a 70 eV ionization source and a quadrupolar mass detector operating in single ion monitoring (SIM) mode. Samples were introduced through an Agilent 6890N gas chromatograph equipped with a Technokroma TRB-5MS column (30 m × 0.25 mm × 0.25 μm). Helium was used as the mobile phase. NMR spectra were recorded at the Nuclear Magnetic Resonance Unit from the Technical Services of the University of Alicante (SSTTI-UA). ^{1}H NMR spectra were acquired at 300 or 400 MHz, whereas proton decoupled ^{13}C NMR experiments were carried out at 75 or 100 MHz with Bruker AV300 Oxford or AV400 NMR spectrometers. The solvent used was deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are expressed in ppm and coupling constants (*J*) are reported in Hz.

Synthesis of 1-butyl-3-(methoxycarbonylmethyl)-imidazolium chloride [b(mcm)imCl]. 1-Butylimidazole (10 mmol, 1.3 mL) and methyl chloroacetate (10 mmol, 0.87 mL) were added to a round bottom flask. The vessel was capped, and the mixture was stirred at 60 °C for 48 h, after which it was washed three times with 5 mL portions of diethyl ether and vacuum dried, affording 2.31 g of pure bmcmimCl (99% yield).

Preparation of iron-based imidazolium salt (IBIS). B(mcm)imCl (4.3 mmol, 1 g) and iron (III) chloride (4.3 mmol, 0.7 g) were added to a vial and stirred overnight at 65 °C. 1.7 g of pure IBIS were obtained (99% yield).

General procedure for the synthesis of quinazolines. A glass tube was charged with 2-aminobenzophenone or aminobenzaldehyde (0.5 mmol), benzylamine (1.5 mmol) and IBIS (10 mol%, 20 mg). A glass nozzle connected to an air pump was inserted into the reaction overlooking the reactants. The air flow was set to 50 mL/min and the reaction mixture was stirred at 130 °C for an adequate amount of time. After completion (monitored by GC/MS), the crude mixture was purified by column chromatography with mixtures of hexane and ethyl acetate.

General procedure for the gram scale synthesis of 1. A glass tube was charged with 2-aminobenzophenone (5 mmol, 986 mg), benzylamine (15 mmol, 1.6 mL) and IBIS (10 mol%, 197 mg). The air flow was set to 50 mL/min and the reaction mixture was stirred at 130 °C for 24 hours. After completion (monitored by GC/MS), the product was isolated by column chromatography with mixtures of hexane and ethyl acetate (69% yield) or by recrystallization (EtOH, 51% yield).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Aerobic oxidation · Catalysis · Imidazolium salt · Nitrogen heterocycles · Sustainable chemistry

[1] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.
[2] T. P. Selvam, P. V. Kumar, *Res. Pharm. Sci.* **2015**, *1*, 1–21.
[3] K. Nepali, S. Sharma, R. Ojha, K. L. Dhar, *Med. Chem. Res.* **2013**, *22*, 1–15.
[4] A. Witt, J. Bergman, *Curr. Org. Chem.* **2003**, *7*, 659–677.
[5] V. G. Ugale, S. B. Bari, *Eur. J. Med. Chem.* **2014**, *80*, 447–501.
[6] a) J. Kuneš, J. Bažant, M. Pour, K. Waisser, M. Šlosárek, J. Janota, *Farmer* **2000**, *55*, 725–729; b) P. M. S. Bedi, V. Kumar, M. P. Mahajan, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5211–5213.
[7] a) S. Parua, R. Sikari, S. Sinha, G. Chakraborty, R. Mondal, N. D. Paul, *J. Org. Chem.* **2018**, *83*, 11154–11166; b) S. Yao, K. Zhou, J. Wang, H. Cao, L. Yu, J. Wu, P. Qiu, Q. Xu, *Green Chem.* **2017**, *19*, 2945–2951.
[8] K. Gopalaiah, A. Saini, A. Devi, *Org. Biomol. Chem.* **2017**, *15*, 5781–5789.
[9] a) Z. Chen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang, H. Wu, *J. Org. Chem.* **2013**, *78*, 11342–11348; b) J. Ma, Y. Wan, C. Hong, M. Li, X. Hu, W. Mo, B. Hu, N. Sun, L. Jin, Z. Shen, *Eur. J. Org. Chem.* **2017**, *2017*, 3335–3342.
[10] a) Z. Ma, T. Song, Y. Yuan, Y. Yang, *Chem. Sci.* **2019**, *10*, 10283–10289; b) H. Yuan, W.-J. Yoo, H. Miyamura, S. Kobayashi, *Adv. Synth. Catal.* **2012**, *354*, 2899–2904; c) R. Gujjarappa, S. K. Maity, C. K. Hazra, N. Vodnala, S. Dhiman, A. Kumar, U. Beifuss, C. C. Malakar, *Eur. J. Org. Chem.* **2018**, *2018*, 4628–4638.
[11] R. Gujjarappa, N. Vodnala, V. G. Reddy, C. C. Malakar, *Eur. J. Org. Chem.* **2020**, *2020*, 803–814.
[12] T. Chatterjee, D. I. Kim, E. J. Cho, *J. Org. Chem.* **2018**, *83*, 7423–7430.
[13] C. Wang, S. Li, H. Liu, Y. Jiang, H. Fu, *J. Org. Chem.* **2010**, *75*, 7936–7938.
[14] a) M. A. McGowan, C. Z. McAvoy, S. L. Buchwald, *Org. Lett.* **2012**, *14*, 3800–3803; b) J.-P. Lin, F.-H. Zhang, Y.-Q. Long, *Org. Lett.* **2014**, *16*, 2822–2825; c) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2010**, *12*, 3963–3965; d) W. Szczepankiewicz, J. Suwiński, *Tetrahedron Lett.* **1998**, *39*, 1785–1786; e) C. Huang, Y. Fu, H. Fu, Y. Jiang, Y. Zhao, *Chem. Commun.* **2008**, 6333–6335.
[15] a) X. Wang, N. Jiao, *Org. Lett.* **2016**, *18*, 2150–2153; b) J. Wang, S. Zha, K. Chen, F. Zhang, C. Song, J. Zhu, *Org. Lett.* **2016**, *18*, 2062–2065.
[16] F. Portela-Cubillo, J. S. Scott, J. C. Walton, *J. Org. Chem.* **2009**, *74*, 4934–4942.
[17] a) Y. Yan, Y. Xu, B. Niu, H. Xie, Y. Liu, *J. Org. Chem.* **2015**, *80*, 5581–5587; b) Z. Zhang, M. Wang, C. Zhang, Z. Zhang, J. Lu, F. Wang, *Chem. Commun.* **2015**, *51*, 9205–9207.
[18] a) X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou, M. Li, *Chem. Commun.* **2013**, *49*, 6752–6754; b) H. Zhao, J. Huang, J. Zhang, Y. Tang, Y. Zhang, *ChemistrySelect* **2020**, *5*, 3007–3010; c) X.-D. Lang, Y.-C. Yu, Z.-M. Li, L.-N. He, *J. CO_2 Util.* **2016**, *15*, 115–122; d) K. Hu, Q. Zhen, J. Gong, T. Cheng, L. Qi, Y. Shao, J. Chen, *Org. Lett.* **2018**, *20*, 3083–3087.
[19] F.-C. Jia, Z.-W. Zhou, C. Xu, Q. Cai, D.-K. Li, A.-X. Wu, *Org. Lett.* **2015**, *17*, 4236–4239.
[20] A. Maleki, T. Kari, M. Aghaei, *J. Porous Mater.* **2017**, *24*, 1481–1496.
[21] E. Eidi, M. Z. Kassaee, Z. Nasresfahani, P. T. Cummings, *Appl. Organomet. Chem.* **2018**, *32*, e4573.
[22] S. Ferrini, F. Ponticelli, M. Taddei, *Org. Lett.* **2007**, *9*, 69–72.
[23] Y. Yan, Y. Zhang, C. Feng, Z. Zha, Z. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 8077–8081; *Angew. Chem.* **2012**, *124*, 8201–8205.
[24] U. P. Saikia, G. Borah, P. Pahari, *Eur. J. Org. Chem.* **2018**, *2018*, 1211–1217.
[25] D. Zhao, Q. Shen, J.-X. Li, *Adv. Synth. Catal.* **2015**, *357*, 339–344.

[26] J. Zhang, C. Yu, S. Wang, C. Wan, Z. Wang, *Chem. Commun.* **2010**, *46*, 5244–5246.
[27] K. Karnakar, J. Shankar, S. N. Murthy, K. Ramesh, Y. V. D. Nageswar, *Synlett* **2011**, 1089–1096.
[28] T. Truong, T. M. Hoang, C. K. Nguyen, Q. T. N. Huynh, N. T. S. Phan, *RSC Adv.* **2015**, *5*, 24769–24776.
[29] a) D. S. Deshmukh, B. M. Bhanage, *Synlett* **2018**, *29*, 979–985; b) J. Zhang, D. Zhu, C. Yu, C. Wan, Z. Wang, *Org. Lett.* **2010**, *12*, 2841–2843.
[30] B. Han, C. Wang, R.-F. Han, W. Yu, X.-Y. Duan, R. Fang, X.-L. Yang, *Chem. Commun.* **2011**, *47*, 7818–7820.
[31] S. Rachakonda, P. S. Pratap, M. V. B. Rao, *Synthesis* **2012**, *44*, 2065–2069.
[32] K. Karnakar, A. V. Kumar, S. N. Murthy, K. Ramesh, Y. V. D. Nageswar, *Tetrahedron Lett.* **2012**, *53*, 4613–4617.
[33] D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.* **2016**, *2016*, 612–632.
[34] a) M. Albert-Soriano, I. M. Pastor, *Adv. Synth. Catal.* **2020**, *362*, 2494–2502; b) P. Gisbert, M. Albert-Soriano, I. M. Pastor, *Eur. J. Org. Chem.* **2019**, *2019*, 4928–4940; c) M. Albert-Soriano, L. Hernández-Martínez, I. M. Pastor, *ACS Sustainable Chem. Eng.* **2018**, *6*, 14063–14070.
[35] P. Trillo, I. M. Pastor, *Adv. Synth. Catal.* **2016**, *358*, 2929–2939.
[36] M. Martos, I. M. Pastor, *J. Mol. Liq.* **2022**, *347*, 118349.
[37] P. Gisbert, I. M. Pastor, *Synthesis* **2018**, *50*, 3031–3040.
[38] a) R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437–1451; b) A. P. Dicks, A. Hent, *Green Chemistry Metrics – A Guide to Determining and Evaluating Process Greenness*, Springer, Cham, **2015**.
[39] R. Sarma, D. Prajapati, *Green Chem.* **2011**, *13*, 718–722.
[40] W. Szczepankiewicz, P. Wagner, M. Danicki, J. Suwiński, *Tetrahedron Lett.* **2003**, *44*, 2015–2017.
[41] J. Andraos, *Reaction Green Metrics – Problems, Exercises, and Solutions*, CRC Press (Taylor & Francis Group), Boca Raton, **2019**.
[42] K. Van Aken, L. Strekowski, L. Patiny, *Beilstein J. Org. Chem.* **2006**, *2*, 3.

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