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**Authors:** Rong Zhou, Ling Han, Honghui Zhang, Rongfang Liu, and Ruifeng Li



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# A Deoxygenative [4 + 1] Annulation Involving *N*-Acyldiazenes for Efficient Synthesis of 2,2,5-Trisubstituted 1,3,4-Oxadiazole Derivatives

Rong Zhou,*[a] Ling Han,[a] Honghui Zhang,[a] Rongfang Liu,*[a] and Ruifeng Li[a]

[a] College of Chemistry and Chemical Engineering, Taiyuan University of Technology, Taiyuan, 030024, P. R. China
Phone: (+ 86)-351-6018564; e-mail: zhourong@tyut.edu.cn; liurongfang0060@link.tyut.edu.cn

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**Abstract:** An unprecedented highly efficient $P(NMe_2)_3$ [tris(dimethylamino)phosphine]-mediated deoxygenative [4 + 1] annulation of *N*-acyldiazenes with α-dicarbonyl compounds such as isatins, α-keto esters, and α-diketones is reported. The annulation reactions proceed smoothly under mild conditions to deliver a broad range of 2,2,5-trisubstituted 1,3,4-oxadiazole derivatives in moderate to excellent yields from readily available starting materials. It represents the first realization of [4 + 1] annulation mode involving *N*-acyldiazenes to construct five-membered heterocycles.

**Keywords:** [4 + 1] annulation; phosphine; *N*-acyldiazenes; α-dicarbonyl compounds; 1,3,4-oxadiazoles

## Introduction

Five-membered heterocycles are ubiquitous structural motifs in natural products, biologically active compounds, as well as functional molecules.[1] 1,3,4-Oxadiazole represents one of the most frequently encountered heterocycles in bioactive molecules and advanced materials (Figure 1). For example, marketed antibiotics such as Furamizole,[2] and HIV-integrase inhibitor Raltegravir[3] contain the oxadiazole nucleus. In addition, the chitin synthase inhibitor, compound DOW416 is also based on the oxadiazole moiety.[4] Other compounds with an oxadiazole core have also exhibited a variety of biological properties such as antitumor,[5] antimicrobial,[6] antifungal and MAO inhibitory activities.[7] Furthermore, the 1,3,4-oxadiazoles are widely used in the construction of electroluminescent and electron-transport materials.[8] The development of synthetic methods for 1,3,4-oxadiazoles has therefore attracted intensive interest from chemists due to their broad bioactivities and utilities. A number of synthetic approaches have been established during the past decade,[1d,9] but the reported methodologies usually require harsh reaction conditions or have limited substrates scope.[1d,9a] Moreover, the majority of the existing synthetic methods are centered upon 2,5-disubstituted 1,3,4-oxadiazoles,[1d,9] and efficient synthetic methodologies to 2,2,5-trisubstituted 1,3,4-oxadiazoles thus far have been underdeveloped although they have comparable bioactivities as that of 2,5-disubstituted 1,3,4-oxadiazoles.[5-7] The development of a practical synthetic strategy with broad scope under mild conditions for oxadiazoles, especially 2,2,5-trisubstituted 1,3,4-oxadiazoles, is therefore highly desirable.

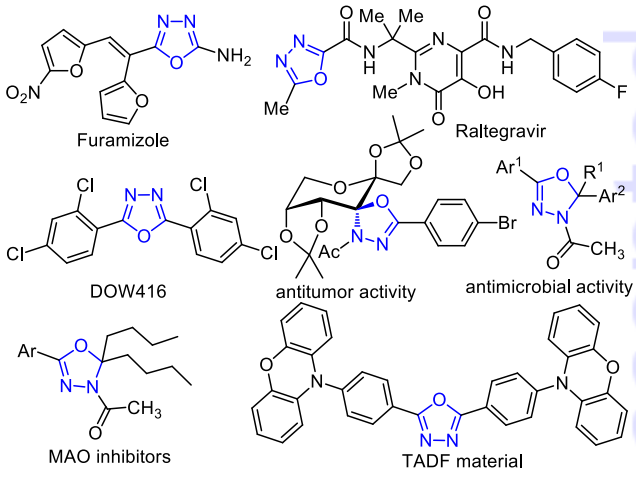
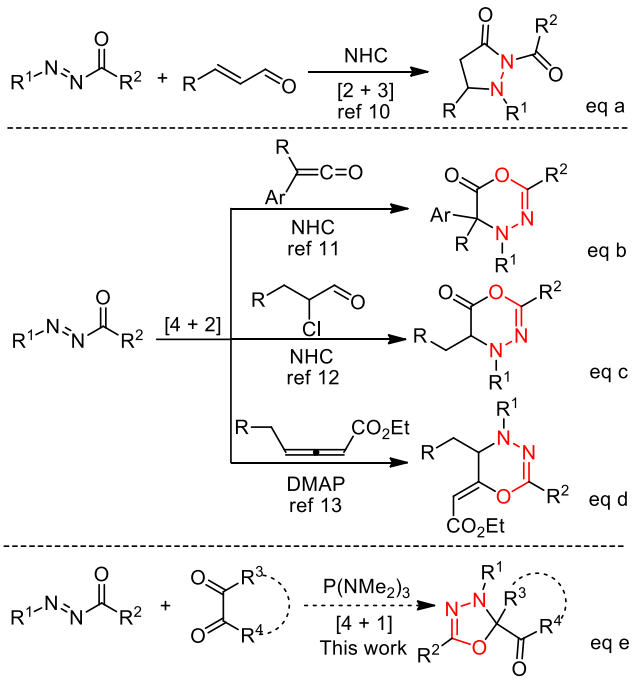



**Figure 1.** Selected bioactive and functional molecules containing a 1,3,4-oxadiazole core.

*N*-Acyldiazenes are an important class of diazenes with distinct reactivity. Recent reports unveiled that *N*-acyldiazenes could serve as good synthons for [2 + 3] and [4 + 2] annulations.[10-13] In 2008, Scheidt and co-workers reported a *N*-heterocyclic carbenes (NHC)-catalyzed [2 + 3] cyclization of *N*-acyldiazenes with α,β-unsaturated aldehydes, affording pyrazolidinones (Scheme 1, eq a).[10] The

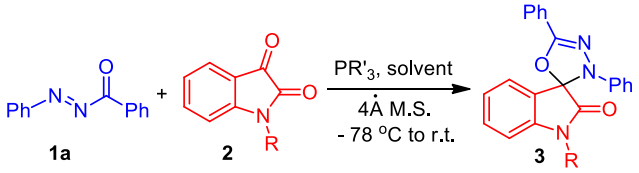
NHC-catalyzed [4 + 2] annulations of *N*-acyldiazenes with ketenes or α-chloroaldehydes leading to 1,3,4-oxadiazin-6-ones were subsequently demonstrated by Ye[11] and Zhong,[12] respectively (Scheme 1, eq b and c). Recently, Wang and co-workers developed a DMAP-catalyzed [4 + 2] cycloaddition between *N*-acyldiazenes and allenoates, providing direct access to 1,3,4-oxadiazines (Scheme 1, eq d).[13] These reactions exhibit distinct annulation reactivity patterns of *N*-acyldiazenes in preparation of heterocycles. However, a [4 + 1] annulation mode involving *N*-acyldiazenes for constructing five-membered heterocycles has by far never been realized, particularly under the influence of phosphines.[14] Considering the broad bioactivities and utilities of 1,3,4-oxadiazoles,[2-7] and also as part of our continuous research efforts in exploring the reactivity patterns of Kukhtin-Ramirez adducts obtained from trivalent phosphorus reagents and α-dicarbonyl compounds,[15] we envisioned that a deoxygenative [4 + 1] annulation between *N*-acyldiazenes and Kukhtin-Ramirez adducts would be feasible to deliver the 1,3,4-oxadiazoles (Scheme 1, eq e). Herein, we report an unprecedented $P(NMe_2)_3$-mediated deoxygenative [4 + 1] annulation of *N*-acyldiazenes with α-dicarbonyl compounds such as isatins, α-keto esters, and α-diketones, leading to a practical synthesis of a board range of 2,2,5-trisubstituted 1,3,4-oxadiazoles in moderate to excellent yields under mild conditions. It also represents the first realization of [4 + 1] annulation mode involving *N*-acyldiazenes to construct five-membered heterocycles.




**Scheme 1.** Different annulation modes involving *N*-acyldiazenes.

## Results and Discussion

**Table 1.** Survey of reaction conditions.[a]




**2a**: R = allyl; **2b**: R = Bn; **2c**: R = Me

| Entry | Isatin **2** | Solvent | PR'$_3$ | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **2a** | $CH_2Cl_2$ | $P(NMe_2)_3$ | **3aa**, 54 |
| 2 | **2a** | $CH_2Cl_2$ | $P(OMe)_3$ | **3aa**, 0 |
| 3 | **2a** | $CH_2Cl_2$ | $PPh_3$ | **3aa**, 29 |
| 4 | **2a** | $CH_2Cl_2$ | $PBu_3$ | **3aa**, 13 |
| 5 | **2a** | THF | $P(NMe_2)_3$ | **3aa**, 33 |
| 6 | **2a** | $CHCl_3$ | $P(NMe_2)_3$ | **3aa**, 37 |
| 7 | **2a** | Toluene | $P(NMe_2)_3$ | **3aa**, 24 |
| 8 | **2a** | $CH_3CN$ | $P(NMe_2)_3$ | **3aa**, 60 |
| 9 | **2a** | $CH_2Cl_2$/ $CH_3CN$ | $P(NMe_2)_3$ | **3aa**, 66[c] |
| 10 | **2b** | $CH_2Cl_2$/ $CH_3CN$ | $P(NMe_2)_3$ | **3ab**, 45[c] |
| 11 | **2c** | $CH_2Cl_2$/ $CH_3CN$ | $P(NMe_2)_3$ | **3ac**, 43[c] |
| 12 | **2a** | $CH_2Cl_2$/ $CH_3CN$ | $P(NMe_2)_3$ | **3aa**, 47[d] |

[a] Reaction conditions: *N*-benzoyldiazene **1a** (0.4 mmol), isatin **2** (0.2 mmol), PR'$_3$ (0.22 mmol), and 4Å molecular sieves in solvent (2.0 mL), -78 °C to r.t., 12 h.
[b] Isolated yield based on **2**.
[c] $V(CH_2Cl_2):V(CH_3CN)$ = 1:1.
[d] The reaction was conducted from 0 °C to r.t.

We initially attempted the annulation reaction by treating *N*-benzoyldiazene **1a** with isatin **2a** in the presence of $P(NMe_2)_3$ under the predetermined conditions listed in Table 1. To our delight, a deoxygenative [4 + 1] annulation reaction between **1a** and **2a** occurred as expected, affording the spirooxindole-1,3,4-oxadiazole **3aa** in 54% isolated yield (entry 1). The structure of compound **3aa** was unambiguous confirmed by X-ray crystallographic analysis (CCDC 1562365).[16] This result therefore demonstrates the first [4 + 1] annulation involving *N*-acyldiazenes and also provides a novel approach to 1,3,4-oxadiazoles. Optimization of the reaction conditions was subsequently conducted to improve the reaction efficiency. Screening of several trivalent phosphorus reagents indicated that $P(NMe_2)_3$ was the optimal phosphorus reagent for the reaction. Phosphite such as $P(OMe)_3$ was ineffective, and phosphines such as $PPh_3$ and $PBu_3$ both gave inferior results (entries 2-4). Among several common solvents including $CH_2Cl_2$, THF, $CHCl_3$, toluene, and $CH_3CN$ surveyed, $CH_3CN$ afforded the best result although the reaction mixture solidified at – 78 °C due to the relatively higher melting point of $CH_3CN$ (entries 5-8). The yield of **3aa** was further improved by adopting a mixture of $CH_2Cl_2$ and $CH_3CN$ (V/V = 1:1) as the reaction medium (entry 9). The influence of substituent R on the nitrogen atom of isatin **2** was examined as well. Although changing the substituent R from an allyl group to a benzyl or a methyl group was all feasible, the corresponding products were afforded in relatively lower yields (entries 10 and 11).

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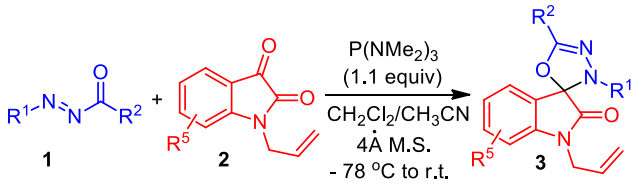
The *N*-allyl isatins were therefore chosen for further investigations. It was found that the yield of **3aa** decreased when elevating the initial reaction temperature to 0 °C(entry 12).

Having identified the optimal conditions in hand, we sought to explore the scope of the annulation reaction (Table 2). A variety of isatins with different substituent on the benzene ring of the oxindole framework were first investigated with representative diazene **1a**. As showed in Table 2, both electron-donating and electron-withdrawing substituted isatins proceeded smoothly to give the corresponding [4 + 1] annulation products in moderate to excellent yields with diazene **1a** (entries 1-9). Experiments to investigate the scope of diazenes **1** unveiled that aryl substituted diazenes with either electron-rich, electron-poor, or heteroaryl group on their substituents $R^1$ and $R^2$ were well tolerated. In the examined cases, the [4 + 1] annulation reactions of diazenes **1b-k** with isatin **2i** uneventfully afforded the corresponding spirooxindole-1,3,4-oxadiazoles in good to excellent yields (entries 10-19).

**Table 2.** [4 + 1] Annulation of *N*-acyldiazenes **1** and isatins **2**.[a]



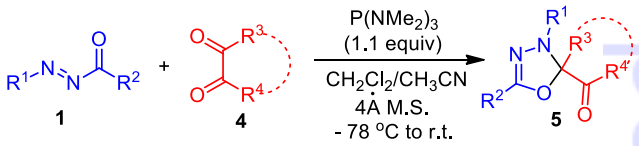

| Entry | $R^1$, $R^2$ in **1** | $R^5$ in **2** | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph, Ph (**1a**) | H (**2a**) | 12 | **3aa**, 66 |
| 2 | **1a** | 5-Me (**2d**) | 8 | **3ad**, 58 |
| 3 | **1a** | 5-OMe (**2e**) | 4 | **3ae**, 46 |
| 4 | **1a** | 4-Br (**2f**) | 11 | **3af**, 93 |
| 5 | **1a** | 5-Br (**2g**) | 12 | **3ag**, 35 |
| 6 | **1a** | 6-Br (**2h**) | 8 | **3ah**, 55 |
| 7 | **1a** | 4-Cl (**2i**) | 11 | **3ai**, 99 |
| 8 | **1a** | 5-Cl (**2j**) | 11 | **3aj**, 49 |
| 9 | **1a** | 5-$NO_2$ (**2k**) | 21 | **3ak**, 42 |
| 10 | Ph, 4-$MeC_6H_4$ (**1b**) | **2i** | 11 | **3bi**, 94 |
| 11 | Ph, 4-$MeOC_6H_4$ (**1c**) | **2i** | 10 | **3ci**, 97 |
| 12 | Ph, 4-$ClC_6H_4$ (**1d**) | **2i** | 11 | **3di**, 77 |
| 13 | Ph, 4-$BrC_6H_4$ (**1e**) | **2i** | 11 | **3ei**, 80 |
| 14 | Ph, 2-Furyl (**1f**) | **2i** | 11 | **3fi**, 94 |
| 15 | Ph, 2-Thienyl (**1g**) | **2i** | 11 | **3gi**, 93 |
| 16 | 4-$MeC_6H_4$, Ph (**1h**) | **2i** | 8 | **3hi**, 89 |
| 17 | 4-$BrC_6H_4$, Ph (**1i**) | **2i** | 11 | **3ii**, 51 |
| 18 | 4-$ClC_6H_4$, Ph (**1j**) | **2i** | 12 | **3ji**, 51 |
| 19 | 4-$CF_3C_6H_4$, Ph (**1k**) | **2i** | 12 | **3ki**, 78 |

[a] Reaction conditions: *N*-acyldiazene **1** (0.4 mmol), isatin **2** (0.2 mmol), $P(NMe_2)_3$ (0.22 mmol), and 4Å molecular sieves in $CH_2Cl_2/CH_3CN$ (2.0 mL, V/V 1:1), -78 °C to r.t.
[b] Isolated yield based on **2**.

We further expanded this protocol to other types of α-dicarbonyl compounds such as α-keto esters and α-diketones (Table 3). Under the standard conditions, ethyl aroylformates bearing either electron-rich or electron-poor aryl groups participated in the [4 + 1] annulation reactions smoothly with diazenes **1** bearing different electronic properties, delivering the corresponding 2,2,5-trisubstituted 1,3,4-oxadiazoles **5** in moderate to excellent yields (entries 1-6). α-Diketones including benzil, acenaphthoquinone, and aceanthrenequinone were all demonstrated to be reliable substrates for this [4 + 1] annulation to afford the corresponding products in moderate to good yields with diazene **1a** (entries 7-9).

The structures of compounds **3** and **5** were fully characterized by $^1H$, $^{13}C$ NMR and HRMS-ESI/MALDI measurements, and further confirmed by single crystal X-ray diffraction analysis of representative compound **3aa**.[16] This deoxygenative [4 + 1] annulation proceeds smoothly under mild conditions using readily available *N*-acyldiazenes and α-dicarbonyl compounds, and particularly exhibiting a broad substrates scope, which makes it an efficient protocol for 2,2,5-trisubstituted 1,3,4-oxadiazoles.

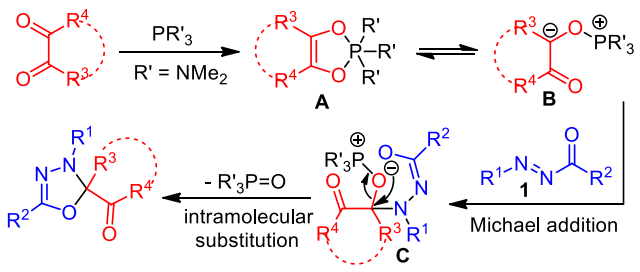
**Table 3.** [4 + 1] Annulation of *N*-acyldiazenes **1** with α-keto esters and α-diketones **4**.[a]




| Entry | $R^1$, $R^2$ in **1** | $R^3$, $R^4$ in **4** | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph, Ph (**1a**) | Ph, OEt (**4a**) | 8 | **5aa**, 86 |
| 2 | Ph, 4$MeC_6H_4$ (**1b**) | **4a** | 11 | **5ba**, 78 |
| 3 | Ph, 4-$ClC_6H_4$ (**1d**) | **4a** | 10 | **5da**, 49 |
| 4 | Ph, 2-Thienyl (**1g**) | **4a** | 11 | **5ga**, 81 |
| 5 | **1a** | 4-$MeC_6H_4$, OEt (**4b**) | 8 | **5ab**, 95 |
| 6 | **1a** | 4-$BrC_6H_4$, OEt (**4c**) | 8 | **5ac**, 85 |
| 7 | **1a** | Ph, Ph (**4d**) | 8 | **5ad**, 84 |
| 8 | **1a** | Acenaphthoquinone (**4e**) | 9 | **5ae**, 53 |
| 9 | **1a** | Aceanthrenequinone (**4f**) | 8 | **5af**, 43 |

[a] Reaction conditions: *N*-acyldiazene **1** (0.4 mmol), α-dicarbonyl compounds **4** (0.2 mmol), $P(NMe_2)_3$ (0.22 mmol), and 4Å molecular sieves in $CH_2Cl_2/CH_3CN$ (2.0 mL, V/V 1:1), -78 °C to r.t.
[b] Isolated yield based on **4**.

Based on the experimental results above and the most related reports from our group[15] and others,[17] a proposed mechanism to account for the formation of 1,3,4-oxadiazole derivatives was depicted in Scheme 2. The initial step involves the addition of $P(NMe_2)_3$ to α-dicarbonyl compound, forming the Kukhtin-Ramirez adduct **A**, which is presumably in equilibrium with dipole **B**.[15] Through its dipolar structure **B**, the Kukhtin-Ramirez adduct can then trigger a Michael addition to diazene **1** to generate the intermediate **C**. Subsequently, the intermediate **C** undergoes an intramolecular substitution through its less hindered oxygen anion to afford the product oxadiazole and release the phosphoric triamide byproduct. The existence of two adjacent carbonyl groups in the substrate is essential for the initial Kukhtin-Ramirez addition step to form the five-membered 1,3,2-dioxaphospholene adduct **A**, which then can trigger the annulation via its dipolar format **B**. Employing other types of activated carbonyl compounds with only one carbonyl group such as 2,2,2-trifluoroacetophenone and benzoyl cyanide failed to give the desired [4 + 1] annulation products with representative diazene **1a** under the standard reaction conditions.




**Scheme 2.** Proposed mechanism for the formation of 1,3,4-oxadiazole.

## Conclusion

In summary, we have demonstrated an unprecedented $P(NMe_2)_3$-mediated deoxygenative [4 + 1] annulation of *N*-acyldiazenes with α-dicarbonyl compounds, which provides a highly efficient synthesis of 2,2,5-trisubstituted 1,3,4-oxadiazole derivatives. It represents the first realization of [4 + 1] annulation mode involving *N*-acyldiazenes to prepare five-membered heterocycles. Features of this annulation include mild conditions, readily available starting materials, as well as broad substrates scope. This work, together with previous reports from our group and others,[15,17] demonstrates the versatility of Kukhtin-Ramirez adduct serving as a new type of dipolar synthon in organophosphorus chemistry. Future efforts will be directly toward application of this methodology for synthesis of pharmaceutically intriguing compounds.

## Experimental Section

### General Information

Unless otherwise noted, all reactions were carried out in nitrogen atmosphere under anhydrous conditions. All solvents were purified according to standard procedures. $^1H$ and $^{13}C$ NMR spectra were recorded in $C_6D_6$ with tetramethylsilane (TMS) as the internal standard. Column chromatography was performed on silica gel (200 ~ 300 mesh) using a mixture of petroleum ether/ethyl acetate as eluant. *N*-Acyldiazenes **1**,[18] isatins **2**,[19] and ethyl aroylformates **4**[20] were prepared according to the literature procedures.

### Typical Procedure for the [4 + 1] Annulation between *N*-Acyldiazenes 1 and α-Dicarbonyl Compounds 2 or 4

Under a $N_2$ atmosphere, to a solution of *N*-acyldiazene **1** (0.4 mmol), α-dicarbonyl compound **2** or **4** (0.2 mmol), and 4Å molecular (150 mg) in a mixture of $CH_2Cl_2$ (1.0 mL) and acetonitrile (0.5 mL) was added $P(NMe_2)_3$ (40 μL, 0.22 mmol) in acetonitrile (0.5 mL) dropwise by means of syringe at -78 °C. The resulting reaction mixture was then slowly warmed up to room temperature and stirred at r.t. until the α-dicarbonyl compound was completely consumed, as monitored by TLC. The solvent was removed on a rotary evaporator under reduced pressure and the residue was subjected to column chromatographic isolation on silica gel by gradient elution using petroleum ether /ethyl acetate (20:1 ~ 3:1) to give the annulation product **3** or **5**.

**1-Allyl-3',5'-diphenyl-3'*H*-spiro[indoline-3,2'-[1,3,4]oxadiazol]-2-one (3aa).** Table 1, entry 9; prepared according to the typical procedure, (*E*)-phenyl(phenyldiazenyl)methanone **1a** (84 mg, 0.4 mmol) and *N*-allylic isatin **2a** (37.4 mg, 0.2 mmol) were employed to give **3aa** (50 mg, 66%) as a yellow solid; mp: 103-105 °C; $^1H$ NMR (400 MHz, $C_6D_6$) δ 8.01 – 7.83 (m, 2H), 7.24 – 7.18 (m, 3H), 7.05 – 6.98 (m, 5H), 6.95 (td, *J* = 7.8, 1.3 Hz, 1H), 6.80 – 6.62 (m, 2H), 6.40 (d, *J* = 7.9 Hz, 1H), 5.40 (ddt, *J* = 17.1, 10.5, 5.4 Hz, 1H), 4.90 (dddd, *J* = 27.2, 10.3, 2.6, 1.4 Hz, 2H), 3.98 (ddt, *J* = 16.2, 5.0, 1.7 Hz, 1H), 3.69 (ddt, *J* = 16.2, 5.7, 1.4 Hz, 1H); $^{13}C$ NMR (101 MHz, $C_6D_6$) δ 169.7, 152.8, 144.1, 143.4, 132.1, 131.0, 130.5, 129.4, 128.7, 126.8, 126.4, 125.6, 124.5, 123.7, 121.7, 117.9, 115.5, 110.1, 95.7, 42.2; HRMS–ESI ($[M + H]^+$) Calcd for $C_{24}H_{20}N_3O_2$ 382.1550, found 382.1544.

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FULL PAPER

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Rong Zhou,* Ling Han, Honghui Zhang, Rongfang Liu,* Ruifeng Li