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Mo-Catalyzed Synthesis of *N*-Polyheterocycles From Functionalized Nitroarenes and Aldehydes

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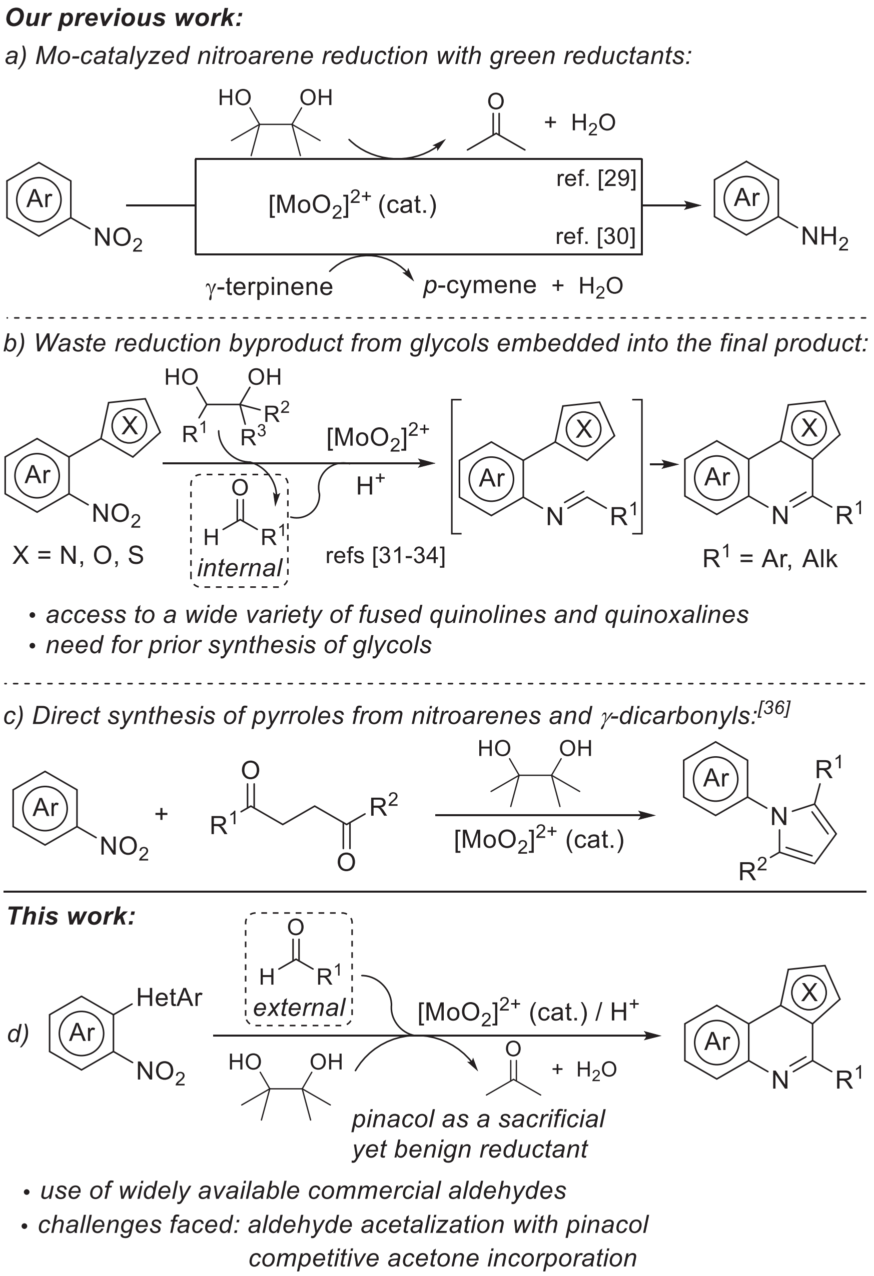
ABSTRACT

The direct preparation of nitrogen-containing polyaromatic heterocycles in a single operational step from readily available nitroarenes represents an attractive and sustainable alternative to traditional multistep approaches. In this context, this work describes an efficient and versatile methodology for the synthesis of fused *N*-polyheterocyclic scaffolds from functionalized nitroarenes and aldehydes catalyzed by dioxomolybdenum(VI) complexes and employing pinacol as a readily available and environmentally benign reductant. The protocol integrates nitro reduction, imine formation, and intramolecular cyclization in a single operational sequence. Careful fine-tuning of the reaction conditions proved crucial to minimizing competing pathways. This molybdenum-catalyzed strategy exhibits broad substrate scope, accommodating aromatic, aliphatic, and *α*,*β*-unsaturated aldehydes, and enabling access to a variety of pharmaceutically relevant frameworks, such as pyrrolo[1,2-*a*]quinoxalines, indoloquinoxalines, *γ*-carbolines, imidazoquinolines, and phenanthridines.

1 | Introduction

Nitrogen-containing heterocycles are highly relevant compounds due to their widespread occurrence in biologically active compounds, drugs, and functional materials. Therefore, the development of efficient, selective, and sustainable methods for the construction of *N*-heterocyclic frameworks remains a major objective in contemporary synthetic chemistry [1–3]. In this field, aza-fused polyheterocyclic frameworks based on quinoxalines and quinolines are key cores in a wide range of compounds possessing relevant biological and pharmaceutical activities [4, 5]. In most cases, these and other *N*-heteroaromatic polycycles are accessed from anilines, which are typically obtained by reduction of nitroarenes using hydrogen or metal-based reductants, strategies that suffer from safety concerns or poor atom economy, generating significant waste [6–8]. In this regard, nitroaromatics represent particularly attractive starting materials that are readily available, easy to handle and display excellent chemical stability, making them ideal building blocks for the synthesis of *N*-containing fine chemicals [9–12]. However, their direct use as nitrogen sources has long been limited by the need for discrete reduction steps prior to C—N bond formation, and so, bypassing the discrete reduction to anilines opens new opportunities for step-economical processes in which the nitro group participates directly in C—N bond formation reactions [13–16]. During the last years, considerable efforts have been made to enable the direct transformation of nitroarenes into *N*-heterocycles through catalytic strategies overcoming the limitation of a prior reduction step [17–19]. In particular, notable advances have been achieved by the successful conversion of *ortho*-functionalized nitroarenes into various *N*-heterocyclic compounds [20–27].

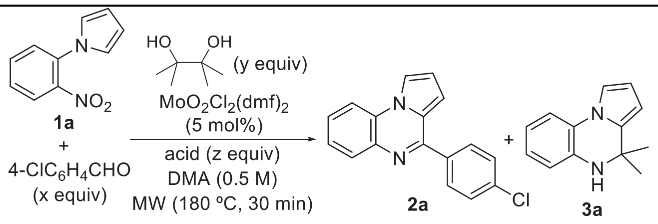
In this area, our group has pioneered the direct exploitation of nitroaromatics, as precursors of value-added *N*-containing compounds, using nontoxic, easily available dioxomolybdenum(VI) complexes as catalysts [28]. We have developed the chemose-



SCHEME 1 | Our previous work on Mo-catalyzed nitroarene reductions and their application to the synthesis of *N*-polyheterocycles from nitroaromatics and glycols. Proposed alternative with pinacol as reductant and external aldehydes.

lective reduction of nitro(hetero)arenes to anilines with pinacol [29] or γ-terpinene [30] as green reducing agents that only generate acetone and water, or *p*-cymene and water as byproducts (Scheme 1a). Subsequently, we demonstrated that different glycols could also behave as reductants in this Mo-catalyzed reduction of nitroarenes, leading to the in situ formation of an imine intermediate by condensation of the resulting aniline with the generated carbonyl byproduct [31], which undergoes annulation with an appropriate *ortho*-substituent of the nitroarene, yielding a variety of *N*-polyheterocycles [32] such as pyrrolo and indoloquinoxalines, thieno and furoquinolines, pyrrolo and indoloquinolines, (benzo)imidazoquinoxalines [33], and substituted quinolines [34]. Interestingly, in these transformations the reduction byproduct is used as a reagent for the subsequent imine generation and is incorporated into the final compound (Scheme 1b) [35]. However, this strategy requires the use of different glycols including symmetric secondary ones, for the introduction of aromatic groups, and mixed secondary–tertiary ones, for the incorporation of alkyl groups, which in several cases have to be previously synthesized. At this point, and considering our reported direct access to pyrroles from nitroarenes and γ-dicarbonyls with glycols as reductants (Scheme 1c) [36], we envisaged that the combination of the Mo-catalyzed reduction of functionalized nitroarenes with pinacol and the subsequent in situ condensation of the resulting aniline with an external aldehyde followed by further Pictet–Spengler cyclization, could lead to a variety of *N*-polyheterocycles (Scheme 1d). Compared with our previous method involving the recycling of the waste reduction byproduct (Scheme 1b), this approach would be susceptible to being employed with a wide variety of carbonyl

TABLE 1 | Optimization of the conditions for the Mo-catalyzed synthesis of **2a**.[a]



Entries	*x*	*y*	Acid	*z*	Conversion (%)[b]	Yield [2a][b]	Yield [3a][b]
1	1	2.2	*p*-TsOH	1	70	54	10
2	1	3	*p*-TsOH	1	90	61	18
3	1	3.5	*p*-TsOH	1	100	67	21
4	1	4	*p*-TsOH	1	100	69	22
5	1.5	3.5	*p*-TsOH	1	100	69	20
6	2	3.5	*p*-TsOH	1	100	77	10
7	2.5	3.5	*p*-TsOH	1	100	76	10
8	2	3.5	*p*-TsOH	—	100	57	28
9	2	3.5	*p*-TsOH	0.5	100	68	11
10	2	3.5	*p*-TsOH	2	100	78	12
11[c]	2	3.5	DNBSA	1	100	35	32
12[d]	2	3.5	CSA	1	100	73	21
13	2	3.5	$BF_3 \cdot OEt_2$	1	100	52	—
14	2	3.5	$Sc(OTf)_3$	1	100	69	26
15	2	3.5	$Bi(OTf)_3$	1	100	27	19
16	2	3.5	$Fe(OTf)_3$	1	100	66	11
17[e]	2.5	3.5	*p*-TsOH	1	100	67	19
18[f]	1	5	*p*-TsOH	1	40	18	—

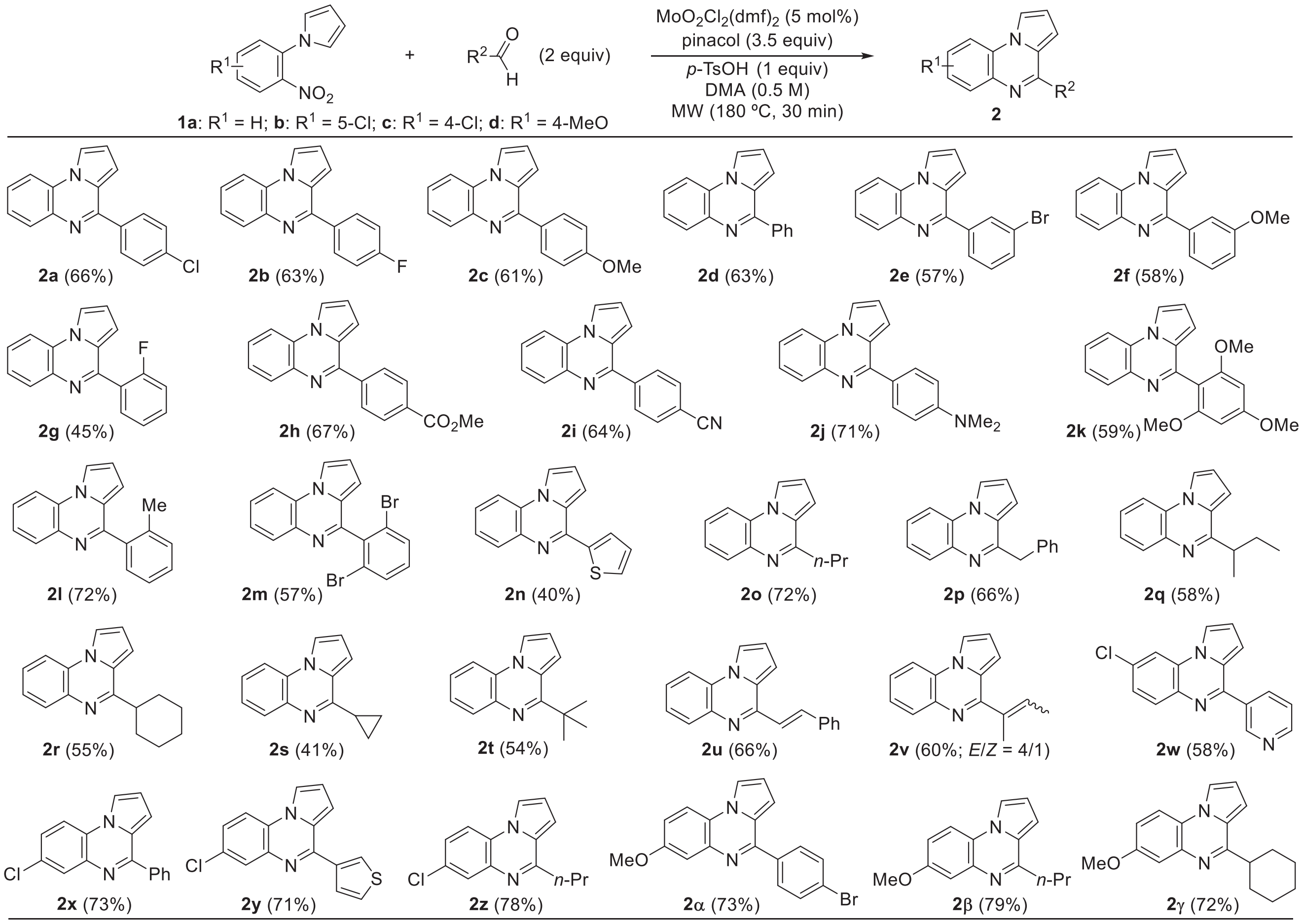
[a] Reaction conditions: **1a** (0.5 mmol) in DMA (1 mL), $MoO_2Cl_2(dmf)_2$ (5 mol%).
[b] Yield calculated by ^{1}H-NMR using CH_2Br_2 as internal standard.
[c] DNBSA = 2,4-dinitrobenzenesulfonic acid.
[d] CSA = 10-camphorsulfonic acid.
[e] Carried out at 180°C for 3 h in DMA (0.5 M) under conventional heating.
[f] γ-Terpinene (5 equiv) were used as reductant.

compounds. In this study, we report the direct synthesis of a selection of *N*-polyheterocycles from functionalized nitroarenes and aldehydes, which further underscores the usefulness of dioxomolybdenum(VI) catalysis in the direct transformation of nitroaromatics to value-added nitrogenated compounds.

2 | Results and Discussion

It should be noted that our proposal presents some challenges that must be addressed to ensure its successful implementation. These include the potential competitive acetalization of the aldehyde with pinacol, which could consume both the reductant and the carbonyl component; a possible aldol reaction between acetone (the byproduct of the reduction) and the aldehyde; as well as the competitive participation of acetone as the carbonyl partner, leading to the formation of a dimethylated dihydroheterocyclic derivative. To evaluate the feasibility of this approach, a model reaction between commercially available (or readily accessible) nitrophenylpyrrole **1a** and 4-chlorobenzaldehyde was selected, employing pinacol as the reducing agent under dioxomolybdenum(VI)-catalysis (Table 1). Based on our previous results on Mo-catalyzed synthesis of *N*-polyheterocycles using glycols as reductants [31–34], reactions were conducted in DMA, under microwave irradiation (180°C, 30 min), using $MoO_2Cl_2(dmf)_2$ as a readily available dioxomolybdenum(VI) catalyst and *p*-toluenesulfonic acid (*p*-TsOH) as a Brønsted acid additive to promote cyclization onto the intermediate imine.

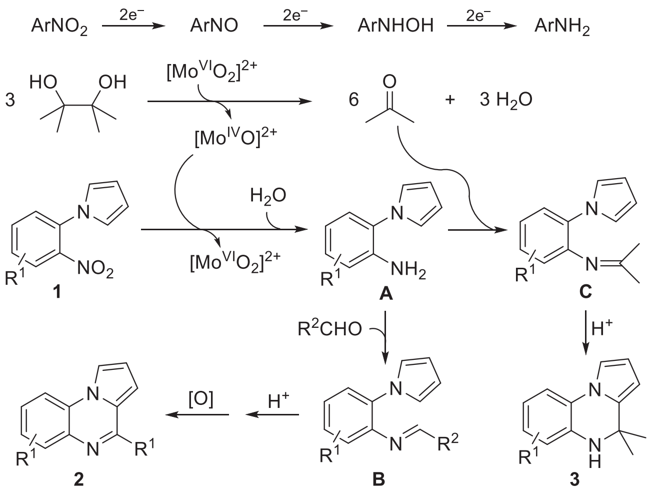
We first investigated the effect of the amount of pinacol using a stoichiometric quantity of the aldehyde (entries 1–4). Although 2 equiv of glycol should, in principle, be sufficient for complete reduction since the additional electron pair would arise from the final oxidation of the intermediate dihydroheterocycle, incomplete conversion was observed (entry 1). Even with 3 equiv of pinacol, a small amount of **1a** remained (entry 2). Increasing the reductant loading to 3.5 equiv led to complete conversion of the starting nitroarene (entry 3). However, in all these exper-



SCHEME 2 | Direct synthesis of pyrrolo[1,2-*a*]quinoxalines **2** from 1-(2-nitroaryl)pyrroles **1** and aldehydes.

iments, significant amounts of dimethyldihydroheterocycle **3a** were detected, thereby decreasing the yield of the desired product **2a**. This outcome is likely attributable to competitive aldehyde consumption via pinacol acetal formation and to the involvement of acetone in imine formation. Further increasing the amount of pinacol to 4 equiv did not improve the outcome (entry 4). Having established 3.5 equiv of pinacol as optimal, we next examined the influence of the aldehyde loading to minimize the competitive formation of **3a** (entries 5–7). Gratifyingly, the use of 2 equiv of aldehyde improved the yield of **2a**, reducing the formation of **3a** to approximately 10% (entry 6). The role of the acid additive was also confirmed, as decreasing the amount of *p*-TsOH resulted in lower yields of **2a** (entries 8 and 9), whereas the use of an excess (2 equiv) provided results comparable to those obtained with a stoichiometric amount (entry 10 vs 6). Other sulfonic acids did not improve the outcome of the process (entries 11 and 12), nor did the use of various Lewis acids as alternative to the Brønsted acid (entries 13–16). Notably, the reaction could also be conducted under conventional heating rather than microwave irradiation; however, longer reaction times were required, and the yield was diminished, with a higher proportion of **3a** formed (entry 17 vs 6). Finally, the use of *γ*-terpinene as an alternative reductant [30] proved ineffective for this transformation under these conditions (entry 18).

With the optimized reaction conditions established (Table 1, entry 6), the scope of the synthesis of pyrrolo[1,2-*a*]quinoxalines **2** was then explored using functionalized 1-(2-nitrophenyl)pyrroles **1a–d** and a variety of aldehydes (Scheme 2). It is worthy to note that this class of aza-fused quinoxalines is typically prepared via Pictet–Spengler-type reactions from 2-(1*H*-pyrrol-1-yl)anilines, with only limited reports describing the use of the corresponding nitroarene precursors [37–42]. We first examined the reaction of commercially available 1-(2-nitrophenyl)pyrrole **1a** with a broad range of aldehydes. Functionalized benzaldehydes bearing halogen or methoxy substituents, as well as heteroaromatic aldehydes, afforded quinoxalines **2a--h** in moderate to good yields. Aliphatic aldehydes, including linear, branched, and cyclic ones, also proved suitable counterparts, enabling the preparation of 4-(*c*)-alkylpyrroloquinoxalines **2i–m** in good yields. Remarkably, this new protocol provides these compounds in a more straightforward manner than our previous methodology [31, 32], which required mixed secondary–tertiary glycols prepared through a three-step sequence from natural amino acids. Interestingly, *α*,*β*-unsaturated aldehydes, such as cinnamaldehyde and tiglic aldehyde, were also compatible under these conditions, delivering 4-alkenylpyrroloquinoxalines **2n,o**. Compound **2n**, for instance, displays antileishmanial activity [43]. Next, functionalized nitroarenes **1b–d**, bearing functional groups on the benzenoid ring. were employed as starting materials. Their reactions with a variety of (hetero)aromatic and aliphatic aldehydes furnished the corresponding functionalized pyrroloquinoxalines **2p–v** in slightly higher yields compared to those obtained from the parent substrate **1a** (Scheme 2).

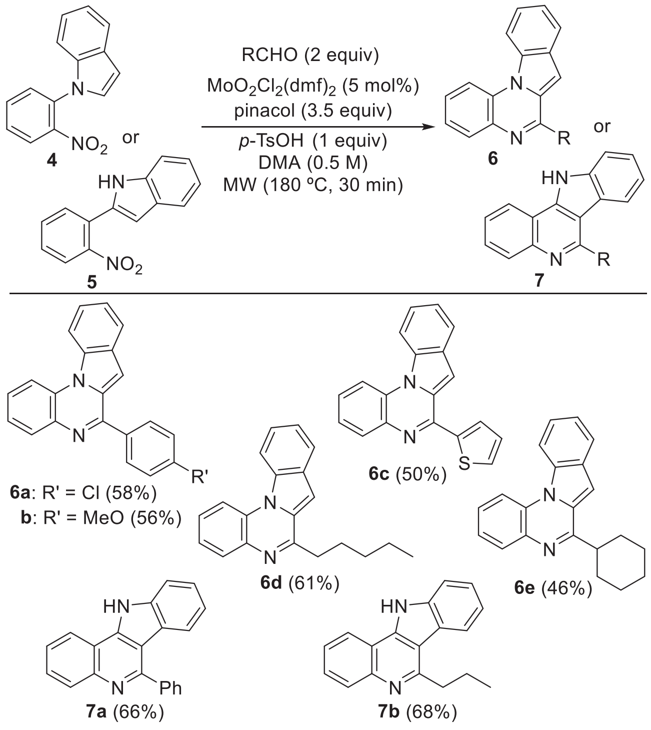


SCHEME 3 | Mechanistic proposal.

This type of heterocyclic derivatives **2**, pyrrolo[1,2-*a*]quinoxalines bearing aryl, alkenyl, or alkyl groups at C4, are of considerable interest due to their reported anticancer, antimycobacterial and antileishmanial activities [44].

At this stage, we propose a plausible mechanism for the formation of quinoxalines **2**, based on our previous DFT studies on the reduction of nitroarenes with pinacol (Scheme 3) [45]. Initially, the dioxomolybdenum(VI) catalyst is reduced by pinacol to a molybdenum(IV) species, which concomitant oxidative cleavage of pinacol to acetone and water as byproducts. Nitroarenes **1** are then reduced by the Mo(IV) complex through three sequential oxygen-transfer steps, involving nitrosoarenes and hydroxylanilines as intermediates. In each reduction step, water is generated via condensation of pinacol with a Mo═O unit and serves as a proton source for the final reduction to the corresponding anilines **A**. Subsequent condensation of **A** with the external aldehyde affords imines **B**, which undergo an intramolecular Friedel–Crafts-type cyclization to form a dihydroquinoxaline intermediate that is readily oxidized to the final quinoxaline **2** under the reaction conditions. The imine formation, cyclization, and oxidation steps are likely facilitated or promoted by the Brønsted acid present in the reaction medium. Alternatively, acetone generated as a byproduct of the reduction may competitively condense with **A** to form imine **C**. A similar acid-promoted Friedel–Crafts-type cyclization of **C** would furnish dihydroquinoxaline **3**, which is observed as side product in these reactions.

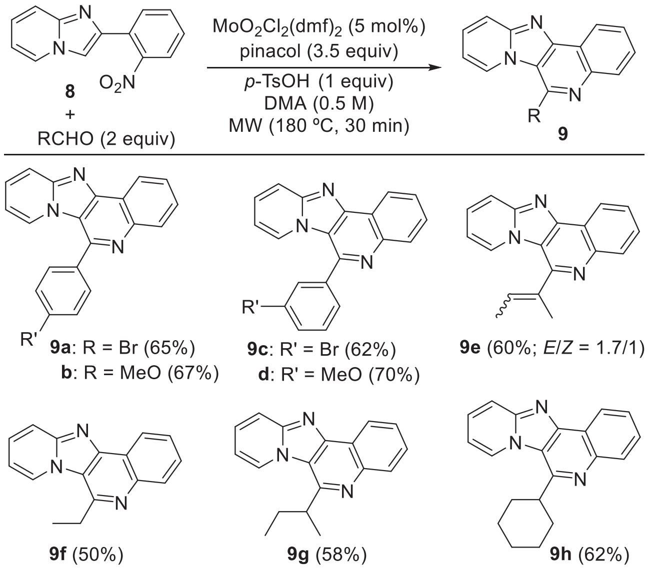
We then investigated 1-(2-nitrophenyl)indole **4** as substrate for this tandem process. Under the same reaction conditions, indolo[1,2-*a*]quinoxalines **6** were obtained efficiently. Functionalized benzaldehydes and 2-thiophenecarboxaldehyde were successfully employed as carbonyl partners, leading to quinoxaline derivatives **6a–c** (Scheme 4). Aliphatic aldehydes were likewise compatible, providing access to (*c*)-alkyl substituted indoloquinoxalines **6d,e**. Given the importance of the indoloquinoline framework, in particular 11*H*-indolo[3,2-*c*]quinolines, as a privileged scaffold in drug discovery owing to their diverse pharmacological properties [46], several synthetic approaches have been developed. These typically involved 2-(2-aminophenyl)indoles as starting materials [47], with some reports using 2-bromophenyl [48] or 2-isocyanophenyl derivatives [49]. In this context, our methodology was further extended to the synthesis of γ-carbolines **7**, starting from 2-(2-nitrophenyl)-1*H*-indole (**5**) [50]. The reaction gave rise to the desired indolo[3,2-*c*]quinolines **7a,b** in good yields, accommodating both aromatic and aliphatic groups at C6 position of the heterocyclic core (Scheme 4).



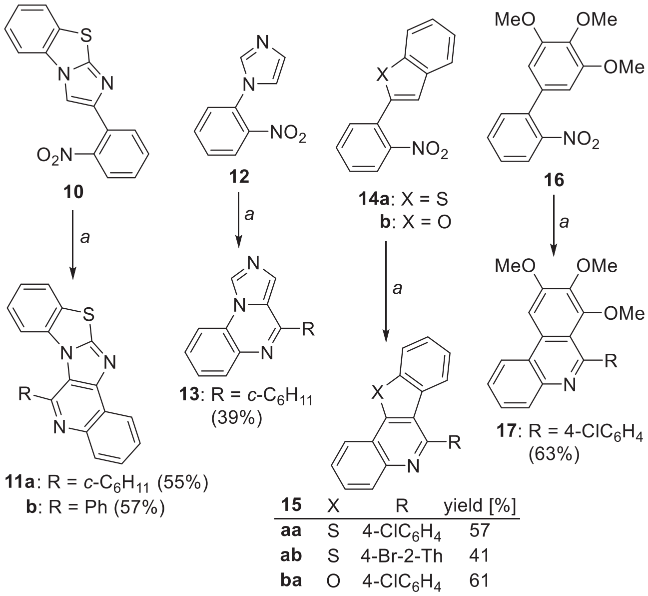
SCHEME 4 | Synthesis of indolo[1,2-*a*]quinoxalines **6** and indolo[3,2-*c*]quinolines **7**.

Imidazo[4,5-*c*]quinolines constitute another important class of fused *N*-heterocycles that have attracted considerable attention due to their distinctive structural features and broad spectrum of biological activities, and they are recognized as key scaffolds in medicinal chemistry [51–53]. Beyond their pharmaceutical relevance, the rigid, π-extended framework of imidazo[4,5-*c*]quinolines endows them with attractive photophysical and electronic properties, rendering them valuable building blocks for functional materials [54]. Consequently, the development of effective, selective, and sustainable synthetic approaches to structurally diverse imidazo[4,5-*c*]quinolines remains an important objective in organic synthesis [55–58]. Among the reported procedures, those based on acid-catalyzed Pictet-Spengler-type cyclizations of the corresponding anilines, via imine intermediates, play a predominant role. These processes typically require prior reduction of nitroarenes, such as **8**, to the corresponding amines. Integrating this reduction step with subsequent imine formation and cyclization would significantly enhance the step economy and overall efficiency of the synthesis of imidazo[4,5-*c*]quinolines. Gratifyingly, when readily available nitroarene **8** was subjected to the optimized reaction conditions in the presence of a range of functionalized aromatic, alkenyl, and aliphatic aldehydes, the corresponding imidazoquinolines **9a–h** were obtained in moderate to good yields (Scheme 5).

Encouraged by these results, we further evaluated the applicability of this methodology to the synthesis of related



SCHEME 5 | Synthesis of imidazo[4,5-*c*]quinolines **9**.



15	X	R	yield [%]
aa	S	4-ClC$_6$H$_4$	57
ab	S	4-Br-2-Th	41
ba	O	4-ClC$_6$H$_4$	61

[a]Reagents and conditions: RCHO (2 equiv), MoO$_2$Cl$_2$(dmf)$_2$ (5 mol%), pinacol (3.5 equiv), *p*-TsOH (1 equiv), DMA (0.5 M), MW (180 ºC, 30 min)

SCHEME 6 | Further application of the developed tandem reaction to the synthesis of *N*-polyheterocycles **11**, **13**, **15**, and **17**.

heterocyclic cores, depending on the position of the *o*-nitroaryl substituent in the starting material (Scheme 6). In this sense, thiazolo[2',3':2,3]imidazo[4,5-*c*]quinolines were readily accessed from 2-(2-nitrophenyl)benzo[*d*]imidazo[2,1-*b*]thiazoles, as demonstrated by the reaction of compound **10** under the standard conditions with either aliphatic or aromatic aldehydes as carbonyl partners, affording products **11a,b** in good yields. Similarly, imidazoles bearing an *o*-nitroaryl substituent at the N1 position, such as compound **12**, provided direct access to imidazo[1,5-*a*]quinoxaline **13**, a relevant heterocyclic scaffold found in numerous biologically active anticancer or anti-HIV compounds [59]. When the *o*-nitroaryl substituent was placed at C2 of a benzo[*b*]thiophene (**14a**) or of a benzo[*b*]furan core (**14b**), the corresponding benzothieno[3,2-*c*]quinolines **15aa–ab** or benzofuro[3,2-*c*]quinoline **15ba** were readily obtained upon reaction with aromatic aldehydes [60]. Finally, we examined the feasibility of synthesizing valuable phenanthridine scaffolds [61, 62], which are commonly found in pharmaceutical agents, natural products, and functional molecules [63]. Thus, subjecting the 2-nitro-1,1'-biphenyl derivative **16** to the optimized reaction conditions in the presence of *p*-chlorobenzaldehyde efficiently furnished phenanthridine **17**, further highlighting the versatility of this methodology for the construction of important heterocyclic architectures.

3 | Conclusion

From a sustainability perspective, the direct conversion of nitroaromatics into *N*-heterocycles offers clear advantages, including improved step economy, reduced waste generation, and enhanced functional group tolerance. In this study, we have developed an efficient and versatile methodology for the synthesis of diverse fused *N*-polyheterocyclic scaffolds directly from functionalized nitroarenes and aldehydes via dioxomolybdenum(VI) catalysis, employing pinacol as a suitable, readily accessible, and benign reductant. The optimization of the reaction conditions enables effective minimization of competing pathways, such as aldehyde acetalization with pinacol, or the competitive condensation of acetone, the byproduct of initial nitro reduction, with the intermediate aniline. Moreover, this methodology enhances step economy by integrating nitro reduction, imine formation, and cyclization into a single operational step. The strategy exhibits broad scope, providing straightforward access to valuable scaffolds such as pyrrolo[1,2-*a*]quinoxalines, indoloquinoxalines, *γ*-carbolines, imidazoquinolines, and phenanthridines, many of which display significant pharmacological relevance. Notably, the protocol tolerates aromatic, aliphatic, and even more challenging *α*,*β*-unsaturated aldehydes, thereby substantially expanding structural diversity. Overall, this work reinforces the potential of nitroarenes as simple and readily available nitrogen sources in sustainable tandem catalytic processes involving nitro-group reduction and C–N bond-forming reactions. In addition, the use of an earth-abundant molybdenum catalyst in combination with a benign reductant further strengthens the environmental appeal of this approach for the construction of highly valuable heterocyclic architectures.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Full experimental procedures, characterization data, and copies of NMR spectra are included. The authors have cited additional references within the Supporting Information [64–75].

Supporting File: ajoc70439-sup-0001-SuppMat.pdf.