ChemInform Abstract: The Synthesis of Cyclic and Acyclic Long-Chain Arylpiperazine Derivatives of Salicylamide as Serotonin Receptor Ligands

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Short Communication

An Efficient Synthesis of Aripiprazole, Buspirone and NAN-190 by the Reductive Alkylation of Amines Procedure

Piotr Kowalski and Jolanta Jaśkowska

Cracow University of Technology, Institute of Organic Chemistry and Technology, Cracow, Poland

The reductive alkylation of amines procedure was applied for the synthesis of aripiprazole **1a**, buspirone **1b**, and NAN-190 **1c**.

Keywords: Aripiprazole / Buspirone / NAN-190 / Reductive alkylation of amines / Sodium triacetoxyborohydride

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Introduction

Aripiprazole (7-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydro-1*H*-quinolin-2-one **1a** and buspirone (8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-8-azaspiro[4.5]decane-7,9-dione hydrochloride **1b** are approved psychotropic drugs; NAN-190 (2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}isoindoline-1,3-dione hydrobromide **1c** is a psychoactive agent (Fig. 1) [1]. From the chemical point of view, **1a**, **1b** and **1c** belong to long-chain arylpiperazine derivatives with terminal aryloxy- (aripiprazole) or the imide (buspirone, NAN-190) functionalities. In general, the syntheses of **1a**, **1b**, and **1c**, are based on three fragments: arylpiperazine (A), four-carbon aliphatic chain (B) and hydroxyaryl or imide moiety (C) (Fig. 1). The synthetic pathways involve two steps (Fig. 2) [2–14]. In the first step the four-carbon chain **2** is coupled with one of the fragments **3** or **4** to form the intermediates **5** or **6**, respectively. Next, attachment of the unit **5** to **4**, or the unit **6** to **3** gives the expected product **1**. In order to prevent formation of a disubstituted product, large excess of **2** is usually used in the first step. This increases costs and the size or number of chemical reactors, which is particularly important in large-scale production of the title compounds.

Results and discussion

In this paper we report the results of our investigations of synthesis of aripiprazole **1a**, buspirone **1b** and NAN-190 **1c** by the reductive alkylation of amines procedure. This procedure allows the conversion of a carbonyl functionality to an amine group by treatment of a mixture of a carbonyl compound and an amine with a suitable reducing agent [15–17]. In our case, the aldehydes **8**, obtained by hydrolysis of the corresponding acetals **7** were used as the carbonyl compounds, while 1-arylpiperazines **3** were used as the amines. Sodium triacetoxyborohydride was applied as the reducing agent (Scheme 1). To date, the preparation of aripiprazole **1a** [2–6, 18–21], buspirone **1b** [7–11, 22–24], and NAN-190 **1c** [12–14] by the reductive alkylation of amines procedure has not been described, neither in scientific literature nor in patents.

The acetals **7a–c** (Scheme 1), the precursors of ω-formylated *O*- or *N*-butyl substituted derivatives of carbostyrile or imides **8**, were easily prepared by *O*-alkylation of 7-hydroxycarbostyrile **4a**, or, *N*-alkylation of the imides **4b** or **4c** with 4-chlorobutyraldehyde dimethyl acetal (1.1–1.2 equiv.). Highest yields of **7a–c** were achieved using DMSO as the solvent; in DMF the reactions were slower and the products were difficult to purify. In the case of the synthesis of **7a** and **7b**, the reaction was accelerated by addition of a catalytic amount (10 mol-%) of TBAB (tetrabutylammonium bromide). So obtained raw acetals **7a–c** were over 94% pure, and were used for the synthesis of **1a–c** without purification.

Hydrolysis of the acetals **7a** and **7b** was carried out in a mixture of 10% hydrochloric acid and dichloromethane, whilst the hydrolysis of **7c** required use of 20% hydrochloric acid. The aldehydes **8a–c**, obtained by hydrolysis of **7a–c**, were condensed with the corresponding 1-arylipiperazines **3a–c** (0.93–0.95 equiv.) without separation, in the presence of sodium triacetoxyborohydride (1.15–1.20 equiv.) (a one-pot reaction). After 20 min the reactions were quenched.

The progress of the reactions was followed by TLC analysis. Full hydrolysis of the acetals **7a–c** was recognized by

Correspondence: Piotr Kowalski, Cracow University of Technology, Institute of Organic Chemistry and Technology, 24 Warszawska Street, 31-155 Kraków, Poland.
E-mail: kowapi@pk.edu.pl
Fax: +4812-628-20-37

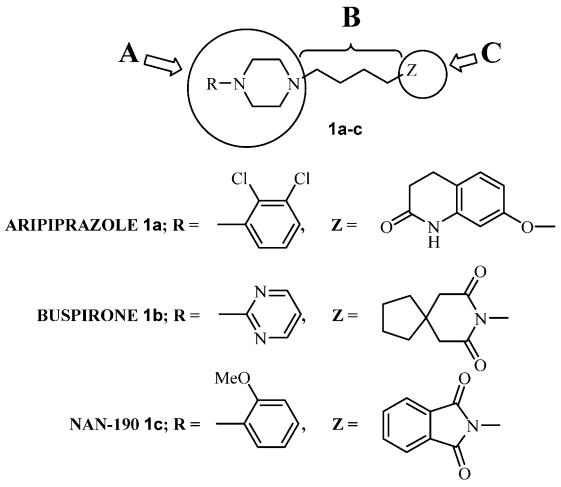


Figure 1. Structures of aripiprazole **1a**, buspirone **1b**, and NAN-190 **1c**.

disappearing of their spots, and along the hydrolysis no additional spots except for those of substrates **7a–c** and products **8a–c** were observed. The reduction of the reaction mixture containing the aldehydes **8a–c** and 1-arylpiperazines **3a–c** in hydrochloride form was performed by solid sodium triacetoxyborohydride. TLC analysis of those reaction mixtures, where only one additional spot corresponding to the final products **1a–c** was detected, indicated that the reductive alkylation took place without prior formation of intermediates iminium salts.

Conclusion

The reductive alkylation of amines procedure was developed for the synthesis of aripiprazole **1a**, buspirone **1b**, and NAN-190 **1c**. Despite the fact that this method is often used in academia and industry, to date it has not been used in the synthesis of these three drugs. Moreover, the reductive

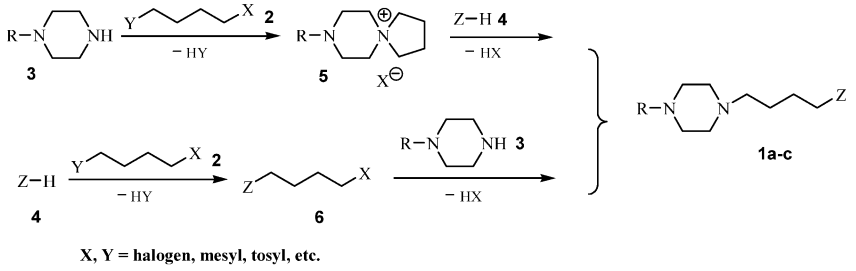
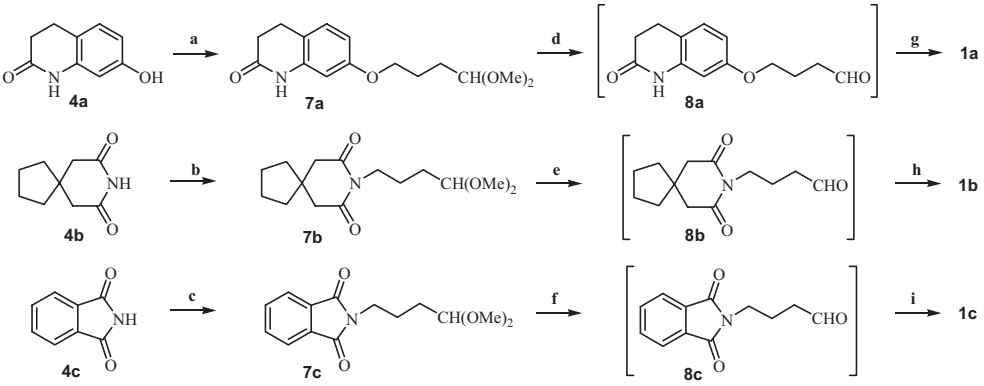


Figure 2. General synthesis of aripiprazole **1a** [2–6], buspirone **1b** [7–11] and NAN-190 **1c** [12–14].



Reagents and conditions: (a) 4-Chlorobutyraldehyde dimethyl acetal, DMSO, K_2CO_3, TBAB, 115 ± 5°C, 4 h; (b) 4-chlorobutyraldehyde dimethyl acetal, DMSO, K_2CO_3, TBAB, 80 ± 5°C, 4 h; (c) 4-chlorobutyraldehyde dimethyl acetal, DMSO, K_2CO_3, 75 ± 5°C, 2.5 h; (d) 10% HCl/CH_2Cl_2, r.t., 2.5 h; (e) 10% HCl/CH_2Cl_2, r.t., 2.5 h; (f) 20% HCl/CH_2Cl_2, r.t., 1 h; (g) 1-(2,3-dichlorophenyl)piperazine hydrochloride **3a**, CH_2Cl_2, $NaBH(OAc)_3$, r.t., 20 min; (h) 1-(2-pyrimidyl)piperazine dihydrochloride **3b**, CH_2Cl_2, $NaBH(OAc)_3$, r.t., 20 min; (i) 1-(2-methoxyphenyl)piperazine hydrochloride **3c**, CH_2Cl_2, $NaBH(OAc)_3$, r.t., 20 min.

Scheme 1. Synthesis of aripiprazole **1a**, buspirone **1b** and NAN-190 **1c** by the reductive alkylation of amines procedure.

alkylation of amines procedure is an attractive synthetic alternative for large-scale production of the title drugs. In these syntheses the products were prepared from commercially available reagents and were isolated in very good yields and purity.

Generally, the experimental results indicate that the described procedure of reductive alkylation of amines allows introduction of an alkyl spacer to a molecule under mild reaction conditions, whilst usually 1,ω-dihalogenalkanes have been applied for construction of the spacers.

Experimental section

General

Melting points were determined on a Boëtius apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian spectrometer, using deuterated chloroform or deuterated dimethylsulfoxide as the solvents. The chemical shifts are expressed as δ values in ppm against TMS as an internal standard. Purities and molecular masses of compounds were determined by Waters Acquity UPLC, coupled to Waters Acquity SQD mass spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 analyzer, and the results are within ±0.4% of the calculated values. The reactions were monitored by TLC on silica-gel plates (Merck 60F_{254}) using chloroform/methanol (9:1) as eluent. Starting materials, solvents, and reagents were purchased from commercial sources and were used without further purification.

UPLC/MS analysis

Samples were dissolved in methanol. The UPLC/MS system consisted of a Waters Acquity UPLC, coupled to Waters Acquity SQD mass spectrometer (electrospray ionization mode, single quadrupole). All analyses were carried out using an Acquity BEH C18, 2.1 × 50 mm, 1.7-μm column. Eluent flow rate of 350 μL/min and a gradient of 5–95% of B over 1.8-min period, followed by holding for 1 min at 95% methanol were used. Eluent A: 0.02% HCOOH in water; eluent B: methanol. Nitrogen was used for both: desolvation and cone gas with flow rates of 800 L/h and 50 L/h, respectively. Source temperature was 120°C and the desolvation temperature was 350°C. The data were obtained in scan mode ranging from 100 to 1100 m/z with a scan rate of 9000 Da/s (alternating both ESI+ and ESI− modes of ESI), giving 4.5 points of TIC per second.

*Procedure for the synthesis of the acetals **7a–c**, illustrated by the preparation of 7-(4,4-dimethoxybutoxy)-3,4-dihydro-1H-quinolin-2-one **7a***

To a solution of 8.16 g (0.050 mol) of 7-hydroxy-3,4-dihydro-1*H*-quinolin-2-one **4a** and 9.15 g (0.060 mol) of 4-chlorobutyraldehyde dimethyl acetal in 15 mL of DMSO, 8.28 g (0.060 mol) of potassium carbonate and 1.61 g (5 mmol) of TBAB were added. The mixture was stirred and heated at 115 ± 5°C for 4 h. Next, the solvent and volatile materials were distilled off under reduced pressure and 50 mL of water was added to the residue. The product was extracted two times with toluene (50 mL and 25 mL). The extract was washed with 10% aqueous solution of sodium hydroxide and toluene was evaporated under reduced pressure. The oil residue was heated up to about 55°C and 15 mL of ethanol was added. Then the solution was cooled down to room temperature. Light beige precipitate formed, which was filtered off, washed with cold ethanol and dried; 13.40 g (96% yield) of raw 7-(4,4-dimethoxybutoxy)-3,4-dihydro-1*H*-quinolin-2-one **7a** was obtained, which was 95% pure (by UPLC). After crystallization from ethanol **7a** had m.p. 85–87°C and 98% (UPLC) purity. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.76–1.85 (m, 4H, 2 CH_2), 2.62 (t, 2H, J = 7.3 Hz, CH_2), 2.89 (t, 2H, J = 7.4 Hz, CH_2), 3.34 (s, 6H, 2 CH_3), 3.95, (t, 2H, J = 6.2 Hz, CH_2), 4.43, (t, 1H, J = 5.5 Hz, CH), 6.38 (d, 1H, J = 2.4 Hz, CH_{Aryl}), 6.51 (d,d, 1H, J = 8.3 Hz, J = 2.4 Hz, CH_{Aryl}), 7.03 (d, 1H, J = 8.3 Hz, CH_{Aryl}), 8.94 (s, 1H, NH). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.39, 24.52, 29.04, 31.02, 52.77 (2C), 67.64, 102.24, 104.21, 108.70, 115.64, 128.51, 138.19, 158.58, 172.22. MS-ESI+: m/z 280 $[M+H]^+$. Anal. calcd. for $C_{15}H_{21}NO_4$ (279.33): C, 64.50; H, 7.58; N, 5.01. Found: C, 64.71; H, 7.39; N, 5.30.

*8-(4,4-Dimethoxybutyl)-8-azaspiro[4.5]dekane-7,9-dione **7b***

Oil, yield 96%, purity (UPLC) 95%. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.48–1.52 (m, 4H, 2 CH_2), 1.56–1.59 (m, 4H, 2 CH_2), 1.70–1.73 (m, 4H, 2 CH_2), 2.58 (s, 4H, 2 CH_2), 3.31 (s, 6H, 2 CH_3), 3.77, (t, 2H, J = 7.1 Hz, CH_2), 4.37, (t, 1H, J = 5.3 Hz, CH). ^{13}C-NMR (125 MHz, $CDCl_3$): 23.04, 24.08 (2C), 29.82, 37.44 (2C), 39.34, 44.73 (2C), 52.68 (2C), 104.06, 172.02 (2C). MS-ESI+: m/z 284 $[M+H]^+$. Anal. calcd. for $C_{15}H_{25}NO_4$ (283.36): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.77; H, 8.62; N, 4.84.

*2-(4,4-Dimethoxybutyl)isoindoline-1,3-dione **7c***

Oil, yield 95%, purity (UPLC) 94%. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.63–1.67 (m, 2H, CH_2), 1.73–1.79 (m, 2H, CH_2), 3.31 (s, 6H, 2 CH_3), 3.71, (t, 2H, J = 7.1 Hz, CH_2), 4.39, (t, 1H, J = 5.7 Hz, CH), 7.76 (d, d, 2H, J = 5.5 Hz, J = 3.1 Hz, 2 CH_{Aryl}), 7.84 (d, d, 2H, J = 5.4 Hz, J = 3.0 Hz, 2 CH_{Aryl}). ^{13}C-NMR (125 MHz, $CDCl_3$): 23.78, 29.83, 37.62, 52.86 (2C), 104.02, 123.13 (2C), 132.07, 133.84 (3C), 168.32 (2C). MS-ESI+: m/z 264 $[M+H]^+$. Anal. calcd. for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.68; H, 6.55; N, 5.09.

*Synthesis of aripiprazole **1a**, buspirone **1b** and NAN-190 **1c** by the reductive alkylation of amines procedure, illustrated by the preparation of 7-{4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydro-1H-quinolin-2-one (aripiprazole) **1a***

To the solution of 5.58 g (0.020 mol) of 7-(4,4-dimethoxybutoxy)-3,4-dihydro-1*H*-quinolin-2-one **7a** in 50 mL of methylene chloride, 150 mL of 10% hydrochloric acid was added. After 2.5 h of stirring at room temperature the layers were separated from each other, and the organic layer, containing 4-[(2-oxo-3,4-dihydro-1*H*-quinolin-7-yl)oxy]butanal **8a** after acetal **7a** hydrolysis, was washed with 5% $NaHCO_3$. The organic layer was diluted with additional amount of methylene chloride (75 mL) and 5.08 g (0.019 mol) of 1-(2,3-dichlorophenyl)piperazine hydrochloride **3a** was added, which was followed by addition of glacial acetic acid till all the components dissolved (about 7 mL). Next, 4.87 g (0.023 mol) of sodium triacetoxyborohydride was dosed at room temperature for several minutes, with intensive stirring, and after further 20 min of stirring, the mixture was treated with 60 mL of 4% hydrochloric acid in order to finish the reduction process. The organic layer was washed with 80 mL of 4% sodium hydroxide to convert the aripiprazole **1a** hydrochloride into free base. The solvent was removed under reduced pressure and the residue was treated with 15 mL of methanol or ethanol to yield 8.25 g (97%) of crude **1a** in the form of light creamy crystals of 94% purity (UPLC). Subsequent crystallization from ethanol afforded 93% yield of aripiprazole **1a** with >99% purity (UPLC). Melting point: 138–139.5°C; [2] m.p. 139–140°C (ethanol); [25] m.p. 138–140°C (ethanol/water); [25] m.p. 139–141°C (ethyl acetate). ^{1}H- and ^{13}C-NMR spectra are consistent with the original sample [4]. MS-ESI+: *m/z* 448 $[M+H]^+$. Anal. calcd. for $C_{23}H_{27}Cl_2N_3O_2$ (448.39): C, 61.61; H, 6.07; N, 9.37. Found: C, 61.50; H, 6.27; N, 9.51.

*8-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl}-8-azaspiro-[4.5]decane-7,9-dione hydrochloride (buspirone) **1b***

Yield 91%, purity (UPLC) >98%. M.p. 202–204°C (ethanol); [10] m.p. 202–204°C (ethanol); [11] m.p. 201.5–202.5°C (ethanol). ^{1}H-NMR spectrum is consistent with the original sample [7, 10]. MS-ESI+: *m/z* 386 $[M+H]^+$. Anal. calcd. for $C_{21}H_{31}N_5O_2 \cdot HCl$ (421.96): C, 59.77; H, 7.64; N, 16.60. Found: C, 59.89; H, 7.51; N, 16.82.

*(2-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-isoindoline-1,3-dione hydrobromide (NAN-190) **1c***

Yield 90%, purity (UPLC) >98%. M.p. 231–234°C (ethanol); [14] m.p. 230–234°C (ethanol). ^{1}H-NMR spectrum is consistent with the original sample [13]. MS-ESI+: *m/z* 394 $[M+H]^+$. Anal. calcd. for $C_{23}H_{27}N_3O_3 \cdot HBr$ (474.39): C, 58.23; H, 5.95; N, 8.86. Found: C, 58.41; H, 5.83; N, 8.69.

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