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Leveraging *in situ* *N*-tosylhydrazones as diazo surrogates for efficient access to pyrazolo-[1,5-*c*] quinazolinone derivatives†

Jun Yan,[a] Pascal Retailleau,[b] Christine Tran*[a] and Abdallah Hamze *[a]

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We developed a transition metal-free methodology for the construction of pyrazoloquinazolinone derivatives. The strategy involves a one-pot reaction wherein the *N*-tosylhydrazone and its corresponding diazo derivative are generated *in situ*, followed by an intramolecular 1,3-dipolar cycloaddition–ring expansion to provide the pyrazolo-[1,5-c]quinazolinone motif. This approach enables straightforward access to a diverse range of highly functionalized N-heterocyclic compounds in good yields (up to 92%).

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Introduction

N-Heterocycles have been a focal point for researchers for several decades, particularly due to their diverse pharmaceutical and agrochemical applications.[1,2] The synthesis of these scaffolds has garnered significant interest among organic chemists, leading to the development of novel synthetic methodologies.[2–5] Among these structures, pyrazolo-[1,5-*c*]quinazolines, with a N-heterocyclic nucleus fusing quinazolines and pyrazoles, have recently emerged as pivotal compounds within the biology and chemistry communities.

These compounds have a range of biological properties, as illustrated in Fig. 1.[1] Specifically, molecules **I** act as antagonists for glycine/NMDA (*N*-methyl-D-aspartic acid) receptors,[6] as well as for AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate[7] receptors, demonstrating high affinities and selectivities toward the corresponding amino acid receptors.[8,9] Additionally, pyrazolo-[1,5-*c*]quinazolinone derivatives **II** also exhibited comparable activities as antagonists for adenosine receptors.[10]

Pyrazolo-[1,5-*c*]quinazolinones **III** emerge as promising antibacterial agents due to their function as DNA gyrase inhibitors.[11] Campiani *et al.* reported molecules **IV** as potent reverse transcriptase inhibitor-type antiviral agents.[12] These aza-heterocycles also acted as efficient ligands with high binding affinities towards benzodiazepine and $GABA_A$ receptors.[13,14] Through virtual screening, Moro and coworkers identified pyrazolo-[1,5-*c*]quinazolinones **V** as novel casein kinase 2 inhibitors.[15]

The Xu group described similar structures with significant antitumor properties and inhibitory activity against cyclin-dependent kinases CDK9 and CDK2.[16] More recently, the photophysical properties of pyrazolo-[1,5-*c*]quinazolines have been scrutinized by Sutherland *et al.*[17] These platforms appeared to be interesting chromophores with high fluorescence quantum yields, paving the way for possible bioimaging applications.

Alongside the widely diverse properties of pyrazolo-[1,5-*c*] quinazolinones depicted above, numerous synthetic strategies have been explored for constructing this N-heterocyclic ring (Scheme 1). One of the earliest methods involves a multi-step

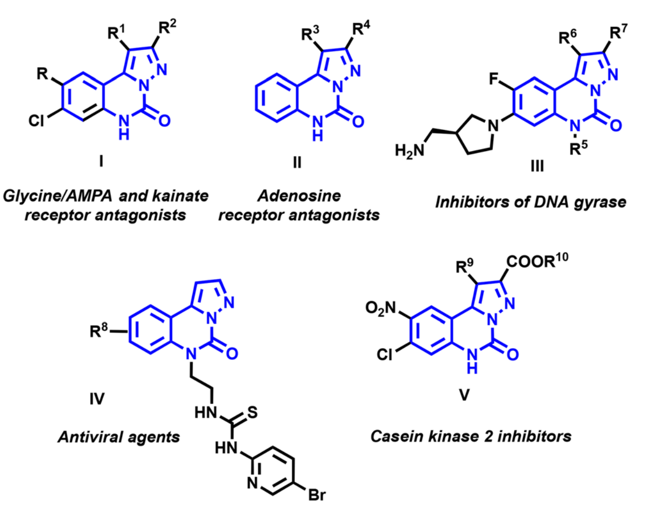

Fig. 1 Biologically active compounds displaying the pyrazolo-[1,5-*c*] quinazolinone scaffold.

[a]*Department of Chemistry and Medicinal Chemistry, Université Paris-Saclay, CNRS, BioCIS, 91400 Orsay, France. E-mail: abdallah.hamze@universite-paris-saclay.fr*
[b]*Department of Chemistry and Natural Products, ICSN, Université Paris-Saclay, UPR 2301, 91198 Gif-sur-Yvette, France*

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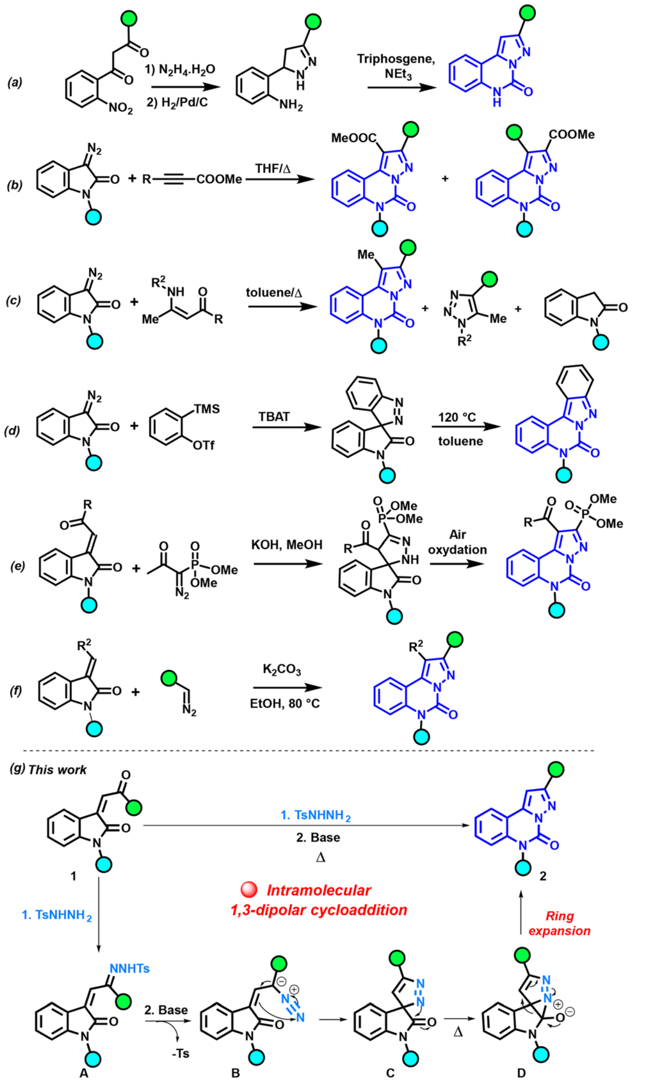

Scheme 1 Reported approaches for synthesizing pyrazolo-[1,5-*c*]quinazolinones, and our approach involving intramolecular 1,3-dipolar cycloaddition for their construction.

synthesis, wherein 4,5-dihydro-3,5-diarylpyrazoles are formed by reacting hydrazine hydrate and 1,3-diaryl-2-propenones, and the reaction is completed with a condensation step using triphosgene (Scheme 1a).[8,10,14,17] Tang and Cao combined 3-diazoindolinones with methyl β-fluoroalkylpropionates to obtain a mixture of two regioisomers of pyrazolo-[1,5-*c*]quinazolinone (Scheme 1b).[18,19] Also, a mixture of three compounds was observed when the reaction was performed between diazooxindole and enaminones (Scheme 1c).[20] Cheng and Zhai developed a [3 + 2] dipolar cycloaddition of arynes with 3-diazoindolin-2-ones in the presence of TBAT (tetrabutylammonium triphenyldifluorosilicate), leading to spiro[indazole-3,3′-indolin]-2′-ones. Their thermal isomerization obtained at 120 °C readily yields indazolo[2,3-*c*]quinazolin-6(5*H*)-ones (Scheme 1d).[21,22] Mohanan *et al.* used the diazo derivative with the Bestmann–Ohira reagent, and the reaction with an isatin derivative afforded the spiropyrazoline derivative through a 1,3-dipolar cycloaddition followed by a 1,3-*H*-shift, and then a spontaneous air-oxidation in the presence of methanol delivered the phosphonated pyrazolo-[1,5-*c*]quinazolinones (Scheme 1e).[23] Nagendra Babu *et al.* used a domino reaction with 3-ylideneoxindoles and diazo partners, leading to pyrazoloquinazolinones (Scheme 1f).[24]

Given our sustained interest in studying the reactivity of *N*-tosylhydrazones (NTHs),[25–32] we formulated plans to investigate reactions involving these reactive species for the construction of N-heterocyclic moieties, specifically the pyrazolo-[1,5-*c*] quinazolinone scaffold. Within this framework, we conceived an original strategy for pyrazolo-[1,5-*c*]quinazolinone synthesis through intramolecular cycloaddition (Scheme 1g). Our protocol was conducted under basic conditions and relied on the transition metal-free one-pot reaction between enone **1** and *p*-toluenesulfonyl hydrazide. The initial condensation of **1** with *p*-toluenesulfonyl hydrazide led to the NTH intermediate **A**. Subsequently, under the influence of a base, **A** was converted into the diazo species **B**. **B** then underwent an intramolecular 1,3-dipolar cycloaddition to generate **C**. Through thermal heating, a nucleophilic attack of the azo on the carbonyl group forms the 5/3 fused heterocyclic scaffold **D**.[22] The final step involved the ring expansion of **D**, resulting in the formation of the pyrazolo-[1,5-*c*]quinazolinone **2**.

Our approach uniquely relies on *p*-toluenesulfonyl hydrazide for the intramolecular 1,3-dipolar cycloaddition, without the need for any co-substrates. In comparison with prior reports, which are often limited to electron-withdrawing group (EWG)-stabilized diazo compounds, this methodology should be applicable for NTHs with electron-donating groups (EDGs). Additionally, this methodology produces only one regioisomer and eliminates the need for toxic reagents such as triphosgene, providing significant advantages for this reaction.

Results and discussion

We initiated the optimization of the reaction using enone **1a** as the substrate (Table 1). The utilization of a strong base, such as *t*BuLi, resulted in the formation of the desired product **2a**, albeit in a low yield of 18% (Table 1, entry 1). It is worth noting that the structure of **2a** was fully confirmed through X-ray crystal analysis (see the ESI† for further details).[33]

Employing a relatively weaker base, LiO*t*Bu, did not result in a significant enhancement in reaction efficiency (entry 2). Subsequently, the exploration continued with an inorganic base such as Cs_2CO_3 (entry 3), which delivered a noteworthy yield of 72%. A further substantial improvement in yield was observed when dioxane was employed, coupled with a switch to K_3PO_4 (entry 4). Compound **2a** was obtained in an excellent NMR yield of 98% and an isolated yield of 92%. Varying the solvent demonstrated the versatility of this transformation in both polar and non-polar solvents (entries 4–6). With a view to improve the sustainability of our system, the green solvent 2-propanol was employed as the reaction medium,[34] resulting

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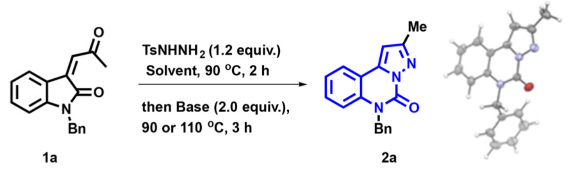
Table 1 Reaction optimization[a]



Entry	Base	Solvent	^{1}HNMR yield (%)	Yield[b] (%)
1	*t*BuLi	Dioxane	18	n.d.[c]
2	LiO*t*Bu	Dioxane	20	n.d.[c]
3	Cs_2CO_3	Dioxane	80	72
4	K_3PO_4	Dioxane	98	92
5	K_3PO_4	Toluene	90	85
6	K_3PO_4	2-Propanol	88	80
7	K_2CO_3	Dioxane	92	87
8	K_3PO_4	Dioxane	91[d]	86

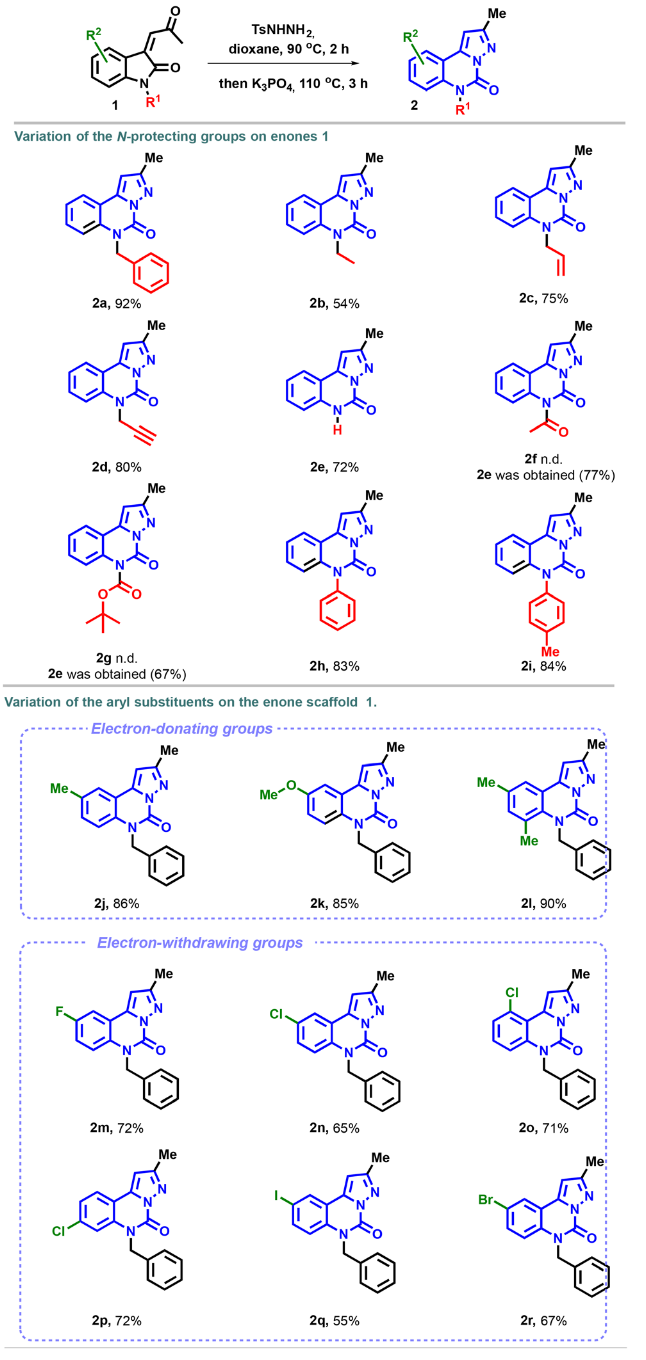
[a] Enone **1a** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 90 °C and stirred for 2 h. Then, base (0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 110 °C for 3 h. [b] Isolated yield after column chromatography. [c] n.d. = not determined. [d] The second step was conducted at 90 °C.

in the corresponding pyrazolo-[1,5-*c*]quinazolinones **2a** in a yield of 80%. Transitioning from K_3PO_4 to K_2CO_3 as the base resulted in a slight decrease in the yield (entry 7). Furthermore, lowering the temperature to 90 °C during the cyclization step led to a marginal decrease in yield to 91% (entry 8).

Consequently, we established the optimal conditions for this transformation, utilizing K_3PO_4 as the base and dioxane as the solvent.

We then began to explore the scope of the reaction. First, we investigated the modification of the amino-protecting groups of enones **1**. As illustrated in Scheme 2, the transformation proved to be well suited for *N*-ethyl, -allyl, -propynyl and -phenyl substrates and afforded the corresponding pyrazolo-[1,5-*c*]quinazolinones **2b–i** in good yields. To our satisfaction, the unprotected enone **1e**, under the optimal reaction conditions, provided the desired product **2e** in 72% yield. In contrast, the expected heterocycles **2f** and **2g** with electron withdrawing protecting groups were not detected. Instead, the unprotected compound **2e** was isolated in satisfactory yields (77% and 67% for acetyl and Boc, respectively), possibly due to the basic conditions of the cyclization step.[35]

Next, the variation of the aryl substituents on the enone scaffold was examined (R^2 group) (Scheme 2). A good tolerance was observed with methyl and methoxy groups, with yields of 86 and 85%, respectively, for molecules **2j** and **2k**. In particular, the presence of electron-donating substituents promoted the formation of the pyrazolo-[1,5-*c*]quinazolinones **2l**. Similarly, the reaction exhibited good compatibility with diverse electron-poor groups, with yields up to 72%. Higher yields were obtained with fluoro (**2m**), chloro (**2n**), and bromo (**2r**) substituents compared to the results observed with the iodo substituent **2q**. The reaction displayed good efficiency



Scheme 2 Substrate scope. [a] Reaction conditions: enone **1** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 90 °C, and stirred for 2 h. K_3PO_4 (0.40 mmol, 2.0 equiv.) was then added to the reaction mixture, which was stirred at 110 °C for 3 h. Isolated yield after chromatographic purification.

with *meta*, *ortho*, and *para*-substituted chloroenones, and compounds **2n**, **2o**, and **2p** were obtained in a good yield.

Next, we expanded the scope of our studies by varying the ketone substituents of enones 1 (Scheme 3).

In order to facilitate the formation of the pyrazolo-[1,5-*c*] quinazoline, we slightly modified the reaction conditions. The

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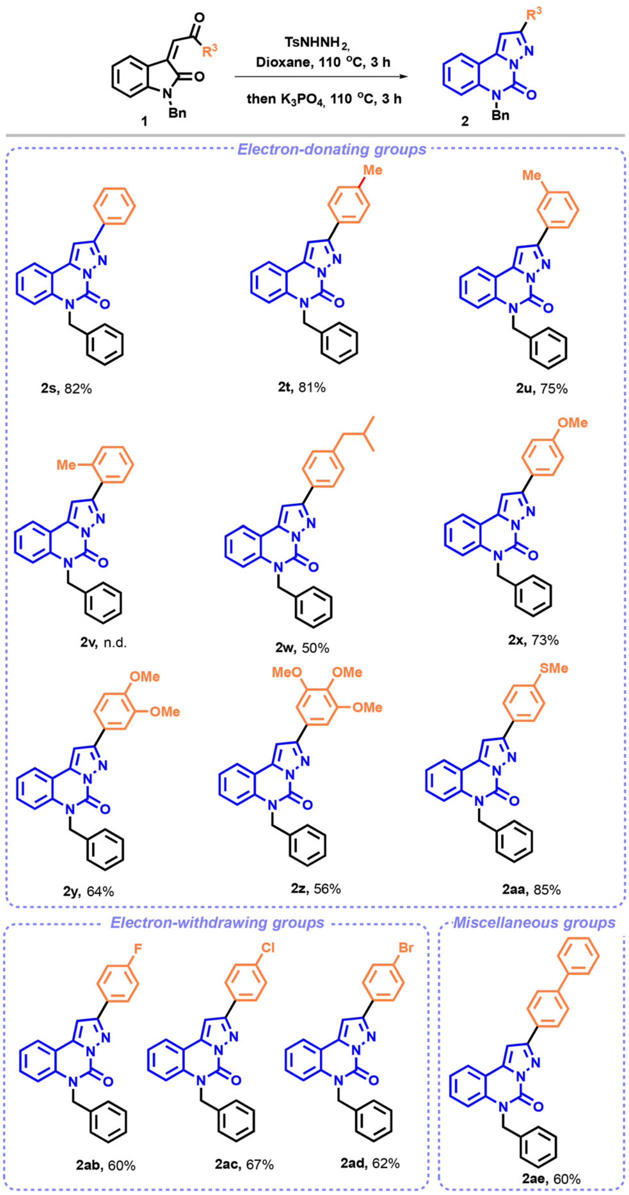
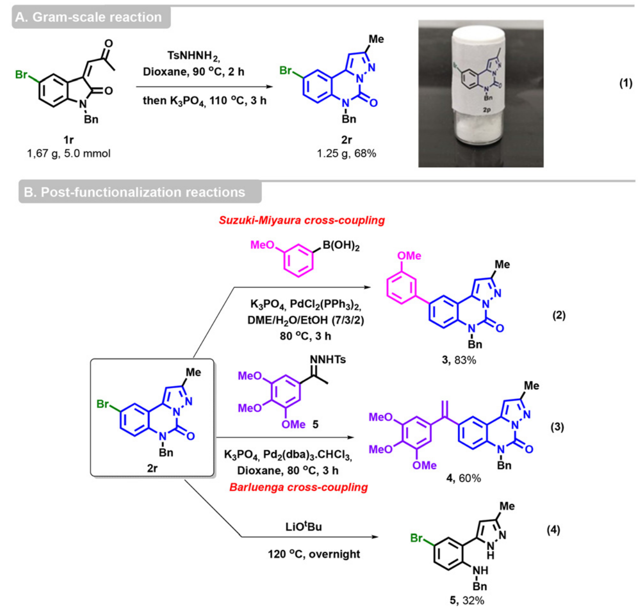


Scheme 3 Substrate scope: variation of the ketone substituents on enones **1**. [a] Reaction conditions: enone **1** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 110 °C and stirred for 2 h. K_3PO_4 (0.40 mmol, 2.0 equiv.) was then added to the reaction mixture, which was stirred at 110 °C for 3 h. Isolated yield after chromatographic purification.



Scheme 4 Gram-scale reaction and post-functionalization reactions.

NTH synthesis was thus carried out at 110 °C for 3 h, instead of 90 °C for 2 h. Upon first examination, as shown in Scheme 3, the reaction proceeded smoothly with both electron-rich and -poor groups. The phenyl group afforded the desired compound **2s** in 82% yield.

Surprisingly, the effectiveness of the reaction decreased upon the addition of a methyl or an isopropyl substituent to the phenyl moiety. While in the presence of the *para* and *meta*-methylated pyrazolo-[1,5-*c*]quinazolinones the desired compounds (**2t** and **2u**) were obtained in good yields, the *ortho*-substituted pyrazolo-[1,5-*c*]quinazolinone **2v** was not isolated under our reaction conditions, probably due to steric hindrance. Only degradation products could be seen on TLC and crude ^1H NMR. Moderate to good yields were achieved with a methoxy or a methylthio group (**2x** and **2aa**) or even in the presence of several electron-donating groups on the phenyl scaffold (**2y** and **2z**). Consistent with the observations made regarding the aryl substituents on substrate **1**, a similar trend was noted for electron-withdrawing substituents, resulting in the formation of compounds **2ab–2ad** in yields ranging from 60 to 67%. Furthermore, we explored a biphenyl substrate, **1ae**, which delivered the expected compound **2ae** in 60% yield.

To confirm the viability of our methodology, we successfully performed a gram-scale reaction with substrate **1r** (5 mmol), delivering the desired cyclized product **2r** in a yield of 68% (1.2 g) (Scheme 4, eqn (1)). Compound **2r** was then subjected to various post-functionalization reactions. A Suzuki–Miyaura cross-coupling was performed with (3-methoxyphenyl)boronic acid, K_3PO_4 as the base and $PdCl_2(PPh_3)_2$ as the catalyst in $DME/H_2O/EtOH$[31] to afford **3** in 83% yield (Scheme 4, eqn (2)).

The Barluenga–Valdés coupling reaction was carried out under the standard conditions between the bromo-derived pyrazoloquinazolinone **2r** and 3,4,5-trimethoxyphenyl NTH **5**, allowing access to the alkene derivative **4** in a satisfactory yield (Scheme 4, eqn (3)). Finally, the hydrolysis of the urea group was also achieved in the presence of LiO*t*Bu at 120 °C, furnishing the expected pyrazole **5** (Scheme 4, eqn (4)).

Conclusions

In summary, the synthesis of pyrazolo-[1,5-*c*]quinazolinone derivatives has been achieved using a convenient methodology.

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The process relied on the *in situ* formation of NTH, followed by the generation of the diazo derivative in a basic medium. This intermediate underwent an intramolecular 1,3-dipolar cycloaddition, leading to the expected pyrazolo-[1,5-*c*]quinazolinones. The wide functional group compatibility (29 diversely functionalized products synthesized in moderate to excellent yields), the transition metal-free process, the bench-stability of substrates, and the step economy of the intramolecular process are significant advantages of this reaction. This one-pot transformation was also validated with the gram-scale synthesis of **2r** in 68% yield. Additionally, various post-functionalization reactions, including pallado-catalyzed cross-couplings, such as the Suzuki–Miyaura and Barluenga–Valdés reactions, were successfully performed with compound **2r**. Further studies are underway to investigate the biological activities of the prepared pyrazolo-[1,5-*c*] quinazolinones.

Conflicts of interest

The authors declare no conflict of interest.

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