

Synthesis of 4-(5-Aryl-1,3,4-oxadiazol-2-yl)phenyl-hydrazine Derivatives from 3-(4-Hydrazinocarbonyl-phenyl)sydnone

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ABSTRACT: The synthesis of potential fluorescent active 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives was accomplished in three steps. The key step was the dehydration cyclization of 1,2-diacylhydrazines to form the 1,3,4-oxadiazole ring by use of acetic anhydride/perchloric acid mixture as the dehydrating agent. The sydnone moiety served as the masked hydrazines, which could be demasked by HCl for further application. © 2007 Wiley Periodicals, Inc. *Heteroatom Chem* 18:438–442, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20318

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INTRODUCTION

1,3,4-Oxadiazoles have been reported to be biologically versatile compounds displaying a variety of biological effects [1–5]. 1,3,4-Oxadiazole-based heterocyclic compounds are also the most widely studied class of electron-injection and/or hole-blocking organic electroluminescent materials [6]. The most common synthetic approach to 1,3,4-oxadiazoles involves cyclodehydration of 1,2-diacylhydrazines by use of a dehydrating agent [11–15]. An alternative route to 1,3,4-oxadiazoles by oxidative cyclization from the corresponding aldehyde *N*-acylhydrazones proceeds with an oxidizing agent [12–17]. Herein, we reported the synthesis of 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives from 3-(4-hydrazinocarbonylphenyl)sydnone in three steps to prepare the precursor of the 1,3,4-oxadiazol derivatives as electroluminescent materials. Description of the formation of the 1,3,4-oxadiazole ring can be found in a previous work, where a mixture of acetic anhydride

and perchloric acid was used as the dehydrating agent [18].

Sydnone attract attention owing to their widely useful properties, including biological and pharmaceutical usage [19], synthetic application [20], photochromic properties [21], and preparation of electroluminescent materials [22]. In this work, sydnones were considered as the masked hydrazines, which could be demasked by HCl for further application [23].

RESULTS AND DISCUSSION

The synthetic pathway of the 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives **4a–4c** is depicted in Scheme 1. 4-Hydrazinocarbonylphenylsydnone **1a–1c** were prepared by the published procedure [24]. The sydnone compounds **1a–1c** were easily converted to the 1,2-diacylhydrazines **2a–2c** by reacting with benzoyle chloride (*para*-R¹ = H, Cl, and OMe) in CH₂Cl₂ solution for 3.0 h. The isolated yields and the results are shown in Table 1.

Treatment of the various 1,2-diacylhydrazines **2a–2c** (*para*-R¹ = H, Cl, and OMe) with the acetic anhydride/perchloric acid mixture gave the 1,3,4-oxadiazole-sydnone hybrids **3a–3c** in 52%–60% yields (see Table 1). The proposed dehydration-cyclization mechanism is shown in Scheme 2. Upon addition of perchloric acid to the acetic anhydride solution, the sequence of the reaction can be generated using the CH₃CO⁺ClO₄[−] and acetic acid species [25]. 1,2-Diacylhydrazines **5** can be reacted with CH₃CO⁺ClO₄[−] in the acidic condition to afford the acetyl hydrazone intermediate (**7**) [26]. Further

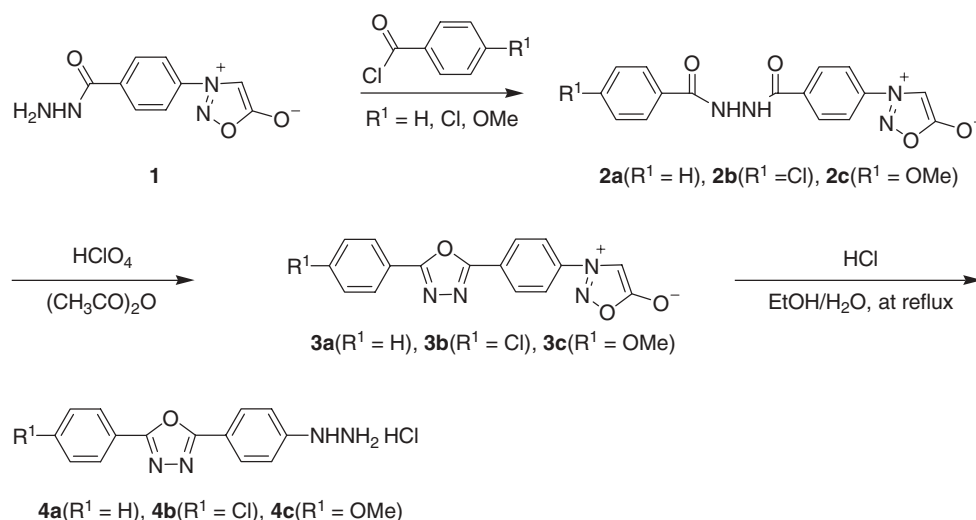
dehydration-cyclization was smoothly performed to yield the 1,3,4-oxadiazole ring (**6**). Finally, reaction of 1,3,4-oxadiazole-sydnone hybrids **3a–3c** with HCl gave products derived from cleavage of the sydnone ring to the corresponding hydrazines **4a–4c**.

In conclusion, we have developed a synthetic route for the precursor of electroluminescent materials of 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives in three steps. The key dehydration cyclization of 1,2-diacylhydrazines was performed with acetic anhydride/perchloric acid mixture to provide the 1,3,4-oxadiazole ring. In the last step, the cleavage of sydnone ring was reacted with HCl aqueous solution to afford the 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazines.

EXPERIMENTAL

General

Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wave numbers reported are referenced to the polystyrene 1601 cm^{−1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker-300 (300 MHz) spectrometer by use of CDCl₃ and *d*₆-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Varian Bruker-300 (75 MHz)



SCHEME 1 The synthetic route of 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives **4a–4c**.

TABLE 1 The Yields of Aldehyde *N*-Acylhydrazones **2a–2c**, 1,3,4-Oxadiazole–sydnone Hybrids **3a–3c**, and 4-(5-Aryl-1,3,4-oxadiazol-2-yl)phenylhydrazines **4a–4c**

Entry <i>R</i> ¹	Compounds 2	Yield (%)	Compounds 3	Yield (%)	Compounds 4	Yield (%)
H	2a	87	3a	52	4a	68
Cl	2b	90	3b	60	4b	77
Ome	2c	91	3c	57	4c	70

spectrometer by use of CDCl₃ as solvent. Carbon-13 chemical shifts are referenced to the center of the CDCl₃ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Standard Procedure for the Substitution Reaction

To a solution of 4-hydrazinocarbonylphenylsydnones (**1**, 0.38 g, 6.00 mmol, 1.0 equiv.) and benzoyl chloride (0.80 mL, 6.00 mmol, 1.0 equiv.) in CH₂Cl₂ (30 mL) was stirred at room temperature for 3 h. After the reaction was completed, the resultant precipitate was filtrated, washed with cold CH₂Cl₂ (10 mL $\times$ 2), and dried in vacuum oven. The residue was purified by recrystallization from EtOAc to give pure 1,2-diacylhydrazines **2a–2c** as light-yellow powder in 87%–91% yields.

3-[4-(*N'*-Benzoylhydrazinocarbonyl)phenyl]sydnone **2a**. mp (recrystallized from EtOAc): 214–216°C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 7.48–7.61 (m, 3H), 7.89 (s, 1H), 7.90–7.99 (m, 2H), 8.12 (d, 2H, *J* = 8.8 Hz), 8.20 (d, 2H, *J* = 8.8 Hz), 10.63 (s, 1H), 10.83 (s, 1H); IR (KBr) 3220 (s, NH), 3130 (s), 1695 (m, C=O) cm^{−1}; FABMS *m/z* (relative

intensity): 325 (*M* + 1, 20), 324 (*M*⁺, 16); Anal. Calcd for C₁₆H₁₂N₄O₄: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.32; H, 3.84; N, 17.27.

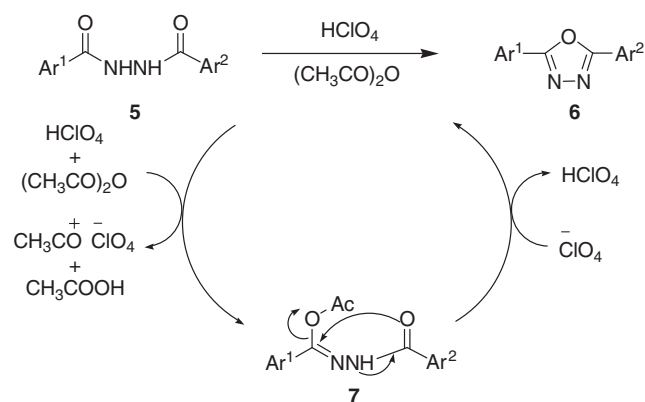
3-[4-(*N'*-4-Chlorobenzoylhydrazinocarbonyl)phenyl]sydnone **2b**. mp (recrystallized from EtOAc): 199–201°C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 7.60 (d, 2H, *J* = 8.8 Hz), 7.88 (s, 1H), 7.90 (d, 2H, *J* = 8.8 Hz), 8.09 (d, 2H, *J* = 8.8 Hz), 8.18 (d, 2H, *J* = 8.8 Hz), 10.74 (s, 1H), 10.87 (s, 1H); IR (KBr) 3214 (s, NH), 3136 (s), 1746 (m, C=O) cm^{−1}; FABMS *m/z* (relative intensity): 361 (*M* + 3, 10), 360 (*M* + 2, 8), 359 (*M* + 1, 32), 358 (*M*⁺, 20); Anal. Calcd for C₁₆H₁₁N₄O₄Cl: C, 53.57; H, 3.09; N, 15.62. Found: C, 53.70; H, 3.21; N, 15.43.

3-[4-(*N'*-4-Methoxybenzoylhydrazinocarbonyl)phenyl]sydnone **2c**. mp (recrystallized from EtOAc): 250–252°C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 3.84 (s, 3H, CH₃), 7.05 (d, 2H, *J* = 8.9 Hz), 7.88 (s, 1H), 7.90 (d, 2H, *J* = 8.8 Hz), 7.91 (d, 2H, *J* = 8.9 Hz), 8.10 (d, 2H, *J* = 8.8 Hz), 8.19 (d, 2H, *J* = 8.8 Hz), 10.47 (s, 1H), 10.74 (s, 1H); IR (KBr) 3214 (s, NH), 3130 (s), 1749 (m, C=O) cm^{−1}; FABMS *m/z* (relative intensity): 355 (*M* + 1, 31), 354 (*M*⁺, 22); Anal. Calcd for C₁₇H₁₄N₄O₅: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.50; H, 4.23; N, 16.69.

Standard Procedure for the Dehydration–Cyclization

1,2-Diacylhydrazines **2a–2c** (0.32 g, 1.00 mmol, 1.0 equiv.) was dissolved in acetic anhydride (5.0 mL) and added to 4 drops of 60% perchloric acid aqueous solution (HClO_{4aq}). The reaction mixture was stirred at room temperature for 36 h. After the reaction was completed, the reaction mixture was filtrated to remove the solid residue. The filtrate was mixed with cold water (10.0 mL) and the resultant precipitate was filtrated, washed with cold EtOAc (10 mL $\times$ 2), and dried in vacuum oven. The residue was purified by recrystallization from EtOAc to give the 1,3,4-oxadiazole–sydnone hybrids **3a–3c** as light-yellow powder in 52%–60% yields.

3-[4-(5-Phenyl-1,3,4-oxadiazol-2-yl)phenyl]sydnone **3a**. mp (recrystallized from EtOAc) > 250°C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ : 7.61–7.67 (m, 3H),

**SCHEME 2** The proposed mechanism of the oxidative cyclization.

7.93 (s, 1H), 8.15–8.22 (m, 4H), 8.43 (d, 2H, $J = 8.8$ Hz), IR (KBr) 3124 (s), 1770 (m, C=O) cm^{-1} ; MS m/z (relative intensity): 306 (M^+ , 3), 280 (4), 276 (11), 248 (100), 221 (10), 164 (21), 105 (53), 88 (33), 77 (63); Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{O}_3$: C, 62.74; H, 3.29; N, 18.29. Found: C, 62.83; H, 3.14; N, 18.18.

3-[4-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-phenyl]sydnone **3b**. mp (recrystallized from EtOAc) $> 250^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 7.70 (d, 2H, $J = 8.5$ Hz), 7.92 (s, 1H), 8.15 (d, 2H, $J = 8.7$ Hz), 8.18 (d, 2H, $J = 8.5$ Hz), 8.41 (d, 2H, $J = 8.7$ Hz); IR (KBr) 3124 (s), 1755 (m, C=O) cm^{-1} ; MS m/z (relative intensity): 340 (M^+ , 10), 310 (11), 282 (100), 255 (15), 198 (15), 164 (16), 139 (40), 90 (39); Anal. Calcd for $\text{C}_{16}\text{H}_9\text{N}_4\text{O}_3\text{Cl}$: C, 56.40; H, 2.66; N, 16.44. Found: C, 56.30; H, 2.67; N, 16.45.

3-[4-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)-phenyl]sydnone **3c**. mp (recrystallized from EtOAc): $241\text{--}243^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 3.87 (s, 3H, CH_3), 7.18 (d, 2H, $J = 8.9$ Hz), 7.92 (s, 1H), 8.10 (d, 2H, $J = 8.9$ Hz), 8.18 (d, 2H, $J = 8.9$ Hz), 8.40 (d, 2H, $J = 8.7$ Hz); IR (KBr) 3142 (s), 1743 (m, C=O) cm^{-1} ; MS m/z (relative intensity): 336 (M^+ , 3), 306 (13), 278 (100), 251 (18), 208 (7), 194 (14), 152 (18), 135 (85), 90 (35); Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_4$: C, 60.71; H, 3.59; N, 16.66. Found: C, 60.53; H, 3.38; N, 16.37.

Standard Procedure for the Demasking Reaction [16]:

1,3,4-Oxadiazole-sydnone hybrids **3a–3c** (1.80 g, 5.88 mmol, 1.0 equiv.) was stirred in EtOH solution (60 mL) and added to 3.0 mL of 37% HCl aqueous solution. The reaction mixture was stirred at reflux for 4 h. After the reaction was completed, the resultant precipitate was filtrated, washed with cold EtOH (10 mL $\times$ 2), and dried in vacuum oven. The residue was purified by recrystallization from EtOH to afford the 4-(5-aryl-1,3,4-oxadiazol-2-yl)phenylhydrazine derivatives **4a–4c** as light-yellow powder in 68%–77% yields.

4-(5-Phenyl-1,3,4-oxadiazol-2-yl)phenylhydrazine Hydrochloride **4a**. mp (recrystallized from EtOH): $247\text{--}249^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 7.18 (d, 2H, $J = 8.8$ Hz), 7.57–7.61 (m, 3H), 7.86 (d, 2H, $J = 8.8$ Hz), 8.02–8.12 (m, 3H), 9.03 (br, 1H), 10.58 (br, 3H); IR (KBr) 3184 (s, NH) cm^{-1} ; MS m/z (relative intensity): 252 ($M^+ - 36$, 59), 180 (9), 165 (17), 135 (100), 119 (16), 105 (46), 90 (22), 77 (72); Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_4\text{OCl}$: C, 58.24; H, 4.54; N, 19.40. Found: C, 58.35; H, 4.47; N, 19.40.

4-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)phenylhydrazine Hydrochloride **4b**. mp (recrystallized from EtOH) $> 250^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ :

7.12 (d, 2H, $J = 8.7$ Hz), 8.95 (br, 1H), 10.47 (br, 3H), IR (KBr) 3208 (s, NH) cm^{-1} ; MS m/z (relative intensity): 286 ($M^+ - 36$, 76), 256 (7), 165 (18), 139 (41), 135 (100), 111 (34), 90 (27), 75 (32); Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{OCl}_2$: C, 52.03; H, 3.74; N, 17.33. Found: C, 52.05; H, 3.70; N, 17.51.

4-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenylhydrazine Hydrochloride **4c**. mp (recrystallized from EtOH): $228\text{--}230^\circ\text{C}$; ^1H NMR ($\text{DMSO}-d_6$, 300 MHz) δ : 3.83 (s, 3H, CH_3), 7.13 (d, 2H, $J = 8.8$ Hz), 7.15 (d, 2H, $J = 8.8$ Hz), 8.01 (d, 2H, $J = 8.8$ Hz), 8.03 (d, 2H, $J = 8.8$ Hz), 8.95 (br, 1H), 10.52 (br, 3H); IR (KBr) 3214 (s, NH) cm^{-1} ; MS m/z (relative intensity): 282 ($M^+ - 36$, 65), 267 (63), 252 (9), 210 (24), 196 (27), 135 (100), 120 (83), 77 (62); Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_4\text{O}_2\text{Cl}$: C, 56.56; H, 4.74; N, 17.58. Found: C, 56.35; H, 4.68; N, 17.39.

REFERENCES

- [1] Omar, F. A.; Mahfouz, N. M.; Rahman, M. A. *Eur Chem Soc* 1996, 31, 819.
- [2] (a) Holla, B. S.; Poojary, K. N.; Kalluraya, B.; Gowda, P. V. *Indian J Heterocycl Chem* 1996, 5, 273; (b) Talawar, M. B.; Dejai, S. R.; Sommanavar, Y. S.; Marihal, S. C.; Bennur, S. C. *Indian J Heterocycl Chem* 1996, 5, 215.
- [3] Omar, M. T. *Arch Pharm Res (Seoul)* 1997, 20, 602.
- [4] (a) Matsumoto, K.; Kuwamura, Y.; Yasuda, Y.; Tanimoto, T.; Matsumoto, K.; Yoshida, T.; Shoji, J. I. *Antibiot (Tokyo)* 1998, 42, 1465; (b) Papakonstantinou, G. S.; Marakos, P.; Tsantili, K. A.; Chytiroglou, L. A. *Pharmazie* 1998, 53, 300.
- [5] (a) Ladduwahetty, T.; Baker, R.; Cascieri, M. A.; Chambers, M. S.; Haworth, K.; Keown, L. E.; MacIntyre, D. E.; Metzger, J. M.; Owen, S.; Rycroft, W.; Sadowski, S.; Seward, E. M.; Shephard, S. L.; Swain, C. J.; Tattersall, F. D.; Watt, A. P.; Williamon, D. W.; Hargreaves, R. J. *J Med Chem* 1996, 39, 2907; (b) Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. *J Med Chem* 1999, 42, 4331.
- [6] (a) Kraft, A. C.; Holmes, A. B. *Angew Chem Int Ed Engl* 1998, 37, 402; (b) Segura, J. L. *Acta Polym* 1998, 49, 319; (c) Thelakkat, M.; Schidt, H.-W. *Polym Adv Technol* 1998, 9, 429; (d) Mitschke, U.; Bäuerle, P. *J Mater Chem* 2000, 10, 1471.
- [7] Golfier, M.; Guillerez, M. *Tetrahedron Lett* 1976, 17, 267.
- [8] (a) John, P. I.; Kathleen, S. G.; John, T. G.; Glenn, N. C. *J Chem Eng Data* 1988, 33, 385; (b) Benthiss, F.; Largrenée, M. *J Heterocycl Chem* 1999, 36, 1029.
- [9] Carlsen, P. H. J.; Jorgensen, K. B. *J Heterocycl Chem* 1994, 31, 805.
- [10] Brown, P.; Best, D. J.; Broom, N. J. P.; Cassels, R.; O'Hanlon, P. J.; Mitchell, T. J.; Osborne, N. F.; Wilson, J. M. *J Med Chem* 1997, 40, 2563.
- [11] Liras, S.; Allen, M. P.; Segelstein, B. E. *Synth Commun* 2000, 30, 437.

- [12] Stolle, R. *J Prakt Chem* 1906, 73, 277.
- [13] Milcent, R.; Barbier, G. *J Heterocycl Chem* 1983, 20, 77.
- [14] Reddy, P. S. N.; Reddy, P. P. *Indian J Chem* 1987, 26B, 890.
- [15] Chiba, T.; Okimoto, M. *J Org Chem* 1992, 57, 1375.
- [16] Yang, R.-Y.; Dai, L.-X. *J Org Chem* 1993, 58, 3381.
- [17] Jedlovská, E.; Leško, J. *Synth Commun* 1994, 24, 1879.
- [18] Lin, S. T.; Yang, M. L.; Tien, H. T. *J Chin Chem Soc* 1999, 1, 63.
- [19] (a) Eicher, T.; Hauptmann, S. In *The Chemistry of Heterocycles*; Georg Thieme: Stuttgart, 1995; p. 184; (b) Chang, E.-M.; Chen, T.-H.; Wong, F. F.; Chang, E.-C.; Yeh, M.-Y. *Synlett* 2006, 6, 901.
- [20] Yeh, M.-Y.; Tien, H.-J.; Huang, L.-Y.; Chen, M.-H. *J Chin Chem Soc* 1983, 30, 29.
- [21] Butkovic, K.; Basaric, N.; Lovrekovic, K.; Marinic, Ž.; Višnjevac, A.; Kojic-Prodic, B.; Šindler-Kulyk, M. *Tetrahedron Lett* 2004, 45, 9057.
- [22] (a) Zhou, J.-X.; Wong, F. F.; Chen, C.-Y.; Yeh, M.-Y. *Bull Chem Soc Ja* 2006, 79, 644; (b) Chang, E.-M.; Lin, C.-J.; Wong, F. F.; Yeh, M.-Y. *Heterocycles* 2006, 68, 733; (c) Shin, M.-H.; Wong, F. F.; Lin, C.-M.; Chen, W.-Y.; Yeh, M.-Y. *Heteroatom Chem* 2006, 17, 160.
- [23] Gelvin, C. R.; Turnbull, K. *Helv Chim Acta* 1992, 75, 1931.
- [24] Pattanashetti, P. P.; Tikare, R. K.; Dambal, D. B.; Badami, B. V.; Puranik, G. S. *Arch Pharm* 1984, 317, 59.
- [25] Gündüz, T.; Yilmaz, S. *Talanta* 1994, 41, 1471.
- [26] Kaim, L. E.; Menestrel, I. L.; Morgentin, R. *Tetrahedron Lett* 1998, 39, 6885.