Original article

Efficient synthesis of functionalized 1,3-dihydroisobenzofurans from salicylaldehydes: Application to the synthesis of escitalopram

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ABSTRACT

An efficient synthesis of substituted 1,3-dihydroisobenzofurans is developed. In this novel route, o-aroylbenzaldehydes, as key intermediates, can be obtained by lead tetraacetate oxidation of N-aroylhydrazones of salicylaldehydes. The mild and general strategy enables the synthesis of various substituted 1,3-dihydroisobenzofurans in high yields. Moreover, this method can be applied to efficiently synthesize escitalopram.

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1. Introduction

Substituted 1,3-dihydroisobenzofurans are an important class of building blocks because such heterocyclic structural moieties are found in a wide range of pharmacologically active compounds [1–3]. Many clinical drugs contain the 1,3-dihydroisobenzofuran ring (Fig. 1), such as siramesine [4], YM-35375 [5], escitalopram [6]. Moreover, 1,3-dihydroisobenzofuran derivatives have been used in perfumes, colorants and the agricultural industry [7–9]. Many methods for the synthesis of 1,3-dihydroisobenzofuran derivatives have been reported [10–14]. However, most of these require strict reaction conditions using the Grignard reagent at very low temperatures while others require expensive fluoride reagents as starting materials, which are not commercially available and have to be prepared via multistep, unconventional syntheses [15–18]. Guiso et al. has also synthesized hydroxyphthalans by a one-pot synthesis based on a modified oxa-Pictet–Spengler reaction [19]. But this method is only applicable to the synthesis of hydroxyphthalans. Hence, there has been a continuous demand to develop synthetic methods for 1,3-dihydroisobenzofuran derivatives.

In recent years, Kotali et al. discovered a very interesting synthesis of o-diacylbenzenes by lead tetraacetate (LTA) oxidation of N-acylhydrazones of o-hydroxyacylbenzenes [20,21]. This carbon-carbon bond forming reaction has been widely used in

the synthesis of tetraacylbenzenes, diacylcoumarins and dioximes [22–24]. To the best of our knowledge, this rearrangement reaction was never applied in the synthesis of substituted 1,3-dihydroisobenzofurans. Herein, we report such an application by utilizing commercially available, functional salicylaldehydes as starting materials.

2. Experimental

Commercial reagents were used as received. Analytical-grade solvents and commercially available reagents were used without further purification. Thin-layer chromatography (TLC) was carried out with 0.2 mm thick silica gel plates (GF$_{254}$). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-300 MHz spectrometer. Chemical shifts are reported relative to TMS; Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets); td (triplet of doublets); br s (broad singlet), etc. and coupling constants are given in hertz. Electrospray mass spectra were obtained on a Finnigan MAT-95 Spectrometer.

General procedure, exemplified by 1-phenyl-1,3-dihydroisobenzofuran (5a): (i) The benzoylhydrazine (1 mmol) was added to a solution of the salicylaldehyde (1 mmol) in 5 mL acetic acid at room temperature. The mixture was stirred for 15 min and then was poured into 15 mL cold water. The resulting solid was filtered, washed with water and dried under vacuum. (ii) The obtained solid (1 mmol) was dissolved in 10 mL THF at room temperature. The solution was cooled to 0 °C and lead tetraacetate (1 mmol) was added under nitrogen. The mixture was stirred 4 h at 0 °C and then

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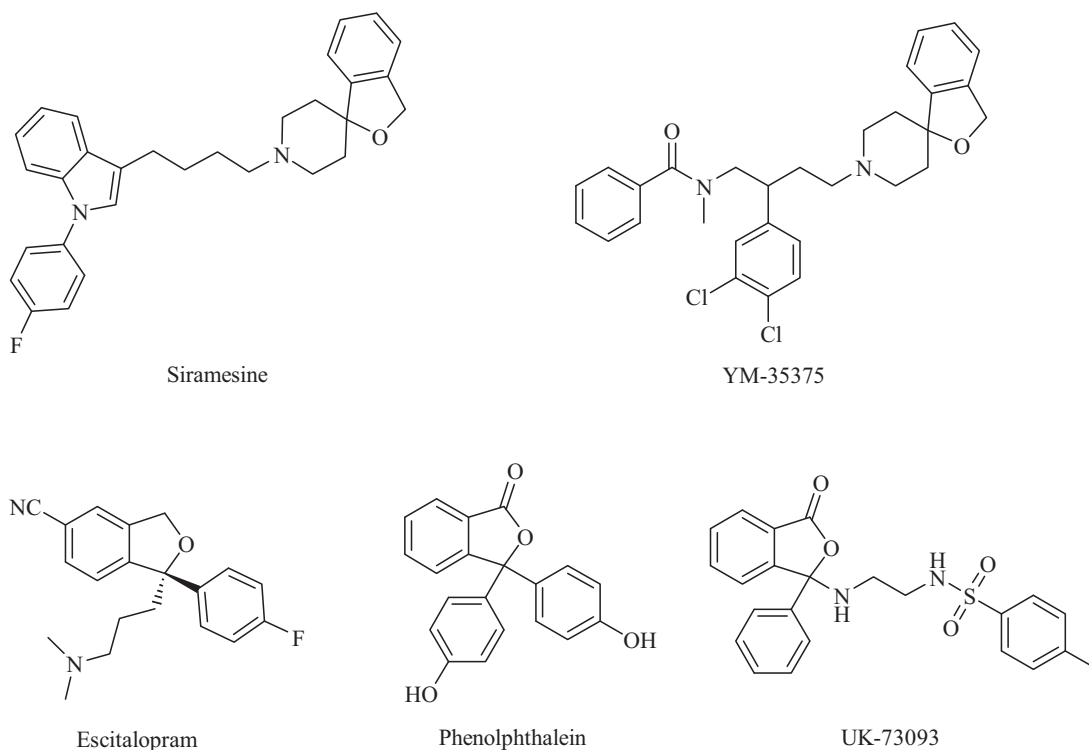E-mail address: jimin@seu.edu.cn (M. Ji).

Fig. 1. Structures of isobenzofuran drugs.

the solvent was removed under reduced pressure. Ethyl acetate was added to the residue and filtered over celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain the 2-benzoylbenzaldehyde as a white solid. (iii) The 2-benzoylbenzaldehyde (1 mmol) was dissolved in 10 mL methanol at room temperature. NaBH$_4$ (0.5 mmol) was added to the solution followed by 1 drop of pyridine and then the mixture was stirred 5 h at room temperature. The solvent was removed under reduced pressure and 0.5 mL hydrochloric acid was added to the residue. The mixture was extracted three times with ethyl acetate. The combined organic phase was distilled under reduced pressure. The residue was used without further purification. The residue was dissolved in 10 mL toluene and p-toluenesulfonic acid (0.1 mmol) was added. The resulting mixture was stirred 3 h under reflux. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give compound 5a.

1-Phenyl-1,3-dihydroisobenzofuran (5a): ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21 (m, 8H), 6.95 (d, 1H, J = 8.0 Hz), 6.09 (s, 1H), 5.27 (d, 1H, J = 12.1 Hz), 5.19 (d, 1H, J = 12.1 Hz). ^{13}C NMR (75 MHz, CDCl$_3$): δ 142.5, 142.3, 139.5, 129.0, 128.4, 128.0, 127.9, 127.4, 122.4, 121.3, 86.3, 73.4. Anal. calcd. (%) for C$_{14}$H$_{12}$O: C 85.68, H 6.16; found: C 85.79, H 6.08.

1-(3-Chlorophenyl)-1,3-dihydroisobenzofuran (5b): ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.24 (m, 7H), 7.03 (d, 1H, J = 7.3 Hz), 6.12 (s, 1H), 5.31 (d, 1H, J = 12.2 Hz), 5.20 (d, 1H, J = 12.2 Hz). ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.3, 141.3, 138.9, 134.5, 129.8, 128.1, 127.8, 127.6, 126.9, 124.9, 122.1, 121.0, 85.4, 73.4. Anal. calcd. (%) for C$_{14}$H$_{11}$ClO: C 72.89, H 4.81; found: C 72.80, H 4.95. MS (ESI): m/z 253 [M+Na]$^+$.

1-(3-Nitrophenyl)-1,3-dihydroisobenzofuran (5c): ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.21 (s, 1H), 8.14 (d, 1H, J = 8.1 Hz), 7.69 (d, 1H, J = 7.6 Hz), 7.51 (m, 1H), 7.32 (m, 2H), 7.24 (m, 1H), 7.03 (d, 1H, J = 7.6 Hz), 6.25 (s, 1H), 5.38 (d, 1H, J = 12.2 Hz), 5.24 (d, 1H, J = 12.2 Hz). ^{13}C NMR (75 MHz, CDCl$_3$): δ 148.4, 144.5, 140.7, 138.8, 132.7, 129.5, 128.1, 127.7, 122.9, 121.9, 121.6, 121.2, 85.0, 73.6.

Anal. calcd. (%) for C$_{14}$H$_{11}$NO$_3$: C 69.70, H 4.60, N 5.81; found: C 69.86, H 4.75, N 5.88. MS (ESI): m/z 264 [M+Na]$^+$.

1-(4-Chlorophenyl)-1,3-dihydroisobenzofuran (5d): ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.25 (m, 7H), 6.99 (d, 1H, J = 7.3 Hz), 6.12 (s, 1H), 5.31 (d, 1H, J = 12.2 Hz), 5.18 (d, 1H, J = 12.2 Hz). ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.5, 140.7, 139.0, 133.8, 128.7, 128.3, 127.8, 127.6, 122.1, 121.0, 85.4, 73.3. Anal. calcd. (%) for C$_{14}$H$_{11}$ClO: C 72.89, H 4.81; found: C 72.76, H 4.93. MS (ESI): m/z 253 [M+Na]$^+$.

1-(4-Nitrophenyl)-1,3-dihydroisobenzofuran (5e): ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.21 (m, 2H), 7.53 (m, 2H), 7.16 (m, 4H), 6.24 (s, 1H), 5.35 (d, 1H, J = 12.2 Hz), 5.21 (d, 1H, J = 12.2 Hz). ^{13}C NMR (75 MHz, CDCl$_3$): δ 148.5, 145.1, 141.6, 138.1, 132.4, 130.5, 129.3, 129.2, 128.9, 122.4, 85.1, 73.7. Anal. calcd. (%) for C$_{14}$H$_{11}$NO$_3$: C 69.70, H 4.60, N 5.81; found: C 69.58, H 4.77, N 5.64. MS (ESI): m/z 264 [M+Na]$^+$.

5-Bromo-1-phenyl-1,3-dihydroisobenzofuran (5f): ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.41 (s, 1H), 7.31 (m, 6H), 6.88 (d, 1H, J = 8.0 Hz), 6.09 (s, 1H), 5.28 (d, 1H, J = 12.5 Hz), 5.15 (d, 1H, J = 12.5 Hz). ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.6, 141.5, 141.2, 130.6, 128.6, 128.3, 126.9, 124.2, 123.8, 121.5, 85.9, 72.6. Anal. calcd. (%) for C$_{14}$H$_{11}$BrO: C 61.11, H 4.03; found: C 61.34, H 3.96. MS (ESI): m/z 273, 275 [M−1]$^-$.

5-Bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran (5g): ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.49 (s, 1H), 7.42 (d, 1H, J = 8.1 Hz), 7.32 (m, 2H), 7.10 (t, 2H, J = 8.6 Hz), 6.92 (d, 1H, J = 8.0 Hz), 6.13 (s, 1H), 5.33 (d, 1H, J = 12.5 Hz), 5.20 (d, 1H, J = 12.5 Hz). ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.6, 141.0, 130.7, 128.9, 128.7, 124.3, 123.8, 121.7, 115.7, 115.4, 85.3, 72.5. Anal. calcd. (%) for C$_{14}$H$_{10}$BrFO: C 57.36, H 3.44; found: C 57.28, H 3.57. MS (ESI): m/z 291, 293 [M−1]$^-$.

3. Results and discussion

In our initial investigation, functional salicylaldehydes were used to give analogs of intermediate 3 (Scheme 1). This preparation of N-acylhydrazones of o-hydroxybenzaldehydes proceeded