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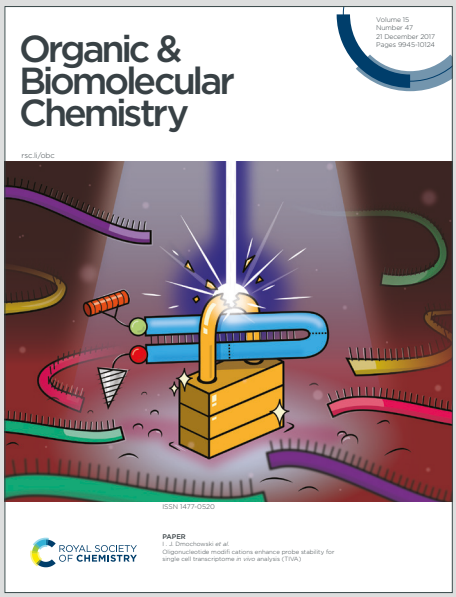

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ARTICLE

Possible competitive modes of decarboxylation in the annulation reactions of ortho-substituted anilines and arylglyoxylates

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Annulation reactions of ortho-substituted anilines and arylglyoxylates in the presence of $K_2S_2O_8$ at 80 °C under metal-free neutral conditions have been investigated, which extended a platform for the tandem synthesis of nitrogen heterocycles. While arylglyoxylic acids are known to undergo decarboxylation to form acyl radical in the presence of $K_2S_2O_8$ and used in the Minisci acylation of electron-deficient (hetero)aromatics, their reactions with electron-rich ortho-substituted anilines to form the nitrogen heterocycles have recently been studied. Depending upon the experimental conditions used in the reactions, the mechanism to the formation of heterocycles involving reactions of acyl radical or aryl iminocarboxylic acids has been postulated. Given subtle understanding of the mechanisms of annulations reactions of 2-substituted anilines and arylglyoxylates in the presence of $K_2S_2O_8$, an extensive mechanistic investigation was undertaken. In the current study, the various mechanistic pathways including the generation of acyl, imidoyl, aminal, and N,O-hemiketal radicals have been postulated based on different possible decarboxylation modes. Some of the proposed intermediates are supported based on available analytical data. The protocol uses a single, inexpensive reagent $K_2S_2O_8$, which offers not only a transition-metal-free condition, but also serves as the reagent for the key decarboxylation step. Taken together, this study complements the current development of the annulations reactions of 2-substituted anilines and arylglyoxylates in terms of synthesis and mechanistic understanding.

INTRODUCTION

Benzodiazines, especially quinazolines (1,3-benzodiazines) represent privileged nitrogen heterocycles ubiquitously found in natural products, pharmaceuticals, and performance materials.[1] Because of their wide prevalence in chemical entities that demonstrate significant antihypertensive, antineoplastic, antidepressant, and antipsychotic activities, an impressive armoury of diverse synthetic routes have been developed for their synthesis.[2] A related class of nitrogen heterocycle, 2*H*-1,2,4-benzothiadiazine-1,1-dioxides, also exhibits considerable biological and pharmaceutical importance.[3] These heterocycles have reportedly been prepared by oxidative amidation although with a certain limitation.[4] Many of the previous reports to the synthesis of these heterocycles involve oxidative annulations of ortho-substituted anilines with a convenient acyl source such as, arylaldehyde, arylmethanol, or even arylmethane, wherein arylimines are often reported to form as the intermediates.[2,4]

Since the discovery of Minisci acylation,[5] arylglyoxylic acids have been extensively studied as the source of acylating agents in decarboxylative acylation reactions.[6] The acyl radical,[7] generated from arylglyoxylic acids by reaction with persulfate at an elevated temperature (>70 °C), undergoes nucleophilic substitution on the electron-deficient heterocycles yielding C-acylated products, often in high regioisomeric ratios.[5] While C-acylation of electron-deficient heteroaromatics using arylglyoxylic acids merits extensive discussion,[6d,8] decarboxylative N-acylation using arylglyoxylic acids largely remained unexplored until a seminal report appeared recently. In 2014, a pioneering work on decarboxylative N-acylation of electron-rich anilines using arylglyoxylic acids under visible light mediated photoredox-catalysis was reported by Lei et al.[9] The annulation reactions of ortho-substituted anilines and arylglyoxylic acids to the synthesis of nitrogen heterocycles, although limited to few examples, was demonstrated first time in this report (Scheme 1). Subsequent to the work of Lei et al., three research groups independently reported the annulations of ortho-substituted anilines and arylglyoxylic acids or salts to the synthesis of nitrogen heterocycles in the same year 2016. Huang *et al*. reported annulation reactions of *o*-phenylenediamine or 2-aminothiophenol and arylglyoxylic acid using electrochemical

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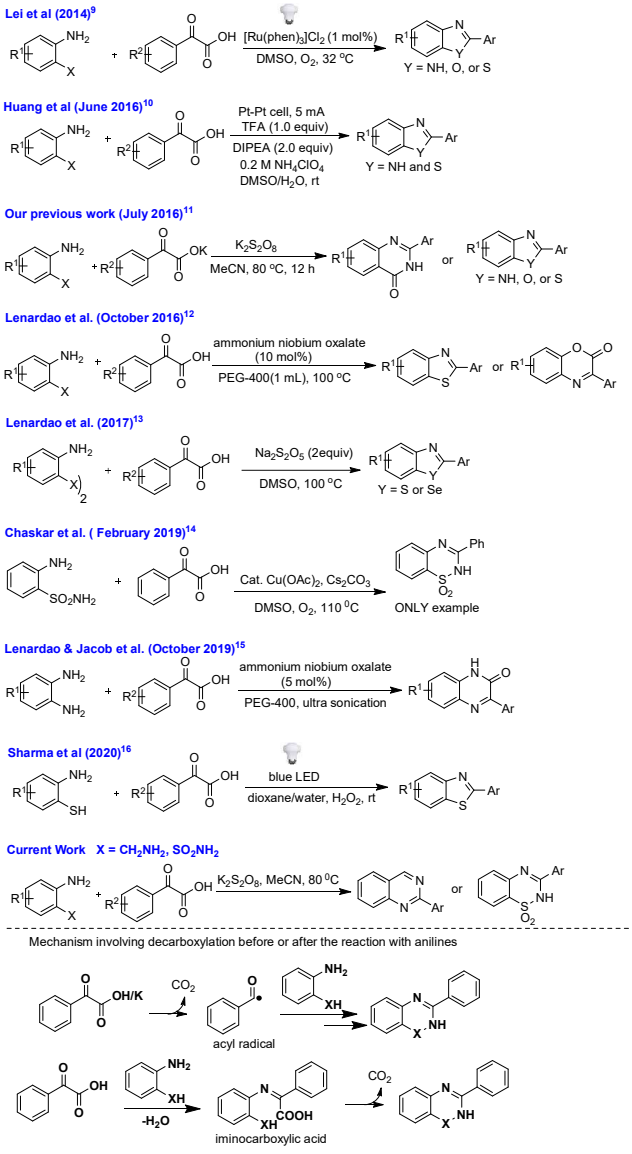
method in aqueous medium demonstrating a convenient, wide access to benzimidazoles and benzothiazoles.[10] We demonstrated an annulation reaction of *ortho*-substituted anilines encompassing broad substrate scope with arylglyoxylates to the synthesis of nitrogen heterocycles using an inexpensive oxidant $K_2S_2O_8$.[11] Concurrently, Lenardao *et al*. reported the annulation reactions using a niobium-catalyst,[12] and later in 2017 by $Na_2S_2O_5$[13] to the general synthesis of benzthiazoles, benoxazin-2-ones, and related heterocycles. A copper-catalyzed reaction of 2-aminobenzenesulfonamide and phenylglyoxylic acid is reported for the synthesis of 2*H*-1,2,4-benzothiadiazine-1,1-dioxide albeit limited to only one example.[14] Subsequent to their earlier contributions, Lenardao and Jacob *et al*. further demonstrated a niobium-catalyzed annulation of ortho-phenelynediamines and phenylglyoxylic acid to the synthesis of 3-arylquinoxalin-2(1*H*)-ones.[15] Very recently, Sharma et al. reported a transition-metal-free visible-light mediated synthesis of benzothiazoles.[16] The mechanistic pathways involving reactions of acyl radical[9,10,11] or aryl iminocarboxylic acids[10,12,13,15,16] have been postulated in these reports. Although a large variety of *ortho*-substituted anilines were covered in previous studies, annulation reactions of *ortho*-substituted aniline containing another ortho-amine functional group, such as 2-aminobenzylamine and arylglyoxylic acid remains unexplored. Such an investigation would be especially interesting and appealing in terms of delivery of product, possibly different modes of annulations, regioselective decarboxylative N-acylation that could occur at aniline or benzylamine nitrogen, and finding a rational mechanism to the product formation. Herein, we describe annulation reactions of 2-aminobenzylamines and arylglyoxylates in the presence of $K_2S_2O_8$ to the tandem preparation of 2-arylquinazolines. The extended substrate scope of the current protocol has been demonstrated with 2-aminobenzenesulfonamides that remained largely uncovered in previous studies. Unlike mechanistic studies previously reported, current mechanistic study reveals substantial difference including $K_2S_2O_8$ aided decarboxylation of iminocarboxylic acids and substrate dependent mechanistic pathway. Based on different possible decarboxylation modes, the formation of reactive intermediates, such as acyl, imidoyl, aminal, and N,O-hemiketal radicals have been proposed in the mechanism. Perhaps most importantly, $K_2S_2O_8$ serves as the reagent for the key decarboxylation step.



Scheme 1. Annulation of ortho-substituted anilines and arylglyoxylic acids or salts to the synthesis of nitrogen heterocycles

RESULTS AND DISCUSSION

The readily available 2-aminobenzylamine **1** and potassium salt of phenylglyoxylic acid **2a** were chosen for the annulation reaction. Reaction of **1** and **2a** in a mixture of solvents [CH_3CN/H_2O (1:1)] in the presence of 3 equiv of $K_2S_2O_8$ at 80 °C gave **3a** in 35% yield (Table 1, entry 1). When MeOH was used, a slightly reduced yield of **3a** was obtained (entry 2). However, a significant improvement in the yield was observed in the absence of any polar protic solvent. Thus, optimized reaction conditions entailed heating **1** and **2a** in the presence of $K_2S_2O_8$ in CH_3CN at 80 °C for 12 h, which afforded **3a** in 89% yield (entry 3). A subordinate amount of $K_2S_2O_8$ was somewhat detrimental (entry 4). Without $K_2S_2O_8$, the reaction did not give even a trace amount of **3a** suggesting the crucial role of

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$K_2S_2O_8$ in this tandem reaction (entry 5). Similar oxidants, such as $Na_2S_2O_8$ or oxone are comparatively less effective in the tandem reaction (entries 6-7).

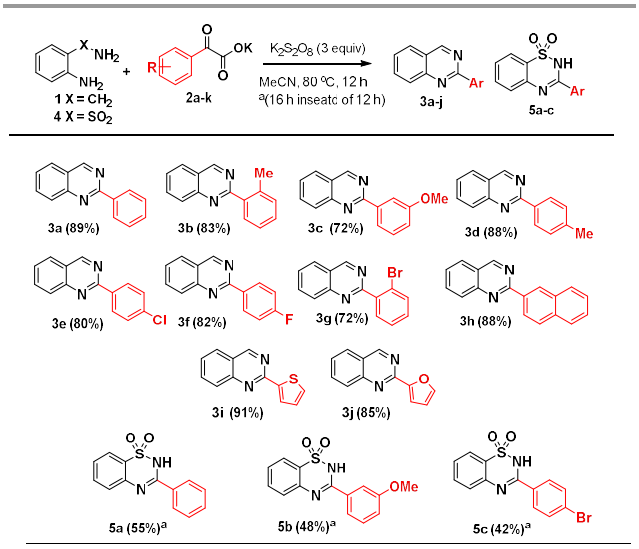
Table 1: Optimization for the synthesis of quinazoline **3a**[a]

Entry	Oxidants	Solvents (mL)	Yield (%)[b]
1	$K_2S_2O_8$	MeCN:H_2O (1:1)	35
2	$K_2S_2O_8$	MeOH	25
3	$K_2S_2O_8$	MeCN	89
4[c]	$K_2S_2O_8$	MeCN	80
5[d]	-	MeCN	0
6[e]	$Na_2S_2O_8$	MeCN	70
7[f]	Oxone	MeCN	67
8	$K_2S_2O_8$	DMF	72

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), oxidant (3 equiv), solvent (2 mL), 80 °C, 12 h. [b]Isolated yield. [c]$K_2S_2O_8$ (2 equiv). [d]No $K_2S_2O_8$ was used. [e]$Na_2S_2O_8$ (3 equiv) was used. [f]oxone (3 equiv) was used.

The effect of a polar aprotic solvent DMF is comparable to that of CH_3CN (entry 8). Perhaps most importantly, $K_2S_2O_8$ was identified as the effective reagent that could promote heterocycle formation via decarboxylation. Despite polymerization is often known to occur with anilines in the presence of $K_2S_2O_8$,[17] reaction of 2-aminobenzylamine **1** and phenylglyoxylate **2a** in our optimized condition delivers 2-arylquinazoline **3a** overcoming such issues. Notably, phenylglyoxylate is used in this annulation reaction in lieu of phenylglyoxylic acid largely used in the literature.

The optimized condition was further utilized to investigate the substrate scope that could participate in tandem annulation reaction for the synthesis of quinazolines (Scheme 2). The arylglyoxylate containing a methyl group at the 2-position also reacted eventfully under the optimized condition affording quinazoline **3b** in 83% yield. An arylglyoxylate containing a 3-OMe group is also compatible with the developed condition affording **3c** in 72% yield. An arylglyoxylate with an electron-donating 4-Me group delivered quinazoline **3d** in 88% yield. The tandem transformation also exhibited tolerance for halogen groups at 2- or 4-positions of arylglyoxylates. 4-Chloro- and 4-fluoro-phenylglyoxylate also reacted with **1** under the optimized conditions affording **3e** and **3f** in 80-82% yield, whereas 2-bromo-phenylglyoxylate afforded **3g** in 72% yield. The halogen substituent in the product could be utilized for further functionalizations. When 2-napthyl-α-oxocarboxylic acid salt was subjected to the reaction with **1** under the optimized condition, 2-napthylquinazoiline **3h** was isolated in 82% yield.



Scheme 2. Synthesis of substituted 2-(hetero)arylquinazolines and benzothiadiazine-1,1-dioxides

Furthermore, more substrate scope was investigated with heterocycles containing an α-oxocarboxylic acid group. Thus, thiophene-3-α-oxocarboxylate and furan-3-α-oxocarboxylate were compatible under the optimized conditions yielding **3i** and **3j** in 85-91% yield. Reaction of 2-aminobenzenesulfonamide **4** and **2a** gave 2*H*-1,2,4-benzothiadiazine-1,1-dioxides **5** under the optimized condition with a little extended time. Thus, when 2-aminobenzenesulfonamide and some aryglyoxylates were subjected to the modified condition, the corresponding annulated products **5a**, **5b**, and **5c** were isolated in 42-55% yields.

Unlike arylglyoxylic acids were used in previous studies,[9,10,12-16] we invariably used arylglyoxylates in the annulations reactions. To understand any difference in reactivity between the free acid and salt in the annulations reactions, we carried out annulation reactions of some ortho-substituted anilines and phenyglyoxylic acid in the presence of $K_2S_2O_8$. The yields of the heterocycles obtained in the annulation reactions of ortho-substituted anilines and phenylglyoxylic acid or phenylglyoxylate are shown in Table 2. The observed yields of the products clearly reflect the different reactivity of phenylglyoxylic acid compared to its salt phenylglyoxylate. This observation may be explained by considering ease of decarboxylation of the free acid/ salt before or after the reaction with aniline. Decarboxylation of arylglyoxylic acids is known to occur at temperature >70 °C in the presence of persulfate.[18] In addition, the current literature supports the relative ease of decarboxylation of arylglyoxylic acid salts compared to their corresponding free acids.[18] An interesting feature of arylglyoxylic acids is that they could undergo condensation with an amino group to form the corresponding aryl iminocarboxylic acids.[19] Because of low pH of the medium, the free acids are likely to undergo condensation with ortho-substituted anilines relatively easily than their salts. From

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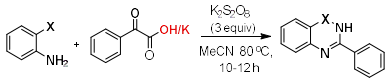
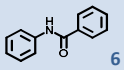
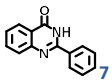
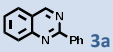
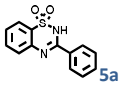
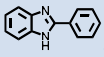
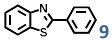
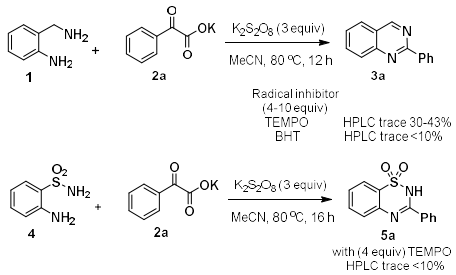
these results, it may be concluded that the reaction mechanism of the annulations reactions involving ortho-substituted anilines and arylglyoxylates could be dissimilar to that of the annulations reactions involving ortho-substituted anilines and arylglyoxylic acids.

Table 2. Comparison of the reactivity of phenylglyoxylic acid and phenylglyoxylate towards reaction with ortho-substituted anilines



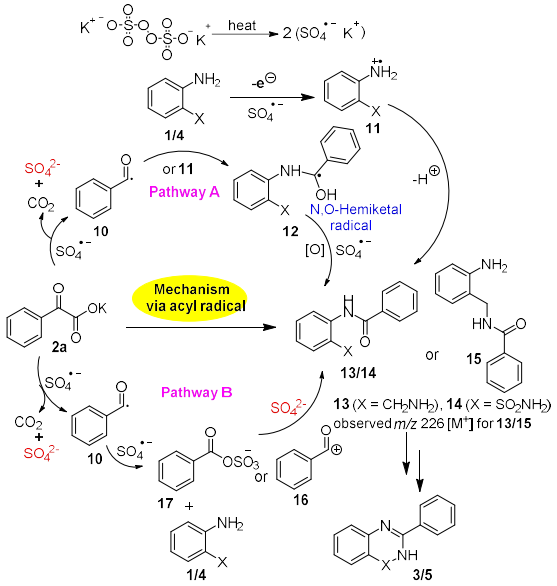
Entry	X	Product	Yield (%) Acid	Yield (%) Salt
1	H	 6	Trace	48[11]
2	$CONH_2$	 7	30	85[11]
3	CH_2NH_2	 3a	40	89
4	SO_2NH_2	 5a	30	55
5	NH_2	 8	60	40[11]
6	SH	 9	80	75[11]

The following experiments were performed to understand whether any radical was indeed involved in the annulation reactions studied herein (Scheme 3). While the annulation reaction of 2-aminobenzylamine and phenylglyoxylate under the optimized condition is only partially affected by TEMPO, a nearly complete inhibition of the reaction was observed with BHT. In stark contrast, the annulation reaction of 2-aminobenzensulfonamide and phenylglyoxylate was completely inhibited by both TEMPO and BHT. The annulations reactions described herein showed ortho-substituted aniline dependent radical inhibition effect with TEMPO and BHT. Although attempted trapping of any radical in these reactions was unsuccessful, the different inhibition effect of the two radical inhibitors augurs possible mechanistic difference of the two annulations reactions.



Scheme 3. Product suppression with radical inhibitors

Based on the results of comparison of decarboxylation of free acid vs. the corresponding salt, radical quenching experiments, and gleaning from previous articulation,[9-13,15-16] the two possibilities including decarboxylation before or after the reaction with anilines have been discussed in the following mechanisms.



Scheme 4. Decarboxylation to form acyl radical before reaction with aniline

The scheme 4 delineates decarboxylation of arylglyoxylate occurs first to form an acyl radical,[7] which upon subsequent reaction with ortho-substituted aniline could give the heterocycle.[20] Initially, homolytic cleavage of $K_2S_2O_8$ under thermal conditions could generate a sulfate radical anion ($SO_4^{\bullet-}$),[21] which upon reaction with phenylglyoxylate **2a** could produce acyl radical **10** via decarboxylation.[6d] The acyl radical **10** could react with ortho-substituted aniline via two different pathways (A & B) leading to N-acylation of ortho-substituted aniline. The aniline **1/4** could form a radical cation **11** by single electron transfer (SET) to $SO_4^{\bullet-}$.[22] The benzoyl radical[23] **10** could react with anilines **1/4** to form N,O-hemiketal radical **12**, which upon oxidation could form an intermediate N-acylated product **13/14** via a radical pathway A.[9-11] The electron-rich benzoyl radical[23] **10** could also react with the radical cation **11** followed by deprotonation to form amide **13/14/15**. The acyl radical also could form an acylium ion **16**,[24] or a similar

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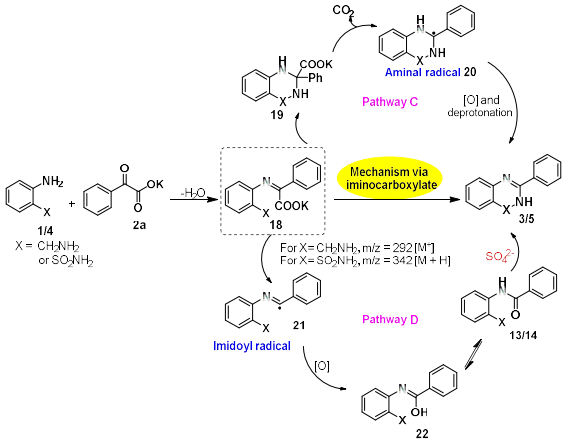
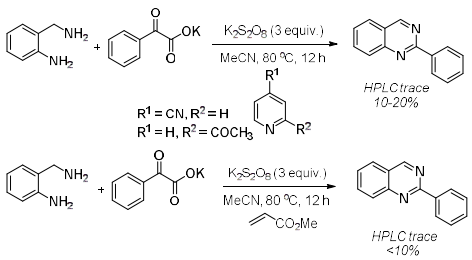
electrophilic species benzoyl sulfate **17**[11] upon capture of a sulfate radical anion ($SO_4^{\cdot-}$), which could undergo nucleophilic substitution with **1/4** to give **13/14** via an ionic pathway B. The intramolecular cyclization of **13/14** in the presence of bases like HSO_4^- or SO_4^{2-}, generated in situ, followed by oxidation could give the final product **3/5**.[25]

Alternatively, the scheme 5 reveals that condensation of both could occur before decarboxylation to form the iminocarboxylate **18**. Based on different modes of decarboxylation, two possibilities that could lead to product formation have been shown (pathways C & D). At this stage, intramolecular cyclization of **18** could directly form a cyclized intermediate **19**, which upon decarboxylation could deliver an aminal radical[26] **20** (pathway C). This aminal radical **20** could give the final product on oxidation and deprotonation. A competitive decarboxylation in **18** could yield imidoyl radical[27] **21**, which upon oxidation could form iminol product **22** (pathway D). The tautomerization of **22** could give **13/14**. The intramolecular cyclization of N-acylated product **13/14** in the presence of bases like HSO_4^- or SO_4^{2-}, generated in situ, followed by oxidation could deliver the heterocycle **3/5**.



Scheme 5. Decarboxylation occurs after reaction with anilines to form iminocarboxylates

To understand whether decarboxylation occurs first to form an acyl radical (pathway A and B), the following experiments were performed. Firstly, the annulation reaction of 2-aminobenzylamine and phenylglyoxylate under the optimized condition in the presence of 2-acetylpyridine or 4-cyanopyridine gave 2-phenylquinazoline albeit in low yield (10-20%) (Scheme 6, upper panel). Secondly, the annulation reaction of 2-aminobenzylamine and phenylglyoxylate under the optimized condition in the presence of methyl acrylate also gave 2-phenylquinazoline in <10% yield (Scheme 6, lower panel).



Scheme 6. Competitive annulation reactions in the presence of electron-deficient species

As acyl radical is known to react with electron-deficient heteroarenes via Minisci acylation,[5] or with methyl acrylate,[28]acyl radical could undergo a competitive reaction in these reactions leading to the lower yield of **3a**. Indeed, 2,4-dibenzoylated pyridine was isolated when 4-cyanopyridine was used (see ESI for ^{1}H NMR and a low-resolution mass data).[29] This suggests that acyl radical was indeed involved in the annulation reactions of **1**.

To trap the formation of N-acylated product **13/14**, we performed mass studies of the reaction mixture with time intervals. The reactions of 2-aminobenzylamine and phenylglyoxylate in the presence of $K_2S_2O_8$ in acetonitrile at 80 °C for 1 h, 2 h, and 4 h were performed and mass data were obtained for all the reaction mixtures. First of all, the mass data of four reaction mixtures were nearly same. An observed mass peak at m/z 226 [M^+] corresponds to amide **13/15**. The other prominent peak observed at m/z 331 [M+H] identified as dibenzoylated product of 2-aminobenzylamine. This experiment could validate both possibilities of acyl radical reactions (pathways A & B). As a radical quencher either slightly or partially inhibits this annulation reaction (Scheme 3), it is likely that acyl radical is transformed into acylium ion **16**[24] or **17**,[11] which drives the reaction further. The intramolecular cyclization of **13/15** could give the final product **3** in the presence of a base like SO_4^{2-}.[25]

To understand whether decarboxylation of arylglyoxylate occurs after reaction with ortho-substituted anilines (pathways C & D), the following experiments were performed. A time course mass analysis of the reaction mixture of 2-aminobenzensulfonamide and phenylglyoxylate under the optimized condition was performed. The mass data for all the reaction mixtures at 1 h, 2 h, and 4 h were nearly same. The mass analysis reveals a mass peak at m/z 304 [M + H], which could correspond to the iminocarboxylate **18** (X = SO_2NH_2). However, similar mass spectroscopic analysis of the reaction mixture of 2-aminobenzylamine **1** and phenylglyoxylate **2a** also revealed a mass peak of iminocarboxylate **18** (X = CH_2NH_2) at m/z 292 [M^+]. These experiments encouraged us to explore further the possibility of the iminocarboxylate formation in the annulation reaction (Scheme 7). Thus, the aryl iminocarboxylates **18** were prepared in situ by the condensation of phenylglyoxylate and 2-aminobenzylamine **1** or 2-aminobenzensulfonamide **4** at room temperature in the absence of $K_2S_2O_8$, which were further treated with $K_2S_2O_8$ at 80 °C. In so doing, two dissimilar observations were recorded.

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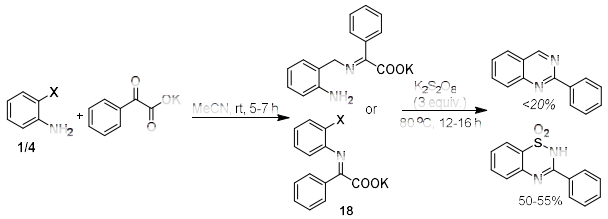
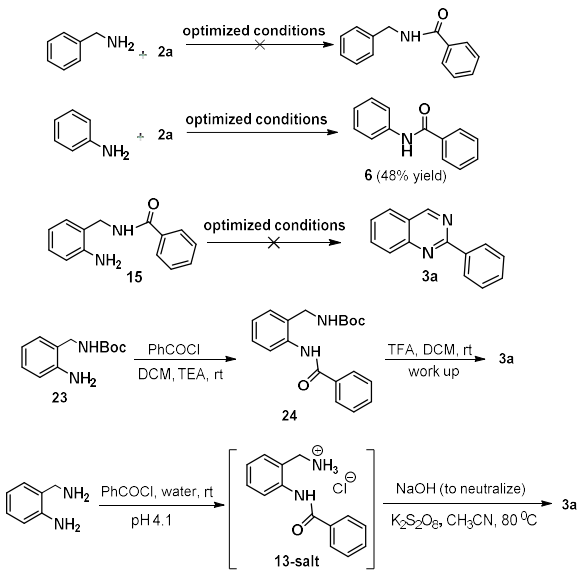
While the reaction involving 2-aminobenzylamine **1** and phenylglyoxylate **2a** gave 2-phenylquinazoline **3a** only in <20% yield, the reaction involving 2-aminobenzensulfonamide **4** and phenylglyoxylate **2a** gave the corresponding heterocycle in a comparable yield to that obtained under the optimized condition. These experiments clearly suggest that iminocarboxylate **18** (X = SO_2NH_2) might involve as an intermediate in the annulation of 2-aminobenzensulfonamide and phenylglyoxylate. Subsequent to iminocarboxylate **18** formation, it could undergo decarboxylation in the presence of sulfate radical anion to form either aminal radical **19** or imidoyl radical **21** as shown in the scheme 4. Unlike in the reaction of 2-aminobenzylamine **1** and phenylglyoxylate, a careful mass analysis of the reaction mixture of 2-aminobenzensulfonamide and phenylglyoxylate does not reveal any mass peak correspond to N-acylated product **14**. Thus, the annulations reaction is more likely to follow the pathway B through the aminal radical.



Scheme 7. Annulation via in situ formation of iminocarboxylate

A radical quencher TEMPO used in this study largely inhibited the annulation reaction of 2-aminobenzensulfonamide and phenylglyoxylate possibly by forming adduct with the proposed aminal radical. The tracking and characterization of the adduct requires further investigation.

A regioselective N-acylation of 2-aminobenzylamine **1** is currently unavailable in the literature. To check whether any regioselective decarboxylative N-acylation takes place at benzylic or aromatic amine of 2-aminobenzylamine **1** although irrelevant in quinazoline synthesis, we carried out reactions involving **2a** and benzylamine, or **2a** and aniline under the optimized conditions. While attempted *N*-acylation of benzylamine itself with **2a** under the optimized condition did not give decarboxylative N-acylated product, aniline yielded N-acylated product **6** of aniline via decarboxylation. Next, we explored the possibility of conversion of the proposed intermediate **13/15** to quinazoline **3a** under the optimized conditions. When *N*-benzoyl-2-aminobenzylamine **15**[30] was exposed to our optimized condition, **3a** didn't form. Next, we investigated the transformation of **13** into product under our optimized condition. As regioselective benzoylation at aniline nitrogen of **1** posed challenging, we protected the benzylamine nitrogen with a *tert*-butoxylcarbonyl (Boc) group. Following a literature report, compound **23** was prepared,[30] which was subjected to benzoylation to obtain **24**.[31] During deprotection of **24** with TFA at room temperature, quinazoline **3a** was obtained directly. Following a literature for the regioselective acylation of 4-aminobenzylamine under a critical pH (4.1),[32] we attempted to make **13** from 2-aminobenzylamine **1** under similar pH controlled conditions. However, direct isolation of an analytically pure **13** was unsuccessful in these experiments. Thus, the crude mixture after neutralization with NaOH was treated with $K_2S_2O_8$ in acetonitrile at 80 °C for 12 h, which afforded quinazoline **3a**. Based on these observations coupled with mass studies, we believe that regioselective decarboxylative N-acylation could occur at aryl amino group to furnish **13**, which upon intramolecular cyclization and oxidation could give quinazoline **3a**.



Scheme 8. Control experiments to understand the regioselective N-acylation

Conclusions

In conclusion, annulation reactions of ortho-substituted anilines and arylglyoxylates described herein feature $K_2S_2O_8$ promoted possible competitive decarboxylation of arylglyoxylates before or after the reactions with anilines. Our study indicated that use of arylglyoxylic acid or its salt may have different outcome in the annulations reactions. Based on substrate dependent radical inhibition experiments and other data available, two different proposed mechanistic pathways are supported for the two substrates. However, it is difficult to ascertain whether a single or competitive deacrboxylative mode is in operational. Using our optimized condition, a regioselective decarboxylative N-acylation of 2-aminobenzylamines could be possible by reaction with arylglyoxylate at the arylamino group. Taken together, the current study is substantially different from the relevant literature in terms substrate variation, product delivery, and mechanistic understanding.

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Experimental Section

General Information: All reagents and solvents were purchased from commercial vendors and used as received. 2-Aminobenzylamine **1** and 2-aminobenzenesulfonamide **4** were purchased from commercial vendors. Arylglyoxylates **2a-k**,[11] compound **15**,[30] and compound **23**[30] were prepared according to the literature procedures. Column chromatography was performed using silica gel 60-120, 100-200, or 230-400 mesh. All ^{1}H NMR and ^{13C} NMR spectra were recorded with 400 MHz and 100 MHz NMR spectrometers, respectively and are reported in δ units. The coupling constants (*J*) are reported in Hz.

General procedure for the synthesis of 2-arylquinazolines illustrated for **3a**: In an oven-dried sealed tube, 2-aminobenzylamine 1 (36.6 mg, 0.30 mmol), phenylglyoxylate (78.5 mg, 0.36 mmol) and potassium persulphate (243.2 mg, 0.90 mmol) were dissolved in CH_3CN (2 mL) and the mixture was heated at 80 ℃ for 12 h. After completion of the reaction, water (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layer was dried over Na_2SO_4. Removal of the solvent with rotary evaporator afforded the crude product, which upon purification by chromatography using hexane/ethyl acetate (8:2) afforded a pale yellow solid.

2-Phenylquinazoline(**3a**):[2] (89% yield); white solid; mp 97-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.62-8.60 (dd, *J* = 7.9, 1.6 Hz, 2H), 8.10-8.08 (d, *J* = 8.5 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.61-7.60 (t, *J* = 7.5 Hz, 1H), 7.60 – 7.56 (m, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.61, 134.24, 130.71, 128.70, 127.31, 77.36, 77.10, 76.85.

2-(o-Tolyl)quinazoline (**3b**):[3] (83% yield); a pale yellow solid; mp 43-45 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.10-8.08 (d, *J* = 8.5 Hz, 1H), 7.99-7.86 (m, 3H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.37-7.32 (dt, *J* = 13.1,6.4 Hz, 3H), 2.60 (s, 3H).

2-(3-Methoxyphenyl)quinazoline (**3c**):[4] (72% yield); a pale yellow solid; mp 119-122°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 8.26-8.24 (d, J = 7.72 Hz, 1H), 8.22 (d, *J* = 2.3 Hz,1H), 8.13-8.11 (d, *J* = 8.44, 1H), 7.96-7.91 (m, 2H), 7.66-7.62 (t, *J* = 7.5 Hz, 1H), 7.49-7.46 (t, *J* = 7.9 Hz, 1H), 7.11-7.08 (dd, J = 8.12, 2.4 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.28, 159.86, 159.46, 150.17, 138.93, 133.52, 129.06, 128.11, 126.63, 123.09, 120.60, 116.68, 112.48, 54.89, 31.36, 29.13, 22.12.

2-(p-Tolyl)quinazoline (**3d**):[5] (88% yield); a yellow solid; mp 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.54-8.52 (d, J = 8.12 Hz, 2H), 8.10-8.09 (d, J = 8.44 Hz, 1H), 7.97-7.87 (m, 2H), 7.64-7.62 (t, *J* = 7.44 Hz, 2H), 7.38-7.36 (d, *J* = 8.0, 1H), 2.47 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 161.15, 160.46, 150.80, 140.89, 134.07, 129.44, 128.54, 127.10, 123.52, 21.55.

2-(4-Chlorophenyl)quinazoline (**3e**):[5] (80% yield); a yellow solid; mp 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.61-8.59 (d, *J* = 8.52 Hz, 2H), 8.11-8.09 (d, J = 8.44 Hz, 1H), 7.96-7.93 (m, 2H), 7.68-7.64 (t, *J* = 7.5 Hz, 1H), 7.54-7.52 (d, *J* = 8.5 Hz, 2H).^{13}C NMR (400 MHz, $CDCl_3$) δ 160.57, 136.85, 134.30, 129.90, 128.85, 128.60, 127.50, 127.18, 123.63, 77.34, 77.03, 76.71.

2-(4-Fluorophenyl)quinazoline (3f):[5] (82% yield); a pale yellow solid; mp 131-133 °C; 1H NMR (500 MHz, $CDCl_3$): δ 9.44 (s, 1H), 8.63-8.61 (m, 2H), 8.07-8.06 (d, J = 8.44 Hz, 1H), 7.94-7.88 (m, 2H), 7.61-7.60 (t, J = 7.4 Hz, 1H), 7.20-7.18 (t, J = 8.76 Hz, 2H).

2-(2-Bromophenyl)quinazoline (3g):[6] (72% yield); a yellow solid; mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 8.18-8.15 (d, J = 8.5 Hz, 1H), 8.06-7.97 (m, 2H), 7.83-7.77(m,3H), 7.51-7.47 (dd, J = 7.5, 6.9 Hz,1H), 7.37-7.35 (dt, J = 15, 1.64 Hz, 1H). ^{13}C NMR (400 MHz, CDCl3) δ 162.82, 160.28, 150.27, 140.16, 134.47, 133.72, 131.67, 130.44, 128.64, 128.12, 127.51, 127.19, 123.31, 121.91, 77.36, 77.04, 76.72, 29.72, 14.15.

2-(Naphthalen-2-yl)quinazoline (**3h**):[7] (82% yield); a pale yellow solid; mp 120-121°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H), 9.18 (s, 1H), 8.77-8.75 (dd, *J* = 8.64 Hz, 1.4 Hz, 1H), 8.18-8.16 (d, *J* = 8.40 Hz, 1H), 8.10-8.06 (m, 1H), 8.04-8.02 (d, *J* = 6.6 Hz, 1H), 7.98-7.92 (dd, *J* = 15.3, 7.7 Hz, 3H), 7.69-7.65 (t, *J* = 7.5 Hz, 1H), 7.60-7.55 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.56, 134.24, 133.42, 129.29, 128.97, 128.50, 127.74, 127.59, 127.03, 126.26, 125.41, 77.34, 77.03, 76.71.

2-(Thiophen-2-yl)quinazoline (**3i**):[7] (91% yield); a yellow solid; mp 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.18-8.17 (d, *J* = 3.6 Hz, 1H), 8.05-8.02 (d, 8.80 Hz, 1H), 7.92–7.89 (m, 2H), 7.62-7.58 (t, *J* = 7.59 Hz, 1H), 7.55-7.54 (d, *J* = 5 Hz, 1H), 7.23-7.21 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.55, 157.86, 150.63, 143.84, 134.38, 129.96, 129.23, 128.40, 128.20, 127.29, 127.02, 123.38, 77.35, 77.04, 76.72.

2-(Furan-2-yl)quinazoline (**3j**):[8] (85% yield); a yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.11-8.09 (d, *J* = 8.9 Hz, 1H), 7.93-7.88 (m, 2H), 7.69 (d, *J* = 0.8 Hz, 1H), 7.63-7.58 (m, 1H), 7.46 (d, *J* = 3.5 Hz, 1H), 6.62 (dd, J = 3.4 Hz, 1.8 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 134.67, 128.49, 127.41, 114.23, 112.45, 77.33, 77.10, 76.85.

General procedure for the synthesis of 2H-1,2,4-benzothiadiazine-1,1-dioxide illustrated for **5a**: In an oven-dried sealed tube, 2-aminobenzenesulphonamide (51.6 mg, 0.30 mmol), phenylglyoxylate (67.7 mg, 0.36 mmol) and potassium persulfate (243.27 mg, 0.90 mmol) were dissolved in CH_3CN (2 mL) and the mixture was heated at 80 ℃ for 16 h. After completion of the reaction, water (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layer was dried over Na_2SO_4. Removal of the solvent with rotary evaporator afforded the crude product, which upon purification by chromatography using hexane/ethyl acetate (3:7) afforded a dark yellow solid.

3-Phenyl-2H-benzo[e][1,2,4]thiadiazine1,1-dioxide (5a):[6] (55% yield); a dark yellow solid; mp. 308-310 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (s, 1H), 8.06-8.04 (d, J = 7.32, 2H), 7.88-7.86 (d, J = 7.88, 1H), 7.77-7.69 (m, 2H), 7.65-7.62 (m, 3H), 7.53-7.49 (t, J = 7.28 Hz, 1H).

3-(3-Methoxyphenyl)-2H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (5b):[6] (48% yield); a dark yellow solid; ; mp. 323-325 °C; 1H NMR (500 MHz, DMSO-d_6): δ 12.13 (s, 1H), 7.84-7.82 (d, J = 7.92, 1H), 7.77-7.73(m, 1H), 7.62-7.57 (m, 2H), 7.55-7.48 (m, 3H), 7.26-7.23 (m, 1H), 3.84 (s, 3H). ^{13}C NMR (500 MHz,

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DMSO-d_6) δ 133.6, 123.87, 121.00, 119.07, 113.87, 41.21, 40.08, 39.52.

3-(4-Bromophenyl)-2H-benzo[e][1,2,4]thiadiazine1,1-dioxide(5c):[6] (42% yield); a dark yellow solid; mp236-238 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.21 (s, 1H), 7.97-7.96 (d, *J* = 8.56, 2H), 7.84-7.81 (m, 3H), 7.73-7.69 (t, *J* = 7.7 Hz, 1H), 7.60-7.58 (m, 1H), 7.49-7.48 (t, *J* = 7.48 Hz, 1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 123.74, 122.65, 109.4, 107.68, 72.78, 72.28, 72.09, 71.70.

N-Phenylbenzamide (6):[11] White solid; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.8 (dd *J* = 7.9, 0.9 Hz, 2H), 7.83 (brs, 1H), 7.64 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.56 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.50-7.46 (m, 2H), 7.40-7.35 (m, 2H), 7.15 (tt, *J* = 7.4, 1.0 Hz, 1H).

2-Phenylquinazolin-4(3*H*)-one (7):[11] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.29 (dd, *J* = 6.3, 2.8 Hz, 2H), 7.93-7.74 (m, 2H), 7.64-7.59 (m, 3H), 7.54 (d, *J* = 6.7 Hz, 1H).

2-Phenyl-1*H*-benzo[*d*]imidazole (8):[11] White solid; ^{1}H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 8.31 (d, *J* = 6.7 Hz, 2H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 21.7, 6.7 Hz, 4H), 7.34 (t, *J* = 8.1 Hz, 2H).

2-Phenylbenzo[*d*]thiazole (9):[11] White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (ddd, *J* = 9.7, 5.0, 3.3 Hz, 3H), 7.94 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.56 – 7.49 (m, 4H), 7.45 – 7.39 (m, 1H).

Preparation of tert-butyl 2-benzamidobenzylcarbamate (**24**): Following a literature,[31] *tert*-butyl 2-aminobenzylcarbamate **23**[30] (444 mg, 2 mmol) and Et_3N (0.2 mL, 1.72 mmol) were dissolved in DCM (4 mL) at 0 ℃. Benzoyl chloride (0.19 mL, 1.72 mmol) was added dropwise at 0 ℃. After 10 min, temperature of the reaction was raised to room temperature and allowed to stir for 1 h. After the completion of the reaction, the mixture was neutralized with aqueous saturated $NaHCO_3$ (10 mL) by constant stirring. It was further extracted with DCM (20 mL x 2). The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography to obtain the desired N-acylated product as a white solid; (600 mg, 92% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 8.02-8.00 (d, J = 7.44 Hz, 2H), 7.62-7.59 (m, 1H), 7.55-7.45 (m, 4H), 7.31-7.21 (m, 3H), 4.17-4.15 (d, 8 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 156.7, 135.9, 134.8, 132.1, 128.85, 128.5, 128.1, 127.5, 126.3, 126.1, 78.6, 28.6. HRMS (ESI) m/z calcd for $C_{19}H_{22}N_2O_3$ [M + Na]$^+$ 349.1528, found 349.1512.

Conflicts of interest

There are no conflicts to declare.

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Possible competitive modes of decarboxylation in the annulations reactions of ortho-substituted anilines and arylglyoxylates

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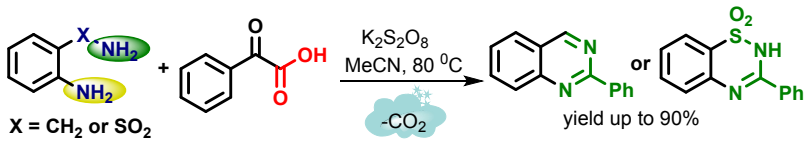

- Competitive decarboxylation, before or after reaction with anilines
- Different outcome with free arylglyxoylic acid or salt
- Substrate dependent inhibition of the reactions by radical quenchers

Annulation reactions of ortho-substituted anilines and arylglyoxylates in the presence of $K_2S_2O_8$ at 80 °C via decarboxylation before or after the reaction with anilines have been investigated, which extended a platform for the tandem synthesis of nitrogen heterocycles.