



Convenient preparation of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles promoted by Dess–Martin reagent

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ABSTRACT

2,5-Disubstituted 1,3,4-oxadiazoles have been conveniently prepared by oxidative cyclization of *N*-acyl-*N*-arylidene-hydrazines promoted by an excess of Dess–Martin periodinane under mild conditions (23 examples, up to 92% isolated yields).

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Among five-membered aromatic heterocycles, 1,3,4-oxadiazoles¹ are of particular interest, since some of the members belonging to this class display various biological activities: 5-HT-receptor antagonists,² muscarinic receptor agonists,³ benzodiazepine receptor agonists,⁴ or tyrosinase inhibitors.⁵

Besides the dehydration of diacylhydrazines, oxidative cyclization of aldehyde *N*-acylhydrazones is the most known method to prepare unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles (Scheme 1), and several reagents have been reported to mediate the named transformation: ceric ammonium nitrate,⁶ chloramine T,⁷ tetravalent lead reagents,⁸ potassium permanganate under microwaves conditions,⁹ ferric chloride,¹⁰ bromine/sodium acetate,¹¹ or yellow mercuric oxide/iodine.¹²

In recent years, hypervalent iodine-containing reagents have been successfully utilized to prepare 1,3,4-oxadiazoles, namely iodobenzene diacetate¹³ or bis(trifluoroacetoxy)-iodobenzene.¹⁴ Besides these trivalent iodine-based reagents, some pentavalent iodine-containing compounds, (i.e., the 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one **1**¹⁵—the Dess–Martin periodinane, DMP, as well as its synthetic precursor 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide—IBX) have proven their usefulness as agents for oxidative cyclizations. Lately, a growing number of reports have revealed their ability to mediate the synthesis of heterocycles from various intermediates based on single-electron transfer (SET) processes.^{16–18} Therefore, we have decided to attempt the preparation

of 1,3,4-oxadiazoles in the presence of DMP via the oxidative cyclization pathway.

To the best of our knowledge, preparation of 1,3,4-oxadiazoles utilizing DMP as the reagent has not been reported yet. Herein we report our first results regarding the preparation of unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles from aldehyde *N*-acylhydrazones mediated by DMP. *N*-benzylidene-*N*-benzhydrazide **2a** was chosen as a model substrate, in order to test the effectiveness of the process. We found that placing **2a** in the presence of an excess of **1** at room temperature resulted in the formation of the desired 2,5-diphenyl-oxadiazole **3a** with complete consumption of the starting material in a few hours. The best solvent for the process was proved to be dichloromethane, while the amount of the oxidant required for a satisfactory yield of product was 2.5 equiv with respect to the substrate (Table 1, entries 1–3).

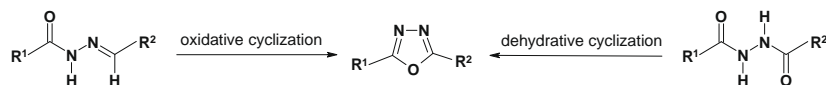
Although the conversion of **1a** was complete even when using 1.5 equiv of reagent (Table 1, entry 1), the yield of the isolated product decreased, probably due to the slow degradation of the substrate under the action of AcOH liberated from the oxidative process. The reaction also takes place in other polar nonprotic solvents, but more slowly and less efficiently (Table 1, entries 4 and 5).

Having these preliminary observations in hand, we have synthesized a series of aldehyde *N*-acylhydrazones **2a–w** in order to test the scope of their oxidative cyclization. These substrates are easily accessible in high yields and purity from aroylhydrazides and aldehydes. Thus, we had subjected this series of acylhydrazones **2** to the optimized reaction conditions.

In all cases, the conversion of the substrates was complete within 4 h in dichloromethane, while the use of DMF required over-

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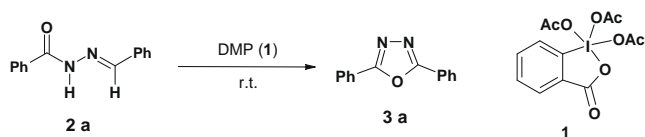


Scheme 1. The main synthetic pathways of access to 1,3,4-oxadiazoles.

night reactions. Chromatographic analysis of the crude mixture indicated the presence of the desired 1,3,4-oxadiazole as the main product, usually with excellent purity, easily separable from the iodinated by-products formed during the reaction. The results obtained are summarized in Table 2.

Table 1

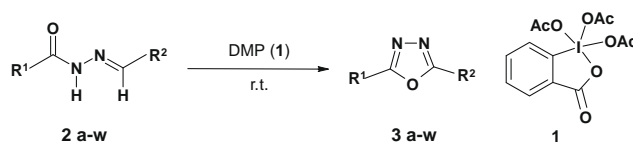
Screening of conditions for the oxidative cyclization of **2a** to 2,5-diphenyl-1,3,4-oxadiazole **3a** in presence of **1**



Entry	Solvent	Equiv of 1	Reaction time	Yield (%)
1	CH ₂ Cl ₂	1.5	4	72
2	CH ₂ Cl ₂	2	4	83
3	CH ₂ Cl ₂	2.5	4	92
4	CH ₃ CN	2	6	71
5	DMF	2	12	59

Table 2

Oxidative cyclization of **2** to 2,5-disubstituted-1,3,4-oxadiazoles **3** in presence of DMP



Entry	R ¹	R ²	Solvent	Product	Yield ^a (%)
1	Ph	Ph	CH ₂ Cl ₂	3a	92
2	Ph	4-MeO-C ₆ H ₄ -	CH ₂ Cl ₂	3b	87
3	Ph	4-Br-C ₆ H ₄ -	CH ₂ Cl ₂	3c	73
4	Ph	2-Furyl	CH ₂ Cl ₂	3d	42
5	Ph	2-Thienyl	CH ₂ Cl ₂	3e	82
6	Ph	4-Pyridyl	CH ₂ Cl ₂	3f	83
7	Ph	3-Thienyl	CH ₂ Cl ₂	3g	85
8	Ph	3-O ₂ N-C ₆ H ₄ -	DMF	3h	53
9	Ph	Pr	CH ₂ Cl ₂	3i	28
10	Ph	^t Pr	CH ₂ Cl ₂	3j	17
11	4-Cl-C ₆ H ₄ -	4-MeO-C ₆ H ₄ -	CH ₂ Cl ₂	3k	87
12	4-Cl-C ₆ H ₄ -	Ph	CH ₂ Cl ₂	3l	76
13	4-Cl-C ₆ H ₄ -	2-O ₂ N-C ₆ H ₄ -	DMF	3m	56
14	4-O ₂ N-C ₆ H ₄ -	4-MeO-C ₆ H ₄ -	DMF	3n	69
15	4-O ₂ N-C ₆ H ₄ -	4-Br-C ₆ H ₄ -	DMF	3o	55
16	2-Furyl	Ph	CH ₂ Cl ₂	3d	81
17	2-Furyl	4-MeO-C ₆ H ₄ -	CH ₂ Cl ₂	3p	88
18	2-Furyl	3-MeO-4-BnO-C ₆ H ₃ -	CH ₂ Cl ₂	3q	51
19	4-Pyridyl	4-MeO-C ₆ H ₄ -	CH ₂ Cl ₂	3r	79
20	4-Pyridyl	Ph	CH ₂ Cl ₂	3f	74
21	3-Chloro-benzo[<i>b</i>]thien-2-yl	Ph	CH ₂ Cl ₂	3s	72
22	3-Chloro-benzo[<i>b</i>]thien-2-yl	4-MeO-C ₆ H ₄ -	CH ₂ Cl ₂	3t	80
23	3-Chloro-benzo[<i>b</i>]thien-2-yl	3-MeO-4-BnO-C ₆ H ₃ -	CH ₂ Cl ₂	3u	65
24	3-Chloro-benzo[<i>b</i>]thien-2-yl	2-O ₂ N-C ₆ H ₄ -	DMF	3v	48
25	3-Chloro-benzo[<i>b</i>]thien-2-yl	3-Thienyl	CH ₂ Cl ₂	3w	81

^a General procedure: Substrate (0.5 mmol) and DMP (0.5 g) are placed in a dried flask and purged twice with vacuum/argon cycles. Dry solvent (10 mL) is syringed and stirring is started, obtaining a clear solution, which develops quickly a color depending on the substrate. After 4 h (of 12 h for DMF as solvent), the mixture is evaporated, the residue is taken in ethyl acetate and washed with water and brine. The organic phase is dried, concentrated, and purified by chromatography on silica. Spectroscopic and physical data for known products agreed with those reported.²⁰

zo[b]thien-2-yl (BBT) group by the dehydration of corresponding diacylhydrazines.¹⁹ In the course of this study, we have encountered difficulties in obtaining several BBT-containing 1,3,4-oxadiazoles (i.e., some nitro-phenyl or pyridyl derivatives) via the dehydrative cyclization. Therefore, we decided to attempt the preparation of some BBT-containing 1,3,4-oxadiazoles using the oxidative cyclization promoted by **1** (Table 2, entries 21–25). To our satisfaction, we observed that most of the substrates tested reacted smoothly in dichloromethane and gave the desired oxadiazoles in good yields. Again, the use of DMF as solvent was required in order to prepare the nitro derivative **3v** in moderate yield.

In summary, we have demonstrated that the preparation of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles via the oxidative cyclization of *N*-acyl-*N'*-arylidene-hydrazines may be effectively accomplished utilizing the DMP, and this method stands as a feasible alternative for convenient access to this class of heterocycles.

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- Compound 3g**: mp 121–122 °C; r_f 0.3 (CH₂Cl₂); IR (KBr, cm⁻¹) 1596, 1551, 1488, 1448, 1266, 860, 723, 688; ¹H NMR (400 MHz, CDCl₃) 8.12–8.1 (m, 3H), 7.73 (dd, 1H, *J* = 5.2 Hz, *J* = 1.2 Hz), 7.55–7.50 (m, 3H), 7.47 (dd, 1H, *J* = 5.2 Hz, *J* = 3.2 Hz); ¹³C NMR (100 MHz, CDCl₃) 163.94, 161.3, 131.65, 129.03 (2C), 127.41, 127.39, 126.88 (2C), 126.04, 125.27, 123.83; MS (CI,%) calcd 228.04, found 229 (100, MH⁺); Anal. Calcd for C₁₂H₈N₂O₅: C, 63.14; H, 3.53; N, 12.27. Found: C, 63.19; H, 3.60; N, 12.33. **Compound 3q**: mp 124–126 °C; r_f 0.3 (AcOEt/pentanes 3:7); IR (KBr, cm⁻¹) 1603, 1507, 1283, 1250; ¹H NMR (400 MHz, CDCl₃) 7.65 (d, 1H, *J* = 2 Hz), 7.60 (dd, 2H, *J* = 8 Hz, *J* = 2 Hz), 7.45–7.35 (m, 3H), 7.33–7.29 (m, 1H), 7.19 (d, 1H, *J* = 4 Hz), 6.98 (d, 1H, *J* = 8.4 Hz), 6.60 (dd, 1H, *J* = 4 Hz, *J* = 2 Hz), 5.22 (s, 2H), 3.98 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 164.04, 157.24, 151.39, 150.06, 145.64, 139.69, 136.38, 128.77 (2C), 128.22, 127.35 (2C), 120.48, 116.55, 113.89, 113.56, 112.24, 110.11, 71.02, 56.34; MS (CI,%) calcd 348.1, found 348 (98, M⁺), 257(100); Anal. Calcd for C₂₀H₁₆N₂O₄: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.00; H, 4.61; N, 8.07. **Compound 3t**: mp 165–167 °C; r_f 0.6 (CH₂Cl₂); IR (KBr, cm⁻¹) 1613, 1588, 1499, 1260; ¹H NMR (400 MHz, CDCl₃) 8.10 (d, 2H, *J* = 8.8 Hz), 7.97–7.94 (m, 1H), 7.86–7.84 (m, 1H), 7.53–7.51 (m, 2H), 7.03 (d, 2H, *J* = 8.8 Hz), 3.89 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 164.85, 162.71, 159.26, 138.13, 136.96, 129.08 (2C), 127.76, 125.79, 123.57, 123.3, 122.8, 119.25, 116.04, 114.69 (2C), 55.58; MS (CI, %) calcd 342.02, found 343.5 (38, (³⁷Cl)M⁺), 341.5(100, (³⁵Cl)M⁺), 250.7(61), 194.7(35), 135(66); Anal. Calcd for C₁₇H₁₁ClN₂O₅: C, 59.56; H, 3.23; N, 8.17. Found: C, 59.51; H, 3.28; N, 8.19. **Compound 3u**: mp 167–169 °C; r_f 0.45 (CH₂Cl₂/MeOH 98:2); IR (KBr, cm⁻¹) 1605, 1582, 1509, 1277; ¹H NMR (400 MHz, CDCl₃) 7.98–7.96 (m, 1H), 7.88–7.85 (m, 1H), 7.71 (s, 1H), 7.67 (d, 1H, *J* = 8.4 Hz), 7.54–7.52 (m, 2H), 7.47–7.43 (m, 2H), 7.39 (t, 2H, *J* = 7.2 Hz), 7.32 (t, 1H, *J* = 7.2 Hz), 7.01 (d, 1H, *J* = 8.4 Hz), 5.25 (s, 2H), 4.01 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) 164.88, 159.37, 151.58, 150.09, 138.17, 136.69, 136.37, 128.79, 128.23, 127.8, 127.33, 125.82, 123.64, 123.32, 122.82, 120.76, 119.19, 116.44, 113.62, 110.22, 71.03, 56.36; MS (CI,%) calcd 448.06, found 449.6 (2, (³⁷Cl)M⁺), 447.6(5, (³⁵Cl)M⁺), 343.8 (19), 295.9 (30), 257.9 (21), 241.9 (97), 211.8 (100), 196.9 (26), 194.9(76); Anal. Calcd for C₂₄H₁₇ClN₂O₅: C, 64.21; H, 3.82; N, 6.24. Found: C, 64.19; H, 3.87; N, 6.27. **Compound 3v**: mp 205–207 °C; r_f 0.7 (CH₂Cl₂); IR (KBr, cm⁻¹) 1582, 1533, 1353, 1286, 1044, 753, 725; ¹H NMR (400 MHz, DMSO-*d*₆) 8.25–8.23 (m, 1H), 8.2–8.18 (m, 1H), 8.01–7.97 (m, 3H), 7.9–7.83 (m, 1H), 7.69–7.64 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) 160.78, 159.8, 148.0, 137.54, 135.92, 133.78 (2C), 131.41, 128.5, 126.51, 124.86, 123.68, 123.33, 122.9, 118.19, 116.38; MS (CI,%) calcd 357.00, found 358.6 (22, (³⁷Cl)M⁺), 356.7(64, (³⁵Cl)M⁺), 194.9(100), 167 (26); Anal. Calcd for C₁₆H₈ClN₂O₅: C, 53.71; H, 2.25; N, 11.74. Found: C, 53.78; H, 2.22; N, 11.80. **Compound 3w**: mp 122–124 °C; r_f 0.5 (CH₂Cl₂); IR (KBr, cm⁻¹) 1583, 1486, 1308, 1266, 1246, 854, 758, 725; ¹H NMR (400 MHz, CDCl₃) 8.18 (dd, 1H, *J* = 2.9 Hz, *J* = 1.2 Hz), 7.99–7.96 (m, 1H), 7.89–7.86 (m, 1H), 7.77 (dd, 1H, *J* = 5 Hz, *J* = 1.2 Hz), 7.55–7.53 (m, 2H), 7.50 (dd, 1H, *J* = 5 Hz, *J* = 2.9 Hz); ¹³C NMR (100 MHz, CDCl₃) 161.56, 159.14, 138.21, 136.95, 128.31, 127.88, 127.65, 126.26, 125.86, 124.92, 123.38, 122.83, 118.97; MS (CI,%) calcd 317.9, found 320.7 (42, (³⁷Cl)MH⁺), 318.7(100, (³⁵Cl)MH⁺); Anal. Calcd for C₁₄H₇ClN₂O₅: C, 52.74; H, 2.21; N, 8.79. Found: C, 52.70; H, 2.26; N, 8.83.