Cobalt(II) nitrate promoted cyclization of benzoyl hydrazone for the synthesis of 2,5-diphenyl-1,3,4-oxadiazole derivatives

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Abstract
A Co(NO₃)₂ method to promote cyclization of benzoyl hydrazone for the formation of 2,5-diphenyl-1,3,4-oxadiazoles has been developed. The reaction proceeded smoothly and was promoted by Co(NO₃)₂ under air at 110 °C in DCE; 16 examples of products were obtained.

Keywords
2,5-Diphenyl-1,3,4-oxadiazoles, benzoyl hydrazone, Co(NO₃)₂, cyclization, synthesis

Introduction
2,5-Disubstituted-1,3,4-oxadiazoles are important scaffolds which have been found in many natural and synthetic molecules with unique physical characteristics¹–³ and remarkable biological activities (Figure 1).⁴,⁵ In view of their great importance, the synthesis of 2,5-diaryl-1,3,4-oxadiazoles has gained much attention in recent decades and many useful synthetic procedures for their preparation have been developed. For example, arylation of 1,3,4-oxadiazoles (Scheme 1(a)),⁶–⁸ aminocarbonylation reaction of aryl halides with chloroform and tetrazoles (Scheme 1(b)),⁹–¹² oxidative dehydrogenation of N-substituted hydrazides (Scheme 1(c)),¹³ oxidations of aldehyde hydrazones and N, N-dimethylamides (Scheme 1(d)),¹⁴ isocyanide insertion/cyclization sequence of hydrazides and aryl halide (Scheme 1(e)),¹⁵ the use of Vilsmeier’s reagent (Scheme 1(f)),¹⁶,¹⁷ decarboxylation and cyclization of α-keto acids with acylhydrazines (Scheme 1(g)),¹⁸,¹⁹ oxidative cyclization using aldehydes and acyl hydrazides (Scheme 1(h)),²⁰–³¹

As shown in Scheme 2, many different methods have been developed for the synthesis of 2,5-substituted-1,3,4-oxadiazoles from aldehydes and acyl hydrazides (Scheme 1(h)). For example, halogen,²⁰–²² organic peroxide,²³,²⁴ inorganic oxides,²⁵ sulfur and oxygen,²⁶ and palladium (0)²⁷ can all promote oxidative cyclization of acylhydrazones to 2,5-substituted 1,3,4-oxadiazoles. Similarly, photooxidation²⁸ and electrooxidation²⁷–³¹ also have been applied to this reaction. In addition, we have shown that cobalt nitrate plays a special role in organic synthesis and is different from other cobalt salts and nitrates of other metals.³²,³³ Inspired by this work and our continuing efforts on C–H bond activation reactions,³⁴–³⁷ we here report the development of an efficient method for the Co(NO₃)₂-mediated, one-pot synthesis of unsymmetrical 2,5-diaryl-1,3,4-oxadiazoles. This method requires mild conditions with high substrate tolerance and good selectivity; high yields of products were obtained.

Results and discussion
Scheme 3. Scale-up experiment
First, we investigated the influence of the nitrate (Table 1, entries 1–5). We observed that the best reproducible yield was obtained when Co(NO₃)₂·6H₂O in DCE was used (Table 1, entry 1). Several other solvents, such as 1,4-dioxane, THF, CH₃CN, toluene, and acetone were examined, but the yield was not as good (Table 1, entries 6–10). Finally, the yield of 2a dropped slightly to 85% when the Co(NO₃)₂·6H₂O loading was increased from 1.5 equiv. to 2.0 equiv. (Table 1, entry 11). When the temperature was reduced to 80 °C and 100 °C or increased to 120 °C, the yield decreased to 57%, 78%, and 84%, respectively (Table 1, entries 12–14).

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we found that Co(NO$_3$)$_2$·6H$_2$O is the only effective one (Table 1, entries 1, 15−17).

With the optimized conditions in hand, we investigated the substrate scope of this reaction, beginning by varying the substituents on the benzene ring of the aromatic aldehyde (Table 2). Substrates derived from aromatic aldehydes with para-substituents 4-Et (2b), 4-C(CH$_3$)$_3$ (2c), 4-Me (2d) and ortho-substituents 2-Br (2f), 2-CF$_3$ (2g), 2-F (2h), 2-OEt (2i), 2-Me (2j) afforded the corresponding products in good yields. Substrates with meta-substituents with diverse electronic properties also worked well, with withdrawing groups 3-CN (2k), 3-CF$_3$ (2l) and electron-donating groups 3-OMe (2m) all providing the oxadiazole in good yields. However, the 2e compound did not give the desired product under standard conditions, probably because the presence of nitro was preventing the promotion of the reaction by Co(NO$_3$)$_2$·6H$_2$O. Similarly, many disubstituted substrates such as 2n, 2o, and 2p also afforded the corresponding products in synthetically useful yields (66−78 %). Unfortunately, both alkyl (2q) and heterocyclic (2r) substituted aldehydes did not give the desired products. In addition, we changed the substituents on the benzene ring of the hydrazide. Methyl substituents (2s, 2u, 2v) all gave good yields, but nitro substituted aroyl hydrazides (2t, 2v, 2x) did not give the desired products.

A gram-scale preparation of 2a was performed, which established the practicality of the method. Happily, under standard conditions (Scheme 3), we managed to isolate the desired product in a 54% yield without any problems. We then wanted to learn more about the mechanism of this reaction and conducted several control experiments to elucidate some of the key steps. First, we found that the reaction was inhibited when a radical scavenger such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction mixture (Scheme 4(a)). Furthermore, employing 1-diphenylethylene as starting material and reacting under the standard conditions...
Table 2. Substrate scope.a

| R1 | R2 | Yield | Ref. |
|----|----|-------|------|
| H  | H  | 96%   | 2b   |
| CH3| H  | 87%   | 2c   |
| Cl | H  | 80%   | 2d   |
| Cl | NO2| 74%   |      |
| CH3| H  | 82%   |      |
| H  | CH3| 78%   |      |
| H  | NO2| 82%   |      |
| H  | Cl  | 73% |      |
| CH3| CH3| 63%  |      |
| CH3| NO2| 69%  |      |
| CH3| NO2| 61%  |      |
| NO2| NO2| 70%  |      |

aReaction conditions: 1 (0.2 mmol), Co(NO3)2·6H2O (1.5 equiv.), and DCE (2.0 mL) at 110 °C in a sealed tube builds pressure, in air for 0.5–4 h, isolated yield.

Scheme 3. Scale-up experiment.

(Scheme 4(b)), we observed a clean transformation to the nitroolefin 4. Because of the competitive oxidation of Co(II) by nitric acid, the reaction did not continue after the addition of TEMPO, and we captured the nitro, further demonstrating that nitric acid generated nitro radicals under heating conditions. We surprisingly found that Cu(NO3)2·3H2O provided the desired oxadiazole in 32% yield (Table 1, entry 4). However, tert-butyl nitrite showed reduced reactivity (Table 1, entry 5). In addition, we did not obtain product 2a when other cobalt salts such as CoCl2, Co(OAc)2, or CoSO4 were used (Table 1, entries 15–17). These results showed that NO3- and certain metal cations (i.e., Co, Cu) were necessary for this cyclization.

On the basis of previous related studies14,38 and the results we obtained, a plausible reaction mechanism for this direct synthesis of 2,5-diarlyl-1,3,4-oxadiazoles is proposed in Scheme 5. Initially, the compound 1a reacts with the Co(II) salt to produce complex A. Next, the complex A can be converted to the Co(II) complex B by an S-endo-trig-type cyclization. Finally, this is further aromatized to give the desired product 2a and Co(0) is oxidized by O2 (Scheme 5(a)) or HNO3 (Scheme 5(b)) giving Co(II).

Conclusion

In conclusion, we have developed a facile synthesis of 2,5-diarlyl-1,3,4-oxadiazoles via a cyclization protocol employing cobalt nitrate and a benzoyl hydrazone. This methodology works under mild conditions and provides a direct approach for the synthesis of various 2,5-diphenyl-1,3,4-oxadiazoles, which are useful in organic and pharmaceutical industries, from commercially available starting materials under mild reaction conditions.

Experimental section

General information

All the chemicals were obtained commercially and used without any prior purification. 1H NMR spectra were recorded on a Bruker Advance II 400 spectrometer. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (60°C–90°C) and ethyl acetate. Unless otherwise noted. All compounds were characterized by 1H NMR and 13C NMR, which are consistent with those reported in the literature.
General procedure for synthesis of various 2,5-substituted 1,3,4-oxadiazoles

A mixture of the 2,5-substituted 1,3,4-oxadiazole (0.2 mmol) and Co(NO\(_3\))\(_2\)•6H\(_2\)O (1.5 equiv.) in CH\(_2\)ClCH\(_2\)Cl (2.0 mL) was stirred in sealed tube at 110 °C for 0.5–4 h. After cooling down to room temperature and concentrating in vacuum, the residue was purified by flash chromatography on a short silica gel column to afford the product.

Declaration of conflicting interests
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