Mo–Catalyzed One-Pot Synthesis of *N*-Polyheterocycles from Nitroarenes and Glycols with Recycling of the Waste Reduction Byproduct. Substituent-Tuned Photophysical Properties

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Dedicated to the memory of Professor Kilian Muñiz

Abstract: A catalytic domino reduction–imine formation–intramolecular cyclization–oxidation for the general synthesis of a wide variety of biologically relevant *N*-polyheterocycles, such as quinoxaline- and quinoline-fused derivatives, and phenanthridines, is reported. A simple, easily available, and environmentally friendly dioxomolybdenum(VI) complex has proven to be a highly efficient and versatile catalyst for transforming a broad range of starting nitroarenes involving several redox processes. Not only is this a sustainable, step-economical as well as air- and moisture-tolerant method, but also it is worth highlighting that the waste byproduct generated in the first step of the sequence is recycled and incorporated in the final target molecule, improving the overall synthetic efficiency. Moreover, selected indoloquinoxalines have been photophysically characterized in cyclohexane and toluene with exceptional fluorescence quantum yields above 0.7 for the alkyl derivatives.

Introduction

Nitroaromatic compounds are readily available nitrogen sources, easily accessed by nitration of parent arenes,[1] and generally less expensive than the corresponding anilines, which are, in addition, typically prepared by reduction of the former.[2] This reduction process is commonly the initial step for accessing more elaborated nitrogen-containing compounds. Therefore, the direct use of air-stable nitroarenes to synthesize value-added nitrogenated derivatives is becoming a powerful and highly efficient tool in organic synthesis saving reagent cost and suppressing at least one process step.[3] When accessing N-heterocyclic compounds, most of the reported examples are related to the catalytic hydrogen transfer reduction of nitroarenes with alcohols,[4] or with Cadogan-type reductive cyclizations[5] and redox neutral Davis-Beirut reaction.[6] These nitrogen-containing heterocycles are privileged motifs extensively present in both natural products and biologically active synthetic compounds. Specifically, aza-fused polyheterocyclic frameworks are indispensable structural units in many different natural products, most of them possessing a wide range of important biological and pharmacological activities. In particular, aza-fused quinoxalines, such as indolo[1,2-*a*]quinoxalines and pyrrolo[1,2-*a*]quinoxalines, are versatile building blocks that appear in different biologically active compounds and are considered to be privileged substructures for drug design.[7] Therefore, several methods have been developed for their synthesis, most of them based on a two-component condensation or oxidative cyclization of *N*-(2-aminophenyl)pyrroles or indoles with different carbonyl equivalents,[8] as well as for their subsequent functionalization.[9] As mentioned above, the development of methods for the direct synthesis of these heterocyclic derivatives from nitroarenes is an appealing challenge in the field that, however, has been scarcely investigated.[10]

On the other hand, combining multistep syntheses into one-pot domino reactions to maximize synthetic efficiency, lower waste generation, save resources and reduce yield losses due to purification processes is a highly desirable but challenging task in organic synthesis with an ever-increasing interest nowadays. In addition, minimizing the production of waste or, alternatively, internally recycling it for subsequent transformations,[11] is a relevant consideration for green

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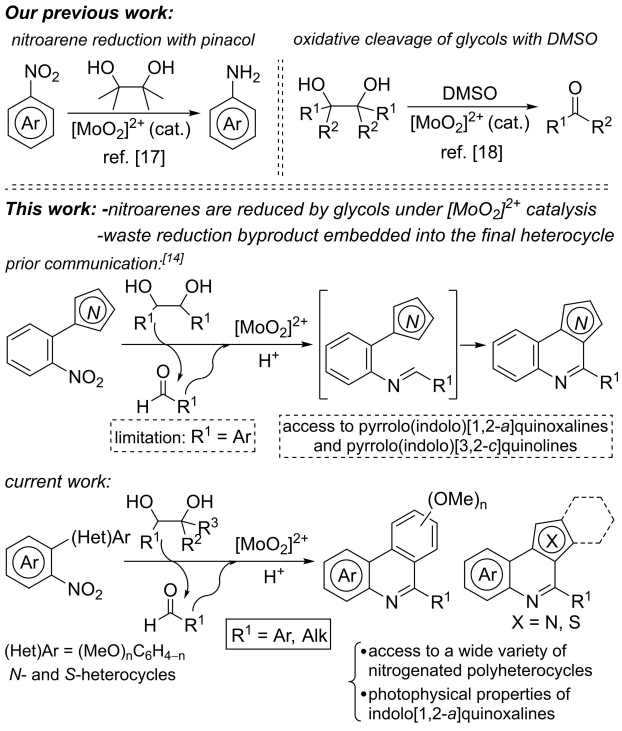
chemistry. In this context, the development of sustainable strategies that internally reuse the waste generated in the first step of a sequence as a catalyst or co-catalyst[12] for the following step is currently a highly interesting topic in organic synthesis. In the pioneering work,[12a] Shibasaki employed the phosphine oxide byproduct from a Wittig reaction to promote a catalytic asymmetric epoxidation. Among all the reported examples, a few of them describe the use of the waste formed in the upstream step, mainly an inorganic salt, as an essential reagent to facilitate or promote a downstream step.[13] However, until our preliminary report,[14] no examples had been reported about the recycling of a byproduct as a reagent that finally is embodied into the final compound.[15]

Based on our experience with the use of inexpensive, non-toxic and readily available dioxomolybdenum(VI) complexes,[16] as catalysts for the reduction of nitroaromatics with pinacol[17] and the oxidative cleavage of glycols (Scheme 1),[18] in our previous report we demonstrated a new Mo(VI)-catalyzed domino process, consisting on a nitro reduction – imine generation – annulation – oxidation that involves the incorporation of the carbonyl reduction byproduct of the first step into the final product. This new concept was applied to the synthesis of pyrrolo(indolo)[1,2-*a*]quinoxalines and pyrrolo(indolo)[3,2-*c*]quinolines from *o*-nitrophenyl pyrroles and indoles.[14] In this work, we aim to extend this methodology to the preparation of a wide variety of nitrogenated polyheterocycles as well as to solve our initial limitation regarding the nature of the glycol reductant that only allowed the presence of aryl groups R^1 groups (Scheme 1). In addition, the photophysical properties of selected indolo[1,2-*a*]quinoxalines have been studied.



Scheme 1. $[MoO_2]^{2+}$-catalyzed reactions of nitroaromatics and glycols.

Results and Discussion

Initially, a model reaction between commercially available *N*-2-nitrophenylpyrrole **1a** and 1,2-di-*p*-tolylethane-1,2-diol **2a** as reducing agent and carbonyl source was chosen to optimize the reaction (Table 1). Based on the previously described conditions for the molybdenum-catalyzed reduction of nitroaromatics to the corresponding anilines,[17] essays were performed under microwave irradiation at 180 °C with DMA as the solvent and 5 mol% of $MoO_2Cl_2(dmf)_2$ as the catalyst for 30 min. First, the influence of variable amounts of glycol was studied using *p*-toluenesulfonic acid as an additive (entries 1–4). The use of 2 equivalents of diol **2a** was proved necessary for the complete conversion of the starting material **1a** (entry 3 vs. entries 1–2), whereas employing a slight excess of the glycol (2.2. equiv) led to a higher yield of the desired pyrroloquinoxaline **3aa** (entry 4).[19] This heterocyclic derivative could be isolated in 85% yield after column chromatography. Under the same reaction conditions, but in the absence of the acid co-catalyst, a slightly lower yield of the targeted *N*-polyheterocycle **3aa** was obtained (entry 5). However, a comparable performance could be achieved with a longer reaction time (entry 6), proving that the added Brønsted acid only serves to enhance reaction rates in the tandem process. Moreover, a higher catalyst loading in the absence of PTSA did not positively impact the outcome of the reaction (entry 7). A decrease of the temperature to 150 °C in the presence and absence of the acid co-catalyst resulted in notably lower yields (entries 8 and 9). Additionally, another experiment was carried out using conventional heating as a successful alternative to microwave irradiation, although longer reaction times and slightly lower yields of **3aa** were observed (entry 10).

As established in the introduction, a significant limitation of our methodology was related to the nature of the C-4 substituent of the pyrroloquinoxaline core that could only be

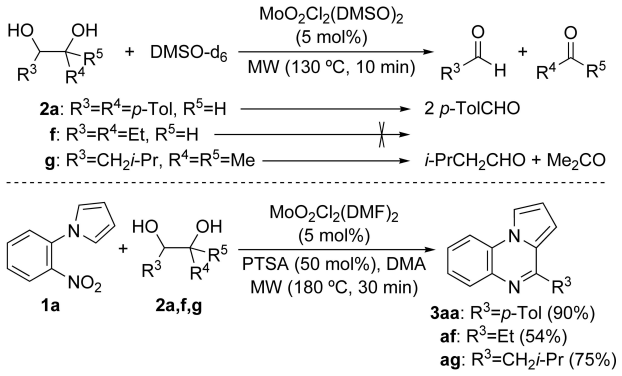
Table 1. Conditions for the reaction of *N*-2-nitrophenylpyrrole **1a** with glycol **2a**.

1a **2a** (n equiv) **3aa**

Entry	additive	n[a]	Conversion [%][b]	Yield [%][b,c]
1	PTSA (50 mol%)	1	83	44
2	PTSA (50 mol%)	1.5	91	64
3	PTSA (50 mol%)	2	100	81
4	PTSA (50 mol%)	2.2	100	95 (85)
5	–	2.2	100	89
6[d]	–	2.2	100	93
7[e]	–	2.2	100	80
8[f]	PTSA (50 mol%)	2.2	100	72
9[f]	–	2.2	88	65[g]
10[h]	PTSA (50 mol%)	2.2	100	90

[a] Number of equivalents of glycol **2a** referred to the starting pyrrole **1a**. [b] Calculated by ^{1}H NMR using CH_2Br_2 as internal standard. [c] In brackets, isolated yield after column chromatography referred to **1a**. [d] Reaction time: 60 min. [e] 20 mol% of catalyst was used. [f] Reaction temperature: 150 °C. [g] ~15% of the dihydro derivative of **3aa** was also obtained. [h] Carried out under conventional heating for 90 min.

an aryl group (Scheme 1). To establish the requirements of the glycols that could be potentially used as reducing agents, we took advantage of our previously described Mo-catalyzed oxidative cleavage of a wide variety of 1,2-diols with DMSO (Scheme 1).[18] This process requires that at least one hydroxyl group is activated as a secondary benzylic or tertiary alcohol. Therefore, although 1,2-di-*p*-tolylethane-1,2-diol **2a** could be effectively cleaved under standard conditions, di-secondary alkyl glycol **2f** could not (Scheme 2).[18] Next, we proceeded to overcome the limitation related to the carbonyl byproduct from the initial reduction of the nitro group, so glycols that after oxidative cleavage generate aliphatic aldehydes could be used. In this sense, we envisaged that a mixed secondary-tertiary diol

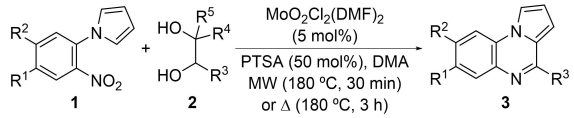


Scheme 2. Glycols **2** able to participate in the reductive cyclization of **1a**.

such as **2g**, which could be easily prepared from the corresponding α-hydroxy ester, would offer a key alternative to allow the presence of alkyl groups at C-4 position in the pyrroloquinoxaline core (R^3 = alkyl) (Scheme 2). As expected, glycol **2g** was effectively cleaved with DMSO leading to isovaleraldeyde and acetone. Next, the corresponding reactions of **1a** with both diols **2f** and **2g** were attempted, despite **2f** not being oxidatively cleaved by DMSO. Surprisingly, treatment of **1a** with diol **2f** led to the formation of 4-ethyl-substituted pyrroloquinoxaline **3af**, probably due to the increase of the reaction temperature (180 vs. 130 °C), although it was obtained with moderate yield (Scheme 2). Gratifyingly, diol **2g** allowed the synthesis of 4-isobutylpyrrolo[1,2-*a*]quinoxaline **3ag** in a higher yield, despite the generation of two different carbonyl byproducts (Scheme 2). As expected, the aldehyde byproduct reacted with the intermediate amine preferentially to the co-generated acetone. Therefore, their easy availability and the higher yield obtained in their cyclization reaction make mixed secondary-tertiary glycols an excellent solution to our initial limitation.

With the optimized reaction conditions established and our previous limitation solved, the substrate scope and effectiveness of the reaction were then explored with different substituted 1-(2-nitrophenyl)pyrroles **1** and a variety of glycols **2** (Table 2). First, model substrate **1a** was tested with different secondary benzylic glycols **2b–e** as reductants and carbonyl sources (entries 1–4). Functionalized secondary benzylic glycols **2c–e** showed no difference in reactivity compared to parent 1,2-diphenylethanediol (**2b**), and the presence of methoxy or

Table 2. Synthesis of pyrrolo[1,2-*a*]quinoxalines **3**.[a]



Entry	1	R^1	R^2	2	R^3	R^4	R^5	Product	Yield [%][b]
1	**1a**	H	H	**2b**	Ph	Ph	H	**3ab**	78 (73)[c]
2	**1a**	H	H	**2c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	**3ac**	71
3	**1a**	H	H	**2d**	4-BrC_6H_4	4-BrC_6H_4	H	**3ad**	83
4	**1a**	H	H	**2e**	2-ClC_6H_4	2-ClC_6H_4	H	**3ae**	60[d]
5	**1a**	H	H	**2h**	*i*-Pr	Me	Me	**3ah**	65
6	**1a**	H	H	**2i**	CH_2Ph	Me	Me	**3ai**	66
7	**1b**	MeO	H	**2a**	*p*-Tol	*p*-Tol	H	**3ba**	71
8	**1b**	MeO	H	**2b**	Ph	Ph	H	**3bb**	66
9	**1b**	MeO	H	**2d**	4-BrC_6H_4	4-BrC_6H_4	H	**3bd**	70
10	**1b**	MeO	H	**2f**	Et	Et	H	**3bf**	55
11	**1b**	MeO	H	**2g**	CH_2*i*-Pr	Me	Me	**3bg**	70
12	**1b**	MeO	H	**2i**	CH_2Ph	Me	Me	**3bi**	85
13	**1b**	MeO	H	**2j**	*n*-Bu	Me	Me	**3bj**	74 (70)[c]
14	**1b**	MeO	H	**2k**	*n*-Hex	Me	Me	**3bk**	79
15	**1b**	MeO	H	**2l**	*c*-C_6H_{11}	Me	Me	**3bl**	75
16	**1b**	MeO	H	**2m**	Me	Me	Me	**3bm**	53
17[e]	**1b**	MeO	H	**2n**	H	Me	Me	**3bn**	66[f]
18	**1c**	Cl	H	**2a**	Ph	Ph	H	**3ca**	80
19	**1d**	H	Cl	**2a**	Ph	Ph	H	**3da**	81
20	**1d**	H	Cl	**2c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	**3dc**	84
21	**1d**	H	Cl	**2m**	Me	Me	Me	**3dm**	52

[a] All reactions were carried out with the corresponding pyrrole **1** (0.3-0.5 mmol) and glycol **2** (0.66-1.1 mmol) and PTSA (0.15-0.25 mmol) in DMA (0.5 M) under microwave irradiation (180 °C, 30 min). [b] Isolated yield based on the starting nitroaromatic **1**. [c] Performed under conventional heating (180 °C, 90 min). [d] Isolated along with ca. 17% of 1-(2-chlorobenzyl)-4-(2-chlorophenyl)pyrrolo[1,2-*a*]quinoxaline. [e] Reaction conditions: **2n** (3 equiv), 20 mol% of catalyst, without PTSA for 90 min. [f] A ca. 10% of the pyrroloquinoxaline with R^3 = *i*-Pr (**3be**) was also obtained.

halide groups at different positions of the aryl moiety was well tolerated leading to pyrroloquinoxalines **3ab–ae** in good to high yields.[20] Remarkably, mixed secondary-tertiary glycols **2h,i**, derived from natural amino acids *L*-valine and *L*-phenylalanine,[21] could also be effectively used to obtain 4-alkyl pyrroloquinoxalines **3ah** and **3ai** in useful yields (entries 5 and 6). Next, the functional group tolerance on the nitroarene ring was analyzed by employing readily accessible pyrroles **1b–d**. Thus, 1-(2-nitrophenyl)pyrroles **1** bearing methoxy (entries 7–17) or chlorine groups at different positions (entries 18–21) could be employed as starting materials under the optimized conditions regardless of the nature of the glycol.

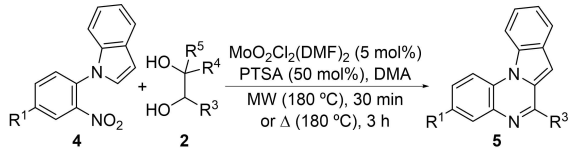
Various glycols **2** were further explored as reducing agents and carbonyl source for this tandem process. Firstly, functionalized pyrrole derivatives **1b–d** were submitted to the reaction with diverse secondary benzylic glycols **2a–d** (entries 7–9 and 18–20). In all of these cases, the final substituted *N*-polyheterocycles **3** were isolated in good to high yields. Again, secondary alkyl glycol **2f** also participated in this tandem methodology and reacted with **1b** under the same optimized conditions leading to the corresponding pyrroloquinoxaline **3bf** although in lower yield (entry 10). To further probe the scope of the method for the synthesis of 4-alkyl-substituted pyrroloquinoxalines, a variety of mixed secondary-tertiary diols **2g–l** were also examined. Mixed glycols **2g–l** bearing a benzyl (entry 12), linear (entries 13 and 14), branched (entry 11), or cyclic (entry 15) alkyl groups on the secondary alcohol reacted efficiently with nitroarenes **1** to provide the desired products **3** possessing (*c*)-alkyl or benzyl groups at C-4 position in high yields. In addition, glycol **2m** bearing a methyl group as R^3 enabled the synthesis of methyl-substituted compounds **3bm** and **3dm**, although in lower yields (entries 16 and 21). Finally, to prepare 4-unsubstituted pyrroloquinoxalines, primary glycol **2n** was employed. However, reaction with **1b** under the standard conditions led to no complete conversion and a ca. 1/1 mixture of the expected product **3bn** and a related pyrroloquinoxaline with $R^3 = i$-Pr (**3bh**). This side-product is likely formed due to a competitive pinacol rearrangement of glycol **2n** to isobutyraldehyde. After some experimentation, we found that a longer reaction time and larger amounts of both glycol and catalyst, in the absence of PTSA, gave rise to a useful yield of **3bn** (entry 17).

Analogously, 1-(2-nitrophenyl)-indoles **4** were also suitable substrates for this tandem reaction, affording indolo[1,2-*a*]quinoxalines **5**, under the same reaction conditions and employing various glycols **2** as reducing agents (Table 3). Thereby, the reaction of nitroaryl indoles **4** with secondary benzylic alcohols (entries 1, 2, and 7) led to the corresponding products **5ab,ac,bb** in good to high yields, whereas the employment of the di-secondary alkyl glycol **2f** gave rise to **5af** in moderate yield (entry 3). Mixed secondary-tertiary alkyl diols reacted well and indoloquinoxalines **5aj–ao,bl** were isolated in good yields (entries 4–6, and 8). Interestingly, the trifluoromethyl group in the nitroaryl moiety is well-tolerated, as shown with the efficient preparation of products **5bb,bl** (entries 7 and 8).

Recently, the synthesis of ullazines (indolizino-[6,5,4,3-*aij*]quinolines) has attracted interest due to the potential applications of such organic materials in optoelectronic devices.[22] These attractive properties encouraged the synthesis of related structures. In this field, the first preparation of aza-ullazines (indolizino[6,5,4,3-*ija*][1,6]naphthyridine), whose optical and electrochemical properties were also investigated, was reported by Langer.[23] However, to the best of our knowledge, there is only one reported method for synthesizing related diaza-ullazines (triazacyclopenta[*c,d*]-phenalenes).[24] Therefore, we hypothesized that our strategy could also provide a route to synthesize this type of electronically engaging heterocycles (Scheme 3). Thus, 1-(2,6-dinitrophenyl)pyrrole **1e** was subjected to our methodology by treating it with an excess of secondary benzylic glycol **2a** (4.4 equiv) to furnish the corresponding 3,9-diaryl-substituted diaza-ullazine **6a** in 50% yield. Under the same reaction conditions, when **1e** reacted with mixed secondary-tertiary alkyl diol **2j**, 3,9-dibutyl-substituted diaza-ullazine derivative **6b** was obtained in a similar yield. It is worth noting that the previous synthesis of diaza-ullazine **6a** by Balli was achieved in three independent steps from the same substrate **1e** with an overall 14% yield.[24]

The value of the developed methodology was further extended to the synthesis of pyrrolo[3,2-*c*]quinolines **8** and indolo[3,2-*c*]quinolines **10**, also known as γ-carbolines, starting respectively from pyrroles **7** and indoles **9**, substituted at C2-

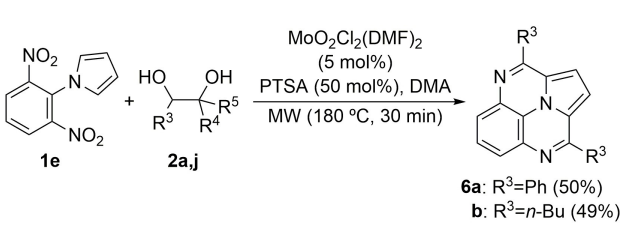
Table 3. Synthesis of indolo[1,2-*a*]quinoxalines **5**.[a]



4 2 5

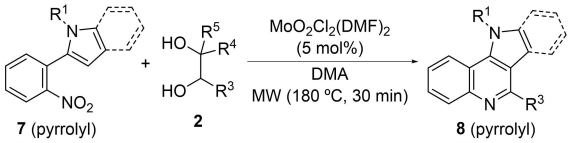
Entry	4	R^1	2	R^3	R^4	R^5	Product	Yield [%][b]
1	**4a**	H	**2b**	Ph	Ph	H	**5ab**	95
2	**4a**	H	**2c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	**5ac**	61
3	**4a**	H	**2f**	Et	Et	H	**5af**	52
4	**4a**	H	**2j**	*n*-Bu	Me	Me	**5aj**	74 (67)[c]
5	**4a**	H	**2l**	*c*-C_6H_{11}	Me	Me	**5al**	69
6	**4a**	H	**2o**	*n*-Pent	Me	Me	**5ao**	71
7	**4b**	CF_3	**2b**	Ph	Ph	H	**5bb**	74
8	**4b**	CF_3	**2l**	*c*-C_6H_{11}	Me	Me	**5bl**	75

[a] All reactions were carried out with the corresponding indole **4** (0.3–0.5 mmol) and glycol **2** (0.66–1.1 mmol) and PTSA (0.15–0.25 mmol) in DMA (0.5 M) under microwave irradiation (180 °C, 30 min). [b] Isolated yield based on the starting nitroaromatic **4**. [c] Carried out under conventional heating (180 °C, 3 h).



Scheme 3. Preparation of diaza-ullazines **6** from *N*-2,6-dinitrophenylpyrrole **1e**.

Table 4. Synthesis of pyrrolo and indolo[3,2-*c*]quinoline derivatives **8** and **10**.[a]



7 (pyrrolyl) **9** (indolyl) | **2** | **8** (pyrrolyl) **10** (indolyl)

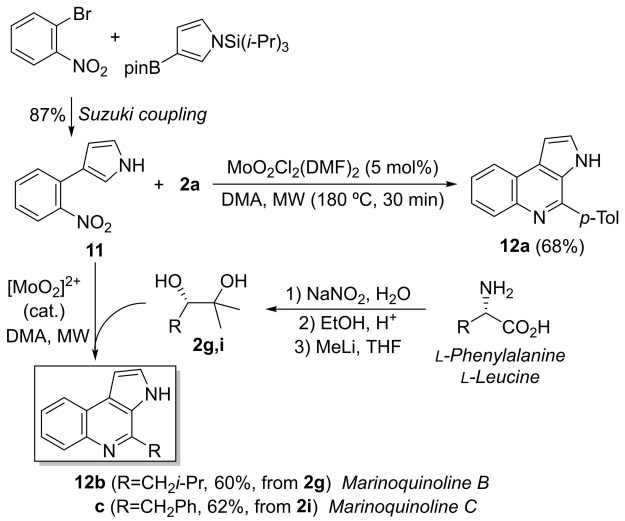
Entry	Nitro	R^1	Diol	R^3	R^4	R^5	Product	Yield [%][b]
1	**7a**	Me	**2b**	Ph	Ph	H	**8ab**	72
2	**7a**	Me	**2d**	4-BrC_6H_4	4-BrC_6H_4	H	**8ad**	94
3	**7a**	Me	**2g**	CH_2*i*-Pr	Me	Me	**8ag**	75
4	**7a**	Me	**2j**	*n*-Bu	Me	Me	**8aj**	66
5	**7a**	Me	**2l**	*c*-C_6H_{11}	Me	Me	**8al**	78
6	**7b**	H	**2b**	Ph	Ph	H	**8bb**	69
7[c]	**9a**	H	**2b**	Ph	Ph	H	**10ab**	83
8[c]	**9a**	H	**2e**	2-ClC_6H_4	2-ClC_6H_4	H	**10ae**	71
9[c]	**9a**	H	**2j**	*n*-Bu	Me	Me	**10aj**	51

[a] Reaction conditions: **7** or **9** (0.5 mmol) was treated with the corresponding glycol **2** (1.1 mmol) in DMA (1 mL) under microwave irradiation (180 °C, 30 min). [b] Isolated yield based on the starting nitroarene **7** or **9**. [c] Reactions carried out in the presence of 25 mol% of PTSA.

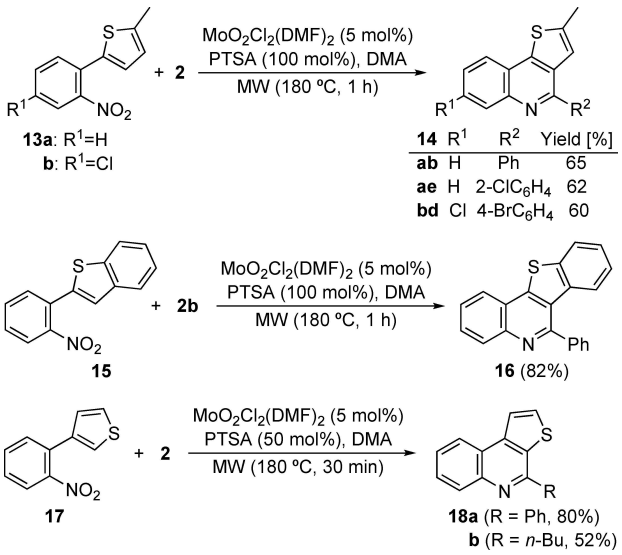
position with a 2-nitrophenyl group, which are easily accessible by known methods.[19] These heterocyclic scaffolds **8** and **10** are important structural units embedded in natural alkaloids and several analogues with a broad range of important biological and pharmaceutical activities.[25] Therefore, different approaches for the synthesis of these types of compounds have been reported in the literature.[26] However, most of these methods suffer from certain drawbacks, including tedious procedures, costly reagents or lack of general applicability. In our case, treatment of the corresponding pyrrolyl (**7**) or indolyl (**9**) nitroarene derivative with a variety of glycols **2** gave effectively rise to the expected quinoline-based heterocycles **8** or **10** in moderate to high yields (Table 4). Our methodology allowed the synthesis of diverse [3,2-*c*]quinoline derivatives **8** and **10** with a substituent R^3 that could be both an aryl (entries 1, 2, and 6–8) or an alkyl (entries 3–5, and 9) group, depending on the glycol **2** used in the reaction. Gratifyingly, an *N*-protecting group was not necessary for these starting nitroarenes to participate in the reaction, allowing direct access to *N*-H heterocycles (entries 6–9). Interestingly, reactions with starting pyrrole derivatives **7** could be conducted without the addition of the Brønsted acid, thus demonstrating that this domino process can be exclusively catalyzed by the dioxomolybdenum (VI) complex when highly reactive substrates are employed.

Next, we envisaged the possibility of the concise total synthesis of Marinoquinolines, a family of natural products that embody the 3*H*-pyrrolo[2,3-*c*]quinoline ring system, a rare structural motif among natural products that is also present in Pyonitrins.[27] Marinoquinolines have been isolated from a range of bacterial sources and have shown antibacterial, antiplasmodial, antifungal activities and moderate cytotoxicity against several cancer lines.[28] Due to this significant variety of biological activities, several synthetic approaches have been developed, although most of them suffer from limitations mainly related to the multistep preparation of starting materials or moderate overall yields.[29] To synthesize Marinoquinolines using our catalytic methodology, the common key intermediate 3-(2-nitrophenyl)-1*H*-pyrrole (**11**) was required and readily prepared through a Suzuki coupling from commercially available materials (Scheme 4). Its reaction with model diol **2a** was performed and, after some optimization, Marinoquinoline unnatural analogue **12a** could be prepared in good yield (Scheme 4). To access selected members of the Marinoquinoline family, we designed mixed secondary-tertiary diols **2g** and **2i**, easily and efficiently prepared from the corresponding natural α-amino acids phenylalanine and leucine, respectively. These diols **2g** and **2i** were then efficiently used as reducing agents and carbonyl source in their reactions with **11** under the optimized conditions, directly producing Marinoquinolines B and C in good yields (Scheme 4).

At this point, to even further evaluate and broaden the scope of this methodology, a selection of thienoquinoline derivatives were synthesized (Scheme 5). Thienoquinolines,



Scheme 4. Preparation of pyrrolo[2,3-*c*]quinolines **12** from 3-(2-nitrophenyl) pyrrole **11**. Synthesis of Marinoquinolines B and C.

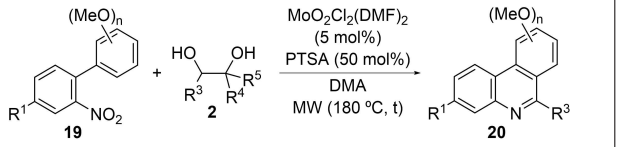


Scheme 5. Preparation of thieno[3,2-*c*]quinoline derivatives **14**, **16** and thieno[2,3-*c*]quinolines **18**.

quinoline fused heterocycles with a sulfur atom, possess different interesting and promising biological activities.[30] The two main types of thienoquinolines depend on the fused sulfur ring position to the quinoline moiety: thieno[*b*]quinolines and thieno[*c*]quinolines.[31] For their synthesis, some methods have been reported,[32] including the reaction of 2-(thiophen-3-yl) anilines with aromatic aldehydes.[33] Based on our previous results, we suggested (2-nitrophenyl)-substituted thiophenes and benzothiophenes **13**, **15**, and **17** as plausible starting materials. Their treatment with different glycols **2**, larger amounts of PTSA (100 mol%) and longer reaction times (1 h), afforded moderate to good yields of the intended (benzo) thieno[3,2-*c*]quinoline derivatives **14** and **16**, and thieno[2,3-*c*] quinolines **18**. The process also revealed to be compatible with glycols bearing halides (**2d,e**). In addition, thieno[2,3-*c*] quinoline **18b** that incorporates an alkyl group at C-4 position, could be obtained by using the mixed secondary-tertiary diol **2j** (Scheme 5).

On the other hand, phenanthridines represent a valuable type of N-heterocyclic structures in organic chemistry, mainly due to their occurrence in natural alkaloids and therapeutically active compounds possessing a wide variety of pharmacological properties including anticancer, antiviral, antimicrobial, antifungal and anti-inflammatory activities.[34] Due to such importance and potential applications, even in material sciences given their optoelectronic properties,[35] a number of methods for the synthesis of regioselectively functionalized phenanthridines have been developed, including photochemical processes, radical cyclizations, anionic ring closure reactions, benzyne mediated cyclizations, transition metal-catalyzed C–H bond arylations and many more.[36] Again, the Brønsted acid-mediated or catalyzed reactions of aldehydes with biphenyl-2-amines, Pictet-Spengler reactions, have been reported as a useful entry to 6-substituted phenanthridines.[37] Therefore, we tried to extend the scope of our strategy to the preparation of these highly interesting functionalized phenanthridines using 2-nitrobiphenyls **19** as starting materials,[38] bearing different degrees of methoxy activation, which was proved to be necessary for the cyclization step to take place effectively (Table 5). A quick optimization process was performed for each methoxy-substitution pattern,[19] and different aromatic secondary glycols **2** were used, affording moderate to good yields of the desired phenanthridines **20**. In the first set of experiments 3′,4′-dimethoxy-2-nitro-1,1′-biphenyl **19a** was treated with a variety of glycols **2** bearing simple aryl groups (**2a,b**), as well as halide-functionalized aryl groups (**2d**,**e**), leading to the corresponding phenanthridines in good yields (entries 1–4). However, in this case, the reaction with a mixed secondary-tertiary diol such as **2j** was unsuccessful delivering an unidentified mixture of products (entry 5). Then, a different methoxy-substitution

Table 5. Synthesis of functionalized phenanthridines **20**.[a]

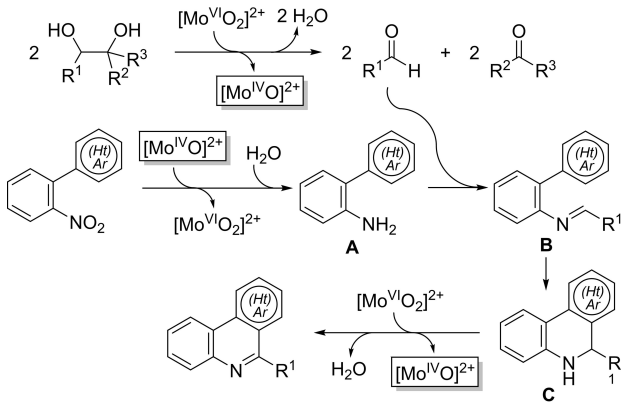


Entry	19	R^1	$(OMe)_n$[b]	2[c]	R^3	t [min]	Product	Yield [%][d]
1	**19a**	H	3,4-$(MeO)_2$	**2a**	*p*-Tol	45	**20aa**	67
2	**19a**	H	3,4-$(MeO)_2$	**2b**	Ph	45	**20ab**	68
3	**19a**	H	3,4-$(MeO)_2$	**2d**	4-BrC_6H_4	45	**20ad**	70
4	**19a**	H	3,4-$(MeO)_2$	**2e**	2-ClC_6H_4	45	**20ae**	82
5	**19a**	H	3,4-$(MeO)_2$	**2j**	*n*-Bu	45	–[e]	–
6	**19b**	H	3,5-$(MeO)_2$	**2b**	Ph	30	**20bb**	72
7	**19c**	Cl	3,5-$(MeO)_2$	**2b**	Ph	30	**20cb**	80 (68)[f]
8	**19d**	CN	3,5-$(MeO)_2$	**2b**	Ph	30	**20db**	78
9[g]	**19e**	H	2,5-$(MeO)_2$	**2b**	Ph	45	**20eb**	50
10	**19f**	H	2,3-$(MeO)_2$	**2b**	Ph	45	**20fb**	61
11	**19g**	H	3,4,5-$(MeO)_3$	**2b**	Ph	30	**20gb**	73
12	**19h**	Cl	3,4,5-$(MeO)_3$	**2b**	Ph	30	**20hb**	72
13[h]	**19i**	H	2,3,4-$(MeO)_3$	**2b**	Ph	90	**20ib**	49
14[h]	**19j**	CF_3	2,3,4-$(MeO)_3$	**2b**	Ph	90	**20jb**	52
15[i]	**19k**	H	3-MeO	**2b**	Ph	60	**20kb**	69
16[i]	**19k**	H	3-MeO	**2e**	2-ClC_6H_4	60	**20ke**	60

[a] Reaction conditions: 2-Nitrobiphenyl derivative **19** (0.5 mmol), the corresponding glycol **2** (1.1 mmol) and PTSA (0.25 mmol) in DMA (1 mL) under microwave irradiation (180 °C, 30 min), unless otherwise stated. [b] Number and positions of methoxy groups referred to the starting nitroaromatic **19**. [c] Glycol **2**: for R^3 = Ar, R^4 = R^3 and R^5 = H; for R^3 = Alk, R^4 = R^5 = Me. [d] Isolated yield based on the starting nitroaromatic **19**. [e] An unidentified mixture of products was obtained under standard conditions and with PTSA (1 equiv, 90 min). [f] Performed under conventional heating (180 °C, 1 h). [g] TfOH was used instead of PTSA. [h] 150 mol% of PTSA was used. [i] 100 mol% of PTSA was used.

pattern was assayed and a good yield of the desired phenanthridine **20bb** was obtained under similar conditions (entry 6). The functional group tolerance in the nitroaromatic counterpart was proved using **19c,d**, bearing chlorine and cyano groups (entries 7 and 8). 2-Nitrobiphenyls **19e,f** were also effectively used to deliver the target N-heterocycles in moderate yields (entries 9 and 10), although **19e** required the use of a stronger acid like TfOH. A good performance was also accomplished with **19g,h** bearing three methoxy groups (entries 11 and 12). However, the reaction with substrates **19i,j**, also bearing a trimethoxy-functionalized aryl ring, required notably higher loads of PTSA and longer reaction times to afford the corresponding phenanthridines in moderate yields (entries 13 and 14). Interestingly, a trifluoromethyl group as a substituent in the nitroaromatic was tolerated (entry 14). Remarkably, the process was also revealed to be compatible with nitrobiphenyl **19k** bearing only one methoxy group (entries 15 and 16). Hence, a wide variety of methoxy-functionalized 6-arylphenanthridines **20** has been synthesized in good yields from readily available 2-nitrobiphenyl derivatives **19**.[39]

With regard to the mechanism of this tandem process, the experimental data and previous knowledge point toward the catalytic reaction sequence depicted in Scheme 6. First, the molybdenum(VI) catalyst promotes the oxidative cleavage of the glycol, giving rise to the corresponding carbonyl compounds.[18] As a result, a molybdenum(IV) species is formed, paired with water release. Reduction of the nitroarene by this molybdenum(IV) complex regenerates the catalyst and delivers the aniline **A** with the protons provided by a water molecule. **A** is subsequently transformed into imine **B** by condensation with the previously released carbonyl byproduct (when unsymmetrical glycols are used, the reaction with an aldehyde is preferred over the condensation with a ketone). An intramolecular Friedel-Crafts-type cyclization would then result in the formation of the corresponding dihydro-*N*-polyheterocycle **C**. At this point, it is worthy to note that the complete reduction of the nitroaromatic starting material requires $6e^-/6H^+$, whereas only two equivalents of the reducing agent (glycol) are employed. The explanation for this apparent inconsistency comes from the fact that the final step consists in the molybdenum(VI)-catalyzed oxidation of dihydro derivative **C** to the final aromatic heterocyclic compound, with the concurrent generation of the required additional pair of electrons/protons.



Scheme 6. Mechanistic proposal.

Photophysical properties of selected indolo[1,2-a] quinoxalines 5ab,ac,bb,al,ao

Small high purity π-conjugated organic molecules with donor-acceptor (D–A) structures such as indolo-quinoxalines are drawing much attention for their technological applications.[40] These compounds, which contain an electron-rich indole unit (D) joined to an electron-deficient quinoxaline moiety (A), exhibit interesting charge-transporting characteristics.[41] Moreover, their optoelectronic properties can be tuned by incorporating electron-donating or electro-withdrawing substituents in their structures.[40] Numerous photophysical studies of functionalized indolo[2,3-*b*]quinoxaline ([2,3-b]IQ) chromophores have been reported.[40–42] However, indolo[1,2-*a*]quinoxalines ([1,2-a]IQ) chromophores photophysically characterized in this work have been scarcely investigated and only limited to studies in which this moiety appears as a substituent on porphyrins.[43]

A stationary and non-stationary photophysical study of five indolo[1,2-*a*]quinoxalines (**5al**, **5ao**, **5ab**, **5bb**, **5ac**) was carried out in two solvents (cyclohexane and toluene) to gain insight into the effect of the substituents and solvent polarity on the emission of these compounds. The structures and photophysical properties are summarized in Table 6.[44] These chromophores show good stability in solution. Their normalized absorption and emission spectra are shown in Figure 1 (**5al** and **5ab**) and in Figures S3 and S4 (**5ao, 5bb** and **5ac**).[19]

The spectra of the alkyl-substituted compounds (**5al** and **5ao**) show a well-resolved vibrational structure and lower Stokes shifts ($\Delta\tilde{\nu}$ = 300–770 cm^{-1}, Table 6). By contrast, the aryl-substituted **5ab**, **5bb** and **5ac** compounds exhibit red-shifted spectra, poorly resolved vibrational structure and higher Stokes shifts (3800–4600 cm^{-1}, Table 6), diminishing the self-quenching processes. As extended conjugated systems lead to

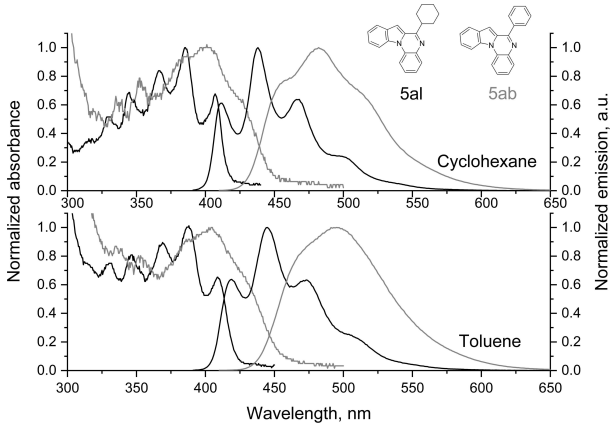
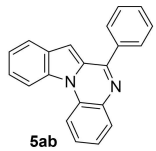
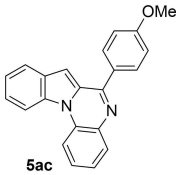
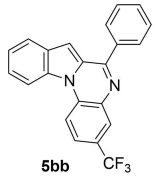
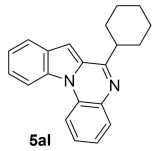
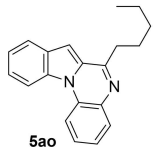


Figure 1. Normalized absorption and emission spectra of **5al** (in black) and **5ab** (in grey) indolo[1,2-*a*]quinoxalines (10^{-5} M) both in cyclohexane (above) and in toluene (below).

Table 6. Maximum absorption wavelength (γ_{abs}), molar absorptivity at the absorption maximum wavelength (ε_{max}), maximum emission wavelength (γ_{em}), Stokes shifts ($\Delta\bar{\nu}$), fluorescence quantum yield (φ_f), average lifetime (τ) and fluorescence (k_f) and non-radiative (k_{nr}) rate constants of selected indolo[1,2-*a*] quinoxalines **5** measured in cyclohexane and toluene.

Compound	Solvent	γ_{abs} [nm]	ε_{max} [L mol^{-1} cm^{-1}]	γ_{em} [nm]	$\Delta\bar{\nu}$ [cm^{-1}][a]	φ_f	τ [ns]	k_f [10^7 s^{-1}]	k_{nr} [10^7 s^{-1}]
 **5ab**	*c*C_6H_{12}	403	4150 ± 40	483	4110	0.38 ± 0.02	10.1 ± 0.1	3.76 ± 0.06	6.13 ± 0.10
	Toluene	404	5380 ± 30	495	4550	0.49 ± 0.02	14.9 ± 0.7	3.28 ± 0.2	3.42 ± 0.20
 **5ac**	*c*C_6H_{12}	400	7820 ± 70	473	3858	0.20 ± 0.01	3.4 ± 0.1	5.83 ± 0.02	23.32 ± 0.08
	Toluene	402	4150 ± 20	484	4215	0.37 ± 0.02	8.7 ± 0.2	4.27 ± 0.10	7.27 ± 0.20
 **5bb**	*c*C_6H_{12}	400	5760 ± 60	482	4253	0.34 ± 0.01	8.4 ± 0.1	4.06 ± 0.02	7.89 ± 0.05
	Toluene	403	6310 ± 30	495	4612	0.46 ± 0.01	15.8 ± 0.1	2.91 ± 0.02	3.41 ± 0.02
 **5al**	*c*C_6H_{12}	386	9680 ± 80	438	298	0.78 ± 0.01	9.7 ± 0.2	8.08 ± 0.20	2.28 ± 0.04
	Toluene	388	9660 ± 80	445	583	0.75 ± 0.03	9.6 ± 0.2	7.85 ± 0.20	2.62 ± 0.06
 **5ao**	*c*C_6H_{12}	385	9230 ± 70	439	359	0.79 ± 0.01	10.0 ± 0.1	7.89 ± 0.09	2.09 ± 0.02
	Toluene	386	6670 ± 70	445	761	0.75 ± 0.02	9.7 ± 0.3	7.72 ± 0.20	2.58 ± 0.08

[a] Stokes shift: $\Delta\bar{\nu} = \bar{\nu}_{abs} - \bar{\nu}_{em}$

long absorption and emission wavelengths,[45] the aryl group of **5ab**, **5bb** and **5ac** is expected to be conjugated with the molecular π-framework.[46] Whereas the aryl-substituted [1,2-a] IQ (**5ab**, **5bb** and **5ac**) present similar Stokes shifts to reported [2,3-b]IQ, to the best of our knowledge, (*c*-)alkyl derivatives (**5al** and **5ao**) show an unprecedented well-resolved vibrational structure and low Stokes compared to previously reported indoloquinoxalines. The highly structured short wavelength emission, with low Stokes shifts, is distinctive of relatively rigid polynuclear aromatic hydrocarbons such as anthracene (at low concentrations to prevent excimer formation).[45]

Additionally, the average molar absorptivities (ε_{max}) of the alkyl-substituted compounds (~9000 L mol^{-1} cm^{-1}) are, generally speaking, higher than those ones of the aryl derivatives (~6000 L mol^{-1} cm^{-1}), which indicates that the probability of the transition between the ground (S_0) and first excited electronic (S_1) state is higher for the alkyl derivatives.

Remarkable differences between the alkyl- and aryl-substituted indolo[1,2-*a*]quinoxalines are also found in the fluorescence quantum yields (φ_f), being on average those of the alkyl-substituted compounds (~0.77), around twice that of the aryl-substituted ones (~0.37), and considerably higher than those reported for [2,3-b]IQ.[41,42b,47] The synthesized alkyl-substituted indolo[1,2-*a*]quinoxalines (**5al** and **5ao**) are quite more efficient fluorophores with higher fluorescence quantum yields.

The molar absorptivities and the fluorescence quantum yields indicate that the indole and quinoxaline fusion and the substituents play a significant role in the studied electronic spectroscopy properties. Additionally, fluorescence decays of the five compounds in cyclohexane and toluene were registered at several wavelengths (emission maxima and shoulders). Mono-exponential decays were obtained for all the cases.[44] Average lifetimes (τ) for each compound in cyclohexane and toluene are listed in Table 6. From the fluorescence quantum yield and lifetimes, the fluorescence (k_f) and non-radiative (k_{nr}) rate constants were calculated (Table 6).[48] Interestingly, for the alkyl-substituted derivatives, $k_f > k_{nr}$ while for the aryl-substituted derivatives $k_f < k_{nr}$. This fact shows the key role of the alkyl substitution of the indolo[1,2-*a*]quinoxalines at the C-6 to improve the efficiency of the radiative deactivation channel while diminishing the efficiency of the non-radiative ones (Table 6).

Being average values considered, k_f of alkyl-substituted indolo[1,2-*a*]quinoxalines are roughly twice those of the aryl-

substituted derivatives (Table 6). However, the k_{nr} of the alkyl derivatives are roughly half the values of the aryl ones (Table 6).

For **5 ac** and **5 bb**, in addition to the internal conversion, which is considered the main non-radiative channel for S_1 deactivation of indolo[2,3-*b*]quinoxaline,[49] the intersystem crossing is expected to contribute to k_{nr},[45] due to the heteroatoms, being particularly efficient for **5 ac** in cyclohexane (Table 6).

The increase in the solvent polarity from cyclohexane to toluene induces a red shift of both the absorption maxima (1–3 nm) and emission maxima (~11 nm for **5 ab, 5 bb** and **5 ac**; ~7 nm for **5 al** and **5 a**), showing that the aryl derivatives are more sensitive to the solvent polarity. As shown in Supporting Information, the Stokes shift of **5 ab** in several solvents follows Lippert-Mataga equation[45] which described a general solvent effect, when no specific chemical interactions between the solvent and fluorophore take place and the fluorophore is considered as a dipole in a continuous medium of uniform dielectric constant.[45] From the slope of the linear plot of the Stokes shift versus orientation polarizability, Δf (which depends on the solvent dielectric constant and refraction index), and assuming a cavity radius of 4 Å, which is comparable to the radius of a typical aromatic fluorophore,[45] the change in dipole momentum upon excitation is around 5 D for **5 ab**.

Aryl substituent allows for a larger charge separation than the alkyl ones upon excitation, leading to compounds with higher polarity. This could explain the fact that the emission quantum yields and lifetimes of the aryl-substituted derivatives are higher in toluene than cyclohexane. Further increases of solvent polarity above that of toluene do not increase the emission quantum yield of **5 ab** (Table S14). The enhancement of φ_f and τ with solvent polarity is higher for the more polar compounds with heteroatoms in their structures [**5 ac** (–OMe) and **5 bb** ($-CF_3$)] (Table 6). On the contrary, for the alkyl derivatives, φ_f and τ are slightly higher in cyclohexane than in toluene.

Conclusion

In summary, we have reported a general, efficient, air- and moisture-tolerant catalytic domino process that allows the synthesis of a wide variety of biologically relevant *N*-polyheterocycles in a single synthetic operation from readily and widely available nitroaromatics by using environmentally friendly glycols as reductants and easily available and non-toxic dioxomolybdenum(VI) complexes as catalysts. As these results demonstrate, not only secondary benzylic diols but also mixed alkyl secondary-tertiary diols could be employed as reductants and carbonyl source, allowing the presence of both aryl and alkyl groups in the final compounds. A wide variety of pyrrolo- and indolo-fused quinoxalines and quinolines, as well as thienoquinolines and phenanthridines has been efficiently accessed in a straightforward manner. It is worth noting that this versatile and practical method allows the reuse of the waste reduction byproduct that is ultimately embodied into the target compounds.

On the other hand, the photophysical properties of indolo[1,2-*a*]quinoxaline can be tuned through the type of substituent at C-6 of the quinoxaline moiety. Alkyl substitution leads to highly fluorescent fluorophores ($\varphi_f > 0.7$) that show absorption and emission spectra with a well-resolved vibrational structure, likely due to hydrogen bonding between quinoxaline nitrogen atom and hydrogen atoms of the substituent, hindering free substituent rotation. On the contrary, aryl substitution gives rise to lower emissive fluorophores (~0.37) with higher sensitivity to solvent polarity owing to a larger charge separation upon excitation.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: dioxomolybdenum · N-heterocycles · nitroaromatics · photophysical properties · reuse of waste

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