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Regioselective ring expansion of 3-ylideneoxindoles with tosyldiazomethane (TsDAM) : A metal-free and greener approach for the synthesis of pyrazolo-[1,5-*c*]quinazolines

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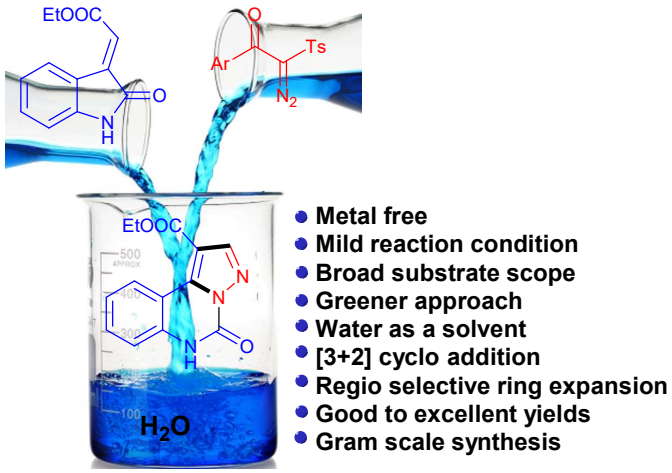


ABSTRACT:

An efficient, metal free approach to access the pyrazolo-[1,5-*c*]quinazolines with 3-ylideneoxindoles and tosyldiazomethane (TsDAM) under mild aqueous reaction conditions has been developed and also the solvent involvement in the present reaction has been explored for the first time. This greener approach involves 1,3-dipolar cycloaddition, regioselective ring expansion followed by the elimination of tosyl group with aqueous base in a single operation and the product can be isolated in high purity without column chromatographic separation. The method is also compatible with a large variety of functional groups, providing good to excellent yields in water, thus offering the decrease of environmental impact in the pharmaceutical industry.

INTRODUCTION

The development of facile strategies to construct diverse complex heterocyclic compounds has intrigued as an important theme in synthetic organic chemistry over the years due to the extensive applications in various fields of science.[1] Among the several synthetic methods to these ends,

those that exploit the use of easily accessible starting materials under domino conditions are highly desirable for their atom and step economy.[2] For instance, quinazolines and pyrazoles are the most significant heterocyclic compounds, widely found in plethora of drug-related molecules, functional materials and natural products.[3] Owing to their unique biological activity and pharmacological properties, they occupy an important position in the family of heterocycles.[4]

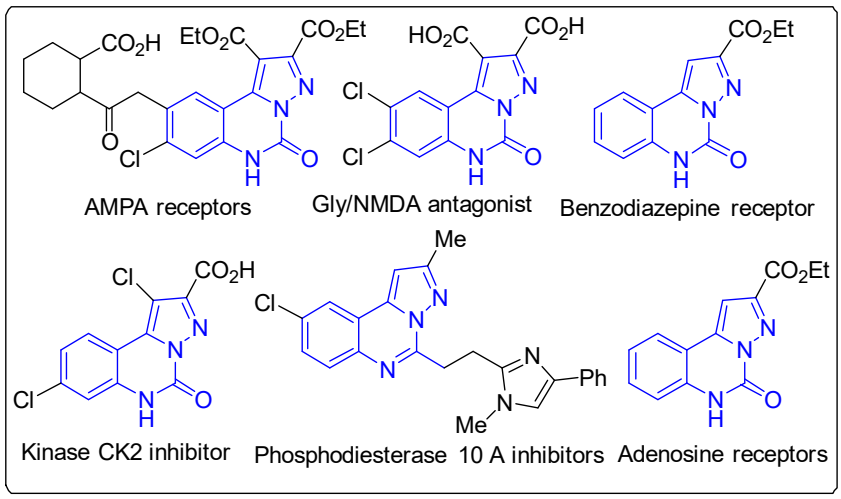


Figure 1. Some Important biologically active molecules

In particular, pyrazolo[1,5-*c*]quinazolines, belonging to a class of N-fused heterocyclic compounds containing quinazoline and pyrazole frameworks, have drawn a great deal of attention from both medicinal as well as synthetic chemists due to their significant biological activities (**Figure 1**), such as benzodiazepine/adenosine receptor,[5] Gly/NMDA antagonist,[6] AMPA receptors,[7] γ-aminobutyric acid type A receptors (GABA),[8] phosphodiesterase 10 A inhibitors,[9] non-nucleoside HIV-1 reverse transcriptase inhibitor,[10] kinase CK2 inhibitor,[11] excitatory amino acid antagonists.[12] They also serve as versatile synthons for the synthesis of various other bioactive molecules.[13]

Accordingly, considerable effort has been devoted to the development of new and novel synthetic approaches to the construction of pyrazolo[1,5-*c*]quinazoline derivatives. Isatin and its synthetic analogues would serve as the versatile synthons in the synthesis of pyrazolo[1,5-*c*]quinazoline derivatives. In the past few years, several methods have been developed by employing complex starting materials, which includes a reactions of 3-diazoindolin-2-ones with electron-deficient alkynes[14] or, enaminones[15] 2-(1*H*-pyrazol-5-yl)anilines with carbonates,[16] 2-aminoacetophenone hydrazones with triphosgene,[17] 1-(2-halophenyl)-3-akylprop-2-yn-1-ones with hydrazine hydrochloride and amidine hydrochlorides,[18] alkyne ketones with sulfonylhydrazones,[19] arynes with 3-diazoindolin-2-ones,[20] 3-aryl/alkylideneoxindoles with Bestmann–Ohira reagent[21] and 3-ylideneoxindoles with diazomethane derivatives.[22] However,

these protocols offer certain limitations, some of them involves the use of metal salts, expensive and complex reagents which require multi step synthesis, harsher reaction conditions, lower yields, and poor chemo selectivity. In view of these aspects as well as from the standpoint of step economy, the development of efficient and practical methods for the construction of pyrazolo-[1,5-*c*]quinazolines *via* an elegant domino strategy with easily accessible precursors is still desirable (**Figure 2**).

Over the past decade, 3-ylideneoxindole core has evolved as an important synthetic intermediate for organic chemists. They have been widely used in the development of several novel methodologies, total synthesis of natural products due to the high reactivity as an electrophile and easy accessibility.[23] On the other hand; substituted diazomethane intermediate is an interesting building block in domino reactions due to its unusual reactivity in the generation of multiple bonds in a single operation.

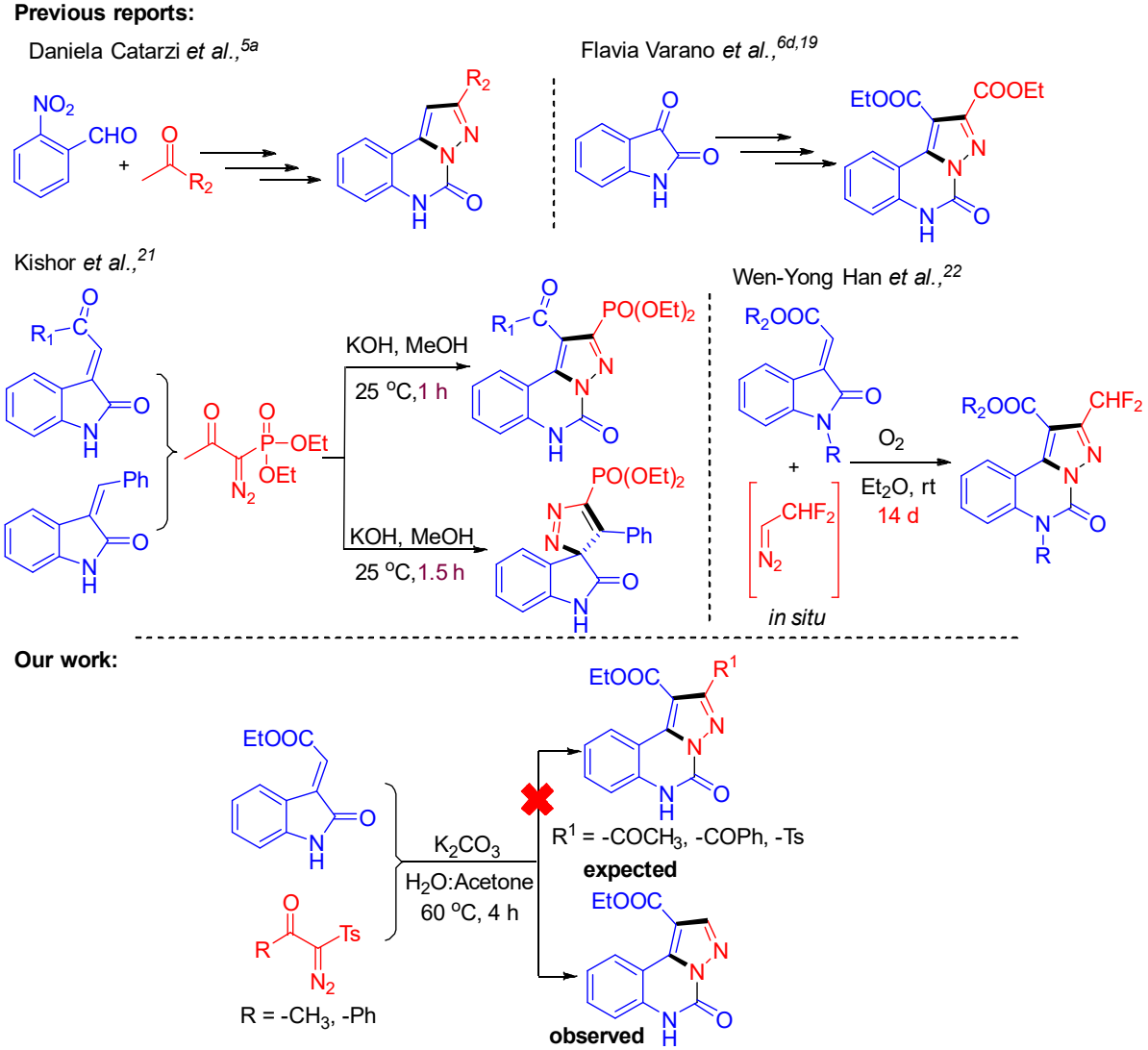
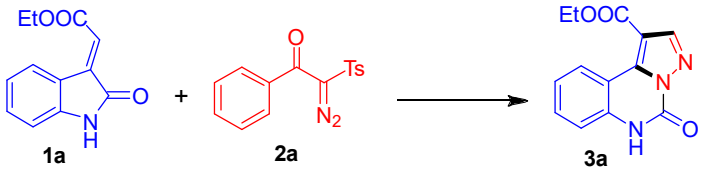


Figure 2. Literature precedents for the synthesis of pyrazoloquinazolines

RESULTS AND DISCUSSION

In our recent studies, we have developed efficient strategies *via* an *in situ* generated diazomethanes with substituted 3-ylideneoxindoles and isatins under metal-free conditions with excellent regio/diastereoselectivity to access the biologically interesting pyrazolo-[1,5-*c*]quinazolines, viridicatin derivatives and marinoquinolines.[24] Inspired by the literature as well as our own work in regioselective ring expansion, 3-ylideneoxindole **(1)** with tosyldiazomethane (TsDAM) **(2)** were chosen for the synthesis of either benzoyl/acylated or tosylated pyrazolo-[1,5-*c*]quinazolines *via* an anticipated 1,3-dipolar cycloaddition followed by a ring expansion under mild reaction conditions. After the X-ray analysis of the resulting product, we concluded that the reaction ended with the formation of unexpected product pyrazolo-[1,5-*c*]quinazoline by the elimination of both benzoyl/acyl and tosyl substituents through regioselective ring expansion.

Table 1: **Optimization of the Reaction Conditions**[a]



Entry	Base	Solvent	Temp(°C)	Time(in h)	Yield (%)[b]
1	K_2CO_3	EtOH	rt	8 h	70
2	K_2CO_3	EtOH	80	1 h	78
3	-	EtOH	80	4 h	-
4	K_2CO_3	MeOH	80	1 h	73
5	K_2CO_3	H_2O	100	24 h	-
6	K_2CO_3	H_2O/Acetone	60	4 h	88
7	Cs_2CO_3	H_2O/Acetone	60	4 h	80
8	^{t}BuOK	H_2O/Acetone	60	4 h	78
9	DBU	H_2O/Acetone	60	4 h	75
10	Et_3N	H_2O/Acetone	60	4 h	68
11	Pyridine	H_2O/Acetone	60	4 h	60
12	K_2CO_3	H_2O/DCM	60	4 h	70
13	K_2CO_3	H_2O/THF	60	4 h	65
14	K_2CO_3	H_2O/CH_3CN	60	4 h	66
15	K_2CO_3	CH_3CN	80	24 h	-
16	K_2CO_3	DMF	100	24 h	-
17	K_2CO_3	DCE	85	24 h	-
18	K_2CO_3	toluene	100	24 h	-
19	K_2CO_3	THF	70	24 h	-

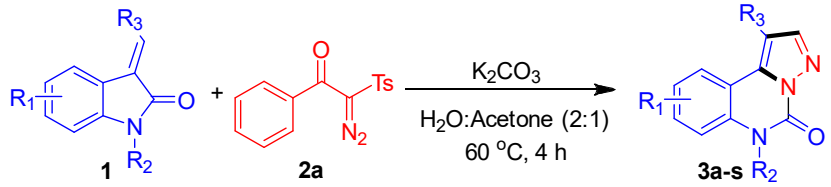
[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), and base (2 mmol) stirred in open air atmosphere. [b]Isolated yield.

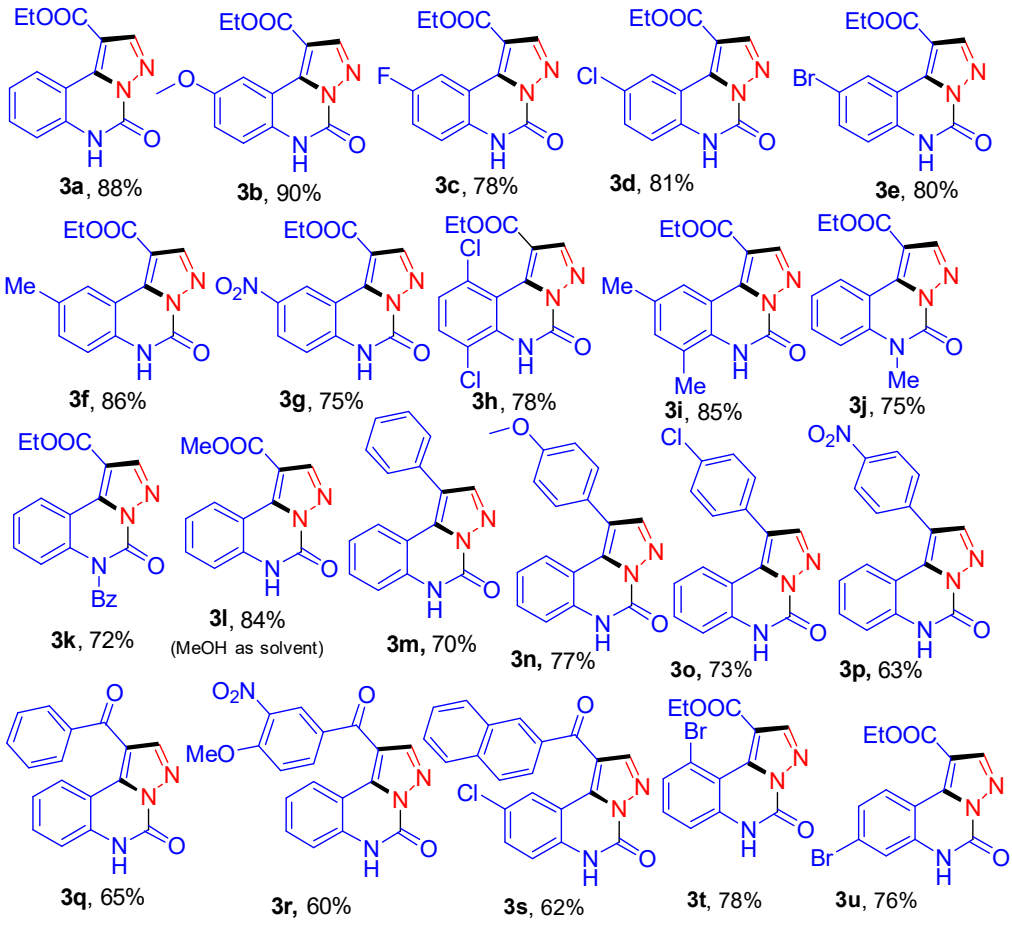
This unusual observation prompted us to further investigate the model reaction between **1a** and **2a** by changing various parameters including the use of bases, solvents, and temperature to evaluate the optimal conditions. We started our studies by treating **1a** (1 mmol) with **2a** (1 mmol) in the presence of K_2CO_3 (2 mmol) in ethanol at room/elevated temperature, the reaction proceeded smoothly and yielded the product **3a** in 70 and 78%, respectively (**Table 1**, entries 1-2). Notably, no desired product formation was observed in the absence of base (**Table 1**, entry 3). Further, when the reaction was performed in methanol (**Table 1**, entry 4), the trans-esterification product was observed in 73% (**3l**, **Table 2**). Next, to avoid the alcoholic solvent and to make the reaction much greener, we performed the reaction in H_2O at 100 ^oC. Unfortunately, due to insolubility of the starting materials the reaction failed to yield the product **3a** (**Table 1**, entry 5). However, to avoid the solubility problem we performed the reaction in H_2O/Acetone (2:1) mixture at 60 ^oC. To our delight, the reaction proceeded smoothly, and the excellent improvement of the yield was observed (**Table 1**, entry 6). Next, a series of experiments were conducted with different bases *viz.,* Cs_2CO_3, ^{t}BuOK, DBU, Et_3N and pyridine to increase the product formation, no significant results were obtained (**Table 1**, entries 7-11). Attempts were also made to improve the product formation by performing the reaction in mixed solvents, none of these were found effective (**Table 1**, entries 12-14). Additionally, we also screened the aprotic solvents, and found to be incompetent (**Table 1**, entries 15-19). It is noteworthy to mention that only protic solvents effected the formation of the products in good to excellent yields. Remarkably, the choice of solvent was crucial for this transformation and affected the yields significantly. Therefore, after careful screening the optimized reaction conditions are the following: 3- ylideneoxindole **1** (1 mmol), tosyldiazomethane (TsDAM) **2** (1 mmol) and K_2CO_3 (2 mmol) H_2O/Acetone (2:1) at 60 °C.

With the optimal conditions in hand, we explored the generality and substrate scope of the reaction by screening different 3-ylideneoxindoles (**Table 2**). Initially, a variety of ethyl 2-(2-oxoindolin-3-ylidene)acetate with different functional groups was screened under the optimized conditions, which provided the corresponding pyrazolo-[1,5-*c*]quinazoline derivatives in good to excellent yields (60−90%). From the results it was clear that, slightly higher yields were obtained with the substrates on benzene ring bearing electron-donating groups than the electron-withdrawing groups. The methyl ester and the halogen-substituted 3-ylideneoxindoles were also applied to the reactions, delivering the desired products in good yields. The *N*-protected 3-ylideneoxindoles resulted in the desired products **3j** and **3k** in 75% and 72% yields. Further, various benzylideneindolin-2-ones and 2-oxo-2-phenylethylideneindolin-2-ones were synthesized from the corresponding 3-ylideneoxindoles. They reacted smoothly with diazomethane substrate **2** and provided the corresponding pyrazolo-[1,5-*c*]quinazoline in moderate to good yield (**Table 2**). The electronic feature of both substrates influenced the reaction yields. The substrates with electron donating

groups on **1** at -R_3 position delivered the corresponding products in slightly higher yields than their counterparts. However, naphthyl substituted 2-oxoethylideneindolin-2-one afforded the corresponding pyrazolo-quinazoline in moderate yield. All the compounds (**3a-u**) were isolated by simple filtration, which did not require any column chromatography technique for purification.

Table 2: **Synthesis of pyrazolo-[1,5-*c*]quinazolines**



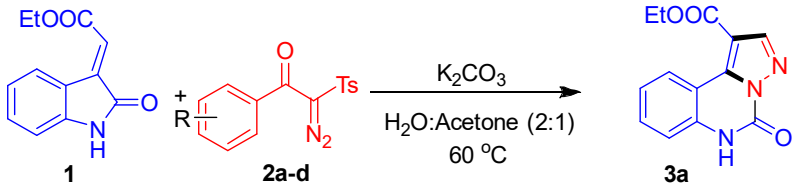


[a]Reaction conditions: **1** (1 mmol), **2a** (1 mmol) and K_2CO_3 (2 mmol), in H_2O:Acetone (2:1), 80 °C, 1 h. [b]Isolated yields

On the other hand, to extend the synthetic feasibility as well as our curiosity, we also examined the reaction between the electronically varied α-benzoyl-TsDAM **2a-d** with ethyl 2-(2-oxoindolin-3-ylidene)acetate **1**. It is to be noted that the electron withdrawing groups (-NO_2, -Cl) on the **2a** delivered the desired product **3a** with the better yields in shorter reaction times than the

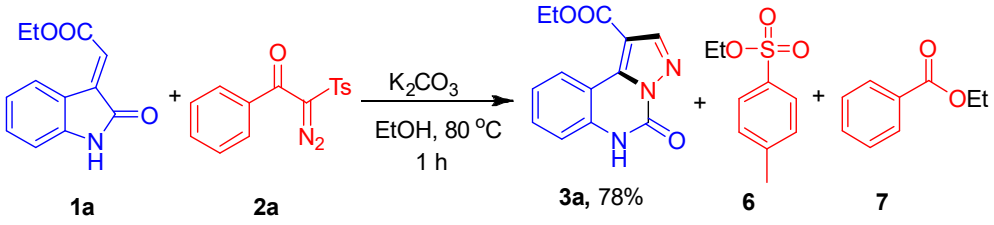
electron donating groups (-Me) (**Scheme 1**). Next, our curiosity further extended to examine the nature of the solvent, systematic comparative experiments were performed in ethanol. Reaction in ethanol displayed faster reaction times than the water with almost same efficacy (**Scheme 2**), which provided the desired product **3a** in 78% yield along with the by-products ethyl 4-methylbenzenesulfonate (**6**) and ethyl benzoate (**7**), which are useful synthetic precursors in the organic synthesis.

Scheme 1. Examination of various tosyldiazomethanes (TsDAM) with ethyl 2-(2-oxoindolin-3-ylidene)acetates

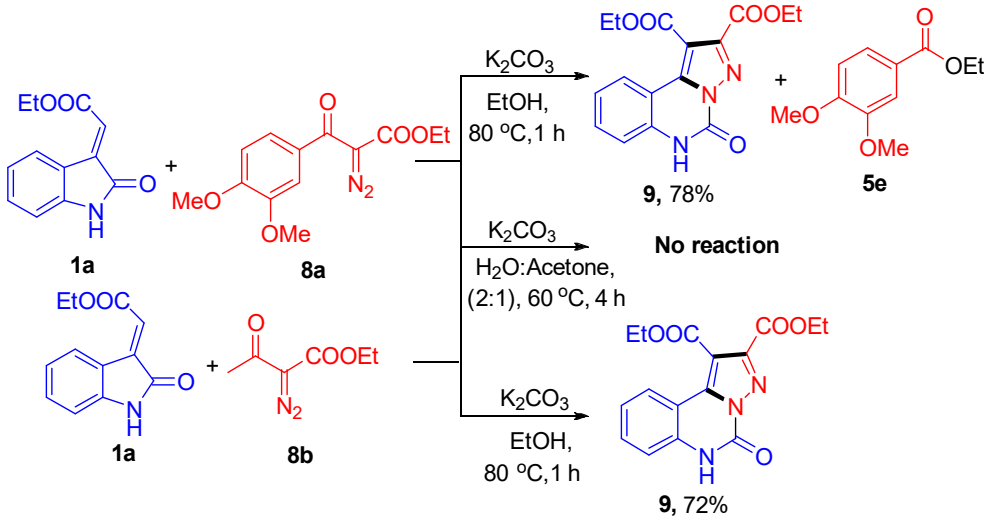


Substrate 2	Time (h)	Yield %
2a, R= H	4 h	88
2b, R= 4-NO_2	2.5 h	86
2c, R= 4-Cl	2.5 h	80
2d, R= 4-Me	8 h	65

Scheme 2. Synthesis of 3a in ethanol

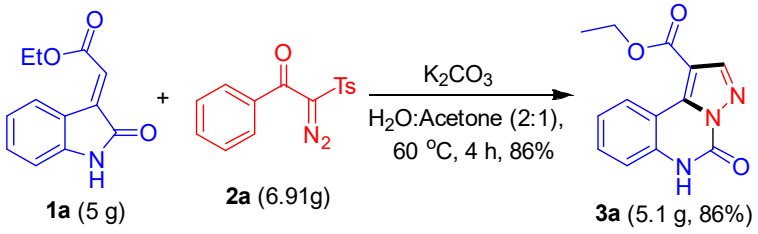


Scheme 3. Synthetic utility of ethyl benzoyl/acyl diazomethane



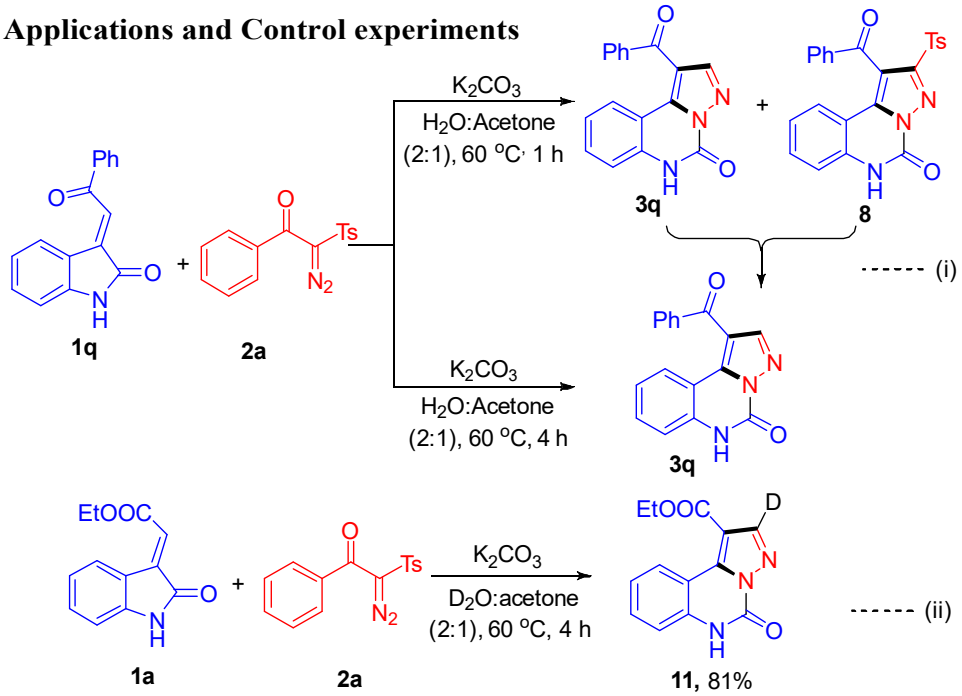
Inspired by the above results, we attempted to synthesize the biologically important dicarboxylates (**Figure 1**) with ethyl 2-diazo-3-(3,4-dimethoxyphenyl)-3-oxopropanoate (**8a**) and 3-diazo-4-ethoxy-2,4-dioxobutan-1-ylium (**8b**) with optimized reaction conditions. Unfortunately, the present base mediated reaction did not work; the lower nucleophilic strength of H_2O and the acyl/donating group containing benzoyl functionality could not be eliminated to produce the key cycloaddition intermediate. Surprisingly, the replacement of H_2O with ethanol in the presence of base at 80 °C afforded the desired product diethyl 5-oxo-5,6-dihydropyrazolo[1,5-*c*]quinazoline-1,2-dicarboxylate **9** in both the cases (**8a** and **8b**) with good yields (**Scheme 3**).

Scheme 4. Gram scale synthesis of 3a



To demonstrate the synthetic utility of the reaction, a gram-scale synthesis was executed using **1a** (5 g, 23.03 mmol) and **2a** (6.9 g, 23.03 mmol) to give the corresponding product **3a** in 86% (5.1 g, **Scheme 4**).

Scheme 5. Applications and Control experiments



Our results prompted us to perform several control experiments to verify the reaction mechanism and the role of the solvents. We could observe the time dependent product formation by isolating the reaction intermediate **8** and the desired product **3a** at different time (**Scheme 5**,

eq. i). Attempts were also made to understand the role of protic solvent by performing the experiments in the acetone- D_2O system, wherein the deuterated product **11** was achieved in good yield (**Scheme 5**, eq. ii). The disappearance of the peak at 8.18ppm in the ^{1}H NMR and the mass of the deuterated compound **11** in HRMS were clear evidence for the product formation as well as the solvent involvement in the reaction (**Figure 3** and ESI).

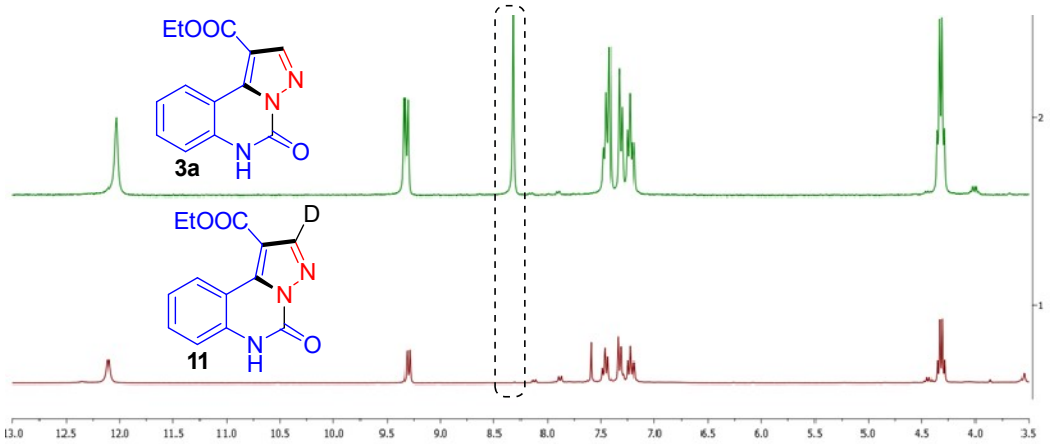


Figure 3. Stacked plot of ^{1}H NMR spectra of **3a** and **11**

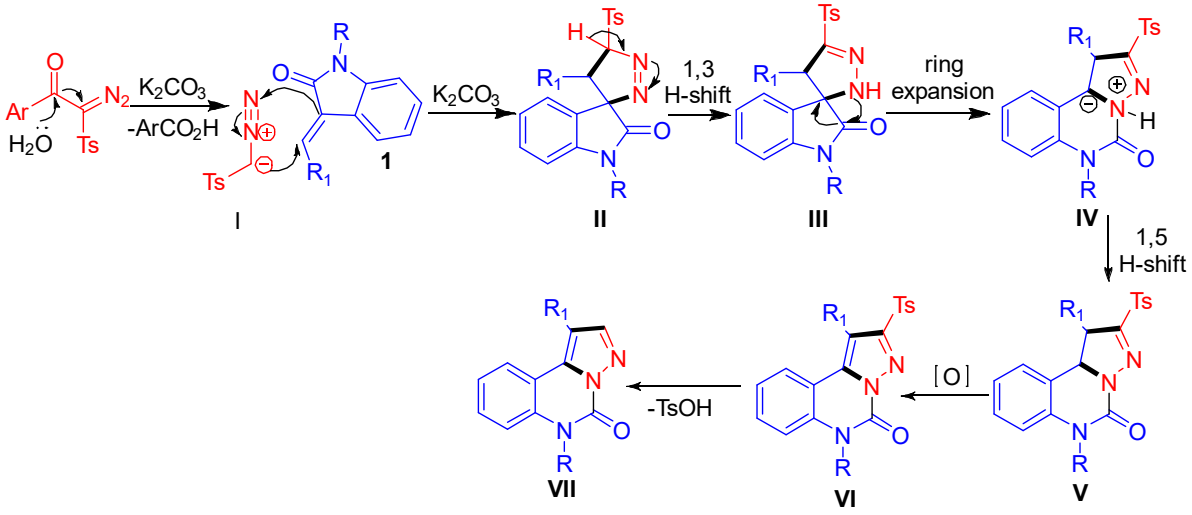


Figure 4: Plausible reaction mechanism

On the basis of deuterated experimental results, by-products formed in Scheme 2 and the relevant literature reports, a plausible mechanism for this transformation is outlined in **Figure 4**. First, the reaction of 2-diazo-1-aryl-2-tosylethanone with H_2O in the presence of base forms the intermediate (**I**),[25] which undergoes a 1,3-dipolar cycloaddition with alkene partner, 3-ylideneoxindole (**1**), leading to the formation of an intermediate (**II**), Next, 1,3-H shift occurred to give the spiro intermediate (**III**). The spiro-Intermediate (**III**) further undergone rearrangement *via* ring expansion to afford the intermediate (**IV**), which was further encountered 1,5- H shift to

yield the intermediate (**V**), undergone oxidative aromatization and afforded the 2-tosylpyrazolo[1,5-*c*]quinazolin-5(6*H*)-ones (**VI**), which was isolated and confirmed by NMR and HRMS. Finally, the formation of the desired product pyrazolo-[1,5-*c*]quinazolines (**VII**) was obtained by the replacement of tosyl group (**Figure 4**).

CONCLUSION

In summary, we developed an efficient, environmentally benign method for the synthesis of pyrazolo-[1,5-*c*]quinazolines *via* regioselective ring expansion of 3-ylidene oxindoles with tosyldiazomethane (TsDAM) in water/protic solvent. The solvent involvement in the present reaction has been explored for the first time. The mild nucleophilic solvent would participate in the reaction and facilitate to generate the key cycloaddition intermediate as well as the replacement of the tosyl group by donating the proton. A wide array of 3-ylideneoxindoles were tolerated in the reaction and afforded pyrazolo-[1,5-*c*]quinazolines in good to excellent yields. The product could be easily isolated in high-purity with simple extraction. Moreover, present protocol is amicable for the scale up synthesis. Further, the current approach is explored for the direct synthesis of biologically important compounds and also having scope for late stage C-H functionalization on pyrazole ring which could facilitate to generate the large library of the pyrazolo-[1,5-*c*]quinazolines.

EXPERIMENTAL SECTION

General Information:

General Procedures.

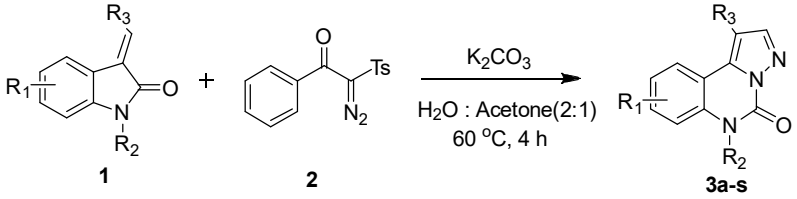
Unless otherwise noted, all reagents were used as received from commercial sources. All air and moisture sensitive reactions were conducted under a nitrogen or argon atmosphere using flame-dried or oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF) was dried over Na, benzophenone and distilled prior to use. Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light, iodine and p-anisaldehyde for visualization. Column chromatography was carried out using silica gel (60-120 mesh or 100- 200 mesh) packed in glass columns. Technical grade EtOAc and petroleum ether used for column chromatography and were distilled prior to use. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Room temperature (r.t.) is 23-25 °C.

Materials. Commercial reagents were purchased from Merck, Alfa, Spectrochem or TCI, and used as received with the following exceptions. Tetrahydrofuran (THF), ethylene glycol dimethyl ether (DME), toluene and 1,4-dioxane were dried over Na with benzophenone-ketyl intermediate as indicator.

Dichloroethane (DCE) and Dichloromethane DCM) were distilled over CaH_2 and acetonitrile (CH_3CN) was distilled over P_2O_5. *N,N*-Dimethylformamide (DMF) was distilled under reduced pressure. Other commercially available reagents and solvents were used without further purification.

Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO as solvent on Bruker AVANCE 400, INOVA instruments with 400, 300 and 500 MHz frequencies spectrometers. The coupling constant J is given in Hz. Chemical shifts (δ) were reported in ppm relative to the residual solvent signal ($CDCl_3$ δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR), DMSO (^{1}H NMR: δ = 2.54and ^{13}C NMR: δ = 39.52 ppm). Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard, or TMS (δ = 0.0) as internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, qd = quartet of doublet, m = multiplet, br = broad, tt = triplet of triplet. IR spectra were recorded on a Bruker Infrared spectrophotometer and are reported as cm-1. High-resolution mass spectra (HRMS) were recorded on a Waters- spectrometer-TOF.

General procedure for the preparation of substituted- pyrazolo-[1,5-*c*]quinazolines (3a-u):



The 3-ylideneoxindoles **1** (0.50 mmol), Substituted 2-diazo-1-phenyl-2-tosylethan-1-ones **2a** (0.50mmol) and K_2CO_3 (1.0 mmol) were stirred in 5.0 mL of (H_2O: Acetone (2:1)) was stirred at 60 ^{o}C for 4 h in an oil bath. Upon the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the product got precipitated, which was isolated by the simple filtration after (3 x 50 ml) water washing (**3a-s)**.

*Ethyl 5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3a**):* Compound **3a** was obtained by the simple filtration as a creamy white solid (103mg, 88%). Mp 287 – 289 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 11.89 (s, 1H), 9.18 (d, *J* = 8.1 Hz, 1H), 8.18 (s, 1H), 7.35 – 7.26 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$+ DMSO-d_6) δ 167.3, 151.1, 149.3, 146.8, 140.5, 136.6, 132.4, 128.0, 120.8, 116.8, 115.5, 65.6, 19.2. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{12}N_3O_3$ 258.0873; Found 258.0874.

*Ethyl 9-methoxy-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3b**):* Compound **3b** was obtained by the simple filtration as a creamy white solid (100 mg, 90%). Mp 275 – 278 ^{o}C.^{1}H NMR (300 MHz, DMSO-d_6) δ 12.16 (s, 1H), 8.92 (d, *J* = 2.3 Hz, 1H), 8.42 (s, 1H), 7.32 – 7.23 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.0, 155.2,

146.3, 144.1, 142.0, 130.1, 120.7, 117.5, 112.6, 110.4, 109.8, 61.2, 55.9, 14.6. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{14}H_{14}N_3O_4$ 288.0978; Found 288.0979.

*Ethyl 9-fluoro-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3c**):* Compound **3c** was obtained by the simple filtration as a creamy white solid (91 mg, 78%). Mp 297 – 302 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 9.10 – 8.99 (m, 1H), 8.41 (s, 1H), 7.51 (dd, J = 11.4, 5.5 Hz, 1H), 7.38 (dd, J = 8.9, 4.9 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 167.5, 162.3(d, $J_{C\text{-}F}$ = 238.2 Hz), 151.0, 148.7, 146.0, 137.6, 124.7(d, $J_{C\text{-}F}$ = 24.4 Hz), 122.8, 117.6, 117.3, 115.6, 66.0, 19.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ -118.4. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{11}O_3N_3F$ 276.07790; Found 258.1074; found: 276.0779.

*Ethyl 9-chloro-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3d**):* Compound **3d** was obtained by the simple filtration as a creamy white solid (93 mg, 81%). Mp 280 – 282 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (s, 1H), 9.35 (s, 1H), 8.45 (s, 1H), 7.70 – 7.64 (m, 1H), 7.39 (d, J = 8.8 Hz, 1H), 4.37 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.8, 146.4, 144.1, 141.0, 135.0, 132.1, 127.3, 126.4, 118.1, 113.3, 111.0, 61.4, 14.6. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{11}O_3N_3Cl$ 292.0483; found: 292.0483.

*Ethyl 9-bromo-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3e**):* Compound **3e** was obtained by the simple filtration as a creamy white solid (90mg, 80%). Mp 285 – 289 °C. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 12.10 (s, 1H), 9.48 (d, J = 2.0 Hz, 1H), 8.26 (s, 1H), 7.45 (dd, J = 8.7, 2.0 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 168.7, 149.4, 148.9, 143.3, 142.6, 136.4, 133.7, 124.6, 120.3, 119.1, 117.4, 66.0, 18.8. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{11}O_3N_3Br$ 335.9978; found: 335.9982.

*Ethyl 9-methyl-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3f**):* Compound **3f** was obtained by the simple filtration as a creamy white solid (100 mg, 86%). Mp 270 – 275 °C. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 11.53 (s, 1H), 8.71 (s, 1H), 7.92 (s, 1H), 6.85 – 6.72 (m, 2H), 3.94 (q, J = 7.1 Hz, 2H), 1.99 (s, 3H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$+ DMSO-d_6) δ 167.5, 151.3, 149.6, 146.8, 138.1, 137.7, 137.6, 132.1, 120.6, 116.7, 115.3, 65.6, 25.9, 19.1. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{14}H_{14}O_3N_3$ 272.1029; found: 272.1030.

*Ethyl 9-nitro-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3g**):* Compound **3g** was obtained by the simple filtration as a pale yellow solid (86 mg, 75%). Mp 300 – 304 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.76 (s, 1H), 10.25 (d, J = 2.3 Hz, 1H), 8.49 (s, 1H), 8.42 – 8.36 (m, 1H), 7.56 – 7.45 (m, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 162.7, 146.5, 144.0, 142.5, 141.1, 140.9, 126.9, 123.7, 117.4, 112.1, 111.4, 61.6, 14.5. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{11}O_5N_4$ 303.0724; found: 303.0729.

*Ethyl 7, 10-dichloro-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3h**):* Compound **3h** was obtained by the simple filtration as a creamy white solid (88 mg, 78%). Mp 260 – 264 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.30 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.6, 145.7, 143.1, 136.3, 132.7, 131.0, 130.6, 126.2, 118.3, 116.1, 112.7, 61.7, 14.1. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{13}H_{10}O_3N_3Cl_2$ 326.0093; found: 326.0095.

*Ethyl 7,9-dimethyl-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3i**):* Compound **3i** was obtained by the simple filtration as a creamy white solid (98 mg, 85%). Mp 250 – 254 °C. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 10.81 (s, 1H), 8.99 (s, 1H), 8.30 (s, 1H), 7.14 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H), 2.32 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8, 147.5, 144.7, 142.3, 134.6, 133.6, 130.6, 126.0, 122.5, 112.3, 111.3, 61.1, 21.2, 17.0, 14.4. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{15}H_{16}O_3N_3$ 286.1186; found: 286.1187.

*Ethyl 6-methyl-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3j**):* Compound **3j** was obtained by the simple filtration as a creamy white solid (87 mg, 75%). Mp 240 – 242 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (dd, J = 8.1, 1.4 Hz, 1H), 8.44 (s, 1H), 7.70 – 7.64 (m, 1H), 7.45 – 7.36 (m, 2H), 4.47 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8, 147.0, 145.3, 140.9, 136.4, 132.1, 128.8, 123.8, 114.3, 113.0, 111.0, 61.1, 31.5, 14.3. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{14}H_{14}O_3N_3$ 272.1029; found: 272.1029.

*Ethyl 6-benzyl-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3k**):* Compound **3k** was obtained by the simple filtration as a creamy white solid (81 mg, 72%). Mp 257 – 259 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (d, J = 8.0 Hz, 1H), 8.49 (s, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.35 – 7.26 (m, 6H), 5.63 (s, 2H), 4.44 (q, J = 7.0 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.9, 147.3, 145.9, 141.1, 135.8, 135.0, 132.0, 129.0, 128.9, 127.8, 126.6, 123.9, 115.3, 113.3, 111.2, 61.1, 48.0, 14.3. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{20}H_{18}O_3N_3$ 348.1342; found: 348.1345.

*Methyl 5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3l**):* Compound **3l** was obtained by the simple filtration as a creamy white solid (100 mg, 84%). Mp 280 – 285 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 9.28 (dd, J = 8.2, 1.1 Hz, 1H), 8.48 (s, 1H), 7.65 (dd, J = 8.4, 7.3, 1.4 Hz, 1H), 7.42 – 7.34 (m, 2H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.3, 146.4, 144.3, 142.2, 136.1, 132.4, 127.4, 123.5, 116.2, 112.0, 110.2, 52.5. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{12}H_{10}O_3N_3$ 244.0716; found: 244.0718.

*1-phenylpyrazolo[1,5-c]quinazolin-5(6H)-one(**3m**):* Compound **3m** was obtained by the simple filtration as a creamy white solid (82mg, 70%). Mp 302 – 304 °C. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 11.97 (s, 1H), 8.29 – 8.22 (m, 1H), 8.07 (s, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.36 (d, J =

7.7 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$+ DMSO-d_6) δ 149.8, 149.6, 140.4, 139.7, 138.1, 136.4, 135.9, 135.4, 134.1, 128.0, 127.6, 122.9, 121.3, 117.6. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{16}H_{12}ON_3$ 262.0974; found: 262.0978.

*1-(4-methoxyphenyl)pyrazolo[1,5-c]quinazolin-5(6H)-one(**3n**):* Compound **3n** was obtained by the simple filtration as a creamy white solid (89 mg, 77%). Mp 290 – 292 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.05 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.39 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.12 – 7.05 (m, 3H), 3.84 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 159.5, 145.4, 144.9, 135.3, 134.9, 131.2, 130.5, 124.2, 123.2, 122.7, 119.2, 116.4, 114.8, 113.2, 55.7. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{17}H_{14}O_2N_3$ 292.1080; found: 292.1085.

*1-(4-chlorophenyl)pyrazolo[1,5-c]quinazolin-5(6H)-one(**3o**):* Compound **3o** was obtained by the simple filtration as a creamy white solid (84 mg, 73%). Mp 287 – 289 °C. ^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ 8.14 (s, 1H), 7.99 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.38 (m, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.08 – 7.01 (m, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 144.5, 144.4, 135.0, 134.4, 131.7, 129.7, 129.2, 128.6, 127.8, 122.4, 122.4, 118.9, 115.9, 112.6. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{16}H_{11}ON_3Cl$ 296.0585; found: 296.0588.

*1-(4-nitrophenyl)-6,10b-dihydropyrazolo[1,5-c]quinazolin-5(1H)-one(**3p**):* Compound **3p** was obtained by the simple filtration as a pale yellow solid (72 mg, 63%). Mp 310 – 312 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.11 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 4.3 Hz, 3H), 7.51 – 7.45 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 145.3, 144.9, 135.4, 135.0, 132.3, 130.6, 129.9, 129.4, 128.6, 123.2, 122.8, 119.5, 116.5, 113.0. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{16}H_{11}N_4O_3$ $[M+H]^+$: 307.0825; found: 307.0829.

*1-benzoylpyrazolo[1,5-c]quinazolin-5(6H)-one(**3q**):* Compound **3q** was obtained by the simple filtration as a creamy white solid (75 mg, 65%). Mp 267 – 269 °C. ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6) δ 12.30 (s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.07 (s, 1H), 7.79 (d, *J* = 10.6 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$+ DMSO-d_6) δ 193.1, 151.5, 149.3, 147.1, 145.6, 140.7, 139.3, 137.5, 137.0, 135.1, 133.9, 132.6, 131.3, 128.0, 122.1, 121.0, 116.8. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{17}H_{12}O_2N_3$ 290.0924; found: 290.0927.

*1-(3-methoxy-4-nitrobenzoyl)pyrazolo[1,5-c]quinazolin-5(6H)-one(**3r**):* Compound **3r** was obtained by the simple filtration as a pale yellow solid (67 mg, 60%). Mp 286 – 288 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.60 (d, *J* = 7.4 Hz, 1H), 8.38 -8.32 (m, 2H), 8.18 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 4.06 (s, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 187.2, 155.8, 146.7, 144.4, 142.0, 139.4, 136.1, 136.1, 132.5,

131.1, 127.1, 126.2, 123.4, 117.2, 116.4, 115.0, 112.0, 57.8. HRMS (ESI) m/z: [M + H]+ Calcd for C_{18} H_{13} O_5 N_4 365.0880; found: 365.0892.

*1-(2-naphthoyl)-9-chloropyrazolo[1,5-c]quinazolin-5(6H)-one(**3s**):* Compound **3s** was obtained by the simple filtration as a creamy white solid (69mg, 62%). Mp 274 – 276 °C. ^{1}H NMR (500 MHz, $CDCl_3$+ DMSO-d_6) δ 12.35 (s, 1H), 9.03 – 8.95 (m, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.25 – 8.21 (m, 1H), 8.05 – 7.98 (m, 2H), 7.99 – 7.91 (m, 2H), 7.69 – 7.63 (m, 1H), 7.59 (dd, J = 15.4, 8.3 Hz, 1H), 7.49 (dd, J = 13.3, 5.3 Hz, 1H), 7.42 (dd, J = 14.2, 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$+ DMSO-d_6) δ 194.95, 152.0, 148.9, 145.7, 141.0, 140.2, 139.7, 137.1, 136.9, 136.7, 134.8, 133.9, 133.7, 132.9, 132.2, 132.0, 130.2, 130.0, 123.2, 123.0, 118.2. HRMS (ESI) m/z: [M + H]+ Calcd for C_{21} H_{13} O_2 N_3 Cl 374.0690; found: 374.0704.

*Ethyl 10-bromo-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3t**)*: Compound **3t** was obtained by the simple filtration as a creamy white solid (87mg, 78%). Mp 286 – 288 °C. ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 12.17 (s, 1H), 8.14 (s, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.36 – 7.24 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 168.7, 149.4, 148.9, 143.3, 142.6, 136.4, 133.7, 124.6, 120.3, 119.1, 117.4, 66.0, 18.8. HRMS (ESI) m/z: [M + H]+ Calcd for C_{13} H_{11} O_3 N_3 Br 335.9978; found: 335.9982.

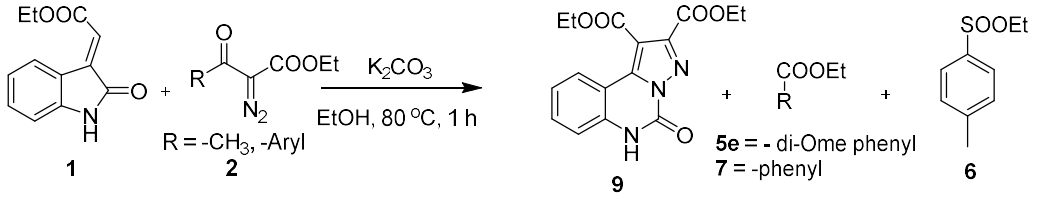
*Ethyl 8-bromo-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate(**3u**):* Compound **3u** was obtained by the simple filtration as a creamy white solid (85mg, 76%). Mp 290 – 292 °C. ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 12.34 (s, 1H), 9.24 (d, J = 8.7 Hz, 1H), 8.32 (s, 1H), 7.52 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 167.4, 151.1, 148.8, 146.2, 142.0, 134.0, 130.9, 129.9, 123.3, 116.0, 115.6, 65.9, 19.3. HRMS (ESI) m/z: [M + H]+ Calcd for C_{13} H_{11} O_3 N_3 Br 335.9978; found: 335.9982.

*1-benzoyl-2-tosylpyrazolo[1,5-c]quinazolin-5(6H)-one(**8**):* Compound **8** was obtained by the simple filtration as a creamy white solid (84 mg, 42%). Mp 256 – 258 °C.^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 12.37 (s, 1H), 7.81 (d, J = 7.4 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.61 (t, J = 6.9 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 4.6 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.0 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 194.7, 158.7, 150.1, 148.6, 144.5, 141.7, 141.3, 140.0, 139.3, 136.3, 134.6, 134.5, 133.8, 133.2, 128.7, 128.6, 121.6, 120.4, 115.9, 26.4. HRMS (ESI) m/z: [M + H]+ Calcd for C_{24} H_{18} N_3 O_4 S 444.1018; found: 444.1021.

*Ethyl 5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1-carboxylate-2-d(**11**):* Compound **11** was obtained by the simple filtration as a creamy white solid (96 mg, 81%). Mp 290 – 292 °C.^{1}H NMR (300 MHz,

$CDCl_3$+DMSO-d_6) δ 12.11 (s, 1H), 9.30 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 167.4, 149.4, 146.8, 140.4, 136.6, 132.4, 128.0, 120.8, 116.8, 65.6, 19.1. HRMS (ESI) m/z: [M + H]+ Calcd for C_{13} H_{11} D N_3 O_3 259.0941; found: 259.0948.

General procedure for the preparation of substituted- pyrazolo-[1,5-*c*]quinazolines (9):



The 3–ylideneoxindoles **1** (0.50 mmol), Substituted 2-diazo-1-phenyl-2-tosylethan-1-ones **2a** (0.50mmol) and K_2CO_3 (1.0 mmol) were stirred in 5.0 mL of ethanol was stirred at 80 °C for 1 h in an oil bath.. Upon the completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with 10 ml of water and extracted with EtOAc (3X10 ml). The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by flash column chromatography on silica gel (petroleum ether/EtOAc) to afford the desired products (**9**)

*Diethyl 5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1,2-dicarboxylate(**9**):* Compound **9** was obtained after column chromatography as a creamy white solid (118 mg, 78%). Mp 242 – 244 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.78 – 8.74 (m, 1H), 7.62 – 7.56 (m, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.39 – 7.34 (m, 1H), 4.48 – 4.43 (m, 4H), 1.43 (td, J = 7.1, 4.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.6, 161.9, 149.0, 145.5, 141.3, 134.2, 132.2, 126.4, 124.7, 116.5, 111.9, 110.8, 62.3, 62.0, 14.2, 14.0. HRMS (ESI) m/z: [M + H]+ Calcd for C_{16} H_{16} N_3 $O_5$330.1084; found: 330.1094.

*Ethyl 4-methylbenzenesulfonate(**6**):* Compound **6** was obtained after column chromatography as a colorless liquid (32mg, 60%).^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.6, 133.3, 129.8, 127.8, 66.8, 21.6, 14.7. HRMS (ESI) m/z: [M + H]+ Calcd for C_9 H_{13} O_3 S 201.0585; found: 201.0571.

*Ethyl benzoate(**7**):* Compound **7** was obtained after column chromatography as a colorless liquid(32 mg, 60%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.57 – 7.53 (m, 1H), 7.46 – 7.41 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.6, 132.8, 130.5, 129.5, 128.3, 60.9, 14.3. HRMS (ESI) m/z: [M + H]+ Calcd for C_9 H_{11} $O_2$151.0754; found: 151.0760.

ethyl 3,4-dimethoxybenzoate(5e): Compound 5e was obtained after column chromatography as a colorless liquid (40 mg, 70%).^1H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 1H), 7.54 (d, J = 6.4 Hz, 1H), 6.94 –

6.83 (m, 1H), 4.45 (q, J = 7.1 Hz, 2H), 3.94 (s, 6H), 1.39 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 152.9, 148.6, 123.5, 123.0, 112.0, 110.2, 60.8, 56.0, 14.4. HRMS (ESI) m/z: [M + H]+ Calcd for C_{11} H_{15} O_4 $[M + H]^+$: 211.0965; found: 211.0976.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data (PDF)

Accession Codes

The **CCDC 1942896** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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