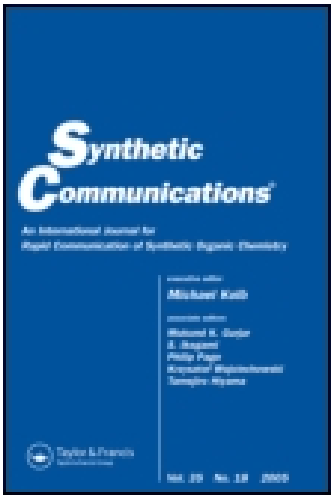

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New Short Synthesis of (5)-2,3-Dimethoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodobenzamide: Dopamine D2 Receptor

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Abstract: A new short and highly efficient synthesis of (5)-2,3-dimethoxy-N[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodobenzamide (epidepride, **1**) from 3-methoxy-salicylaldehyde (o-vanillin, **2**) and 3-methoxysalicyclic acid (**6**) was achieved by employing a new iodination method with iodine monochloride and iodine nitrate under basic conditions.

Keywords: dopamine D2 receptor, epidepride, iodine monochloride, iodine nitrate

INTRODUCTION

Epidepride [(5)-2,3-dimethoxy–N[(1-ethyl-2-pyrrolidinyl)methyl]-5-iodobenzamide] (**1**) is a neuroleptic possessing selective and high binding affinity toward dopamine D2 receptor sites in vitro.[1] The ^{123}I-labeled form of **1** combined with single-photon emission computed tomography (SPECT) can serve as a superior in vivo imaging agent for the dopamine D2 receptors in the human brain.[2] Several syntheses of **1** have been reported, all in low to moderate yieds.[3–5] These methods involve low-yielding direct iodination of a salicyl-type phenol precursor[3] and the anion-mediated exchange of bromine to iodine at the 5-position at some stage in the synthetic sequence.[3a,5] The latter method suffers from the rather unreactive nature of iodine toward 5-lithio

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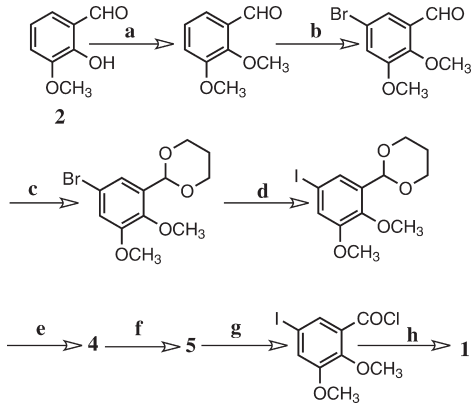


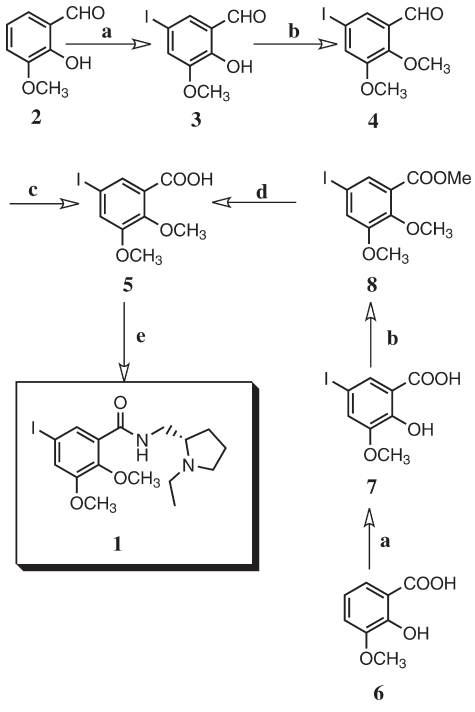
Scheme 1. Reagent and conditions: (a) MeI, K_2CO_3, DMF, 60°C, 16 h, 98%; (b) Br_2, 64%; (c) $CH_2(CH_2OH)_2$, H^+; (d) t-BuLi, I_2; (e) HCl; (f) $KMnO_4$, K_2HPO_4; (g) $(COCl)_2$, DMF; (h) (S)-2-aminomethyl-1-ethylpyrrolidine, CH_2Cl_2, 1 h, 63%.

derivatives and the propensity of the pyrrolidine fragment to undergo decomposition. The overall yield (54%) of epidepride (**1**) by this approach has been somewhat improved by the use of 5-bromo-2,3-dimethoxy-1-(1,3-dioxacin-2-yl) benzene as a substrate (Scheme 1).[5,6] Although methods involving aryltin intermediates are satisfactory for the preparation of labeled epidepride, they are less than satisfactory for the preparation of unlabeled **1**, because the procedures are too long with low overall yields.

Thus, a shorter and more efficient synthesis of epidepride (**1**) is highly desirable. A major problem in the synthesis of epidepride and related iodinated compounds has been the lack of suitable methods for the direct iodination of salicyl-type phenol substrates. Yue et al.[5] investigated the reaction of several known iodinating agents with 3-methoxysalicylaldehyde and methyl-3-methoxysalicylate and found that none gave satisfactory yields of the desired iodinated products. Thus, a good and high-yielding iodination method for salicyl-type phenol compounds would greatly simplify the synthesis of these compounds. Such a method and its applications to the synthesis of epidepride (**1**) are the subjects of this communication.

RESULTS AND DISCUSSION

Reaction of 3-methoxysalicylaldehyde (o-vanillin, **2**) with pyridine complexes of iodine monochloride[6] or iodine nitrate[7] (generated in situ from iodine monochloride and silver nitrate in chloroform-pyridine) at room temperature proceeded cleanly and efficiently to yield 5-iodo-3-methoxysalicylaldehyde (**3**, yield 96%) (Scheme 2). It is to be noted that the reaction of iodine monochloride in acetic acid with o-vanillin gave predominantly 5-chloro-3-



Scheme 2. Reagent and conditions: (a) $AgNO_3$, ICl, pyridine, $CHCl_3$, rt, 2 h, 96%; (b) MeI, K_2CO_3, DMF, 60°C, 16 h, 98%; (c) $KMnO_4$, K_2HPO_4, t-BuOH, rt, 1.5 h; (d) NaOH, THF, H_2O, 20 h, reflux, 98%; (e) (S)-2-aminomethyl-1-ethylpyrrolidine, CDI, CH_2Cl_2, rt, 20 h, 99%.

methoxysalicylaldehyde.[5] For the conversion of **3** to the methoxy derivative **4**, the reported methods[3,8,9] for the corresponding bromoaldehyde and bromo acid was unsatisfactory because a very large excess (<25 molar excess) of dimethyl sulfate was required, and the reaction never went to completion. On the other hand reaction of **3** with methyl iodide and anhydrous potassium carbonate in anhydrous DMF at 60°C for 16 h gave the dimethoxy derivative **4**[5] in 98% yield. Masamune oxidation [5,9] ($KMnO_4$, t-BuOH, K_2HPO_4) gave 5-iodo-2,3-dimethoxybenzoic acid (**5**) [5] in 98% yield after chromatographic purification. Alternatively, reaction of 3-methoxysalicyclic acid (**6**) with either iodine monochloride in pyridine or iodine nitrate gave 5-iodo-3-methoxy salicylic acid (**7**) in quantitative yield. Methylation of **7** (CH_3I, K_2CO_3, DMF) to **8** proceeded smoothly in 98% yield. Hydrolysis of **5** (NaOH, H_2O, THF) provided 5-iodo-2,3-dimethoxy benzoic acid (**8**) in 98% yield.

Both iodine nitrate-pyridine and iodine monochloride-pyridine complexes gave comparable yields of the iodoaldehyde **3** and the iodo acid **7**. The iodine nitrate-pyridine complex is considerably faster (2 h) than with iodine monochloride-pyridine complex (20 h).

The acid chloride coupling method[5,10] on **5** (oxalyl or thionyl chloride followed by reaction with (S)-2-aminomethyl-1-ethylpyrrolidine) gives excellent yield of epidepride (**1**), but it involves the use of a relatively large excess of the chiral diamine. We have used a more convenient and less wasteful procedure without any sacrifice in yield by using carbonyldiimidazole as the coupling agent.[11] Thus treatment of **5** with carbonyldiimidazole (1.05 equivalent) to generate the imidazole derivative in situ and subsequent reaction with (S)-2-aminomethyl-1-ethylpyrrolidine[10] (1.05 equivalent) gave epidepride **1**, homogeneous by thin-layer chromatography (TLC) in 99% yield.

CONCLUSION

The use of iodine monochloride-pyridine complex or iodine nitrate-pyridine complex for the key iodination step of o-vanillin (**2**) or 3-methoxysalicylic acid (**6**) has yielded a three-step synthesis of 5-iodo-2,3-dimethoxybenzoic acid **5** in 98% overall yield. Using carbonyldiimidazole as a coupling agent we have achieved the shortest and most efficient (95% overall) synthesis of epidepride (**1**) to date.

EXPERIMENTAL

Method A

To a solution of silver nitrate (7.14 g, 42 mmol) dissolved in a mixture of $CHCl_3$ (50 mL) and pyridine (20 mL), iodine monochloride (6.82 g, 42 mmol) in $CHCl_3$ (10 mL) was added dropwise over a period of 5 min with constant stirring at room temperature. The stirring was continued for another 10 min, and to this solution o-vanillin (**2**, 6.08 g, 40 mmol) dissolved in $CHCl_3$ (10 mL) was added dropwise with stirring. The reaction mixture was stirred at room temperature for 2 h and then diluted with ether (50 mL). The mixture was filtered, the residue was washed with a mixture of $CHCl_3$–ether (1:1), and the combined filtrate was evaporated at 30°C, resulting in a white residue. The residue was redissolved in $CHCl_3$ (50 mL), and washed successively with 5% HCl (50 mL), 5% sodium thiosulfate (50 mL), and finally water (50 mL). The organic layer was separated, collected, dried over sodium sulfate, and filtered, and the solvent was evaporated at 30°C. The residual solid was purified by passing through a short silica-gel column ($CHCl_3$) to give compound **3**, which was crystallized from ethylacetate hexane (50 mL, 40:10) to give 10.68 g (96%) of **3**. The mixture of **2** (3.39 g, 12.2 mmol), anhydrous K_2CO_3 (8.42 g, 61 mmol), and methyl iodide (8.66 g, 61 mmol) in anhydrous DMF (30 mL) was heated at 68°C with continuous stirring under nitrogen for 16 h. The solvent was removed; the residue was taken up in dichloromethane (3 × 30 mL) and washed with water (50 mL). The organic layer was collected and dried over Na_2SO_4, filtered, and

concentrated. The residue was passed through a column of neutral alumina (in EtOAc) and eluted by the same to give **4** as a white solid (3.63 g, yield 90%), with mp 100–101°C (lit. 100–101°C).[10] The oxidation of **4** to give 5-iodo-2,3-dimethoxybenzoic acid (**5**) was achieved by Masamune oxidation.[5,10] The aldehyde **4** (1.22 g, 4.18 mmol) was dissolved in tert. butanol (30 mL), and dipotassium hydrogen phosphate (1.25 M, 16.5 mL) and potassium permanganate (1 M, 25.5 mL) were added. The mixture was stirred at room temperature for 90 min. The reaction was quenched with saturated Na_2SO_3, and the pH of the reaction mixture was adjusted to 1–2 with a few drops of conc. HCl, extracted with $CHCl_3$ (5×25 mL). The combined organic extract was dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting solid was purified on a silica-gel column; pure compound **5** came in 5% MeOH–$CHCl_3$ as a white solid (1.26 g, yield 98%), with mp 126–128°C.

Method B

Iodine monochloride (1.95 g, 12 mmol) in $CHCl_3$ (5 mL) was added dropwise to pyridine (20 mL) with stirring. After stirring for another 15 min, the resulting brownish-yellow solution was added to a solution of o-vanillin (**2**, 1.52 g, 10 mmol) in $CHCl_3$ (10 mL) and stirred at room temperature for 20 h. The reaction mixture was concentrated in vacuo. The residue was redissolved in $CHCl_3$ (50 mL) and washed successively with 5% HCl (50 mL), 5% sodium thiosulfate (50 mL), and finally with water (50 mL). The organic layer was separated and collected, dried over sodium sulfate, and filtered, and the solvent was evaporated at 30°C. The residual solid was purified by passing through a short silica-gel column (20 cm packed length to remove the color impurity) ($CHCl_3$) to give compound **3**, which was crystallized from ethyl acetate hexane (50 mL, 40:10) to give 2.665 g of **3** in 96% yield.

Selected Data for Compound **3**

Mp 124–126°C (sharp), anal. calcd. for $C_8H_7IO_3$ C, 34.56; H, 2.54. Found C, 34.74; H, 2.54. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.20 (s, 1H, OH, exchanged with D_2O), 10.16 (s, 1H, CHO, exchanged with D_2O), 7.48 and 7.43 (dd, 2H, Ar-H), 3.85 (S, 3H, OCH_3). EI (mass) [M + 1] 278.

Synthesis of Epidepride (1)

To a stirred suspension of 5-iodo-2,3-dimethoxybenzoic acid (5, 308 mg, 1.0 mmol) in dichloromethane (5 mL), 1,1-carbonyldiimidazole (170 mg, 1.05 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. To this, (S)-2-aminomethyl-1-ethylpyrrolidine (141 mg, 1.1 mmol) was added. The stirring was continued at room temperature for 20 h. The reaction

mixture was washed with 1 N sodium hydroxide solution (10 mL) and water (20 mL). The organic layer was dried over sodium sulphate and filtered, and the solvent was evaporated at 30°C. The residual solid was purified by silica-gel column (20 cm); pure compound was eluted in $CHCl_3$–MeOH (9:1), as yellow oil (415 mg, 99.3% yield). Anal. calcd. for $C_{16}H_{23}IN_2O_3$: C, 45.94; H, 5.54; N, 6.70. Found: C, 45.98; H, 5.59; N, 7.78. ^{1}H NMR (DMSO-d_6) δ (ppm): 8.58 (s, 1H, NH, exchanged with D_2O), 7.29 and 7.78 (dd, 2H, Ar-H), 3.85 and 3.73 (S, 3H, OCH_3), 1.64–2.80 (m, 7H, PyrrolidineH) EI (mass) [M + 1] 419.

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