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Iron(III)/TEMPO-Catalyzed Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles by Oxidative Cyclization under Mild Conditions

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Abstract A simple and efficient cationic Fe(III)/TEMPO-catalyzed oxidative cyclization of aroyl hydrazones has been developed for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives. The reaction offers a broad scope, good functional-group tolerance, and high yields under mild conditions in the presence of O_2.

Key words oxadiazoles, iron catalysis, cyclization, oxidation, aroyl hydrazones

The 1,3,4-oxadiazole motif is a prevalent heterocyclic structure in many biologically active compounds and photoelectric materials (Figure 1).[1,2] Consequently, the development of protocols for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives has received significant attention. These compounds are usually prepared by oxidative cyclization of benzoyl hydrazones in the presence of oxidants.[3,4]

Recently, a transition-metal-catalyzed oxidative cyclization strategy has been developed as an effective route to the formation of 1,3,4-oxadiazoles (Scheme 1, a and b).[5a,b] Interestingly, Yadav and Yadav reported a novel route to 2,5-disubstituted 1,3,4-oxadiazoles directly from aldehydes and acyl hydrazides by using visible-light irradiation under air in the presence of eosin Y as an organophotoredox catalyst at room temperature (Scheme 1, c).[5c]

In 2009, Miura and co-workers described a copper-catalyzed direct arylation of 1,3,4-oxadiazoles with aryl iodides by using phosphorus ligands with the aid of carbonate bases.[6] Other progress in this field involves electrophilic substitution of 2-substituted 1,3,4-oxadiazoles,[7] cyclodehydration of 1,2-diacyl hydrazines,[8] and reactions of carboxylic acids or acyl chlorides with hydrazides.[9] However, these

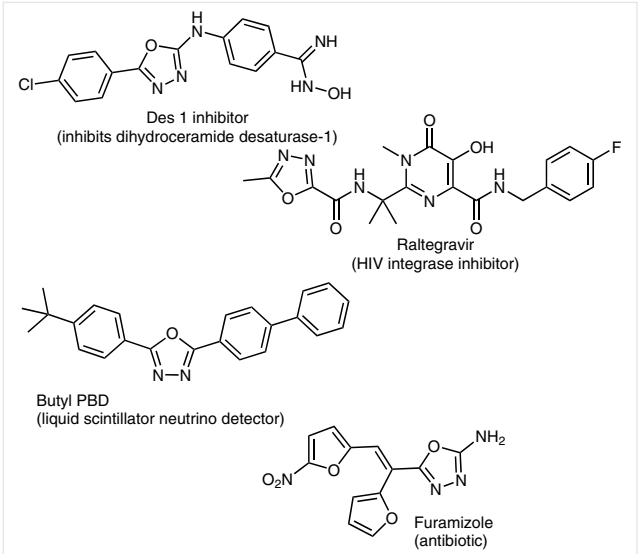
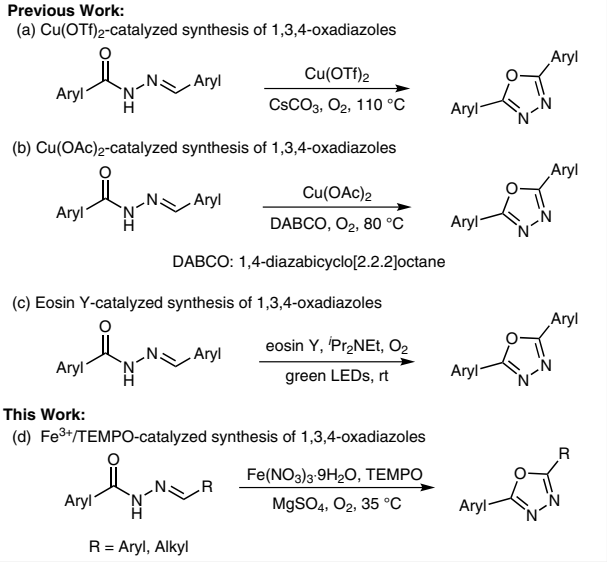


Figure 1 Pharmaceuticals and materials containing the 1,3,4-oxadiazole motif

strategies require the use of expensive or toxic oxidants, such as tetravalent lead reagents,[3a,c] Br_2,[3b] chloramine T,[3d] $FeCl_3$,[3e] HgO/I_2,[3f] $KMnO_4$,[3g] ceric ammonium nitrate,[3h] or H_2O_2/I_2,[3i] or they require high reaction temperatures.[5a,b] We previously described an efficient approach to the aerobic oxidative deoximation of various ketoximes under mild conditions by using commercially available $FeCl_3$/TEMPO as a catalyst with oxygen as the terminal oxidant.[10] On the basis of this previous work, we surmised that a Fe^{3+}/TEMPO-catalyzed oxidative cyclization of aroyl hydrazones might be established.

To test our hypothesis, we began an investigation by using *N*′-(2,2-dimethylpropylidene)benzohydrazide (**1a**) as a model substrate. To our delight, the desired oxadiazole **2a**

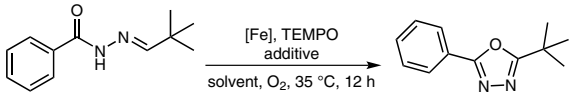


Scheme 1 Catalyzed oxidative cyclization approaches to 1,3,4-oxadiazoles in the presence of O_2

was obtained in 74% isolated yield when 10 mol% $Fe(NO_3)_3{\cdot}9H_2O$/TEMPO was used as a catalyst under O_2 in dichloromethane at 35 °C (Table 1, entry 1). Subsequently, other reaction parameters, such as the solvent, additive, Fe salt, reaction temperature, and reaction atmosphere, were surveyed. Among the tested solvents (entries 1–5), dichloroethane was found to be the most effective for this reaction, providing the desired product **2a** in 87% isolated yield (entry 2). Surprisingly, we found that $MgSO_4$ as an additive increased the yield to 92% (entry 6; for further details see Table S2 in the Supporting Information). With iron(III) triflate as the Fe salt, the yield of the desired product **2a** dropped dramatically to less than 10% (entry 14), and none of the desired product was obtained when $FeBr_3$, FeF_3, $FeSO_4{\cdot}7H_2O$, $Fe(acac)_2$, $Fe(OAc)_2$, or $FeCl_2{\cdot}4H_2O$ was using in the transformation (entries 15–20). In addition, none of the desired product **2a** was obtained in the absence of an Fe catalyst (entry 21), and the yield fell to 26% in the absence of TEMPO (entry 22), demonstrating that the Fe salt and TEMPO play essential roles in promoting the reaction. As can be seen, the reaction is aerobic, as yields of product **2a** were also reduced under molecular nitrogen or air (entries 23 and 24). Fortunately, the progress of the reaction was unaffected by shortening the reaction time (entries 25 and 26).

To test the scope of our method, we surveyed a variety of aryl aldehyde derived benzohydrazides **1** (Scheme 2). Substrates bearing electron-withdrawing groups such as chloro, bromo, trifluoromethyl, or iodo on the aromatic rings were all easily converted into the corresponding products **2f–i** in good to excellent yields (Scheme 2); other substrates with electron-donating groups also gave high yields

Table 1 Optimization of the Reaction Conditions[a]



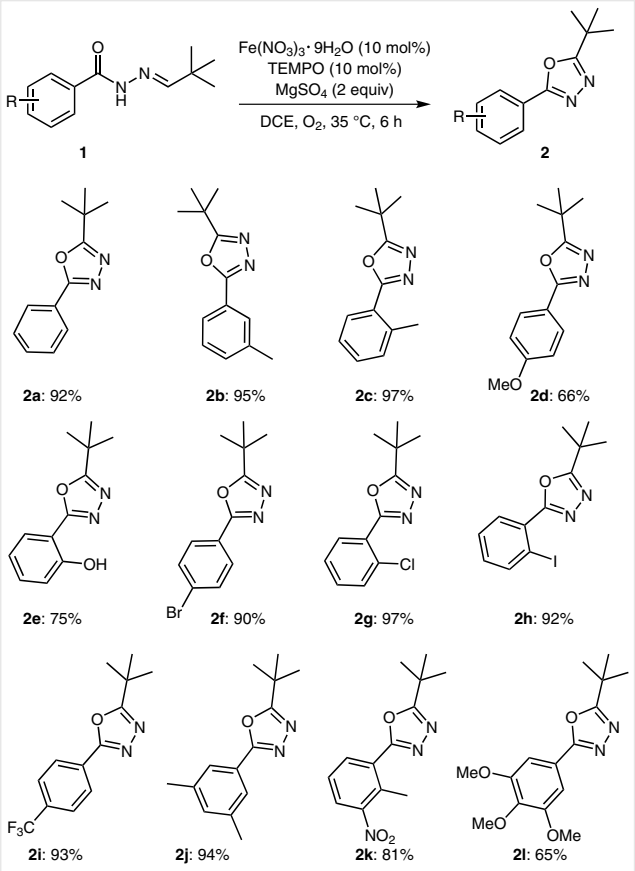
1a **2a**

Entry	Solvent	Temp (°C)	[Fe]	Additive	Yield[b]
1	CH_2Cl_2	35	$Fe(NO_3)_3{\cdot}9H_2O$	–	74%
2	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	–	87%
3	$CHCl_3$	35	$Fe(NO_3)_3{\cdot}9H_2O$	–	62%
4	EtOAc	35	$Fe(NO_3)_3{\cdot}9H_2O$	–	59%
5	toluene	35	$Fe(NO_3)_3{\cdot}9H_2O$	–	54%
6	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	$MgSO_4$	92%
7	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	4 Å MS[c]	86%
8	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	Na_2SO_4	51%
9	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	NaOH	–
10	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	Na_2CO_3	–
11	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	$NaHCO_3$	–
12	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	K_2CO_3	24%
13	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	NaOAc	<10%
14	DCE	35	$Fe(OTf)_3$	$MgSO_4$	<10%
15	DCE	35	$FeBr_3$	$MgSO_4$	–
16	DCE	35	FeF_3	$MgSO_4$	–
17	DCE	35	$FeSO_4{\cdot}7H_2O$	$MgSO_4$	–
18	DCE	35	$Fe(acac)_2$	$MgSO_4$	–
19	DCE	35	$Fe(OAc)_2$	$MgSO_4$	–
20	DCE	35	$FeCl_2{\cdot}4H_2O$	$MgSO_4$	–
21	DCE	35	–	$MgSO_4$	–
22[d]	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	$MgSO_4$	26%
23[e]	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	$MgSO_4$	36%
24[f]	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	$MgSO_4$	74%
25[g]	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	$MgSO_4$	92%
26[h]	DCE	35	$Fe(NO_3)_3{\cdot}9H_2O$	$MgSO_4$	90%
27[i]	DCE	30	$Fe(NO_3)_3{\cdot}9H_2O$	$MgSO_4$	88%

[a] Reaction conditions: **1a** (0.5 mmol), [Fe] (10 mol%), TEMPO (10 mol%), additive (2 equiv), solvent (5 mL), 12 h, in 100 mL sealed tube.
[b] Isolated yield.
[c] 0.5 g.
[d] Without TEMPO.
[e] Under N_2.
[g] Under air.
[h] 6 h.
[i] 9 h.

of the corresponding products **2b**, **2c**, and **2j**, showing that electronic effects in the aromatic moiety had no significant effect on the reaction. Curiously, when the aromatic group was connected to one or more oxygen atoms, the yields of **2d**, **2e**, and **2l** were reduced to 65–75%. Some results suggested that steric hindrance in the aromatic substrate appeared to have no effect (**2g** and **2h**). Meanwhile, substrate

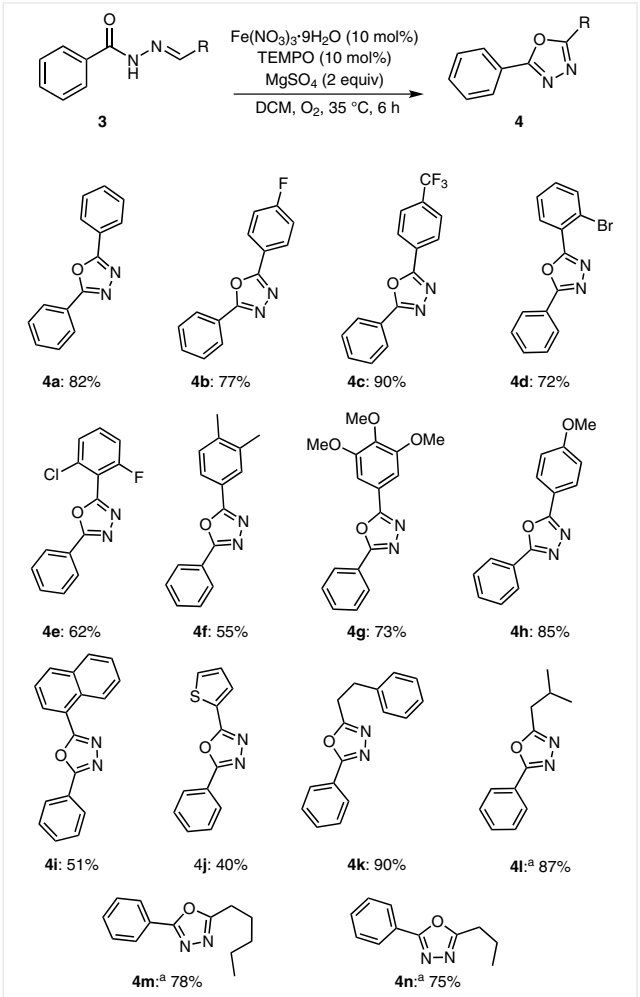
1k possessing both an electron-donating methyl group and an electron-withdrawing nitro group gave product **2k** in a satisfactory yield (81%).



Scheme 2 Scope of the reactions of *N*′-(2,2-dimethylpropylidene)benzohydrazides **1**. *Reagents and conditions*: **1** (0.5 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (10 mol%), TEMPO (10 mol%), $MgSO_4$ (2 equiv), DCE (5 mL), 6 h, 100 mL sealed tube. The isolated yields are reported.

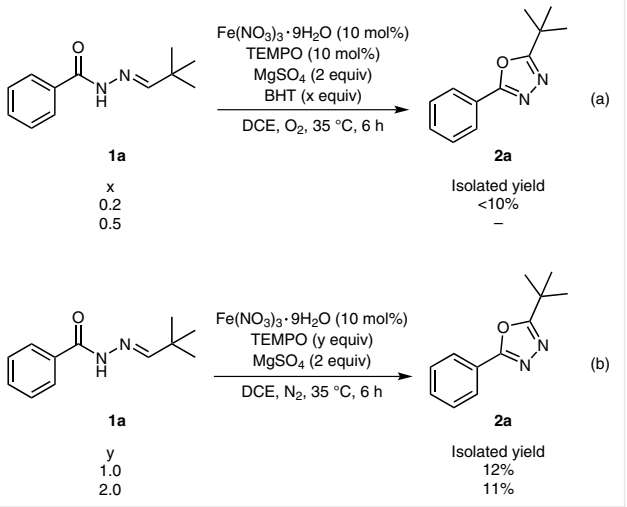
Next, we investigated the scope of substrates by replacing the *tert*-butyl group in the substrate (Scheme 3). Disappointingly, we found that the reactions of *N*′-(arylmethylene)benzohydrazides under our previously optimized conditions did not reach our expectations. We therefore reinvestigated the optimization of the reaction conditions with *N*′-benzylidenebenzohydrazide as a substrate (for details, see Table S6 of the Supporting Information), and we identified the following optimal conditions: $Fe(NO_3)_3{\cdot}9H_2O$ (10 mol%), TEMPO (10 mol%), $MgSO_4$ (2 equiv), CH_2Cl_2 (5 mL), O_2, 35 °C, 6 h.

With these optimal conditions in hand, we investigated the scope of the oxidative cyclization of various *N*′-(alkylidene)benzohydrazides **3** (Scheme 3). Gratifyingly, we found that substrates with electron-withdrawing substituents gave the corresponding products **4b–e** in moderate to excellent yields (62–90%) in six hours, whereas those with electron-donating substituents gave the corresponding products **4f–h** in moderate to good yields (55–85%). When the aromatic ring had *ortho*-substituents, yields were reduced to 62–72% (**4d** and **4e**), suggesting that steric hindrance is a major factor. Substrates **3** with 1-naphthyl, 2-thienyl, or 2-phenylethyl substituents gave products **4l** (51%), **4j** (40%), and **4k** (90%), respectively. Intriguingly, compounds with aliphatic substituents gave products **4l–n** in good yields (75–87%) when 15 mol% of TEMPO was used.



Scheme 3 Scope with *N*′-(alkylidene)benzohydrazides. *Reagents and conditions*: **3** (0.5 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (10 mol%), TEMPO (10 mol%), $MgSO_4$ (2 equiv), CH_2Cl_2 (5 mL), 6 h, 100 mL sealed tube. Isolated yields are reported. [a] TEMPO (15 mol%), DCE (5 mL).

To gain insight into the mechanism, we conducted some preliminary control experiments (Scheme 4). When 0.2 equivalents of 2,6-di-*tert*-butyl-4-methylphenol (BHT), a known radical-trapping reagent, were present in the reaction of substrate **1a**, the amount of product **2a** that was formed was markedly reduced to <10%, and when the amount of BHT was increased to 0.5 equivalents, none of the desired product **2a** was obtained, implying that a single-electron transfer pathway is involved in this reaction



Scheme 4 Control experiments. *Reagents and conditions*: **1a** (0.5 mmol), $Fe(NO_3)_3·9H_2O$ (10 mol%), $MgSO_4$ (2 equiv), DCE (5 mL), 6 h, 100 mL sealed tube. BHT = 2,6-di-*tert*-butyl-4-methylphenol.

(Scheme 4, a). Furthermore, when 1.0 or 2.0 equivalents of TEMPO were added to the reaction system under N_2, the desired product **2a** was obtained in only 12% and 11%, yield, respectively (Scheme 4, b), revealing that the reaction involves a radical pathway.

On the basis of these control experiments and related reports in the literature,[10,11] a plausible mechanism is proposed, as outlined in Scheme 5. Initially, TEMPO captures a hydrogen atom from the acyl hydrazone **A** to form TEMPO-H, which regenerates TEMPO in the presence of O_2. Meanwhile, acyl hydrazone **A** generates intermediate **B**. Subsequently, single-electron oxidation of **B** by $Fe(NO_3)_3$ affords intermediate **C**, which gives the intermediate **D** through addition of an oxygen radical to the carbon atom of the C=N moiety. Finally, compound **D** is converted into the desired product **E** by TEMPO-assisted dehydrogenation.

In conclusion, we have developed an economical and green Fe(III)/TEMPO-catalyzed oxidative cyclization of aroylhydrazones to form 1,3,4-oxadiazoles[12,13] under mild conditions in the presence of inexpensive and convenient O_2 as an oxidant. In addition, both arylalkylidene and alkylidene benzohydrazides exhibited good compatibility with the reaction conditions. From preliminary mechanistic studies, a plausible pathway is proposed.

Acknowledgment

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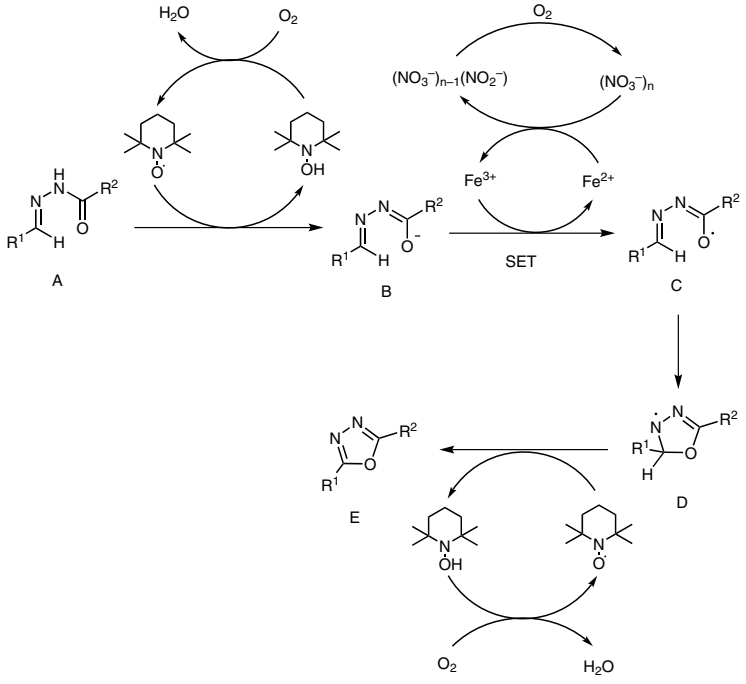
Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588747.



Scheme 5 Possible mechanism

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(12) **2-*tert*-Butyl-5-phenyl-1,3,4-oxadiazole (2a); Typical Procedure**

A mixture *N*′-(2,2-dimethylpropylidene)benzohydrazide (**1a**; 0.1021 g, 0.5 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (0.0202 g, 0.05 mmol), $MgSO_4$ (0.1204 g, 1.0 mmol), TEMPO (0.0078 g, 0.05 mmol), and DCE (5.0 mL) was added to a 100 mL sealed tube and vigorously stirred under O_2 at 35 °C for 6 h. H_2O (20.0 mL) was then added to the tube and the product was extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated under a vacuum. The residue was purified by column chromatography to give a light yellow liquid; yield: 0.0931 g (92%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.99 (dd, *J* = 8.0, 1.6 Hz, 2 H), 7.63–7.54 (m, 3 H), 1.42 (s, 9 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.67, 163.77, 131.71, 129.29, 126.37, 123.58, 32.02, 27.77. HRMS: *m/z* [M + 1]$^+$ calcd for $C_{12}H_{15}N_2O$: 203.1179; found: 203.1178.

(13) **2,5-Diphenyl-1,3,4-oxadiazole (4a**): **Typical Procedure**

A mixture of *N*′-(benzylidene)benzohydrazide (0.1120 g, 0.5 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (0.0202 g, 0.05 mmol), $MgSO_4$ (0.1204 g, 1.0 mmol), TEMPO (0.0078 g, 0.05 mmol), and CH_2Cl_2 (5.0 mL) was added to a 100 mL sealed tube and vigorously stirred under O_2 at 35 °C for 6 h. H_2O (20.0 mL) was then added to the tube and the product was extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated under a vacuum. The residue was purified by column chromatography to give a light yellow solid; yield: 0.0911 g (82%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.15–8.08 (m, 4 H), 7.66–7.60 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.99, 131.99, 129.37, 126.65, 123.33. HRMS: *m/z* [M + 1]$^+$ calcd for $C_{14}H_{11}N_2O$: 223.0871; found: 223.0867.