Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2317–2320

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A Practical Synthesis of 3,4-Diethoxybenzthioamide Based on Friedel–Crafts Reaction with Potassium Thiocyanate in Methanesulfonic Acid

Shinji Aki,* Takafumi Fujioka, Masashi Ishigami and Jun-ichi Minamikawa

Process Research Laboratory, 2nd Tokushima Factory, Otsuka Pharmaceutical Co., Ltd., 224-18, Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771-0182, Japan

Received 28 February 2002; accepted 1 June 2002

Abstract—The synthesis of 3,4-diethoxybenzthioamide, the key intermediate for **OPC-6535**, is achieved by employing Friedel–Crafts reaction of 1,2-diethoxybenzene with potassium thiocyanate in methanesulfonic acid at ambient temperature.

6-[2-(3,4-Diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid (**OPC-6535**; **1**)[1] is a thiazole derivative, which has an inhibitory activity of superoxide production by human neutrophils, and is now under clinical trials. We realized the construction of the thiazole moiety by a condensation reaction[1,2] of 3,4-diethoxybenzthioamide (**2a**)[1,3] and α-haloketone derivative (**3**).[1,4] One of the several challenges we faced was to produce a large amount of **2a** required for pharmacological and toxicological evaluation of **1** by using transthioamidation reaction of 3,4-diethoxybenzonitrile with thioacetamide, which was our initially proposed synthesis of **2a**.[1] Evidently unsatisfactory yield and the complicated workup of the transthioamidation reaction in a large-scale process prompted us to search for an alternative synthetic method for benzthioamide. Moreover, it seemed useful to investigate the practical synthetic method of benzthioamide derivatives, possessing alkoxy groups such as **2a**, since these derivatives have been used as important intermediates for the preparation of several biologically active compounds.[5] Namely, 4-methoxybenzthioamide (**2c**), which was mostly derived by transthioamidation reaction or thionation reaction to benzamides with thionating reagents such as Lawesson's reagent,[6] is a useful compound in the field of medicinal chemistry.[5c–e] Herein, we disclose the results of our study on one step practical synthesis of **2a** from 1,2-diethoxybenzene and potassium thiocyanate by using Friedel–Crafts type reaction (Fig. 1).

A variety of synthetic methods for the benzthioamide derivatives, other than transthioamidation methods, have been reported in the literature, ranging from Friedel–Crafts reaction of aromatic compounds with potassium thiocyanate or ethoxycarbonyl isothiocyanate,[7] addition reaction of benzonitriles bearing hydrogen sulfide, and thioamidation reaction of benzyl chlorides bearing sulfur, ammonia, and sodium methoxide.[8] Among these reactions, we have selected the Friedel–Crafts strategy for the synthesis of **2a**, since this method seemed to be most straightforward approach to directly introduce thioamide group to the aromatic ring. Reported Friedel–Crafts conditions are summarized as follows. (1) The

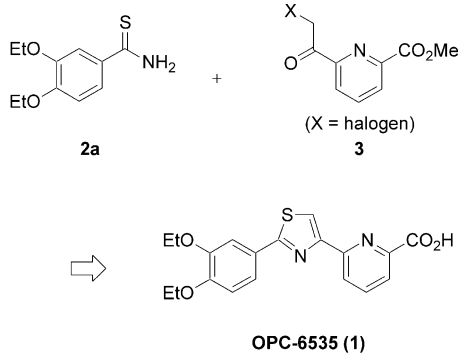


Figure 1. Synthesis of **OPC-6535**.

*Corresponding author. Tel.: +81-665-2126; fax: +81-637-1144; e-mail: shinaki@fact.otsuka.co.jp

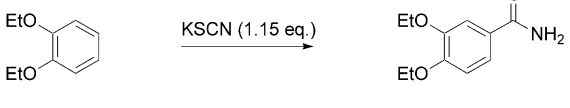
0960-894X/02/$ - see front matter
PII: S0960-894X(02)00398-0

benzene derivatives are treated with potassium thiocyanate in aqueous 80% sulfuric acid,[7a] polyphosphoric acid,[7a] or liquid hydrofluoric acid.[7b] (2) The benzene derivatives are treated with ethoxycarbonyl isothiocyanate in the presence of aluminum chloride to yield *N*-ethoxycarbonylbenzthioamide derivatives, which are subsequently hydrolyzed.[7c] As with any other case, each reaction condition has advantages and disadvantages. The latter method (2) seemed more generalized, since it can be applied to the benzene derivatives having not only the electron-donating substituents but also the electron-withdrawing substituents. Additionally, the methods (1) reacting in either 80% sulfuric acid or polyphosphoric acid are not satisfactory in yields (in 50–60% yield:[9] indeed, the reaction in polyphosphoric acid at 60 °C gave our compound **2a** in only 11% yield, and in 80% sulfuric acid at room temperature gave it in 6% yield), and the harsh cryogenic condition is required for storing hydrofluoric acid as a liquid phase. However, the method (1) seemed to be economically promising for the large-scale production of **2a** in view of the cost (availability and inexpensive thioamidation regent). Thus, we focused on the method (1) using potassium thiocyanate.

We searched for a superior acid to reported aqueous 80% sulfuric acid, polyphosphoric acid, or hydrofluoric acid for the improvement. After several trials, methanesulfonic acid was the best acid to meet our purpose.

The desired **2a** was given in good yield after an easy workup (the reaction mixture was poured into cold water and the precipitates were purified by recrystallizing from ethyl acetate), when excess methanesulfonic acid was used (Table 1, entry 1). The efficiency of this improved method was conveyed to a scale-up trial. **4a** (2.53 kg) resulted to give the desired **2a** (2.90 kg) with high purity[10] in 85% yield. Reducing the amount of methanesulfonic acid lowered the yields (Table 1, entries 2 and 4). Trifluoroacetic acid was not available for this reaction (Table 1, entry 5).

Table 1. Friedel–Crafts thioamidation reaction of 1,2-diethoxybenzene with potassium thiocyanate



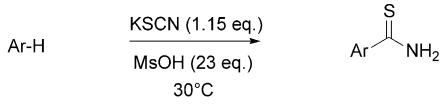
4a **2a**

Entry	Reagent and solvent	Temp. (°C)	Time (h)	Yield[a] (%)
1	$MeSO_3H$ (23 equiv)	30	4.3	85 (93)[b]
2	$MeSO_3H$ (10 equiv)	30	17.0	60
3	$MeSO_3H$ (10 equiv), AcOH (1.2 M)	30	2.5,	0
4	$MeSO_3H$ (2 equiv), CH_2Cl_2 (0.6 M)	30 then reflux	4.0 then 1.5	13
5	CF_3CO_2H (19 equiv)	30	2.0	0

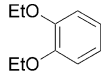
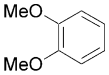
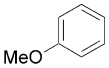
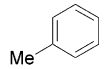
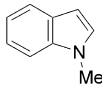
[a]Isolated yield after recrystallization of crude product from ethyl acetate.
[b]Isolated yield after the purification by column chromatography.

We next tried to extend the reaction to other aromatic compounds, and the results are summarized in Table 2. From Table 2, it is found that methanesulfonic acid mediated Friedel–Crafts thioamidation reactions of aromatic compounds with potassium thiocyanate have following characteristics: (1) Activated aromatic compounds such as anisole derivatives underwent thioamidation reaction smoothly in satisfactory yields (Table 2, entries 1–3). (2) Neither weakly activated nor nonactivated aromatic compounds gave the desired corresponding thioamide derivatives (Table 2, entries 5 and 6). (3) π-Electron-excessive heteroaromatic compounds, except for furan that decomposed in acidic

Table 2. Methanesulfonic acid mediated Friedel–Crafts thioamidation reaction of aromatic compounds with potassium thiocyanate



4 **2**

Entry	Ar–H	Time (h)	Yield (%)[a]
1		4.3	85 (93)[b] (**2a**)[c]
2		5.3	68[d] (83)[b] (**2b**)[e]
3		5.0	65[f] (72)[b] (**2c**)[g]
4		28.5	0
5		5 days	0
6		—	0[h]
7		5.5	(75)[b] (**2g**)[i]
8		4.5	(35)[b] (**2h**)[j]
9		5.3	(42)[b] (**2i**)[k]
10		39[l]	(77)[b] (**2i**)

[a]Isolated yield after recrystallization of crude product from ethyl acetate.
[b]Isolated yield after the purification by column chromatography.
[c]See ref 11.
[d]Isolated yield after recrystallization of crude product from acetone.
[e]See ref 12.
[f]Isolated yield of the *p*-isomer. The *o*-isomer was obtained in 2% yield.
[g]See ref 13.
[h]Furan decomposed under the conditions.
[i]Thiophene-2-thiocarboxamide was obtained; see ref 14.
[j]Pyrrole-2-thiocarboxamide was obtained; see ref 15.
[k]1-Methyl-1*H*-indole-3-thiocarboxamide was obtained; see ref 16.
[l]After stirring for 29 h, further 1.15 equiv of KSCN was added.

media, underwent thioamidation reaction in satisfactory yields (Table 2, entries 7–10).

In conclusion, we have developed a facile and practical method in good yield for preparing the benzthioamide derivative **2a**, which is the key intermediate for the synthesis of **OPC-6535**, by taking advantage of Friedel–Crafts reaction using potassium thiocyanate in methanesulfonic acid at ambient temperature. This method could be done by using inexpensive starting materials and reagents in ordinary reaction vessels and could be extended to other activated aromatic compounds having alkoxy groups, especially toward the important compounds such as **2c,** in the field of medicinal chemistry.

Typical experimental procedure for the preparation of **2a** is as follows: Potassium thiocyanate (33.60 g, 345.8 mmol) was added to a solution of **4a** (50.00 g, 300.8 mmol) in methanesulfonic acid (371 mL) with ice-cooling bath. After stirring at room temperature (about 30 °C) for 4.3 h, the reaction mixture was poured into cold water (1.0 L). The precipitates were filtered and dried to give crude **2a** (65.62 g). The crude **2a** was recrystallized from ethyl acetate (522 mL) to give 57.53 g of **2a** (85% yield).[11] The aqueous filtrate was extracted with dichloromethane. The combined dichloromethane extract and mother liquid of the recrystallization was purified by SiO_2 column chromatography (methanol/dichloromethane = 1/20; $R_f = 0.56$, methanol/dichloromethane = 1/9) to give further 5.39 g of **2a** (total 62.92 g, 93% yield).

Caution: Concerning the use of potassium thiocyanate, it is reported that cyanic acid is discharged from thiocyanic acid when the solution is either hot or in high concentration.[17] During our production campaign, no cyanic acid was detected; however, it is recommended to prepare an alkaline trap.

Acknowledgements

We thank Ms Kyoko Sejiyama at our Analytical Section for skillful analysis.

References and Notes

1. (a) Chihiro, M.; Nagamoto, H.; Takemura, I.; Kitano, K.; Komatsu, H.; Sekiguchi, K.; Tabusa, F.; Mori, T.; Tominaga, M.; Yabuuchi, Y. *J. Med. Chem.* **1995**, *38*, 353. (b) Chihiro, M.; Komatsu, H.; Tominaga, M.; Yabuuchi, Y. *Chem. Abstr.* **1994**, *121*, 9391c. WO93 24,472, 1993.
2. Hantzsch, A.; Weber, J. H. *Chem. Ber.* **1887**, *20*, 3118.
3. (a) Taylor, E. C.; Zoltewicz, J. A. *J. Am. Chem. Soc.* **1960**, *82*, 2656. (b) Chaudhari, D. T.; Sabnis, S. S.; Patel, M. R.; Deliwala, C. V. *Bull. Haff. Instt.* **1976**, *4*, 8. (c) Lin, P.-Y.; Ku, W.-S.; Shiao, M.-J. *Synthesis* **1992**, 1219.
4. Aki, S.; Ishigami, M.; Fujioka, T.; Minamikawa, J. Jpn. Kokai Tokkyo Koho. *Chem. Abstr.* **2000**, *133*, 177026d. JP2000 229,920.
5. For recent examples, see (a) Einsiedel, J.; Thomas, C.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2041. (b) Nötzel, M. W.; Labahn, T.; Es-Sayed, M.; De Meijere, A. *Eur. J. Org. Chem.* **2001**, 3025. (c) Ito, K.; Glen, S. W.; Yamada, A.; Toshima, M.; Kato, M. *Chem. Abstr.* **2001**, *135*, 180630t. Jpn. Kokai Tokkyo Koho, JP2001 220,375. (d) Ishizuka, N.; Nagata, K.; Yamamori, T.; Sakai, K. *Chem. Abstr.* **2001**, *135*, 190413p. Jpn. Kokai Tokkyo Koho, JP2001 233,767. (e) Yu, D. T.; Macina, O. T.; Sircar, I.; Sircar, J. C.; Riviello, C. M. *Chem. Abstr.* **2001**, *134*, 29412g. U.S. Patent, US6,156,776.
6. (a) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229. (b) Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* **1984**, *40*, 2047. (c) Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, *1*, 697 and references therein.
7. (a) Sastry, S.; Kudav, N. A. *Indian J. Chem., Sect. (B)* **1979**, *18B*, 455. (b) Feiring, A. E. *J. Org. Chem.* **1976**, *41*, 148. (c) Papadopoulos, E. P. *J. Org. Chem.* **1976**, *41*, 962.
8. Becke, F.; Hagen, H. *Chem-Ztg.* **1969**, 474.
9. These yields were for 1,2-dimethoxybenzene (**4b**: veratrol), 1,3-dimethoxybenzene (resorcinol dimethyl ether), and anisole (**4c**) as starting materials; see: ref 7a.
10. 99.87% purity on HPLC analysis; Column: Tosoh TSKgel ODS-80Ts; eluent: CH_3CN/aqueous 10 mM Na_2SO_4 solution/H_3PO_4 (500/500/1) phase; detection: 254 nm. Flow rate: 1.0 mL/min, $R_t = 4.0$ min.
11. Mp 151.5–153.0 °C (lit.:[3b] 157–158 °C); IR (KBr): 1271, 1592, 1630, 3273, 3317 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.33 (3H, t, $J = 6.9$ Hz), 1.34 (3H, t, $J = 6.9$ Hz), 4.06 (4H, q, $J = 6.9$ Hz), 6.95 (1H, d, $J = 9.1$ Hz), 7.6 (1H, d, $J = 1.9$ Hz), 7.62 (1H, dd, $J = 9.6$, 1.9 Hz), 9.31 (1H, br.s), 9.64 (1H, br.s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.7, 14.8, 64.0, 64.2, 111.8, 113.1, 121.4, 131.4, 147.1, 151.4, 198.8.
12. Mp 190.5–191.5 °C; IR (KBr): 850, 1270, 1595, 1641, 3336 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.79 (3H, s), 3.80 (3H, s), 6.98 (1H, d, $J = 8.4$ Hz), 7.60 (1H, d, $J = 1.7$ Hz), 7.62 (1H, dd, $J = 8.4$, 1.7 Hz), 9.34 (1H, br.s), 9.67 (1H, br.s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.7, 55.8, 110.7, 111.4, 121.3, 131.5, 147.7, 151.8, 198.8.
13. Mp 151.5–152.0 °C (lit.:[3a] 148.5–149.5 °C); IR (KBr): 887, 1258, 1597, 1626, 3276, 3365 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.80 (3H, s), 6.95 (2H, d, $J = 8.8$ Hz), 7.96 (2H, d, $J = 8.8$ Hz), 9.33 (1H, br.s), 9.66 (1H, br.s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.5, 113.1 (× 2), 129.5 (× 2), 131.5, 162.0, 198.8.
14. This ^1H NMR spectrum was identical with that reported in lit.; see: Chihiro, M.; Komatsu, H.; Tominaga, M.; Yabuuchi, Y. *Chem. Abstr.* **1993**, *118*, 191726d. WO92 09,586, 1992. It was recrystallized from toluene to give an analytical sample; mp 107.7–108.3 °C (lit. 107–109 °C; see: Uhlendorf, J.; Betzing, H.; Winkelmann, J. *Chem. Abstr.* **1983**, *98*, 160703e. German Patent, DE3,128,452); IR (KBr): 868, 1277, 1518, 1626, 3158, 3279, 3328 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (1H, dd, $J = 5.0$, 3.9 Hz), 7.51 (1H, dd, $J = 3.9$, 1.1 Hz), 7.57 (1H, dd, $J = 5.0$, 1.1 Hz), ca. 7.15 (1H, br.s), ca. 7.51 (1H, br.s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.8, 128.3, 134.0, 144.7, 192.1.
15. This ^1H NMR spectrum was identical with that reported in lit.; see (a) Chihiro, M.; Komatsu, H.; Tominaga, M.; Yabuuchi, Y. *Chem. Abstr.* **1993**, *118*, 191726d. WO92 09,586, 1992. (b) Papadopoulos, E. P. *J. Org. Chem.* **1973**, *38*, 667. It was recrystallized from toluene to give an analytical sample; mp 158.0–159.7 °C (lit. 162–164 °C; see: Papadopoulos, E. P. *J. Org. Chem.* **1973**, *38*, 667.); IR (KBr): 841, 1537, 1630, 3176, 3279, 3332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (1H, dd, $J = 2.6$, 2.6 Hz, H-4 or H-4′), 6.32 (1H, dd, $J = 2.6$, 2.6 Hz, H-4′ or H-4), 6.64 (1H, dd, $J = 2.6$, 1.3 Hz, H-3 or H-3′), 6.65 (1H, dd, $J = 2.6$, 1.3 Hz, H-3′ or H-3), 6.94 (1H, br.s, NH_2 or NH'_2), 6.98 (1H, br.s, NH'_2 or NH_2), 7.04 (1H, dd, $J = 2.6$, 1.3 Hz, H-5 or H-5′), 7.05 (1H, dd $J = 2.6$, 1.3 Hz, H-5′ or H-5),

9.66 (2H, br.s, H-1 and H-1′); ^{13}C NMR (75 MHz, DMSO-d_6) δ 109.4, 109.5, 124.4, 131.0, 187.0.

16. This ^{1}H NMR spectrum was identical with that reported in lit.; see: (a) Baker, L.; Saunders, J.; Swain, C. Eur. Patent, EP328,200. *Chem. Abstr*. **1990**, *112*, 139035q. (b) 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. It was recrystallized from ethyl acetate to give an analytical sample; mp 135.6–137.0 °C; IR (KBr): 862, 1523, 1623, 3163, 3272, 3423 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (3H, s), 7.17 (1H, ddd, J = 7.0, 6.8, 1.4 Hz), 7.23 (1H, ddd, J = 7.8, 7.0, 1.4 Hz), 7.49 (1H, dd, J = 7.8, 1.4 Hz), 8.09 (1H, s), 8.57 (1H, dd, J = 6.8, 1.4 Hz), 8.78 (1H, br.s), 8.98 (1H, br.s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.9, 110.3, 115.3, 121.0, 121.7, 122.1, 125.8, 132.5, 137.2, 193.0.

17. *Kagakujitan*, 1st ed.; Ohki, M., Ohsawa, T., Tanaka, M., Chihara, H. Eds.; Tokyo Kagaku Dozin Co. Ltd: Tokyo, 1994; p 838.