EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202400145

Chemistry Europe
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Molybdenum-Catalyzed One-Pot Multi-Step Synthesis of *N*-Polyheterocycles from Nitroarenes and Glycols

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Dedicated to the memory of Prof. Rafael Pedrosa

We report the efficient, sustainable one-pot synthesis of a wide variety of *N*-polyheterocycles, such as imidazo-quinolines and quinoxalines, and furoquinolines, from easily available nitroaromatics and glycols via a molybdenum catalytic domino reduction-imine formation-intramolecular cyclization-oxidation sequence. It is worth highlighting that the recycling and incorporation of the waste carbonyl byproduct, generated in the reduction step, into the final compound is realized. In addition, the overall efficiency and atom economy of the process are further improved owing to the participation of one reaction intermediate as reductant that allows lowering the amount of external reducing agent employed.

Introduction

Nitroaromatic compounds are readily available nitrogen sources,[1] easily accessible and less expensive than their corresponding anilines. However, the latter are, in fact, usually employed as starting materials for accessing more elaborated *N*-containing compounds.[2] Therefore, directly using nitro compounds to access such value-added nitrogenated derivatives in one-pot tandem reactions, avoiding their prior reduction, is becoming a powerful and attractive tool in synthesis.[3]

On the other hand, waste prevention is considered to be the primary one of the Twelve Principles of Green Chemistry.[4] Hence, the design of synthetic methods that combine multistep syntheses into one-pot processes represents a relevant strategy that reduces waste generation, maximizing synthetic efficiency and reducing yield losses associated to intermediate purification processes. Although this one-pot approach has been widely used in synthetic organic chemistry for a long time, a dramatic increase in one-pot syntheses has occurred over the past decades.[5] In this context, the development of sustainable strategies capable of internal reuse of the waste generated in the initial step of a reaction sequence as a catalyst or co-catalyst for the following step is an interesting topic in synthetic chemistry. Shibasaki and co-workers reported a pioneering work where the phosphine oxide byproduct of the Wittig reaction was used to promote a catalytic asymmetric epoxidation.[6] Inspired by this work, several one-pot sequences where the waste generated in a previous step can be recycled as a promoter or catalyst for the downstream reaction have been developed.[7] Nevertheless, one-pot reactions can be further improved by the use of the generated waste byproduct not only as promoter or catalyst but as reagent or reactant in subsequent transformations. To the best of our knowledge, Zhou *et al* reported the first example in which a waste salt byproduct was recycled as reagent for the next step.[8] Similarly, other authors have described several processes in which the byproduct participates as a reagent in a subsequent step.[9] However, until our preliminary report,[10] no examples had been reported about the reuse of a byproduct as reactant being embodied into the final compound.[11]

By its part, *N*-heterocycles are privileged motifs extensively present in both natural products and biologically active synthetic compounds. In particular, aza-fused quinolines and quinoxalines, such as pyridoimidazoquinolines, benzothiazoleimidazoquinolines, benzoimidazoquinoxalines, triazoquinoxalines, and furoquinolines, are important natural molecular scaffolds that appear in different biologically active compounds (Figure 1).[12] On account of the great importance and usefulness of these heterocycles, their synthesis has received much attention. As already stated, the traditional methods for their construction rely on anilines as starting materials, which are usually prepared by reducing the corresponding nitroarenes. In this context, and following our interest in the development of new clean and efficient one-pot synthetic methodologies catalyzed by nontoxic, easily available and affordable dioxomolybdenum(VI) complexes,[13] we reported the Mo-catalyzed chemoselective reduction of nitroaromatic compounds to anilines with pinacol, that only generates acetone and water as byproducts.[14] In a further development of this reaction, it was

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202400145

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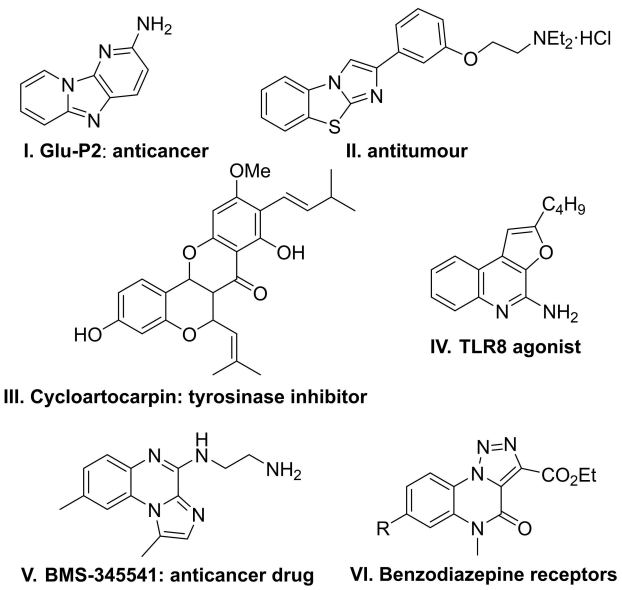
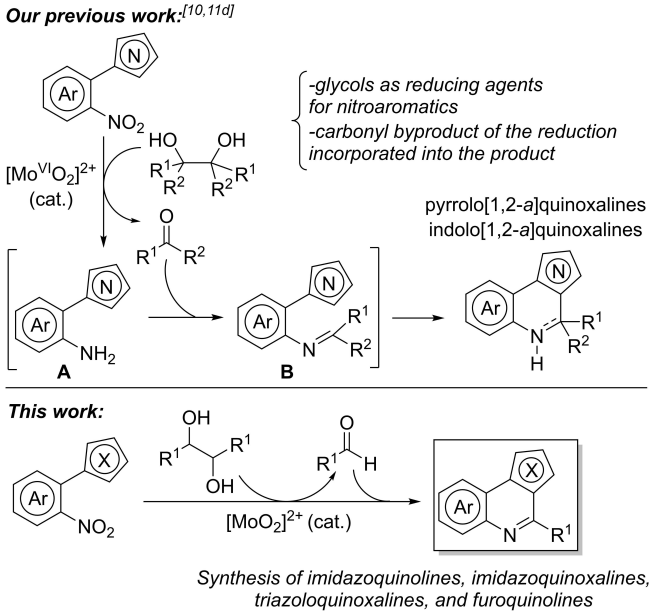


Figure 1. *N*-polyheterocycles compounds with biological activity.

demonstrated that also different glycols could be used as reductants leading to subsequent *in situ* imine **B** formation, by condensation of the resulting aniline **A** with the generated carbonyl byproduct, which could eventually evolve through an intramolecular cyclization with an appropriate *ortho*-substituent of the nitroarene yielding different nitrogenated polyheterocycles like pyrrolo and indolo[1,2-*a*]quinoxalines (Scheme 1).[10,11d] In view of the potential of this strategy, herein we aim to expand its applicability for the synthesis of other *N*-polyheterocycles such as imidazoquinolines and quinoxalines, triazoloquinoxalines and furoquinolines, from easily accessible



Scheme 1. Our previous work on Mo-catalyzed synthesis of pyrrolo and indoloquinoxalines, and proposed synthesis of diverse *N*-polyheterocycles (this work).

ortho-functionalized nitroarenes and glycols under Mo-catalysis via a domino reaction consisting of a nitro reduction-imine generation-annulation-oxidation, where the reduction byproduct of the first step is embodied into the final structure (Scheme 1).[15]

Results and Discussion

Synthesis of Imidazo[4,5-c]quinolines 3-6

Imidazo[4,5-*c*]quinolines are structural motifs that can be found in numerous biologically active compounds and are considered privileged substructures for drug design and material science.[16] Therefore, several methods have been developed for their synthesis, mostly based on the reduction of the nitro group of the adequate substrate to the corresponding aniline and a subsequent Pictet-Spengler cyclization, via an imine intermediate and usually catalyzed by acid. Several modifications of this process have been developed by changing the acid additive employed to promote the intramolecular cyclization, such as cyanuric chloride in water,[17] *p*-TsOH[18] or I_2-DMSO.[19] Trying to improve synthetic efficiency, Chanda *et al* developed a three step one-pot procedure based on a Pictet-Spengler variant, avoiding amine isolation, catalyzed by TFA and under microwave heating.[20] Another approximation consists in the reaction of the corresponding bromide with an aldehyde and an external nitrogen source under copper-catalysis.[21] In addition, the reaction of anilines with benzylamines[22] or 2-methyl azaarenes[23] catalyzed by molecular iodine also led to the formation of imidazo[4,5-*c*]quinolines. At this point, we envisaged that the reduction of nitroaromatic compounds **1a**,**b** with different glycols **2** under Mo-catalysis and subsequent cyclization of the intermediate imine could afford the corresponding imidazo[4,5-*c*]quinolines **3** and **5**, which incorporate the waste carbonyl byproduct of the first step into their structures.

With this goal in mind, and based on the conditions we had previously reported for the synthesis of pyrrolo and indoloquinoxalines,[10,11d] we found that the treatment of nitroarene **1a** with glycol **2a** (2.2 equiv) in the presence of *p*-TsOH (0.5 equiv), a catalytic amount of dioxomolybdenum(VI) complex ($MoO_2Cl_2(dmf)_2$) and *N*,*N*-dimethylacetamide (DMA) as solvent, under microwave heating led to the formation of pyridoimidazoquinoline **3a** (see Table S1), isolated in 70% yield (Table 1, entry 1). Next, a variety of functionalized glycols **2** were evaluated. Firstly, aromatic glycols (entries 1 and 2), with both electron-withdrawing (entries 3-6) and electron-donating groups (entry 7), were reacted with nitroarene **1a** obtaining imidazoquinolines **3a**–**g** in good to high yields. Glycols bearing a heteroaromatic substituent were tested leading to the corresponding quinolines **3h**,**i** with good yields (entries 8 and 9). Finally, alkyl groups could also be introduced as R^1 substituents, by using mixed secondary-tertiary diols as reducing agents, accessing products **3j**,**k** in moderate to good yields (entries 10 and 11). Surprisingly, when a mixed benzylic alkyl disecondary diol was employed, such as 1-(*p*-tolyl)butane-1,2-diol (**2l**), a moderate yield of **3a** was obtained, without competitive

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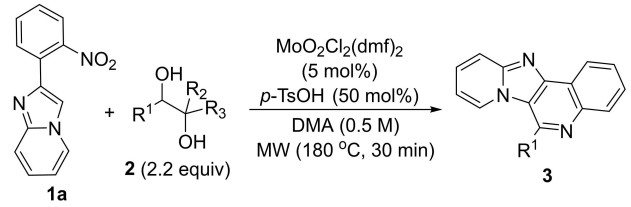
Table 1. Synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*c*]quinolines **3**.[a]



1a + **2** (2.2 equiv) → **3**

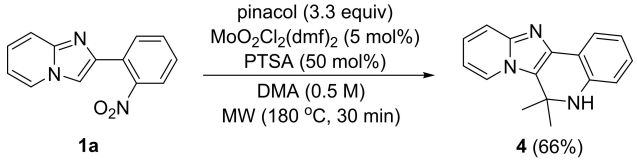
Entry	**2**	R^1	R^2	R^3	Product	Yield (%)[b]
1	**2a**	*p*-Tol	*p*-Tol	H	**3a**	70
2	**2b**	Ph	Ph	H	**3b**	63
3	**2c**	4-BrC_6H_4	4-BrC_6H_4	H	**3c**	55
4	**2d**	4-ClC_6H_4	4-ClC_6H_4	H	**3d**	72
5	**2e**	4-FC_6H_4	4-FC_6H_4	H	**3e**	64
6	**2f**	2-ClC_6H_4	2-ClC_6H_4	H	**3f**	68
7	**2g**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	**3g**	71
8	**2h**	2-furyl	2-furyl	H	**3h**	50
9	**2i**	2-thienyl	2-thienyl	H	**3i**	71
10	**2j**	*n*-Bu	Me	Me	**3j**	66
11	**2k**	CH_2Ph	Me	Me	**3k**	40
12	**2l**	*p*-Tol	Et	H	**3a**	40
13[c]	**2a**	*p*-Tol	*p*-Tol	H	**3a**	57

[a] Reaction conditions: nitroarene **1a** (0.5 mmol), glycol **2** (1.1 mmol) and *p*-TsOH (0.25 mmol) in DMA (0.5 M) under microwave irradiation (180 °C, 30 min). [b] Isolated yield based on starting nitroaromatic **1a**. [c] Carried out under conventional heating at 180 °C for 5 h.

incorporation of the co-generated propanal (entry 12). Remarkably, the reaction could also be performed under conventional heating with slightly lower yield, although a longer reaction time was required (entry 13).

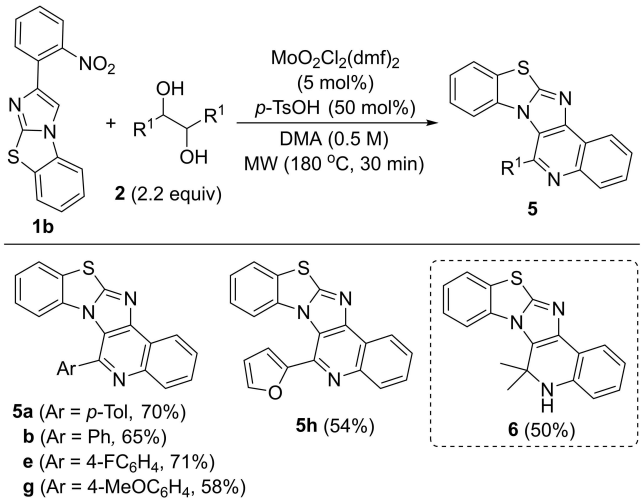
Moreover, di-tertiary glycols, such as pinacol (**2m**), also participated in this tandem reaction under the same conditions. In this case, dihydropyrido[2′,1′:2,3]imidazo[4,5-*c*]quinoline **4** was obtained due to the generation of acetone as byproduct in the initial reduction step (Scheme 2).

In an analogous way, the reaction of nitroarene **1b** with a selection of secondary glycols **2a,b,e,g,h** enables facile access to related benzothiazoloimidazoquinolines **5**, which were isolated in good yields (Scheme 3). Disappointingly, in this case, the employment of alkyl glycols **2j,k** led to decomposition. However, reaction using pinacol (**2m**) as reductant successfully afforded the corresponding dihydrobenzo[4′,5′]thiazolo[2′,3′:2,3]imidazo[4,5-*c*]quinoline **6**.



1a → **4** (66%)

Scheme 2. Synthesis of dihydropyrido[1′,2′:2,3]imidazo[4,5-*c*]quinoline **4** from **1a** and pinacol.



1b + **2** (2.2 equiv) → **5**

5a (Ar = *p*-Tol, 70%)
b (Ar = Ph, 65%)
e (Ar = 4-FC_6H_4, 71%)
g (Ar = 4-$MeOC_6H_4$, 58%)

5h (54%)

6 (50%)

Scheme 3. Synthesis of benzo[4′,5′]thiazolo[2′,3′:2,3]imidazo[4,5-*c*]quinolines **5** and **6**.

Synthesis of Benzo[4,5]imidazo[1,2-a]quinoxalines 7

The quinoxaline core is a structural motif that appears in different molecules with biological and pharmaceutical properties. Their derivatives also have important applications in materials science, such as fluorescence or photovoltaics.[24] Although different synthetic methods have been described to access fused quinoxalines, the synthesis of benzo[4,5]imidazo[1,2-*a*]quinoxalines is still underexplored, and only a few protocols have been reported. Ma *et al* communicated a new method for their synthesis from *N*-tosyl-2-haloanilines and 2-(chloromethyl)-1*H*-benzo[*d*]quinoxalines catalyzed by copper.[25] In 2020, Chang *et al* developed a new route that gives access to this quinoxaline framework via an iodine-mediated sp^3 C–H amination of 2-(benzimidazole-1-yl)anilines.[26] Based on our previous results, we suggested 1-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole **1c** as plausible starting material for the obtention of this valuable *N*-polyheterocycle. Its treatment with glycol **2a**, under identical conditions as above, afforded expected quinoxaline **7a** as the minor product (10% yield), being the corresponding imine derivative **B** the major one. After a brief optimization of the reaction conditions (see Table S2), benzo[4,5]imidazo[1,2-*a*]quinoxaline **7a** was obtained in good yield when **1c** was treated with glycol **2a** and excess of *p*-TsOH (1.5 equiv) under microwave heating at 200 °C for 30 minutes (Scheme 4). With these optimized conditions in hand, a selection of benzoimidazoquinoxalines **7a–c,e,f** were synthesized with moderate yields using different glycols **2**. Notably, the synthesis of **7f** represents an example of the successful use of a glycol possessing a substituent at the *ortho* position of the aryl group (**2f**) as reductant, showing the tolerance of this methodology to the presence of halide groups at this synthetically useful position. The lower yields obtained in these cases could be due to the harsher conditions required.

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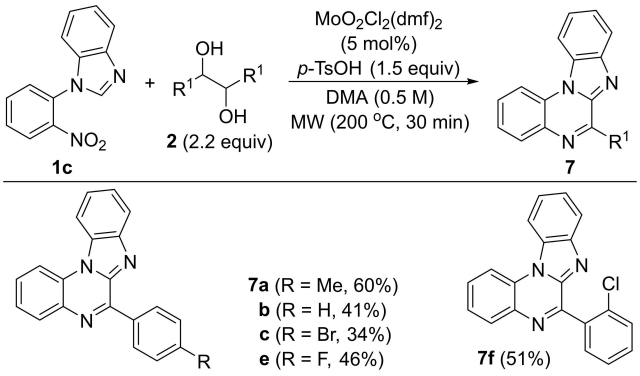


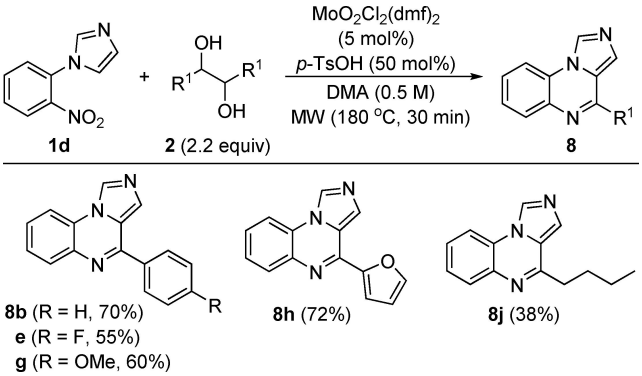
Scheme 4. Synthesis of benzo[4,5]imidazo[1,2-*a*]quinoxalines **7**.

Synthesis of Imidazo[1,5-a]quinoxalines 8

Imidazoquinoxalines are important heterocyclic skeletons that appear in numerous compounds with biological activity like anti-cancer or anti-HIV agents.[27] Therefore, developing new methodologies to prepare these heterocyclic molecules is an interesting goal in synthesis. Most of the approaches for the preparation of imidazoquinoxalines consist in the modified Pictet-Spengler reaction between 2-imidazolilarilamines and an aldehyde catalyzed by acids such as *p*-TsOH,[28] or Wang-OSO_3H resin.[29] In this field, Akula *et al* reported a one-pot, two-step synthesis of quinoxalines from nitrocompounds employing *D*-glucose as reductant and subsequent condensation of the amine catalyzed by acetic acid.[30] In addition, Hulme *et al* have developed a multicomponent reaction for the synthesis of imidazo[1,5-*a*]quinoxalines from aryldiamines and 1,2-ketoaldehydes.[31]

Continuing with our interest in developing a general method for accessing different *N*-heterocycles from nitroarenes by a Mo-catalyzed one-pot multi-step reaction, 1-(2-nitrophenyl)-1H-imidazole (**1 d**) was treated with diol **2 b** in the presence of *p*-TsOH (50 mol%) under microwave irradiation at 180 °C for 30 minutes (see Table S3). In this way, phenylimidazo[1,5-*a*]quinoxaline **8 b** was isolated in good yield (Scheme 5).

Next, other aromatic glycols were evaluated, and the corresponding quinoxalines **8 e,g** were obtained with good yields (Scheme 5). Furthermore, heteroaromatic glycol **2 h** also led to the corresponding quinoxaline derivative **8 h** with a good yield. Finally, imidazoquinoxaline **8 j** was isolated with moderate yield when mixed secondary-tertiary diol **2 j** was employed as reductant (Scheme 5).



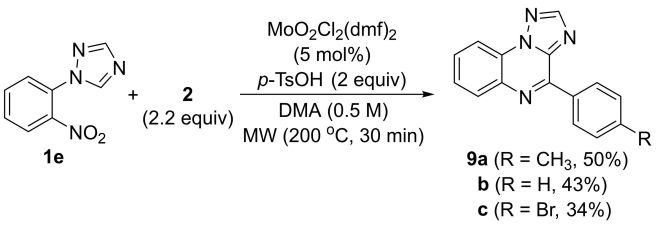
Scheme 5. Synthesis of imidazo[1,5-*a*]quinoxalines **8**.

Synthesis of Triazolo[1,5-a]quinoxalines 9

Triazoloquinoxalines are important structural moieties, which could be found in numerous molecules with physiological and biological activity such as antiviral, anticancer, antibacterial, benzodiazepine or adenosine receptors.[32] Despite their importance in pharmaceutical science, few methods have been developed for their synthesis and, remarkably, the Pictet-Spengler reaction has not been applied to this heterocyclic system. Methodologies developed to access triazoloquinoxalines involve the rearrangement of benzyl bromide with *N*-(benzotriazole-1-yl)arylimidoyl chlorides in the presence of *t*-BuOK,[33] or the tandem Cu-catalyzed azide-alkyne cycloaddition and Ullmann-type coupling of *N*-propargyl-*N*-(2-iodoaryl)amides.[34] Therefore, we hypothesized that our strategy could also provide a synthetic route to this heterocyclic core (Scheme 6). Thus, 1-(2-nitrophenyl)-1*H*-1,2,4-triazole (**1 e**) was subjected to our methodology by treating it with glycol **2 a**, *p*-TsOH (50 mol%) at 180 °C for 30 minutes to furnish the quinoxaline **9 a** in 15% yield. After a brief study of the reaction conditions (Table S4), a small selection of triazolo[1,5-*a*]quinoxalines **9 a**–**c** could be obtained, although with moderate yields, when treating nitroarene **1 e** with glycols **2**, *p*-TsOH (2 equiv) at 200 °C for 30 minutes.

Synthesis of chromeno[3,2-c]quinolin-7-one 10 a

Chromones are important structural units embedded in organic molecules with diverse medicinal properties as antimicrobial, antitumor and anti-inflammatory activity.[35] Currently, chromone-fused heterocycles have garnered a lot of attention. However, there are scarce reports on the synthesis of these molecules. To the best of our knowledge, the only reported example for the synthesis of chromeno[3,2-*c*]quinolin-7-ones is based on an iron(III)-catalyzed Pictet-Spengler reaction of the suitable amine, which had been previously obtained by reduction from the corresponding nitroarene.[36] Hence, we envisaged that the treatment of nitro derivative **1 f** with glycol **2 a**, under Mo(VI)-catalysis would deliver 6-(*p*-tolyl)-7*H*-



Scheme 6. Synthesis of triazolo[1,5-*a*]quinoxalines **9**.

chromeno[3,2-*c*]quinoline-7-one (**10a**). Under standard conditions [*p*-TsOH (50 mol%), 180 °C, 30 min], the intermediate imine derivative was generated as the major product. However, gratifyingly after a brief optimization (Table S5), **10a** was isolated with moderate yield using excess of acid and a higher reaction temperature, further demonstrating the usefulness of this protocol (Scheme 7).

Synthesis of Furo[3,2-c]quinolines 11

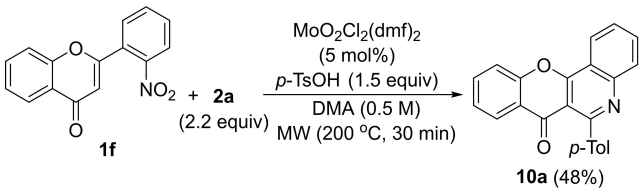
Annulated furoquinolines are important structural building blocks of more complex molecules due to their myriad biological properties. Particularly, these substructures have been shown to possess potential as antimalarial, antibacterial, and anticancer agents,[37] which encouraged the synthesis of related structures. In this field, Usui *et al* prepared furo[3,2-*c*]quinolines from 3-(2-nitrophenyl)5-methyl-2-furoate.[38] Moreover, Zhu *et al* reported the synthesis of furoquinolines by a three multicomponent approach of *o*-alkynylanilines, α-isocyanoacetamides and aldehydes.[39] Yang described a furoquinoline synthesis based on the cross-coupling of 2-formyl-3-furanboronic acid and haloarenes catalyzed by Pd(0).[40] In 2016, Bhattacharya reported the synthesis of furo[3,2-*c*]quinolines via the Pictet-Spengler reaction of the *o*-(3-furyl)anilines, which were obtained from the corresponding nitro derivatives, and an aldehyde catalyzed by $FeCl_3$.[41] Moreover, Maji developed a new route for accessing furoquinolines from the corresponding 2-(furan-3-yl)aniline with arylamines.[12d] However, most of these methods suffer from certain drawbacks, including multi-step processes and tedious procedures.

In our case, treatment of the corresponding furyl nitroarene derivative **1g** with a variety of glycols **2** gave rise to the expected furoquinolines **11** (Scheme 8). A variety of diols **2** bearing simple aryl groups (**2b**), as well as halide-functionalized aryl groups (**2e**) or heteroaromatic ones (**2i**), led to the corresponding furoquinolines **11** with moderate to good yields. In addition, a mixed alkyl secondary-tertiary glycol was also tested providing the corresponding furoquinoline **11j** in good yield. Moreover, when pinacol (**2m**) was used as reducing agent the corresponding desired dihidrofuroquinoline **12** could be isolated in moderate yield (Scheme 8).

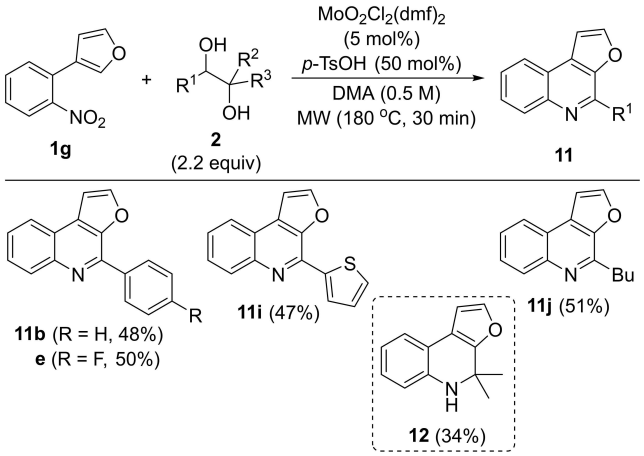
Proposed Mechanism for the Multi-Step Reaction

Herein, we propose a possible mechanism for the reaction based on our previous knowledge (Scheme 9). First, the molybdenum(VI) catalyst promotes the oxidative cleavage of the glycol **2**, giving rise to the corresponding carbonyl compounds.[42]

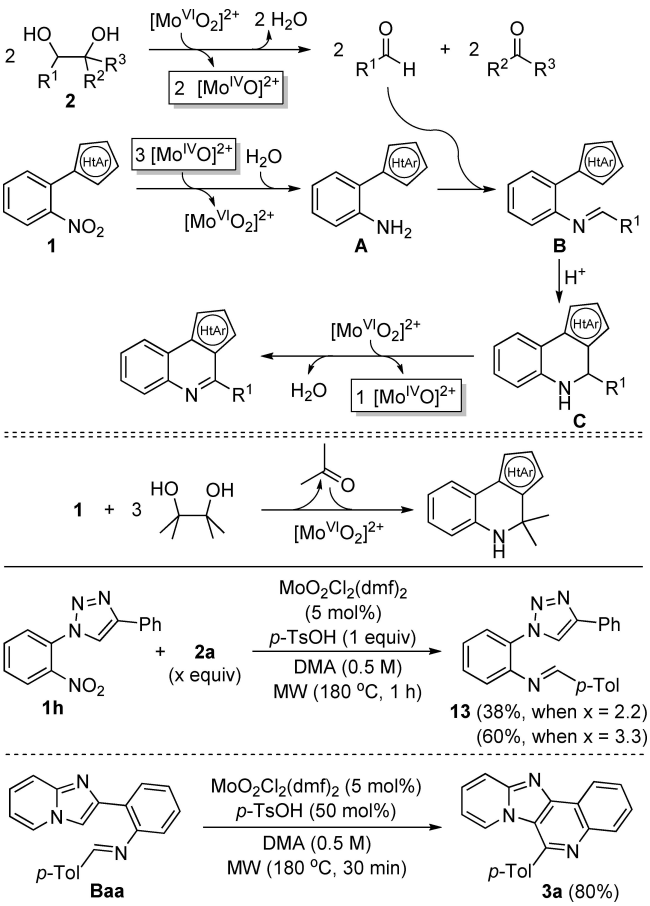
As a result, a molybdenum(IV) species is formed, paired with water release. Reduction of nitroarene **1** by this molybdenum(IV) complex, through sequential oxygen-transfer



Scheme 7. Synthesis of chromeno[3,2-*c*]quinoline-7-one **10a**.



Scheme 8. Synthesis of furo[3,2-*c*]quinoline derivatives **11** and **12**.



Scheme 9. Mechanistic proposal.

processes, regenerates the catalyst and delivers the corresponding 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 acid-promoted cyclization would then result in the formation of the corresponding dihydro-*N*-polyheterocycle **C**. Eventually, the final step involves the molybdenum(VI)-catalyzed oxidation of this dihydro derivative to the final aromatic heterocyclic compound. At this point, it is worth noting that the complete reduction of the nitroaromatic starting material requires three pairs of electrons, whereas only two equivalents of the reducing agent (glycol) are employed. The explanation lies in the fact that the dihydro derivative **C** provides the additional pair of electrons required for the complete reduction of nitroarene **1**. This hypothesis was supported by the fact that when pinacol (a di-tertiary glycol) is used as reductant, three equivalents are needed for the complete reduction of the nitroaromatic to the corresponding aniline as no final dehydroaromatization step can take place. In addition, when nitroaromatic **1h** was reacted with glycol **2a** and *p*-TsOH under molybdenum catalysis, imine **13** was isolated from the crude reaction in moderate yield, which could be improved as expected by using 3 equiv. of reductant. Moreover, the evolution of imine **Baa**, independently synthesized by condensation of the corresponding amine **Aa** with *p*-tolualdehyde, under the standard reaction conditions also led to high yield of **3a**. These facts also support the mechanistic proposal where the final polyheterocycle is formed via cyclization of the corresponding imine intermediate **B**.[43]

Conclusions

In summary, we have reported a general, efficient, and air-tolerant catalytic domino process that involves nitro reduction, imine generation, annulation with heterocycle formation, and final oxidation that allows the synthesis of a wide variety of relevant *N*-polyheterocycles in a one-pot process from easily available *o*-functionalized nitroaromatics by using a dioxomolybdenum(VI)-complex as catalyst and different glycols as reducing agents. A wide variety of imidazoquinolines and quinoxalines, triazoloquinoxalines, as well as furoquinolines have been efficiently and straightforwardly accessed. Remarkably, the reuse of the initial reduction byproduct that is ultimately embodied into the final compound, as well as the lowered amount of the stoichiometric reductant by the participation of the intermediate dihydroheterocycles as reducing agents enhance the overall atom economy of the process.

Experimental Section

General procedure for the synthesis of *N*-polyhterocylces. In a 10 mL microwave tube, nitroaromatic compound **1** (0.5 mmol), glycol **2** (1.1 mmol for **2a-k**, 1.65 mmol for **2l**), *p*-TsOH (0.5–1.5 equiv), and $MoO_2Cl_2(dmf)_2$ (8.6 mg, 0.025 mmol) were dissolved in DMA (1 mL), and the tube was sealed with a septum. The reaction mixture was stirred at the temperature established for each substrate for 30 minutes under microwave irradiation (120 W). After completion of the reaction, monitored by GC-MS, the residue was purified by flash column chromatography using silica gel and mixtures of hexane/EtOAc as eluent to afford the corresponding *N*-polyheterocycles **3**–**12**.

Supporting Information

Full experimental procedures, characterization data, and copies of NMR spectra are included. The authors have cited additional references within the Supporting Information.[44–51]

Acknowledgements

We gratefully acknowledge Ministerio de Ciencia e Innovación (PID2020-115789GB–C21/AEI/10.13039/501100011033), and Junta de Castilla y León and FEDER (BU028P23) for financial support. S.G.-G. thanks Ministerio de Educación for a FPU predoctoral contract. S.S.-P. thanks a Ramón y Cajal (RYC2021-031533-I) contract funded by MCIN/AEI/10.13039/501100011033 and European Union "NextGenerationEU"/PRTR.

Conflict of Interests

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: catalysis · dioxomolybdenum · nitroaromatics · *N*-polyheterocycles · reuse of waste

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Manuscript received: February 5, 2024
Revised manuscript received: March 14, 2024
Accepted manuscript online: March 15, 2024
Version of record online: April 17, 2024