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

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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%).

### Introduction

*N*-Heterocycles have been a focal point for researchers for several decades, particularly due to their diverse pharmaceutical and agrochemical applications.<sup>1,2</sup> The synthesis of these scaffolds has garnered significant interest among organic chemists, leading to the development of novel synthetic methodologies.<sup>2–5</sup> 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.<sup>1</sup> Specifically, molecules **I** act as antagonists for glycine/NMDA (*N*-methyl-D-aspartic acid) receptors,<sup>6</sup> as well as for AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate<sup>7</sup> receptors, demonstrating high affinities and selectivities toward the corresponding amino acid receptors.<sup>8,9</sup> Additionally, pyrazolo-[1,5-*c*]quinazolinone derivatives **II** also exhibited comparable activities as antagonists for adenosine receptors.<sup>10</sup>

Pyrazolo-[1,5-*c*]quinazolinones **III** emerge as promising antibacterial agents due to their function as DNA gyrase inhibitors.<sup>11</sup> Campiani *et al.* reported molecules **IV** as potent reverse transcriptase inhibitor-type antiviral agents.<sup>12</sup> These aza-heterocycles also acted as efficient ligands with high binding affinities towards benzodiazepine and GABA<sub>A</sub>

receptors.<sup>13,14</sup> Through virtual screening, Moro and coworkers identified pyrazolo-[1,5-*c*]quinazolinones **V** as novel casein kinase 2 inhibitors.<sup>15</sup>

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

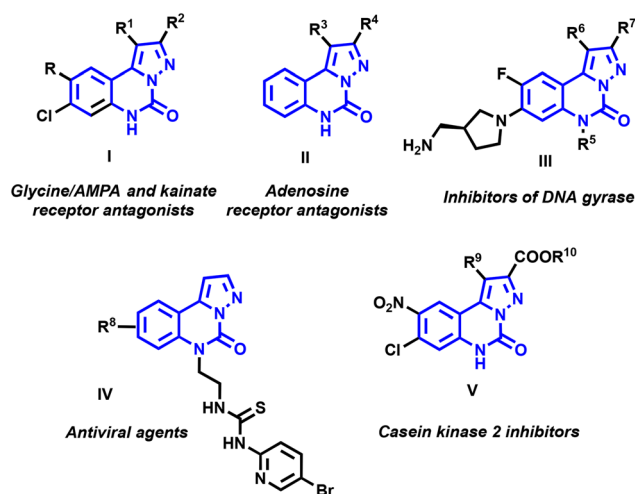


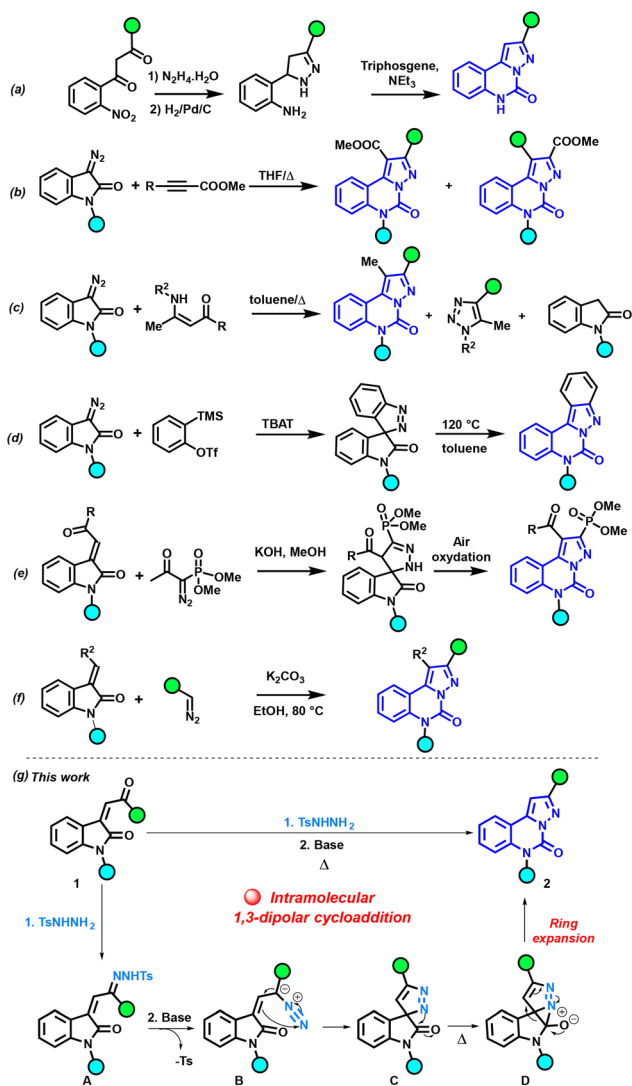
Fig. 1 Biologically active compounds displaying the pyrazolo-[1,5-*c*]quinazolinone scaffold.

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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).<sup>8,10,14,17</sup> Tang and Cao combined 3-diazoindolinones with methyl  $\beta$ -fluoroalkylpropionates to obtain a mixture of two regioisomers of pyrazolo-[1,5-c]quinazolinone (Scheme 1b).<sup>18,19</sup> Also, a mixture of three compounds was observed when the reaction was performed between diazoindole and enaminones (Scheme 1c).<sup>20</sup> 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).<sup>21,22</sup> 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).<sup>23</sup> Nagendra Babu *et al.* used a domino reaction with 3-ylideneoxindoles and diazo partners, leading to pyrazoloquinazolinones (Scheme 1f).<sup>24</sup>

Given our sustained interest in studying the reactivity of *N*-tosylhydrazones (NTHs),<sup>25–32</sup> 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**.<sup>22</sup> The final step involved the ring expansion of **D**, resulting in the formation of the pyrazolo-[1,5-c]quinazolinone **2**.

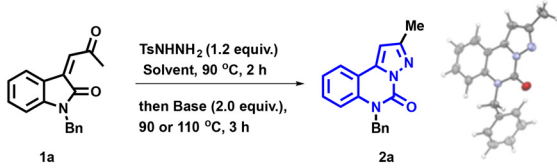
Our approach uniquely relies on *p*-toluenesulfonyl hydrazide for the intramolecular 1,3-dipolar cycloaddition, without the need for any co-substrates. In comparison with prior reports, which are often limited to electron-withdrawing group (EWG)-stabilized diazo compounds, this methodology should be 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).<sup>33</sup>

Employing a relatively weaker base, LiOtBu, did not result in a significant enhancement in reaction efficiency (entry 2). Subsequently, the exploration continued with an inorganic base such as Cs<sub>2</sub>CO<sub>3</sub> (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<sub>3</sub>PO<sub>4</sub> (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,<sup>34</sup> resulting



Table 1 Reaction optimization<sup>a</sup>


Entry	Base	Solvent	<sup>1</sup> HNMR yield (%)	Yield <sup>b</sup> (%)
1	<i>t</i> BuLi	Dioxane	18	n.d. <sup>c</sup>
2	LiO <i>t</i> Bu	Dioxane	20	n.d. <sup>c</sup>
3	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	80	72
4	K <sub>3</sub> PO <sub>4</sub>	Dioxane	98	92
5	K <sub>3</sub> PO <sub>4</sub>	Toluene	90	85
6	K <sub>3</sub> PO <sub>4</sub>	2-Propanol	88	80
7	K <sub>2</sub> CO <sub>3</sub>	Dioxane	92	87
8	K <sub>3</sub> PO <sub>4</sub>	Dioxane	91 <sup>d</sup>	86

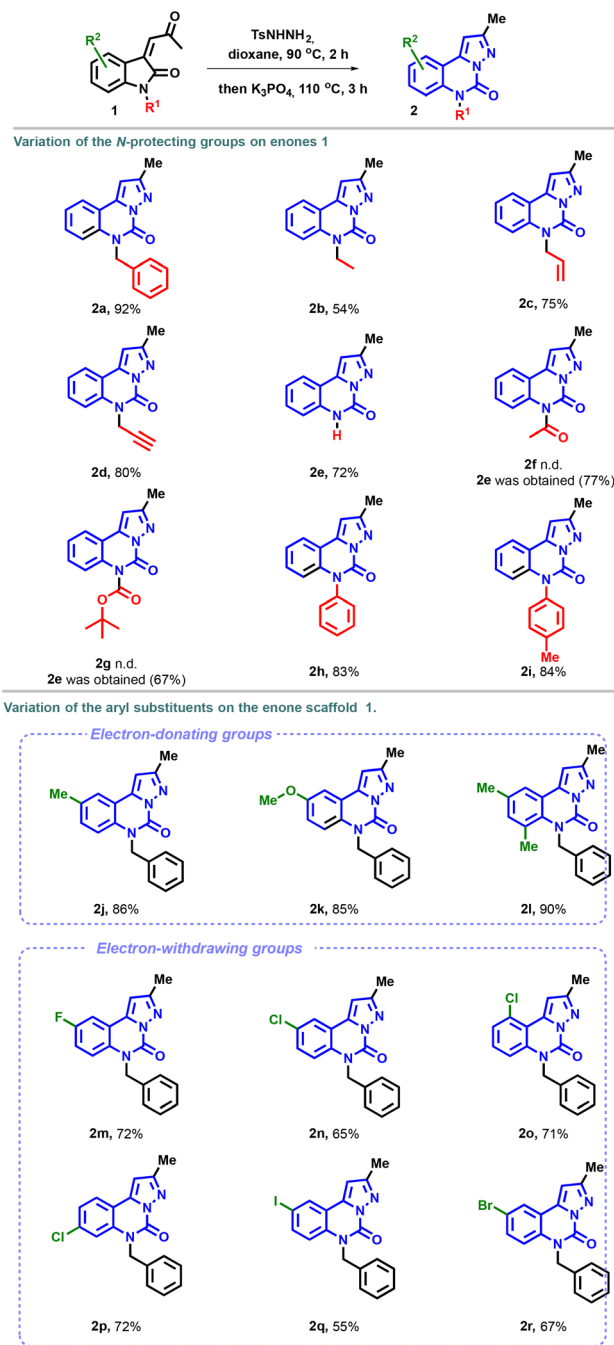
<sup>a</sup> Enone **1a** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 90 °C and stirred for 2 h. Then, base (0.40 mmol, 2.0 equiv.) was added, and the reaction mixture was stirred at 110 °C for 3 h. <sup>b</sup> Isolated yield after column chromatography. <sup>c</sup> n.d. = not determined. <sup>d</sup> 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<sub>3</sub>PO<sub>4</sub> to K<sub>2</sub>CO<sub>3</sub> 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<sub>3</sub>PO<sub>4</sub> 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.<sup>35</sup>

Next, the variation of the aryl substituents on the enone scaffold was examined (R<sup>2</sup> 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



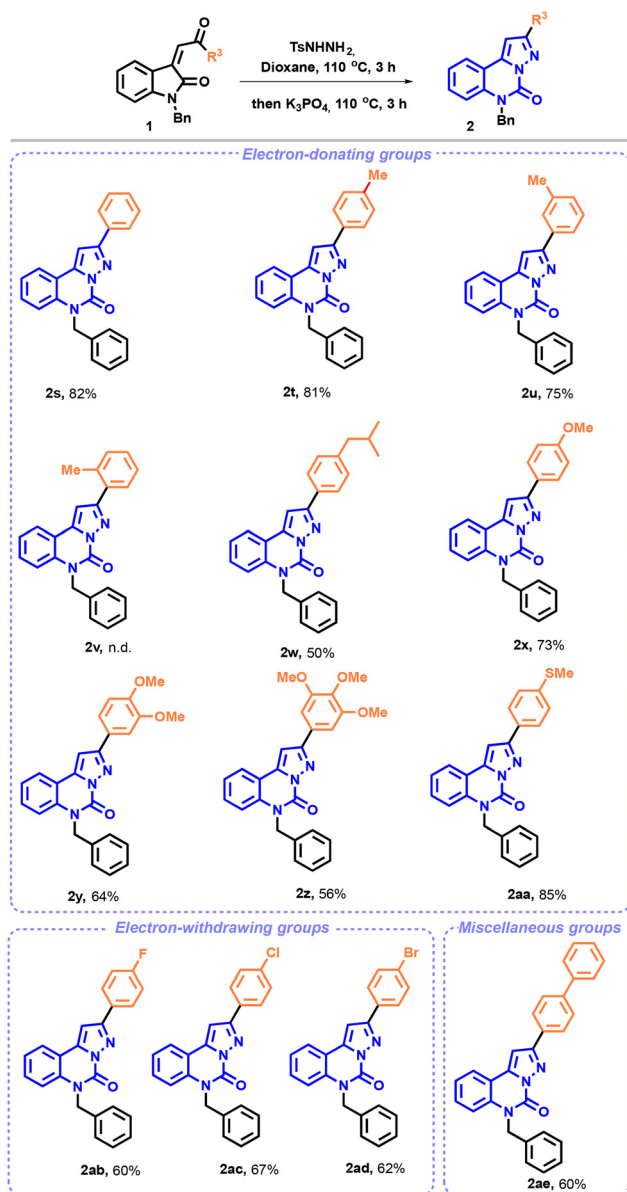
Scheme 2 Substrate scope. <sup>a</sup> Reaction conditions: enone **1** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 90 °C, and stirred for 2 h. K<sub>3</sub>PO<sub>4</sub> (0.40 mmol, 2.0 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*]quinazolinone, we slightly modified the reaction conditions. The

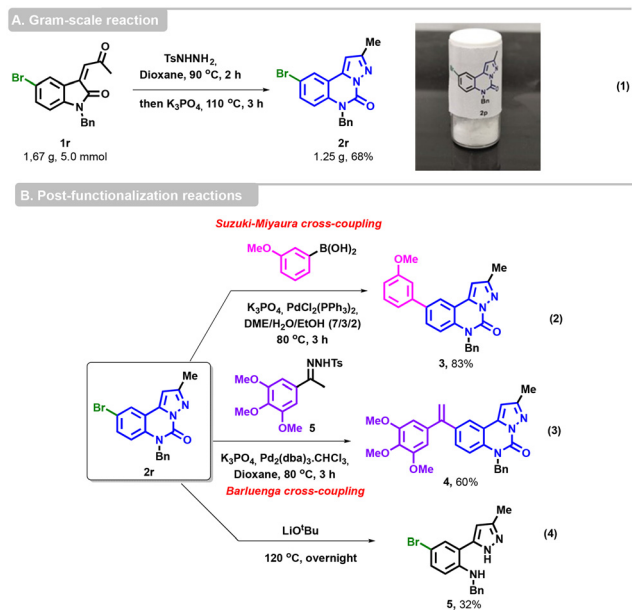




**Scheme 3** Substrate scope: variation of the ketone substituents on enones **1**. <sup>a</sup> Reaction conditions: enone **1** (0.20 mmol, 1.0 equiv.) and *p*-toluenesulfonyl hydrazide (0.24 mmol, 1.2 equiv.) were dissolved in dioxane (2 mL). The reaction was heated in an oil bath at 110 °C and stirred for 2 h. K<sub>3</sub>PO<sub>4</sub> (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.

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*-



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

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 <sup>1</sup>H 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<sub>3</sub>PO<sub>4</sub> as the base and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst in DME/H<sub>2</sub>O/EtOH<sup>31</sup> 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 LiOtBu 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.



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.

## Acknowledgements

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