EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201200127

Direct Amination of Nitro(pentafluorosulfanyl)benzenes through Vicarious Nucleophilic Substitution of Hydrogen

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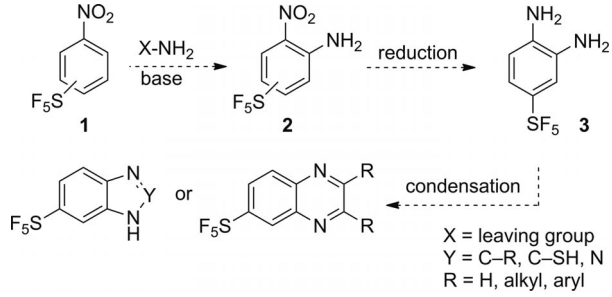
Keywords: Nitrogen heterocycles / Sulfur / Nucleophilic substitution / Amination

1-Nitro-4-(pentafluorosulfanyl)benzene underwent direct amination with 1,1,1-trimethylhydrazinium iodide in the presence of *t*BuOK in DMSO to give 2-nitro-5-(pentafluorosulfanyl)aniline in good yield. 1-Nitro-3-(pentafluorosulfanyl)benzene, under similar conditions, gave 2-nitro-4-(pentafluorosulfanyl)aniline, also in good yield. Reduction of either product with hydrogen in the presence of Raney nickel provided 4-(pentafluorosulfanyl)benzene-1,2-diamine, which served as a precursor for the efficient synthesis of SF_5-containing benzimidazoles, quinoxalines, and benzotriazoles.

Introduction

Compounds with the pentafluorosulfanyl group (SF_5) are becoming increasingly important in organic chemistry. This is because of their unique behavior arising from the unusual properties of the SF_5 group, such as its high thermal and hydrolytic stability, high lipophilicity, and strong electron-withdrawing character. Applications of compounds with the SF_5 group are beginning to appear in the pharmaceutical and agrochemical industries, as well as in polymeric products, energetic materials, liquid crystals, and other materials.[1] Although SF_5 compounds have been known for more than 50 years, progress in the exploration of their chemistry and the development of applications has been hampered by a lack of availability of key SF_5-containing building blocks.

Aliphatic SF_5 compounds are usually prepared by the radical addition of expensive and toxic SF_5X (X = Cl, Br) to unsaturated compounds,[2] and the chemistry of SF_5 aliphatics is being developed.[3] In the subclass of SF_5-benzene derivatives, *para*- and *meta*-nitro(pentafluorosulfanyl)benzenes (**1a** and **1b**, respectively) are made on a large scale by direct fluorination of bis(nitrophenyl) disulfides by using F_2/N_2 (1:9, v/v) in acetonitrile.[4] The reduction of the nitro group in **1** to (pentafluorosulfanyl)anilines followed by acylation, S_EAr halogenation, or diazotization (with follow-up reactions) allowed the synthesis of a number of SF_5-benzene derivatives.[4b,5] Several of these are now commercially available. Recently disclosed two-step conversions of diaryl disulfides to SF_5-aromatics could also represent an important source in the future.[6] Very recently, we have reported the S_NAr reaction of the nitro group in compounds **1** with alkoxides and thiolates[7] and vicarious nucleophilic substitution (VNS) of the hydrogen in **1** with carbon[8] or oxygen[9] nucleophiles. This chemistry gave rise to a number of previously unknown SF_5-benzene derivatives. As a continuation of our investigations into synthetic pathways to novel SF_5-benzene derivatives, we began the search for the ideal conditions for the direct amination of compounds **1** to give nitro(pentafluorosulfanyl)anilines **2**. Nitro group reduction of compounds **2** would give 4-(pentafluorosulfanyl)benzene-1,2-diamine (**3**), which could be used as a precursor of novel nitrogen heterocycles as shown in Scheme 1.



Scheme 1. Proposed access to SF_5-containing nitrogen heterocycles from nitro(pentafluorosulfanyl)benzenes **1** through 4-(pentafluorosulfanyl)benzene-1,2-diamine (**3**) as a common intermediate.

2-Nitro-4-(pentafluorosulfanyl)aniline (**2b**) and 4-(pentafluorosulfanyl)benzene-1,2-diamine (**3**) have been previously prepared by a different route. In 2004, Thrasher and co-workers reported the nucleophilic aromatic substitution of 1-chloro-2-nitro-4-(pentafluorosulfanyl)benzene with aqueous ammonia in a sealed tube at 130–135 °C to give **2b** in 72% yield followed by reduction to **3** in 87% yield by using iron powder in the presence of hydrochloric acid (reflux in ethanol).[10]

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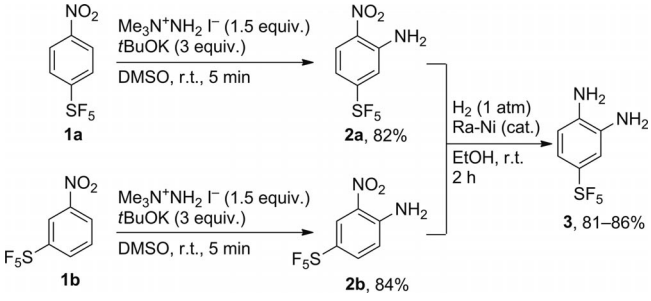
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200127.

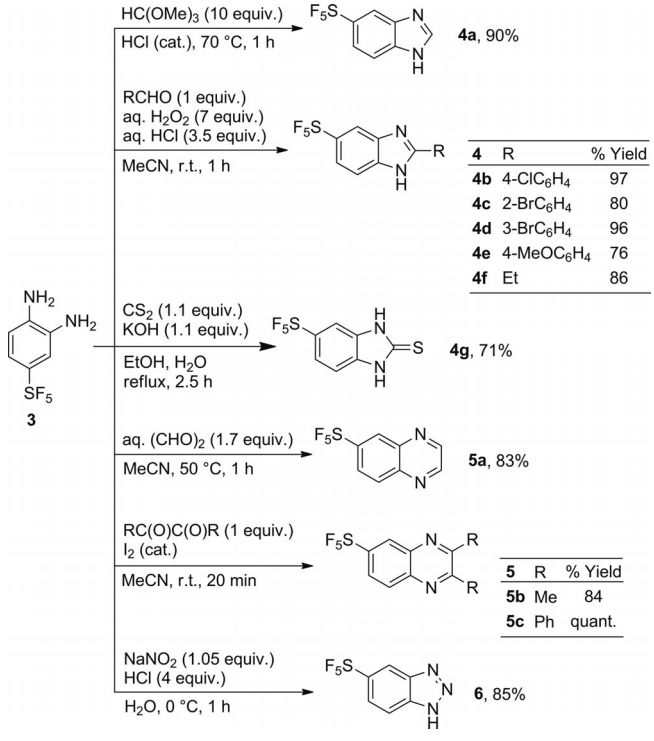
Results and Discussion

Initial investigations into the direct amination of compounds **1** using Chichibabin[11] reaction conditions or oxidative amination[12] were not successful. For example, reaction of **1a** with $NaNH_2$ (6 equiv.) in DMF at room temperature or in liquid ammonia at –33 °C did not provide desired aniline derivative **2a** after acid or potassium permanganate quenching. Next, we turned our attention to vicarious nucleophilic substitution. The use of methoxyamine hydrochloride, an excess amount of *t*BuOK and CuCl or CuBr (0.1–3 equiv.) in DMF or DMSO at room temperature, that is, the VNS amination conditions developed by Seko and co-workers,[13] gave no more than 9% conversion to **2a**. Amination of **1b** with 4-amino-1,2,4-triazoles according to Katritzky[14] (excess amount of *t*BuOK, DMSO, r.t.) provided only trace amounts of **2b**. Finally, 1,1,1-trimethylhydrazinium iodide (TMHI) proved to be a highly reactive amination reagent.[15] The addition of *t*BuOK (2.5 equiv.) to a DMSO solution of **1b** and an equimolar amount of TMHI at room temperature resulted in a slightly exothermic reaction, with the evolution of trimethylamine and the formation of deep red reaction mixture. After 4 h, a single regioisomer of substituted aniline **2b** was formed and isolated in 31% yield (43% yield based on recovered **1b**). Increasing the amount of the base and TMHI improved the reaction yield to 84%; it was found that the reaction was complete in 5 min. Applying the same reaction conditions to **1a** gave isomeric aniline derivative **2a** in 82% yield (Scheme 2). In both cases, these VNS aminations were highly regioselective and no other isomers of SF_5-containing nitroanilines were formed. Nitro group reduction in compounds **2** was achieved by hydrogenation with hydrogen in the presence of a Raney nickel catalyst giving 4-(pentafluorosulfanyl)benzene-1,2-diamine (**3**) in good yields.



Scheme 2. Synthesis of nitroaniline derivatives **2** by VNS amination of nitro(pentafluorosulfanyl)benzenes **1** and nitro group reduction to benzene-1,2-diamine **3**.

Diamine **3** was used as a precursor for the synthesis of new SF_5-containing nitrogen heterocycles such as benzimidazoles, quinoxalines, and benzotriazole. It is well known that the benzimidazole ring is an important pharmacophore in medicinal chemistry and agrochemistry.[16] The quinoxaline ring is a part of a number of pharmacologically active compounds,[17] and benzotriazole derivatives are found in some antiemetic (Alizapride) and antineoplastic (Vorozole) drugs.[18] In drug discovery, the presence of a strongly electron-withdrawing and highly lipophilic pentafluorosulfanyl group can offer advantages in terms of bioavailability, metabolic stability, and better binding to a biological target, and it can also positively influence pK_a. However, to the best of our knowledge, SF_5-containing benzimidazoles, quinoxalines, and benzotriazoles are not known, and our efficient synthesis of diamine **3** has provided access to these nitrogen heterocycles. The following condensation reactions were successful, despite the reduced nucleophilicity of both amino groups in **3**, due to the presence of the strongly electron-withdrawing SF_5 group. Unsubstituted (pentrafluorosulfanyl)benzimidazole **4a** was prepared in high yield by the reaction of **3** with an excess amount of trimethylorthoformate in the presence of catalytic amounts of hydrochloric acid (Scheme 3).[19] 2-Substituted SF_5-containing benzimidazoles **4b**–**f** were prepared according to Bahrami and co-workers[20] by condensation of **3** with aldehydes in the presence of an aqueous H_2O_2/HCl system in acetonitrile. In this reaction, aromatic aldehydes with electron-withdrawing or electron-donating groups as well as an aliphatic aldehyde gave good yields of products (Scheme 3). 5-Pentafluorosulfanyl-1,3-dihydrobenzoimidazole-2-thione (**4g**) was prepared in good yield by the reaction with carbon disulfide and KOH.[21] The ΔG_{298} values calculated in vacuo by the DFT/B3LYP/6-31G* method revealed that the compound exists as 1,3-dihydrobenzimidazole-2-thione **4g** rather than 2-mercaptobenzimidazole **4g′** or **4g′′** (Figure 1). The results suggest that **4g** is by about 10 kcal mol^{-1} more stable than tautomers **4g′** and **4g′′**. Additionally, a better correlation between calculated ^{13}C NMR shielding constants and ex-



Scheme 3. Preparation of SF_5-containing benzimidazoles **4**, quinoxalines **5**, and benzotriazole **6** from benzene-1,2-diamine derivative **3**.

perimental differences of chemical shifts was shown for **4g** than for **4g′** or **4g′′** (Supporting Information, Table S1). These findings are in accordance with the literature X-ray crystal structure of unsubstituted 1,3-dihydrobenzoimidazole-2-thione, showing that the fused ring system is planar and aromatic and that the thione is the predominant tautomer in the solid state.[22] Condensation of **3** with an aqueous solution of glyoxal was used for the synthesis of quinoxaline **5a**.[23] Quinoxaline derivatives **5b** and **5c** were prepared in excellent yield by using 1,2-diketones and catalytic amounts of iodine in acetonitrile.[24] Finally, benzotriazole **6** was synthesized in high yield by the reaction of **3** with nitrous acid (Scheme 3).

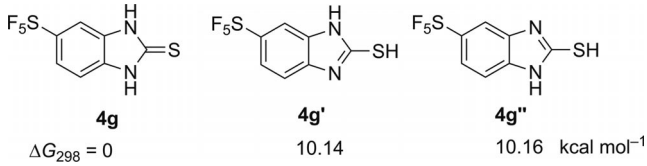


Figure 1. Possible tautomers of **4g** and their ΔG_{298} values calculated at the B3LYP/6-31G* level of theory.

Conclusions

In conclusion, nitro(pentafluorosulfanyl)benzenes underwent regioselective vicarious nucleophilic amination with 1,1,1-trimethylhydrazinium iodide in the presence of *t*BuOK to give nitro(pentafluorosulfanyl)anilines in high yields. Catalytic reduction with hydrogen in the presence of Raney nickel provided 4-(pentafluorosulfanyl)benzene-1,2-diamine in high yields, and simple condensation reactions afforded new SF_5-containing benzimidazoles, quinoxalines, and benzotriazole.

Experimental Section

General Procedure for the VNS Amination Reaction: A drying tube with anhydrous $CaCl_2$ was attached to a round-bottomed flask (250 mL) with a stirring bar. The flask was charged with **1** (1.478 g, 5.93 mmol), TMHI (1.80 g, 8.90 mmol, 1.5 equiv.), and DMSO (35 mL), and the flask was then immersed in a water bath (r.t.). *t*BuOK (2.00 g, 17.8 mmol, 3.0 equiv.) was added, and the resulting deep red mixture was stirred for 5 min, followed by the addition of an aqueous saturated solution of NH_4Cl (100 mL) and extraction with EtOAc (3 × 80 mL). The combined organic phase was washed with water (2 × 80 mL) and brine (80 mL), dried using anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (silica gel, PE/EtOAc) gave desired product **2**.

2-Nitro-5-(pentafluorosulfanyl)aniline (2a): Pale orange solid (1.285 g, 82%); m.p. 92–93 °C; R_f = 0.42 (PE/EtOAc, 80:20). IR (film): $\tilde{\nu}$ = 3506, 3393, 1633, 1569, 1499, 1435, 1333, 1248, 846, 839 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.30 (br. s, 2 H), 7.05 (dd, J = 9.4, 2.3 Hz, 1 H), 7.29 (d, J = 2.3 Hz, 1 H), 8.19 (dquint., J = 9.4, 1.0 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 113.8 (quint., J = 4.6 Hz), 117.1 (quint., J = 4.9 Hz), 127.0, 132.7, 144.2, 158.2 (quint., J = 18.7 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 61.2 (d, J = 150.5 Hz, 4 F), 81.3 (quint., J = 150.5 Hz, 1 F) ppm. MS (EI): *m/z* (%) = 264 (100) $[M]^+$, 218 (25), 137 (15), 91 (13), 83 (26). HRMS (CI): calcd. for $C_6H_6F_5N_2O_2S$ $[M + H]^+$ 265.0070; found 265.0068.

2-Nitro-4-(pentafluorosulfanyl)aniline (2b):[10] Pale brown solid (1.316 g, 84%); m.p. 134–135 °C; R_f = 0.43 (PE/EtOAc, 70:30). IR (film): $\tilde{\nu}$ = 3483, 3356, 1633, 1568, 1512, 1354, 1271, 1133, 1084, 909, 847, 829 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.52 (br. s, 2 H), 6.89 (dquint., J = 9.3, 0.9 Hz, 1 H), 7.69 (dd, J = 9.3, 2.6 Hz, 1 H), 8.56 (d, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 118.5, 125.1 (quint., J = 5.0 Hz), 129.9, 132.3 (quint., J = 4.3 Hz), 142.1 (quint., J = 20.7 Hz), 146.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 63.6 (d, J = 151.1 Hz, 4 F), 83.9 (quint., J = 151.1 Hz, 1 F) ppm. MS (EI): *m/z* (%) = 264 (100) $[M]^+$, 245 (13), 234 (7), 218 (22), 110 (22), 91 (20), 83 (30). HRMS (CI): calcd. for $C_6H_6F_5N_2O_2S$ $[M + H]^+$ 265.0070; found 265.0066.

4-(Pentafluorosulfanyl)benzene-1,2-diamine (3):[10] A suspension of Raney nickel (ca. 200 mg) in water was washed with ethanol (2 × 20 mL). Ethanol (25 mL) and **2** (1.00 g, 3.79 mmol) were added, a balloon filled with hydrogen was attached, and the mixture was stirred at room temperature for 2 h, followed by filtration, washing with THF (3 × 20 mL), and concentration of the filtrate under reduced pressure. The resulting residue was purified by column chromatography (silica gel, PE/EtOAc) to give **3** as an orange solid (719–764 mg, 81–86%); m.p. 72–74 °C; R_f = 0.26 (PE/EtOAc, 60:40). IR (film): $\tilde{\nu}$ = 3425, 3358, 3255, 3215, 1627, 1515, 1298, 832, 804 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.53 (br. s, 4 H), 6.62 (dquint., J = 8.5, 1.0 Hz, 1 H), 7.08 (d, J = 2.5 Hz, 1 H), 7.11 (dd, J = 8.5, 2.5 Hz, 1 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 114.3, 114.4 (quint., J = 4.7 Hz), 118.5 (quint., J = 4.7 Hz), 133.1, 138.1, 145.6 (quint., J = 16.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 64.1 (d, J = 150.0 Hz, 4 F), 87.3 (quint., J = 150.0 Hz, 1 F) ppm. MS (EI): *m/z* (%) = 234 (100) $[M]^+$, 126 (34), 107 (23), 98 (14), 80 (22). HRMS (CI): calcd. for $C_6H_8F_5N_2S$ $[M + H]^+$ 235.0328; found 235.0321.

Supporting Information (see footnote on the first page of this article): General procedures, full characterization, and copies of the ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra of compounds **2**–**6**.

Acknowledgments

This work was supported by the Academy of Sciences of the Czech Republic (Research Plan AVZ40550506) and the Grant Agency of the Czech Republic (P207/12/0072).

[1] a) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim **2004**, pp. 146–156; b) R. W. Winter, R. A. Dodean, G. L. Gard in *ACS Symposium Series, 911: Fluorine-Containing Synthons* (Ed.: V. A. Soloshonok) American Chemical Society, Washington, DC, **2005**, pp. 87–118; c) P. Kirsch, G. V. Röschenthaler in *ACS Symposium Series, 949: Current Fluoroorganic Chemistry* (Eds.: V. A. Soloshonok, K. Mikami, T. Yamazaki, J. T. Welch, J. F. Honek), American Chemical Society, Washington, DC, **2007**, pp. 221–243.

[2] a) S. Aït-Mohand, W. D. Dolbier Jr., *Org. Lett.* **2002**, *4*, 3013–3015; b) W. D. Dolbier Jr., S. Aït-Mohand, T. D. Schertz, T. A. Sergeeva, J. A. Cradlebaugh, A. Mitani, G. L. Gard, R. W. Winter, J. S. Thrasher, *J. Fluorine Chem.* **2006**, *127*, 1302–1310.

[3] a) R. W. Winter, G. L. Gard, *J. Fluorine Chem.* **2006**, *127*, 1188–1194; b) V. K. Brel, *J. Fluorine Chem.* **2007**, *128*, 862–867; c) W. R. Dolbier Jr., Z. Zheng, *J. Fluorine Chem.* **2011**, *132*, 389–393; d) M. V. Ponomarenko, Y. A. Serguchev, G.-V. Röschenthaler, *J. Fluorine Chem.* **2010**, *131*, 270–273; e) S. Gard, J. Shreeve, *J. Mater. Chem.* **2011**, *21*, 4787–4795; f) Y.

Huang, G. L. Gard, J. M. Shreeve, *Tetrahedron Lett.* **2010**, *51*, 6951–6954; g) W. S. Husstedt, J. S. Thrasher, G. Haufe, *Synlett* **2011**, 1683–1686.
[4] a) R. D. Bowden, M. P. Greenhall, J. S. Moilliet, J. Thomson, WO 9705106, **1997** [*Chem. Abstr.* **1997**, *126*, 199340]; b) R. D. Bowden, P. J. Comina, M. P. Greenhall, B. M. Kariuki, A. Loveday, D. Philp, *Tetrahedron* **2000**, *56*, 3399–3408; c) R. D. Chambers, R. C. H. Spink, *Chem. Commun.* **1999**, 883–884.
[5] a) P. J. Crowley, G. Mitchell, R. Salmon, P. A. Worthington, *Chimia* **2004**, *58*, 138–142; b) P. Kirsch, M. Bremer, M. Heckmeier, K. Tarumi, *Angew. Chem.* **1999**, *111*, 2174; *Angew. Chem. Int. Ed.* **1999**, *38*, 1989–1992; c) W. A. Sheppard, *J. Am. Chem. Soc.* **1962**, *84*, 3064–3072.
[6] a) T. Umemoto, WO 2008/118787, **2008** [*Chem. Abstr.* **2008**, *149*, 402044]; b) T. Umemoto, WO 2010/014665 A1, **2010**; c) T. Umemoto, WO 2010/033930 A1, **2010**.
[7] P. Beier, T. Pastýříková, N. Vida, G. Iakobson, *Org. Lett.* **2011**, *13*, 1466–1469.
[8] P. Beier, T. Pastýříková, G. Iakobson, *J. Org. Chem.* **2011**, *76*, 4781–4786.
[9] P. Beier, T. Pastýříková, G. Iakobson, *Tetrahedron Lett.* **2011**, *52*, 4392–4394.
[10] A. M. Sipyagin, V. S. Enshov, S. A. Kashtanov, C. P. Bateman, D. B. Mullen, Y.-T. Tan, J. S. Thrasher, *J. Fluorine Chem.* **2004**, *125*, 1305–1316.
[11] a) A. F. Pozharskii, A. M. Simonov, V. N. Doronkin, *Usp. Khim.* **1978**, *47*, 1933–1970; b) H. J. W. van den Haak, H. C. van der Plas, B. van Veldhuizen, *J. Org. Chem.* **1981**, *46*, 2134–2137.
[12] a) M. Wozniak, A. Baranski, B. Szpakiewicz, *Liebigs Ann. Chem.* **1991**, 875–878; b) P. Ji, J. H. Atherton, M. I. Page, *J. Org. Chem.* **2011**, *76*, 3286–3295.
[13] S. Seko, N. Kawamura, *J. Org. Chem.* **1996**, *61*, 442–443.
[14] A. R. Katritzky, K. S. Laurenzo, *J. Org. Chem.* **1986**, *51*, 5039–5040.
[15] P. F. Pagoria, A. R. Mitchell, R. D. Schmidt, *J. Org. Chem.* **1996**, *61*, 2934–2935.
[16] a) V. C. Emery, A. F. Hassan-Walker, *Drugs* **2002**, *62*, 1853–1858; b) H. Kagechika, *Curr. Med. Chem.* **2002**, *9*, 591–608; c) S. Bhattacharya, P. Chaudhuri, *Curr. Med. Chem.* **2008**, *15*, 1762–1777; d) A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1998**, *41*, 1252–1262; e) M. Roth, M. L. Morningstar, P. L. Boyer, S. H. Hughes, R. W. Bukheit, C. J. Michejda, *J. Med. Chem.* **1997**, *40*, 4199–4207; f) M. T. Migawa, J. L. Giradet, J. A. Walker, G. W. Koszalka, S. D. Chamberlain, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1998**, *41*, 1242–1251.
[17] a) R. Sarges, H. R. Howard, R. C. Browne, L. A. Label, P. A. Seymour, *J. Med. Chem.* **1990**, *33*, 2240–2254; b) L. E. Seitz, W. J. Suling, R. C. Reynolds, *J. Med. Chem.* **2002**, *45*, 5604–5606.
[18] M. J. O'Neil, P. E. Heckelman, C. B. Koch, K. J. Roman (Eds.), *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 14th ed., Merck & Co., Inc., Whitehouse Station, NJ, USA, **2006**.
[19] S. Venkatraman, G. N. Anilkumar, K. X. Chen, F. Velazquez, Q. Zeng, D. Liu, Y. Jiang, J. A. Kozlowski, F. G. Njoroge, S. B. Rosenblum, S. J. Gavalas, P. A. Pinto, O. B. Selyutin, B. Vibulbhan, WO 2009/152200 A1, **2009** [*Chem. Abstr.* **2009**, *152*, 57333].
[20] K. Bahrami, M. M. Khodaei, I. Kavianinia, *Synthesis* **2007**, 547–550.
[21] J. A. VanAllan, B. D. Deacon, *Org. Synth., Coll. Vol.* **1963**, *IV*, 569.
[22] G. R. Form, E. S. Raper, T. C. Dowhie, *Acta Crystallogr., Sect. B* **1976**, *32*, 345–348.
[23] G. A. Strohmeier, W. M. F. Fabian, G. Uray, *Helv. Chim. Acta* **2004**, *87*, 215–226.
[24] S. V. Moore, M. N. V. Sastry, C.-C. Wang, C.-F. Yao, *Tetrahedron Lett.* **2005**, *46*, 6345–6348.

Received: February 3, 2012
Published Online: March 5, 2012

