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Metal-Free C−H [5 + 1] Carbonylation of 2-Alkenyl/Pyrrolylanilines Using Dioxazolones as Carbonylating Reagents

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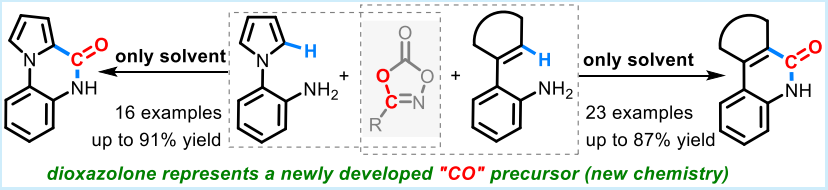

ABSTRACT: A novel metal-free C−H [5 + 1] carbonylative annulation of 2-alkenyl/pyrrolylanilines with dioxazolones has been established for the assembly of the privileged quinolinones and pyrrolyl-fused quinoxalinones. Entirely differing from the existing reports, the dioxazolones herein behave with an innovative chemistry and first emerge as carbonylating reagents to participate in annulation reactions. Moreover, this process features exceedingly simple operation (only solvent) and tolerates both vinyl and aryl substrates. Comprehensive mechanistic studies indicate that the formed isocyanate intermediate plays a crucial role in enabling the carbonylation annulation.

The carbonylation process comprises one of the most fundamental and promising tactics for building up the privileged carbonyl-containing organic molecules and derivatives, which has greatly benefited both academia and industry application.[1] Meanwhile, CO gas as the most direct C1 source in organic syntheses has been extensively exploited for over a half century, especially with respect to the transition-metal catalyzed version, and has gained remarkable achievements,[2] even benefiting the total synthesis of a myriad of natural products.[3] Notwithstanding its robustness, this conversion still encounters several non-negligible restraints such as a difficult system (toxicity, flammability, and high pressure)[4] as well as aspects affecting reaction efficacy (poison metal catalyst).[5] Again, in recent years, seeking new carbonylating agent candidates in lieu of gaseous CO has been gaining increasing focus in the organic community.[6] The current CO surrogates predominantly encompass the matured $M(CO)_n$ and CO_2 reagents as well as the evolving $(CH_2O)_n$, $CHCl_3$, TFBen, $COCl_2$, HCO_2R, CH_3NO_2, and so forth (Scheme 1A),[7] each of which is practically applied as CO alternatives through the specific reaction fashion. Nonetheless, consistent with the model of CO gas transformation, inevitably capitalizing on the transition metals combined with external oxidants appears imperative in the majority of these cases. Thus, exploring more CO substitutions and new carbonylation tactics will continue to be highly demanded.

Alternatively, the chemical reactivity of dioxazolone has more recently increasingly captured substantial attention,[8] largely due to its phenomenal reaction performance in constructing new C−N bonds. This blooming reagent, featuring concise preparation, easy handling, as well as environmental friendliness by generating only CO_2 and H_2O as chemical wastes, typically applies to homogeneous catalysis systems as quite a "smart" nitrene transfer agent. In this arena, Chang,[9] Li,[10] Bolm,[11] and others[12] have had numerous successes associated with implementing a plethora of intriguing amidating reactions (Scheme 1B, left). As a dramatic comparison, the other chemical properties of dioxazolones are scarcely documented, and only two studies described that the dioxazolones were capable of coupling with amines to access ureas without metal catalysts,[13] which selectively formed a challenging N−C(O) bond by means of the Curtius-type rearrangement (Scheme 1B, right). Inspired by these seminal works, we speculate whether the further intramolecular transformation could take place to construct complicated and value-added cyclic carbonyl molecules by installing an appropriate nucleophilic unit on the urea species.

In this paper, in line with our ongoing interest in heterocyclic chemistry,[14] we communicate a novel [5 + 1] cycloaddition example of 2-alkenyl/pyrrolylanilines with dioxazolones (Scheme 1C), thus resulting in a broad collection of ubiquitous quinolinone and pyrrolyl-fused quinoxalinone derivatives frequently found in pharmaceutical chemistry (Scheme 1D).[15] Most strikingly, the dioxazolone herein

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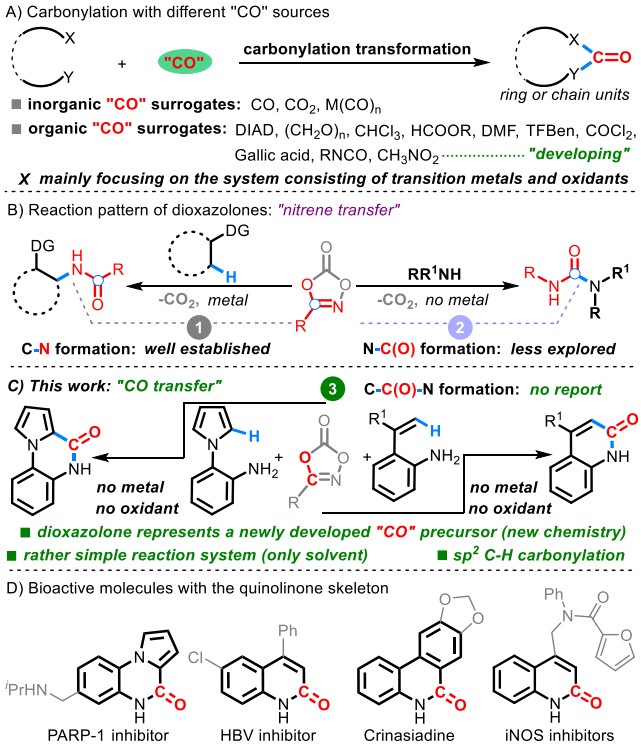
Scheme 1. Carbonylation Reaction and Dioxazolone Chemistry

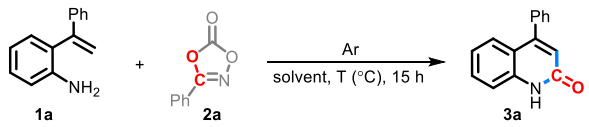


behaves with a new chemistry and represents a CO surrogate to participate in cyclization transformation for the first time via simultaneously constructing C−C(O) and N−C(O)bonds.

Initially, the reaction was optimized by employing 2-(1-phenylvinyl)aniline **1a** to react with phenyl-ligated dioxazolone **2a** as a potential carbonyl source. Some representative experiments are summarized in Table 1. A comprehensive screening of reaction solvents was first conducted (entries 1−8). Although cases such as HFIP, EtOH, TFE, 1,4-dioxane, MeCN, toluene, DCE, and DMF were all feasible to perform this titled [5 + 1] conversion, the toluene solvent was identified as the better choice and delivered the anticipated product **3a** in 73% yield (entry 6). Further adjusting the temperature to higher or lower level proved to be ineffective for higher productivity (entries 9 and 10). In the end, it was found that the ratio of reaction substrates could affect the reaction performance (entries 11 and 12), improving the yield of **3a** to 73% when modifying the ratio of **1a**:**2a** to 1:1.2 (entry 12). In addition, the air atmosphere resulted in a diminished outcome (entry 13).

To further harness this modest synthetic methodology at this stage, we proceeded to optimize transformation efficiency by tuning the C3-substituent of carbonylation agent **2a**. A sequence of differentially substituted dioxazolones was prepared, including electronically or sterically diverse aromatic (**2b**−**k**) and aliphatic (**2l**) reagents, to react with substrate **1a** for executing this [5 + 1] annulation according to the aforementioned reaction conditions (Scheme 2). All of these

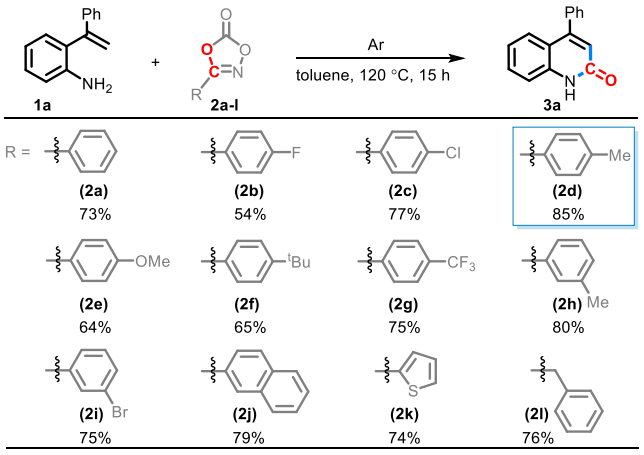
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	**2a** (mmol)	*T* (°C)	yield[b] (%)
1	HFIP	0.4	120	65
2	EtOH	0.4	120	30
3	TFE	0.4	120	68
4	1,4-dioxane	0.4	120	49
5	MeCN	0.4	120	67
6	toluene	0.4	120	73
7	DCE	0.4	120	66
8	DMF	0.4	120	38
9	toluene	0.4	110	64
10	toluene	0.4	130	69
11	toluene	0.3	120	68
12	**toluene**	**0.24**	**120**	**73**
13[c]	toluene	0.24	120	55

[a]Reaction conditions: **1a** (0.2 mmol) and **2a** in solvent (1.5 mL) were stirred for 15 h under Ar atmosphere. [b]Isolated yield. [c]Air instead of Ar.

Scheme 2. Optimization of the Dioxazolones[a]



[a]Isolated yield of **3a** (reacting 0.2 mmol **1a** with 0.24 mmol **2**).

cases took place properly to furnish the target **3a** in 54−85% yields, and the electronic effect on the reaction productivity appeared inconspicuous, in which adapting **2d** as the carbonylation reagent presented a comparatively preferential reaction performance (85% isolated yield).

Having established the optimal conditions, the generality and scope of this novel [5 + 1] reaction was next investigated. As depicted in Scheme 3, with substrate **2d** as the carbonylating reagent, a broad range of 2-alkenylanilines (**1a**−**w**) participated quite well in this protocol, constructing the corresponding products (**3a**−**w**) in moderate to good yields. First, with regard to the alkenyl segment, it accommodated diversified organic functionalities such as substituted phenyl with distinct electron traits (**3b**−**d**), naphthyl (**3e**), thienyl (**3f**), methyl (**3g**), ethyl (**3h**), phenylmethyl (**3i**), and even fused-cyclohexyl (**3j**) groups, rapidly assembling the respective quinolinone derivatives in 70−87% yields. Subsequently, studies on decorating the phenylamine ring were also performed. Satisfyingly, a large number of functional groups was able to be introduced and capable of resulting in the titled [5 + 1] carbonylation issue smoothly, encompassing electron-donating groups such as methyl (**3k**), methoxyl (**3l**), thiomethyl (**3m**), methylenedioxyl (**3u**), and

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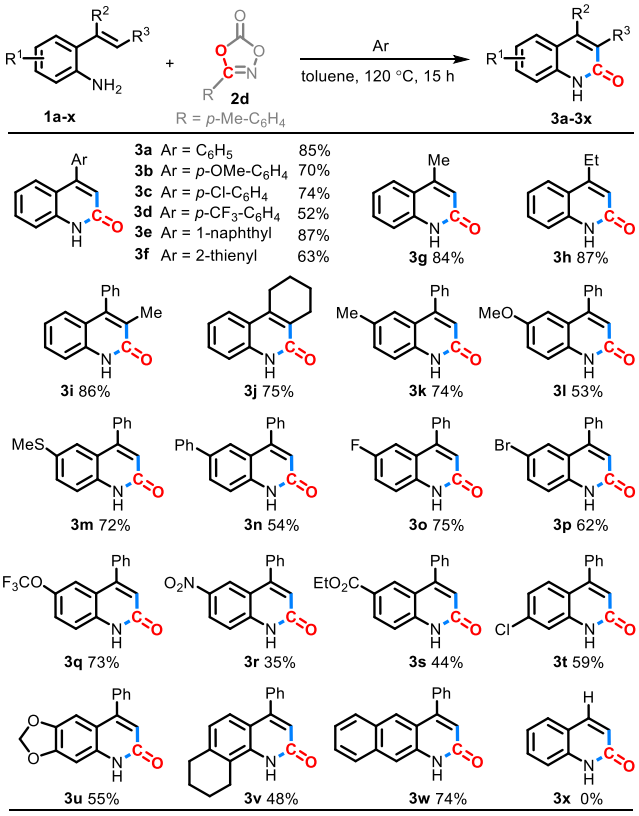
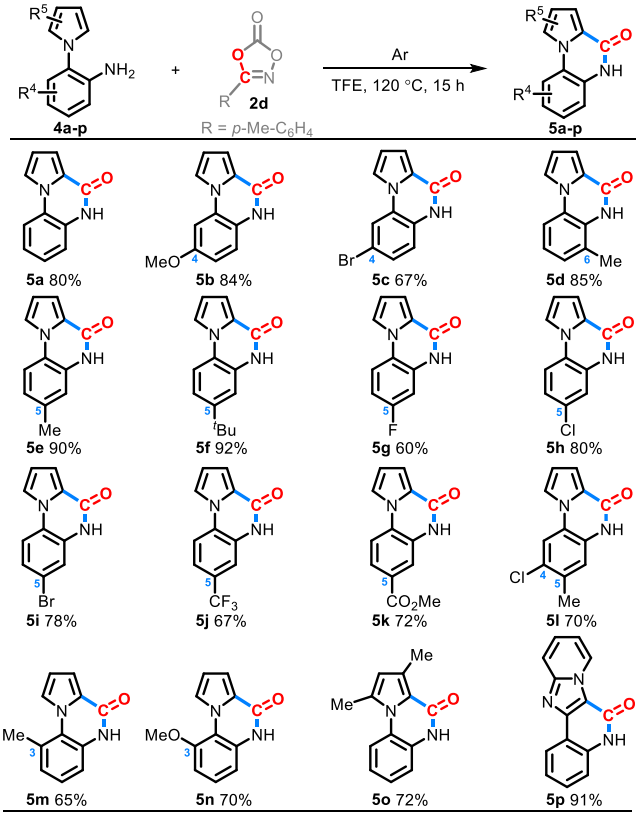
Scheme 3. Substrate Scope of 2-Alkenylanilines



Scheme 4. Substrate Scope of 2-Pyrrolylanilines

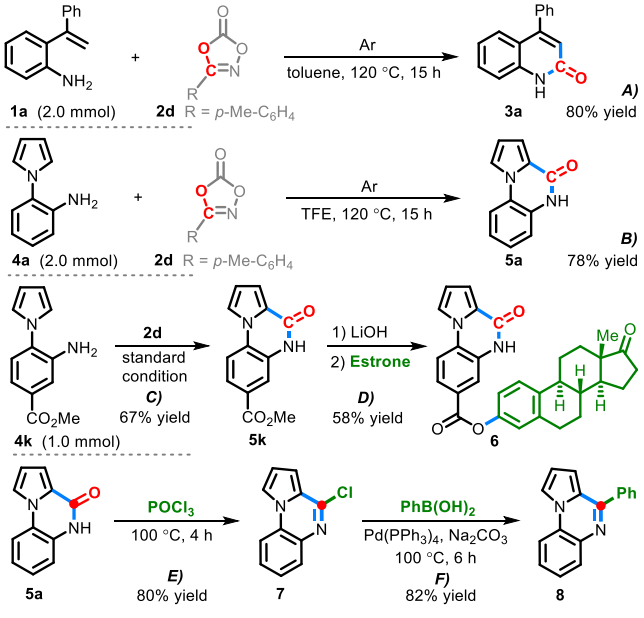


cyclohexyl (**3v**) and electron-withdrawing moieties such as phenyl (**3n**), fluoro (**3o**), bromo (**3p**), trifloromethyloxyl (**3q**), nitro (**3r**), ester (**3s**), and chloro (**3t**) groups. Furthermore, the π-system-expanded **3w** could be readily obtained. Unfortunately, the simplest substrate **1x** failed to run in this protocol.

Inspired by the success of this new carbonylation reagent in the [5 + 1] annulation reaction, we set out to survey the feasibility of using this tactic to execute 2-arylaniline derivatives (Scheme 4). After slightly modifying the reaction parameters (replacing toluene with TFE as solvent, see details in the Supporting Information), we observed that the 2-(1*H*-pyrrol-1-yl)aniline **4a** remained in this carbonylation procedure and potently generated the pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **5a**, which has generally served as a core skeleton in numerous bioactive molecules such as the PARP-1 inhibitor (Scheme 1D). By coupling with **2d**, various 2-pyrrolylanilines (**4b**−**o**) performed smoothly to provide the anticipated products (**5b**−**o**) in 65−92% yields. A multitude of substituents appended to the possible sites of the aniline ring were all tolerated properly, including methoxyl (**5b** and **5n**), bromo (**5c** and **5i**), methyl (**5d**, **5e** and **5m**), *tert*-butyl (**5f**), fluoro (**5g**), chloro (**5h** and **5l**), trifluomethyl (**5j**), and ester (**5k**) groups, wherein the electron-rich compounds expressed relatively preferential outcomes. In this theme, incorporating dimethyl into the pyrrolyl portion was allowable. Additionally, replacing pyrrolyl with imidazo[1,2-*a*]pyridine was also subjected to this envisioned [5 + 1] lactamization reaction and led to the formation of polyheterocycle **5p** in 91% yield.

Afterward, we embarked on assessing the potential utility of this established methodology. The larger scale experiments with the aforementioned two types of representative reaction precursors (**1a** and **4a**) in a 2.0 mmol amount were carried out, respectively, in which the two runs were both able to accomplish the desired transformation with good yields (Scheme 5A and B). In addition, the reaction with 2-pyrrolylaniline **4k** was also amenable to perform scale-up conversion, resulting in **5k** with comparable yield and efficiency (Scheme 5C). To our delight, exposed to the adduct **5k**, the late-stage functionalization of estrone ran smoothly to

Scheme 5. Gram-Scale Reaction and Synthetic Utilization



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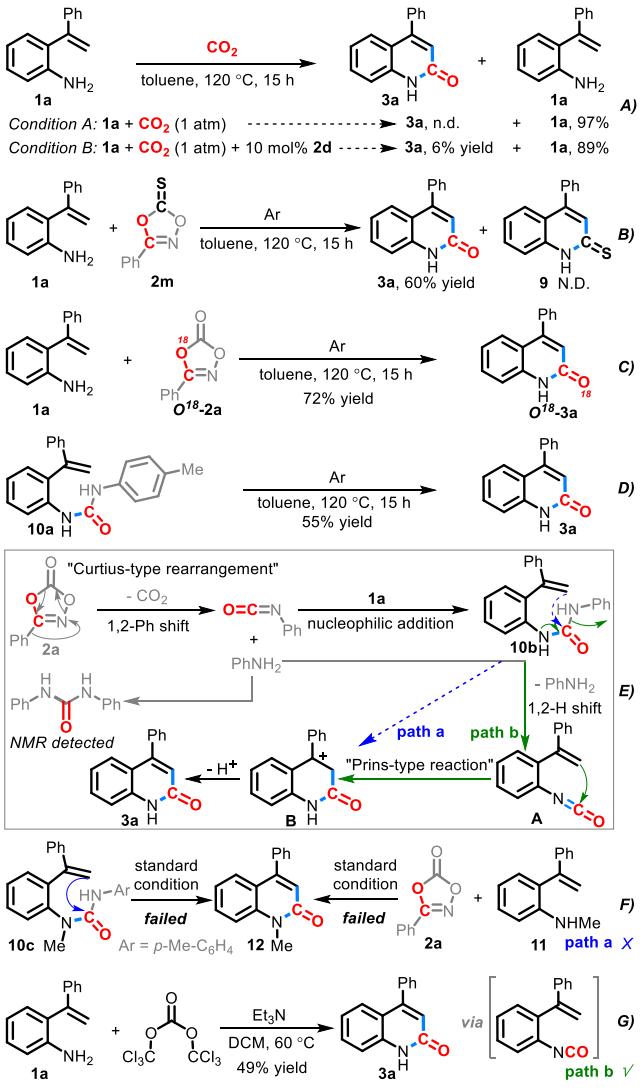
build a new type of complicated ester **6** in 58% yield (Scheme 5D). Moreover, when **5a** was treated with $POCl_3$ reagent, the 4-chloropyrrolo[1,2-*a*]quinoxaline **7** was accessed in 80% yield (Scheme 5E). Next, the C−Cl bond could be further functionalized to furnish product **8** by Suzuki−Miyaura cross-coupling (Scheme 5F).

To gain more insights into the mechanistic rationality, additional experiments were undertaken. In view of the verified fact that the dioxazolones could readily decompose into CO_2, we introduced CO_2 gas, another typical CO resource, into the reaction system in the absence or catalytic amount of **2d**, respectively. Both of these cases failed to generate the titled product smoothly, which unequivocally obviated the involvement of CO_2 as the carbonylation source (Scheme 6A). The

Scheme 6. Mechanistic Studies



reaction with **2m** still delivered the wanted **3a**, but no 4-phenylquinoline-2(1*H*)-thione **9** was made (Scheme 6B). Furthermore, the isotope-labeling experiment with diaxazolone ^{18}O-**2a** led to the formation of product ^{18}O-**3a** in 72% yield (Scheme 6C). These findings provided solid evidence for the viewpoint that the carbonyl group appended to the product arose from the C3−O4 fragment. Subsequently, urea compound **10a** was synthesized to execute the reaction, in which product **3a** could be generated properly (Scheme 6D). This result supported that the urea species were involved in this cyclization procedure.

On the basis of these findings, the reaction mechanism was then put forward (Scheme 6E). The thermal decomposition of dioxazolones initially takes place to generate isocyanate accompanied by dislodging the CO_2 molecule,[13,16] followed by reacting with 2-alkenylaniline via nucleophilic addition to access the key intermediate urea **10b**. At this stage, two pathways might be employed, involving a direct cyclization (path a) or sequential forming isocyanate species/Prins-type reaction (path b). To further probe the exact reaction path, the Me-protected 2-alkenylaniline **11** or its corresponding urea **10c** was used to undergo this issue. Notably, the envisioned quinolinone **12** failed to occur (Scheme 6F), which proved that the urea species was futile to enable this reaction by one-step cyclization. Alternatively, to affirm the feasibility with respect to isocynate, the reaction between substrate **1a** with bis(trichloromethyl) carbonate agent, which is able to *in situ* generate the relevant isocyanate smoothly, was carried out and indeed released quinolione product **3a** (Scheme 6G), so the path b was rational.

In summary, we discovered a class of new carbonylating agents resulting from the dioxazolones, by which the metal-free [5 + 1] carbonylation of 2-alkenylanilines or 2-pyrrolylanilines with dioxazolones is accomplished, leading to a variety of quinolinones (23 examples) and pyrrolyl-fused quinoxalinones (16 examples) in good yields with excellent functionality tolerance. This study represents an unprecedented chemistry reactivity with dioxazolones via simultaneously constructing new N−C(O) and C(O)−C bonds. Mechanistic investigations clearly illustrate that the generated double isocyanate species are pivotal in this carbonylation conversion. Extensive studies into the scope of the carbonylation reaction generated from dioxazolones are currently ongoing in our laboratory and will be presented in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01147.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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