SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 6, pp. 1041–1048, 2004

Synthesis of *ortho*-Methoxyphenylsulfonylsemicarbazides

N. Lebegue,* G. Bethegnies, and P. Berthelot

Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques de Lille, Lille Cedex, France

ABSTRACT

The synthesis of a new series of phenylsulfonylsemicarbazide which was substituted in ortho position by a methoxy group is described. The protection of the phenyl ring by a bromine, in order to eliminate the obtention of undesired regioisomers, is necessary to afford final compounds.

Key Words: Phenylsulfonylsemicarbazide; Sulfonylurea; Ortho position; Methoxy group.

Sulfonylurea derivatives are the most widely prescribed drugs for the treatment of the maturity onset form of diabetes melitus.[1–3] Compounds **1** were also described in the literature like hypoglycemic agents[4] (Fig. 1).

*Correspondence: N. Lebegue, Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques de Lille, 3 rue du Professeur Laguesse, B.P. 83, 59006 Lille Cedex, France; E-mail: nlebegue@phare.univ-lille2.fr.

DOI: 10.1081/SCC-120028635 0039-7911 (Print); 1532-2432 (Online)

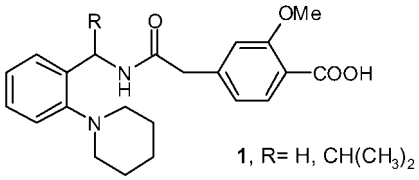


Figure 1. Compound **1** structure.

In regard with these structures, we decided to bring a sulfonylsemicarbazide moiety by replacement of the carboxylic acid (Fig. 2). Sulfonylureas are well known to increase endogenous insulin secretion.[5] The difficulty of the synthesis was to obtain sulfonylsemicarbazide substituted by a methoxy in ortho position of the sulfonyl group in the phenyl ring.

The first step of the synthesis to obtain 2-piperidinobenzylamine derivatives **2a–b** are well known[4] (Sch. 1). Condensation of this amine with 3-methoxyphenylacetic acid, using dicyclohexylcarbodiimide (DCC) in toluene, furnishes the corresponding amides **3a–b** which are then treated with chlorosulfonic acid in dichloromethane. 90% of the chlorosulfonylation takes place at the 2-position (**4a–b**), which is more reactive than the 4-position (**5a–b**).

The blocking of this position by addition of bromine on 3-methoxyphenylacetic acid following by condensation with amines **2a–b** affords the amides **7a–b** in 50–60% yield (Sch. 2). Addition of chlorosulfonic acid to dichloromethane (stabilized with amylene) solution of amide **7** supplies the chlorosulfonyl compound which is directly treated with gaseous ammonia. The isomers **8a–b**, bearing the sulfonamide group at the 4-position of the ring, are obtained with 45–55% yield.

Displacement of the bromine is realized in the presence of ammonium formate and Pd/C.[6,7] Synthesis of phenylsulfonylcarbazides from phenylsulfonylisocyanate and the corresponding hydrazines is described in the literature.[8] We have undertaken the synthesis by reacting sulfonamides **9a–b**

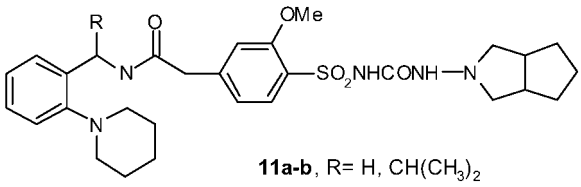
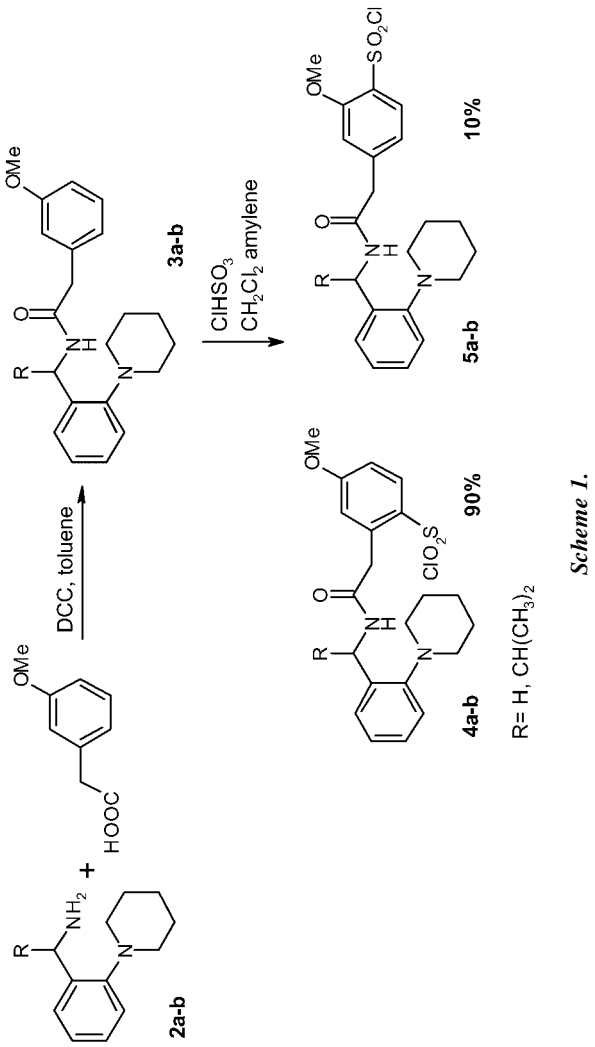


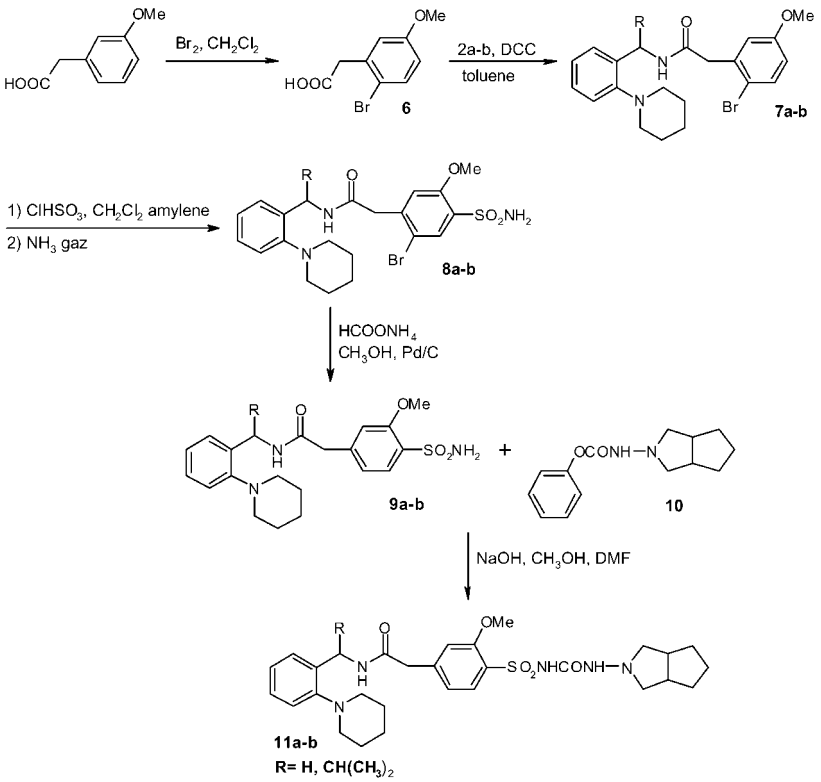
Figure 2. Sulfonylsemicarbazide moiety by replacement of carboxylic acid.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 2.

with carbamate **10** in the presence of NaOH in DMF to provide final compounds **11a–b** in 80–90% yield (Sch. 2).[9,10]

EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were recorded as thin films on potassium bromide disks on a Beckman Acculab IV spectrophotometer. Mass spectra were performed on a Applied Biosystems API 3000 LC/MS/MS (electrospray-ionspray method) (Laboratoire d'Application de Spectrométrie de Masse, Faculté de Medecine Henri Warembourg de Lille). ^{1}H NMR spectra were recorded on a Bruker AC 300 P and 2D NMR spectra on a Bruker DPX 300 (LARMN, Universite de Lille 2), using tetramethylsilane as internal

standard. Elemental analyses were performed by C.N.R.S.—Vernaison, and were in agreement with the calculated values within ± 0.4.

2-Bromo-3-methoxyphenylacetic acid (6). 1.7 mL of bromine (33 mmol) was added at 0°C to a solution of 5 g of 3-methoxyphenylacetic acid (30 mmol) in 25 mL of dichloromethane and the mixture was stirred at room temperature for 2 hr. The red solution was discolored with sodium thiosulfate, washed with water and extracted with dichloromethane. The organic layers were dried and evaporated under vacuo. Yield: 95%; mp = 114–115°C (Lit. 114°C)[11]; IR (cm^{-1}): 3200–2600 (OH), 1700 (C═O), 1600, 1490 (C═C); ^1H NMR ($CDCl_3$): δ (ppm) = 3.77–3.82 (m, 5H), 6.75 (dd, 1H, $J = 8.8, 2.9$), 6.85 (d, 1H, $J = 2.9$), 7.45 (d, 1H, $J = 8.8$). Anal. Calcd for $C_9H_9BrO_3$ ($M = 245$): C, 44.11; H, 3.7; Found: C, 44.23; H, 3.65.

General procedure for synthesis of amides (7). 1.9 g of **2a** or 2.3 g of **2b** (10 mmol) was added portionwise to a solution of 2.5 g of DCC (12 mmol) and 2.7 g of **6** (11 mmol) in 100 mL of toluene at room temperature and stirred for 10 hr. The reaction mixture was filtered, the filtrate was evaporated and the residue was recrystallized from hexane. The following compounds were obtained:

3-(2-Bromo-5-methoxyphenyl)-N-(2-piperidinobenzyl)acetamide (7a). Yield 62%; mp = 104–105°C; IR (cm^{-1}): 3300 (NH), 2900 (CH), 1650 (C═O), 1600, 1490 (C═C); ^1H NMR ($CDCl_3$): δ (ppm) 1.48–1.62 (m, 6H), 2.72–2.80 (m, 4H), 3.72 (s, 2H), 3.75 (s, 3H), 4.51 (d, 2H, $J = 6.5$), 6.55 (t, 1H, $J = 6.5$), 6.72 (dd, 1H, $J = 8.7, 2.7$), 6.89 (d, 1H, $J = 2.7$), 7.05 (m, 2H), 7.25 (m, 2H), 7.45 (d, 1H, $J = 8.7$). Anal. Calcd for $C_{21}H_{25}BrN_2O_2$ ($M = 417.34$): C, 60.44; H, 6.04; N, 6.71; Found: C, 60.19; H, 6.14; N, 6.84.

3-(2-Bromo-5-methoxyphenyl)-N-[1-(2-piperidinophenyl)-2-methylpropyl]acetamide (7b). Yield 52%; mp = 128–130°C; IR (cm^{-1}): 3300 (NH), 2900 (CH), 1650 (C═O), 1600, 1490 (C═C); ^1H NMR ($CDCl_3$): δ (ppm) 0.73 (d, 3H, $J = 8.5$), 0.95 (d, 3H, $J = 8.5$), 1.50–1.75 (m, 7H), 1.95 (m, 1H), 2.62 (m, 2H), 2.95 (m, 2H), 3.65 (s, 2H), 3.7 (s, 3H), 4.98 (m, 1H), 6.70 (dd, 1H, $J = 8.5, 2.7$), 6.88 (d, 1H, $J = 2.7$), 6.95 (m, 1H), 7.05 (m, 2H), 7.23 (m, 2H), 7.45 (d, 1H, $J = 8.5$). Anal. Calcd for $C_{24}H_{31}BrN_2O_2$ ($M = 459.42$): C, 62.74; H, 6.80; N, 6.10; Found: C, 62.98; H, 6.84; N, 6.27.

General procedure for synthesis of sulfonamides (8). 4 mL of chlorosulfonic acid (60 mmol) was added dropwise to a solution of 4.2 g of **7a** or 4.6 g of **7b** (10 mmol) in 15 mL of CH_2Cl_2 (stabilized with amylene) at 0°C. The mixture was then refluxed for 5 hr. After cooling, 150 mL of CH_2Cl_2 was added to the solution which was cooled to 0°C and treated with gaseous ammonia to form a white precipitate. The precipitate was filtered, washed with CH_2Cl_2 and the filtrate was evaporated under vacuo and used without further purification. The following compounds were obtained:

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

3-(4-Aminosulfonyl-2-bromo-5-methoxyphenyl)-N-(2-piperidinobenzyl)acetamide (8a). Yield 53%; mp = 187–188°C; IR (cm^{-1}): 3280, 3100 (NH), 2900 (CH), 1640 (C═O), 1600, 1490 (C═C), 1170, 1350 (SO_2N); ^1H NMR ($CDCl_3$): δ (ppm) 1.62–1.79 (m, 6H), 2.71–2.83 (m, 4H), 3.73 (s, 2H), 3.95 (s, 3H), 4.55 (d, 2H, $J = 6.5$), 5.09 (s, 2H), 7.12 (m, 3H), 7.25 (m, 2H), 8.05 (s, 1H). Anal. Calcd for $C_{21}H_{26}BrN_3O_4S$ ($M = 496.42$): C, 50.81; H, 5.28; N, 8.46; Found: C, 51.02; H, 5.34; N, 8.62.

3-(4-Aminosulfonyl-2-bromo-5-methoxyphenyl)-N-[1-(2-piperidinophenyl)-2-methyl-propyl]acetamide (8b). Yield 45%; mp = 249–250°C; IR (cm^{-1}): 3400, 3350 (NH), 2900 (CH), 1670 (C═O), 1600, 1500 (C═C), 1175, 1335 (SO_2N); ^1H NMR ($CDCl_3$): δ (ppm) 0.73 (d, 3H, $J = 8.5$), 1.02 (d, 3H, $J = 8.5$), 1.58–1.79 (m, 7H), 1.99 (m, 1H), 2.69 (m, 2H), 2.97 (m, 2H), 3.68 (m, 2H), 3.91 (s, 3H), 4.85 (m, 1H), 5.11 (s, 2H), 7.12 (m, 3H), 7.25 (m, 2H), 7.60 (m, 1H), 8.05 (s, 1H). Anal. Calcd for $C_{24}H_{32}BrN_3O_4S$ ($M = 538.5$): C, 53.53; H, 5.99; N, 7.80; Found: C, 53.60; H, 5.79; N, 7.86.

General procedure for synthesis of (9). 1 g of **8a** or 1.1 g of **8b** (2 mmol) and 130 mg of ammonium formate (2 mmol) were dissolved in 30 mL of methanol. 100 mg of palladium 10% on charcoal was then added and the mixture was heated under reflux for 4 hr. After cooling, the palladium was eliminated and the filtrate concentrated under reduced pressure. 50 mL of NaOH 1 N was added to the residue and the solution was stirred for 1 hr at room temperature. The resulting mixture was acidified with acetic acid 10% until pH 6 and extracted twice with $CHCl_3$. The combined extracts were dried, concentrated under reduced pressure and recrystallized from ethanol. The following compounds were obtained:

3-(4-Aminosulfonyl-3-methoxyphenyl)-N-(2-piperidinobenzyl)acetamide (9a). Yield: 95%; mp = 198–199°C; IR (cm^{-1}): 3400, 3300 (NH), 2950, 2850 (CH), 1655 (C═O), 1610, 1495 (C═C), 1160, 1345 (SO_2N); ^1H NMR (CD_3OD): δ (ppm) 1.64–1.82 (m, 6H), 2.91–3.08 (m, 4H), 3.84 (s, 2H), 4.05 (s, 3H), 4.65 (s, 2H), 7.12 (dd, 1H, $J = 8.1, 2.1$), 7.23 (m, 2H), 7.35 (m, 3H), 7.95 (d, 1H, $J = 8.1$); MS m/e 418.2. Anal. Calcd for $C_{21}H_{27}N_3O_4S$ ($M = 417.52$): C, 60.41; H, 6.52; N, 10.06; Found: C, 60.52; H, 6.48; N, 10.15.

3-(4-Aminosulfonyl-3-methoxyphenyl)-N-[1-(2-piperidinophenyl)-2-methylpropyl]acet-amide (9b). Yield: 90%; mp = 205–207°C; IR (cm^{-1}): 3400, 3300 (NH), 2950, 2800 (CH), 1650 (C═O), 1600, 1500 (C═C), 1155, 1350 (SO_2N); ^1H NMR ($CDCl_3$): δ (ppm) = 0.72 (d, 3H, $J = 8.5$), 0.98 (d, 3H, $J = 8.5$), 1.56–1.80 (m, 7H), 1.95 (m, 1H), 2.63 (m, 2H), 2.90 (m, 2H), 3.56 (s, 2H), 3.91 (s, 3H), 4.85 (m, 1H), 5.08 (s, 2H), 6.91 (d, 1H, $J = 8.1$), 7.02 (s, 1H), 7.09 (m, 2H), 7.25 (m, 2H), 7.52 (m, 1H), 7.85 (s, 1H); MS m/e 460.3. Anal. Calcd for $C_{24}H_3N_3O_4S$ ($M = 459.6$): C, 62.72; H, 7.24; N, 9.14; Found: C, 62.79; H, 7.09; N, 9.23.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Phenyl hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylcarbamate (10). A solution of 6.3 g of hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-amine (50 mmol) and 7 mL of triethylamine (50 mmol) was added dropwise to a solution of 7.5 mL of phenyl chloroformate (60 mmol) in 150 mL of CH_2Cl_2. The reaction mixture was heated under reflux for 2 hr, evaporated, taken with water and the resulting precipitate was filtered and washed with petroleum ether. Yield: 86%; mp = 138–140°C; IR (cm^{-1}): 3260 (NH), 2900, 2840 (CH), 1730 (C═O), 1600, 1500 (C═C); ^1H NMR ($CDCl_3$): δ (ppm) 1.45–1.71 (m, 6H), 2.45 (m, 2H), 2.65 (m, 2H), 3.35 (m, 2H), 5.82 (s, 1H), 7.15 (m, 3H), 7.35 (m, 2H). Anal. Calcd for $C_{14}H_{18}N_2O_2$ (M = 246.3): C, 68.27; H, 7.37; N, 11.37; Found: C, 68.40; H, 7.32; N, 11.41.

General procedure for synthesis of sulfonylsemicarbazides (11). 80 mg of NaOH (2 mmol) dissolved in 5 mL of methanol was added to 0.83 g of **9a** or 0.92 g of **9b** (2 mmol) in solution in 4 mL of DMF and the solution was stirred at room temperature for 1 hr. The methanol was evaporated and 0.54 g of carbamate **10** (2.2 mmol) dissolved in 1 mL of DMF was added to the resulting mixture which was stirred at 50°C for 12 hr. After evaporation, the residu was taken into 3 mL of CH_2Cl_2 and isopropylic ether was added until precipitation of the sodium salt of the sulfonylsemicarbazide which was filtered. The resulting powder was dissolved in CH_2Cl_2 and acidified with acetic acid until pH 5 followed by addition of aqueous ammonia. The solution was washed with water and the organic layers were dried, filtered and evaporated. Recrystallization from acetone furnished the finals sulfonylsemicarbazides.

2-[4-[[[(hexahydrocyclopenta[*c*]pyrrol-2(1H)amino)carbonyl]amino]-sulfonyl]-3-methoxy phenyl], N-(2-piperidinobenzyl)acetamide (11a). Yield: 88%; mp = 175–176°C; IR (cm^{-1}): 3390, 3340, 3100 (NH), 2950, 2860 (CH), 1700, 1660 (C═O), 1600, 1495 (C═C), 1160, 1330 (SO_2N); ^1H NMR ($CDCl_3$): δ (ppm) 1.52–1.76 (m, 12H), 1.98 (m, 1H), 2.61 (m, 2H), 2.84 (m, 6H), 3.32 (m, 1H), 3.63 (s, 2H), 3.92 (s, 3H), 4.56 (d, 2H, J = 6.3), 5.42 (m, 1H), 6.92 (d, 1H, J = 8.0), 7.05 (m, 4H), 7.23 (m, 2H), 7.98 (d, 1H, J = 8.0), 9.03 (m, 1H); MS m/e 570.2; Anal. Calcd for $C_{29}H_{39}N_5O_5S$ (M = 569.7): C, 61.14; H, 6.9; N, 12.29; Found: C, 61.32; H, 6.84; N, 12.15.

2-[4-[[[(hexahydrocyclopenta[*c*]pyrrol-2(1H)amino)carbonyl]amino]-sulfonyl]-3-methoxy phenyl], N-[1-(2-piperidinophenyl)-2-methylpropyl]-acetamide (11b). Yield: 78%; mp = 198–203°C; IR (cm^{-1}): 3400, 3340, 3120 (NH), 2950, 2860 (CH), 1710, 1660 (C═O), 1600, 1490 (C═C), 1150, 1335 (SO_2N); ^1H NMR ($CDCl_3$): δ (ppm) 0.72 (d, 3H, J = 8.1), 0.98 (d, 3H, J = 8.1), 1.48–1.72 (m, 13H), 1.99 (m, 1H), 2.53 (m, 4H), 2.84 (m, 4H), 3.31 (m, 1H), 3.55 (s, 2H), 3.85 (s, 3H), 4.82 (t, 1H, J = 6.3), 5.33 (m, 1H), 6.92 (d, 1H, J = 8.0), 7.01 (s, 1H), 6.98 (m, 2H), 7.22 (m, 2H), 7.48 (m, 1H), 7.98

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

(d, 1H, $J = 8.0$), 9.03 (m, 1H); MS m/e 612.2; Anal. Calcd for $C_{32}H_{45}N_5O_5S$ ($M = 611.8$): C, 62.82; H, 7.41; N, 11.45; Found: C, 62.78; H, 7.35; N, 11.53.

REFERENCES

1. Brown, G.R.; Foubister, A.J. J. Med. Chem. **1984**, *27*, 79–81.
2. Rufer, C.; Biere, H.; Ahrens, H.; Loge, O.; Schroder, E. J. Med. Chem. **1974**, *17*, 708–715.
3. Biere, H.; Rufer, C.; Ahrens, H.; Loge, O.; Schroder, E. J. Med. Chem. **1974**, *17*, 716–721.
4. Grell, W.; Hurnaus, R.; Griss, G.; Sauter, R.; Rupprecht, E.; Mark, M.; Luger, P.; Nar, H.; Wittneben, H.; Muller, P. J. Med. Chem. **1998**, *41*, 5219–5246.
5. Satin, L.S. Endocrine **1996**, *4*, 191–198.
6. Cortese, N.A.; Heck, R.F. J. Org. Chem. **1977**, *42*, 3491.
7. Cortese, N.A.; Heck, R.F. J. Org. Chem. **1978**, *43*, 3985.
8. Jensen, K.A. Acta. Chem. Scand. **1966**, *20*, 2795.
9. Venkatraman, S.; Kong, J.S.; Nimkar, S.; Wang, Q.M.; Aube, J.; Hanzlik, R.P. Bioorg. Med. Chem. Lett. **1999**, *9* (4), 577–580.
10. Gil, M.J.; Manu, M.A.; Arteaga, C.; Migliaccio, M.; Encio, I. Bioorg. Med. Chem. Lett. **1999**, *9* (16), 2321–2324.
11. Amupitan, J.O.; Stanfield, F. J. Chem. Soc. Perkin. Trans. 1. **1974**, 1949–1951.

Received in Poland July 5, 2003

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016