Tetrahedron Letters 50 (2009) 1886–1888

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Cristian Dobrotă *, Codruţa C. Paraschivescu, Ioana Dumitru, Mihaela Matache, Ion Baciu, Lavinia L. Ruţă

University of Bucharest, Department of Chemistry, Division of Organic Chemistry, Şoseaua Panduri, No. 90–92, Sector 5, 050657 Bucharest, Romania

ARTICLE INFO

Article history:
Received 12 December 2008
Revised 28 January 2009
Accepted 3 February 2009
Available online 13 February 2009

Keywords:
1,3,4-Oxadiazoles
Oxidative cyclization
Dess–Martin periodinane
Heterocycles

ABSTRACT

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

Among five-membered aromatic heterocycles, 1,3,4-oxadiazoles[1] 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 diacetate[13] 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).

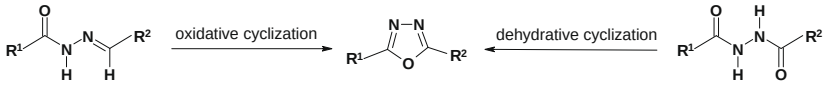
Although the conversion of **1a** was complete even when using 1.5 equiv of reagent (Table 1, entry 1), the yield of the isolated product decreased, probably due to the slow degradation of the substrate under the action of AcOH liberated from the oxidative process. The reaction also takes place in other 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-

* Corresponding author at present address: Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany. Tel.: +49 089 289 13 206.
E-mail address: cristian.dobrota@ch.tum.de (C. Dobrotă).

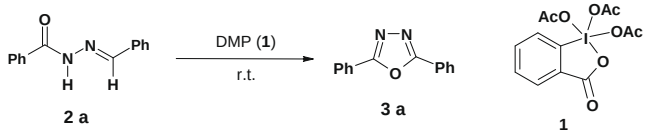
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.054



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**



2 a **3 a** **1**

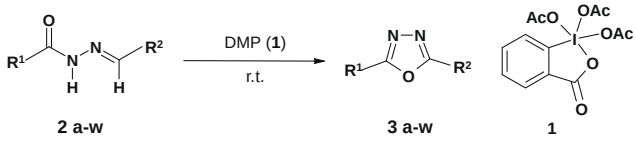
Entry	Solvent	Equiv of **1**	Reaction time	Yield (%)
1	CH_2Cl_2	1.5	4	72
2	CH_2Cl_2	2	4	83
3	CH_2Cl_2	2.5	4	92
4	CH_3CN	2	6	71
5	DMF	2	12	59

We have firstly studied variations of the nature of the aldehyde moiety participating in the formation of oxadiazoles **3**, preserving the same aroyl part (i.e., benzoyl, Table 2, entries 1–10). Thus, we have observed that the best results were obtained with hydrazones derived from aromatic aldehydes possessing electron-donating groups. The solvent of choice was dichloromethane. For the cases where the substrate was poorly soluble in dichloromethane, DMF was a suitable alternative, although the presence of an electron withdrawing group on the aromatic ring decreased the yield (Table 2, entry 8). The benzoyl hydrazones bearing an aliphatic chain in the aldehyde part gave very low yields (entries 9 and 10) probably due to the decomposition of the substrate during the reaction. Hydrazones derived from some heterocyclic aldehydes gave good yields (Table 2, entries 5–7). However, the cyclization of furyl derivative **2d** led to the desired oxadiazole **3d** in modest yield (Table 2, entry 4).

Subsequently, we have tested several *N*-aroyl-*N*′-aryliden-hydrazines bearing substituted benzoyl as well as some heterocyclic aromatic groups (Table 2, entries 11–20). The yields obtained were usually good to excellent, improvements being noticed in the case of the furyl- or nitro derivatives.

Very recently, we have reported the synthesis of a series of 2,5-disubstituted 1,3,4-oxadiazoles bearing the 3-chloro-ben-

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



2 a-w **3 a-w** **1**

Entry	R^1	R^2	Solvent	Product	Yield[a] (%)
1	Ph	Ph	CH_2Cl_2	**3a**	92
2	Ph	4-MeO–C_6H_4–	CH_2Cl_2	**3b**	87
3	Ph	4-Br–C_6H_4–	CH_2Cl_2	**3c**	73
4	Ph	2-Furyl	CH_2Cl_2	**3d**	42
5	Ph	2-Thienyl	CH_2Cl_2	**3e**	82
6	Ph	4-Pyridyl	CH_2Cl_2	**3f**	83
7	Ph	3-Thienyl	CH_2Cl_2	**3g**	85
8	Ph	3-O_2N–C_6H_4–	DMF	**3h**	53
9	Ph	Pr	CH_2Cl_2	**3i**	28
10	Ph	^{i}Pr	CH_2Cl_2	**3j**	17
11	4-Cl–C_6H_4–	4-MeO–C_6H_4–	CH_2Cl_2	**3k**	87
12	4-Cl–C_6H_4–	Ph	CH_2Cl_2	**3l**	76
13	4-Cl–C_6H_4–	2-O_2N–C_6H_4–	DMF	**3m**	56
14	4-O_2N–C_6H_4–	4-MeO–C_6H_4–	DMF	**3n**	69
15	4-O_2N–C_6H_4–	4-Br–C_6H_4–	DMF	**3o**	55
16	2-Furyl	Ph	CH_2Cl_2	**3d**	81
17	2-Furyl	4-MeO–C_6H_4–	CH_2Cl_2	**3p**	88
18	2-Furyl	3-MeO-4-BnO–C_6H_3–	CH_2Cl_2	**3q**	51
19	4-Pyridyl	4-MeO–C_6H_4–	CH_2Cl_2	**3r**	79
20	4-Pyridyl	Ph	CH_2Cl_2	**3f**	74
21	3-Chloro-benzo[*b*]thien-2-yl	Ph	CH_2Cl_2	**3s**	72
22	3-Chloro-benzo[*b*]thien-2-yl	4-MeO–C_6H_4–	CH_2Cl_2	**3t**	80
23	3-Chloro-benzo[*b*]thien-2-yl	3-MeO-4-BnO–C_6H_3–	CH_2Cl_2	**3u**	65
24	3-Chloro-benzo[*b*]thien-2-yl	2-O_2N–C_6H_4–	DMF	**3v**	48
25	3-Chloro-benzo[*b*]thien-2-yl	3-Thienyl	CH_2Cl_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*′-aryliden-hydrazines may be effectively accomplished utilizing the DMP, and this method stands as a feasible alternative for convenient access to this class of heterocycles.

Acknowledgments

The authors thank the Romanian Ministry for Education and Research for financial support by a Grant CEEX-VIASAN 43/2005. We also thank Mrs. Ulrike Ammari (Mikroanalytisches Labor, LSAC, Technische Universität München) for performing the elemental analyses.

References and notes

1. (a) Weaver, G. W.. In *Science of Synthesis*; Storr, R. C., Gilchrist, T. L., Eds.; Thieme: Stuttgart, 2004; Vol. 13, pp 219–251; (b) Hill, J.. In *Comprehensive Heterocyclic Chemistry II*; Storr, R. C., Ed.; Pergamon: Oxford, 1996; Vol. 4,. pp 267–287 and 905–1006.
2. Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. *J. Med. Chem.* **1991**, *34*, 140–151.
3. (a) Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsworth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726–2735; (b) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1128–1138.
4. Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060–2067.
5. Khan, M. T. H.; Choudhary, M. I.; Khan, K. M.; Rani, M.; Ahman, A.-u. *Bioorg. Med. Chem.* **2005**, *13*, 3385–3395.
6. Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Bahramnejad, M. *Tetrahedron Lett.* **2006**, *47*, 6983–6986.
7. Jedlovska, E.; Lesko, J. *Synth. Commun.* **1994**, *24*, 1879–1885.
8. (a) Milcent, R.; Barbier, G. *J. Heterocycl. Chem.* **1983**, *20*, 77–80; (b) Saikahi, H.; Shimojo, N.; Uehara, Y. *Chem. Pharm. Bull.* **1972**, *20*, 1663–1668.
9. Rostamizadeh, S.; Ghasem Housaini, S. A. *Tetrahedron Lett.* **2004**, *34*, 8753–8756. and the references cited therein.
10. Mruthyunjayaswamy, B. H. M.; Shanthaveerappa, B. K. *Indian J. Heterocycl. Chem.* **1998**, *8*, 31–38.
11. Werber, G.; Bucherri, F.; Noto, R.; Gentile, M. *J. Heterocycl. Chem.* **1977**, *14*, 1385–1388.
12. Faidallah, H. M.; Sharshira, E. M.; Basaif, S. A.; A-Ba-Oum, A. E.-K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 67–79.
13. (a) Yang, R.-Y.; Dai, L.-X. J. *Org. Chem.* **1993**, *58*, 3381–3383; (b) Rao, V. S.; Sekhar, K. *Synth. Commun.* **2004**, *34*, 2153–2157.
14. (a) Shang, Z. *Synth. Commun.* **2006**, *36*, 2927–2937; (b) Shang, Z.; Reiner, J.; Chang, J.; Zhao, K. *Tetrahedron Lett.* **2005**, *46*, 2701–2704.
15. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
16. Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261–8263.
17. Janza, B.; Studer, A. *J. Org. Chem.* **2005**, *70*, 6991–6993.
18. Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233–2244. and the references cited therein.
19. Paraschivescu, C. C.; Dumitrascu, F.; Draghici, C.; Ruta, L. L.; Matache, M.; Baciu, I.; Dobrota, C. *Arkivoc* **2008**, *xiii*, 198–206.
20. *Compound* **3g**: mp 121–122 °C; r_F 0.3 (CH_2Cl_2); IR (KBr, cm^{-1}) 1596, 1551, 1488, 1448, 1266, 860, 723, 688; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{12}H_8N_2OS$: 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{16}N_2O_4$: 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 (CH_2Cl_2); IR (KBr, cm^{-1}) 1613, 1588, 1499, 1260; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, (^{37}Cl)M$^+$), 341.5(100, (^{35}Cl)M$^+$), 250.7(61), 194.7(35), 135(66); Anal. Calcd for $C_{17}H_{11}ClN_2O_2S$: 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 (CH_2Cl_2/MeOH 98:2); IR (KBr, cm^{-1}) 1605, 1582, 1509, 1277; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, (^{37}Cl)M$^+$), 447.6(5, (^{35}Cl)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 $C_{24}H_{17}ClN_2O_3S$: 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 (CH_2Cl_2); 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); ^{13}C 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, (^{37}Cl)M$^+$), 356.7(64, (^{35}Cl)M$^+$), 194.9(100), 167 (26); Anal. Calcd for $C_{16}H_8ClN_3O_3S$: 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 (CH_2Cl_2); IR (KBr, cm^{-1}) 1583, 1486, 1308, 1266, 1246, 854, 758, 725; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, (^{37}Cl)MH$^+$), 318.7(100, (^{35}Cl)MH$^+$); Anal. Calcd for $C_{14}H_7ClN_2OS_2$: C, 52.74; H, 2.21; N, 8.79. Found: C, 52.70; H, 2.26; N, 8.83.