Tetrahedron Letters 52 (2011) 1557–1560

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A convenient synthesis of benzofuro[3,2-*c*]isoquinolines and naphtho[1′,2′:4,5]furo[3,2-*c*]isoquinolines

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ARTICLE INFO

Article history:
Received 28 June 2010
Revised 9 December 2010
Accepted 17 December 2010
Available online 24 December 2010

ABSTRACT

A convenient method for the preparation of benzofuro[3,2-*c*]isoquinoline derivatives is described. The condensation reaction of methyl 2-(chloromethyl)-benzoate with substituted salicylonitriles **7a–c** and intramolecular cyclization of the resulting substituted methyl 2-[(2-cyanobenzyl)oxy]benzoates **10a–c** using potassium *tert*-butoxide results in the substituted benzofuro[3,2-*c*]isoquinolin-5(6*H*)-ones **1a–c**. The same sequence of reactions starting from 2-(chloromethyl)benzonitrile and compounds **7a–c** gave substituted 5-aminobenzofuro[3,2-*c*]isoquinolines **13a–c**. In addition, this method is useful for the synthesis of other heterocycles. For example, using 1-cyano-2-naphthol **16,** instead of the salicylonitriles **7a–c**, gives naphtho[1′,2′:4,5]furo[3,2-*c*]isoquinolines.

1. Introduction

Cell necrosis observed in inflammatory diseases, such as arthritis, colitis and autoimmune diabetes, and in reperfusion diseases, such as stroke and heart attack involves activation of the nuclear enzyme poly (ADP-ribose) synthetase (PARS). This activation is an important step in the cell-mediated death observed in inflammation and reperfusion diseases,[1] and the search for new PARS inhibitors and methods for their synthesis has gained much interest.

Preclinical tests[2] on benzofuro[3,2-*c*]isoquinolin-5(6*H*)-one (**1a**) have demonstrated PARS inhibitor activity, and potential ability for the treatment and prevention of inflammatory diseases, such as arthritis, rheumatoid arthritis, diabetes, osteoarthritis, and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis and ulcerative colitis; asthma, and inflammatory diseases of the eye including corneal dystrophy and trachoma; reperfusion disease, such as myocardial infarction or stroke. This compound also demonstrated very low or no peripheral toxicity.[2]

There are a few reported methods for the synthesis of benzofuroisoquinolinone **1a**. One example[3] requires a multistage process involving the condensation of diethyl α-bromohomophthalate (**2**) with methyl salicylate (**3**) to afford ester **4**, which was converted into the acid **5** via alkaline cyclization. Thermolysis of **5** gave the corresponding benzofuroisocoumarin **6**. Benzofuroisoquinolinone **1a** was obtained by treatment of **6** with gaseous ammonia at 100 °C for 24 h in a sealed tube (Scheme 1).[3]

The second method involved the condensation of **2** with salicylonitrile (**7**) under the action of anhydrous potassium carbonate in acetone, which gave a mixture of nitrile **8** (65%) and benzofuroisoquinolinone **1a** (6%)[4] (Scheme 2).

Compound **8** was converted into benzofuroisoquinolinone **1a** by a treatment with sodium hydride in refluxing toluene. Furthermore, the condensation of **2** with **7** using triethylamine in refluxing acetonitrile for 24 h gave **1a** in 47% yield.[5]

These methods have the disadvantages of long reaction times and poor to moderate overall yields of **1a**.

Herein, we describe a convenient method for the synthesis of substituted benzofuro[3,2-*c*]isoquinolin-5(6*H*)-ones **1a–c,** which involves the condensation of methyl 2-(chloromethyl)benzoate[6] (**9**) with salicylonitrile (**7a**), 5-methylsalicylonitrile[7] (**7b**), or 5-chlorosalicylonitrile[8] (**7c**) in the presence of anhydrous potassium carbonate in DMF to afford the substituted methyl 2-[(2-cyanobenzyl)oxy]benzoates **10a–c**. Products **1a–c** were obtained by treating **10a–c** with potassium *tert*-butoxide in DMF (Scheme 3).

This method is useful for the preparation of other benzofuro[3,2-*c*]isoquinoline derivatives. The condensation reactions of 2-(chloromethyl)benzonitrile[9] (**11**) with salicylonitriles **7a–c** gave 2-[(2-cyanobenzyl)oxy]benzonitriles **12a–c**. Subsequent treatment of **12a–c** with potassium *tert*-butoxide in DMF afforded 5-aminobenzofuro[3,2-*c*]isoquinolines **13a–c** in good yields (Scheme 4).

We propose that the mechanism of the intramolecular cyclization of compounds **10** and **12** proceeds via a domino reaction, which involves the formation of benzofuran intermediates **14** or **15** by Thorpe–Ziegler reaction, and subsequent annulation to give benzofuro[3,2-*c*]isoquinolines **1** or **13** (Scheme 5).

This method for the preparation of benzofuro[3,2-*c*]isoquinolines **1a–c** and **13a–c** can also be used for the synthesis of other heterocyclic systems. For example, the same sequence of reactions

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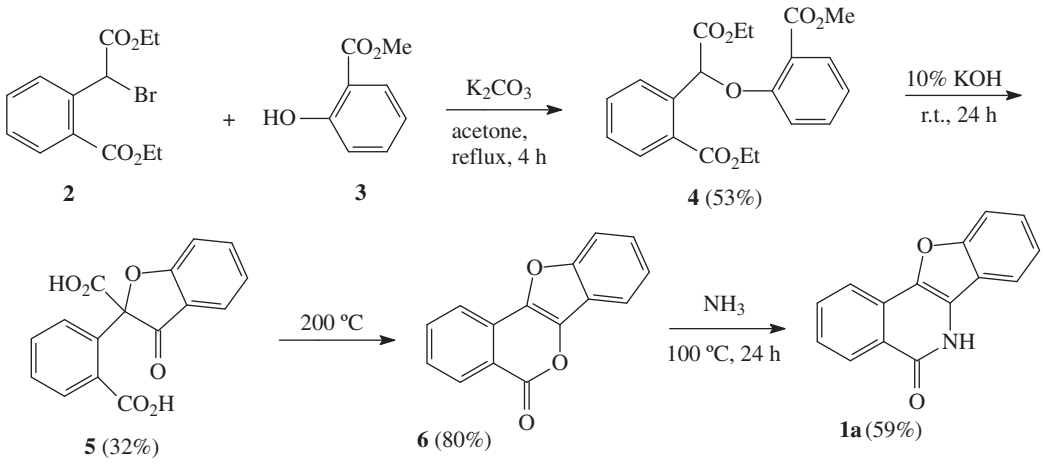
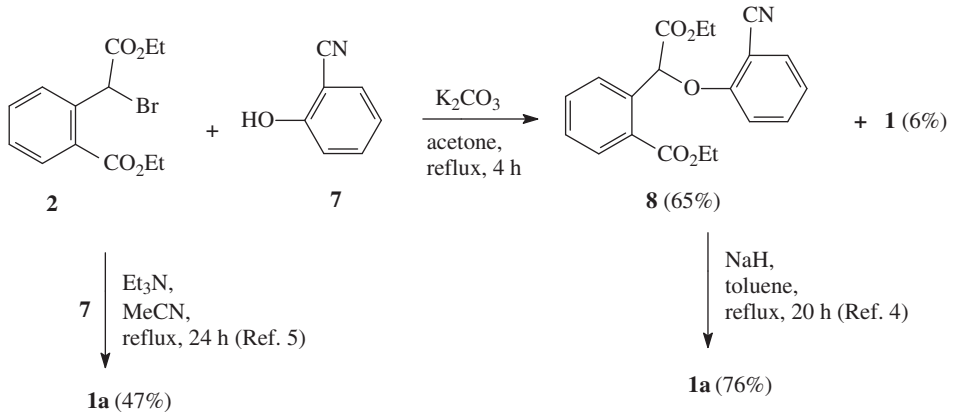
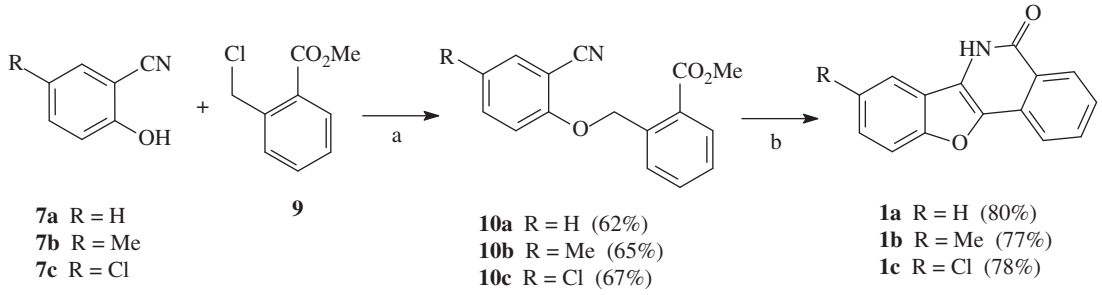
0040-4039/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.12.080



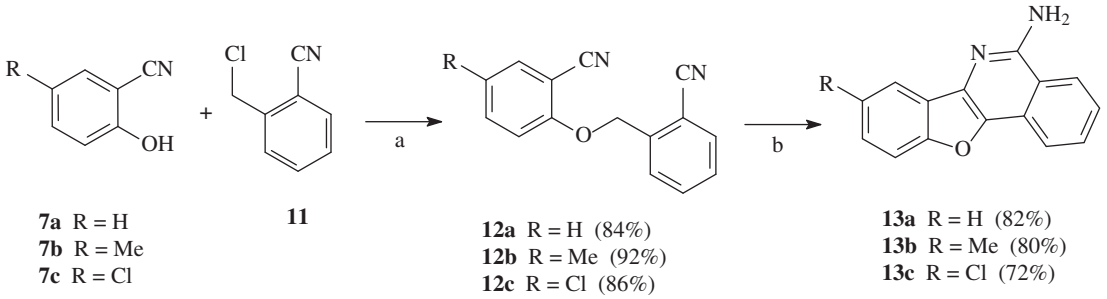
Scheme 1.



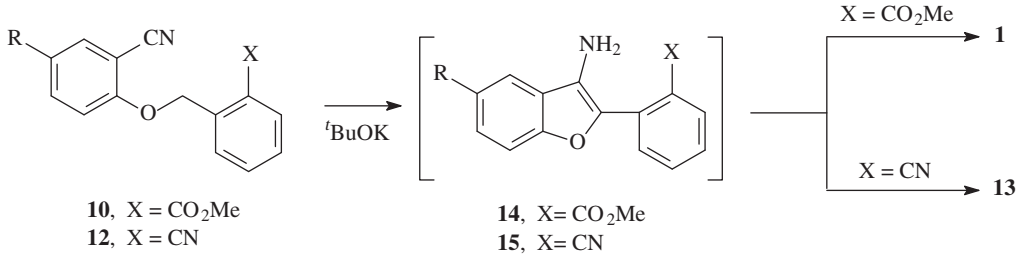
Scheme 2.



Scheme 3. Reagents and conditions: (a) 2 equiv K_2CO_3, DMF, 50–55 °C, 40 min; (b) 1.5 equiv ^tBuOK, DMF, 40 °C, 30 min.



Scheme 4. Reagents and conditions: (a) 2 equiv K_2CO_3, DMF, 50–55 °C, 40 min; (b) 1 equiv ^tBuOK, DMF, 40 °C, 30 min.



Scheme 5. Proposed mechanism for the formation of benzofuro[3,2-*c*]isoquinolines **1** and **13**.

starting from 1-cyano-2-naphthol[10] (**16**) and methyl 2-(chloromethyl)benzoate (**9**) or 2-(chloromethyl)benzonitrile (**11**) gave naphtho[1′,2′:4,5]furo[3,2-*c*]isoquinoline-5(6*H*)-on (**18**) or 5-amino naphtho[1′,2′:4,5]furo[3,2-*c*]isoquinoline (**20**) in good yields (Scheme 6).

In conclusion, we have developed a convenient method for the synthesis of benzofuro[3,2-*c*]isoquinolines **1a–c** and **13a–c** in good yields and short reaction times, using substituted salicylonitriles **7a–c** and methyl 2-(chloromethyl)benzoate (**9**) or 2-(chloromethyl)benzonitrile (**11**) as starting materials. This method was also useful for the synthesis of novel fused naphtho[1′,2′:4,5]furo[3,2-*c*]isoquinoline heterocycles **18** and **20**.

1.1. General procedure for the synthesis of compounds 10a–c and 17

To a solution of **7a–c** or **16** (4 mmol) and methyl 2-(chloromethyl)benzoate[6] (**9**) (0.74 g, 4 mmol) in DMF (4 ml) was added dry K_2CO_3 (1.1 g, 8 mmol). The mixture was stirred at 50–55 °C for 40 min, poured into H_2O (30 ml), and extracted with $CHCl_3$ (15 ml × 3). The extract was washed with H_2O (20 ml × 2) and dried over Na_2SO_4. The solvent was evaporated in vacuo and the product crystallized from an appropriate solvent.

1.1.1. Compound 10a

Yield 62%, mp 96–97 °C ($CHCl_3$–hexane). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 5.56 (s, 2H, OCH_2), 7.11 (t, J = 7.3 Hz, 1H, ArH), 7.27 (d, J = 8.1 Hz, 1H, ArH), 7.51 (t, J = 8.8 Hz, 1H, ArH), 7.69 (m, 4H, ArH), 7.93 (d, J = 7.3 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 52.68, 69.13, 100.97, 113.71, 116.81, 121.93, 129.02, 129.22, 129.41, 130.90, 133.00, 134.18, 135.69, 137.05, 160.29, 167.47. IR (KBr) ν: 2948, 2224, 1720, 1584, 1496, 1260, 1024, 748 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.86; H, 4.61; N, 4.53.

1.2. General procedure for the synthesis of compounds 1a–c and 18

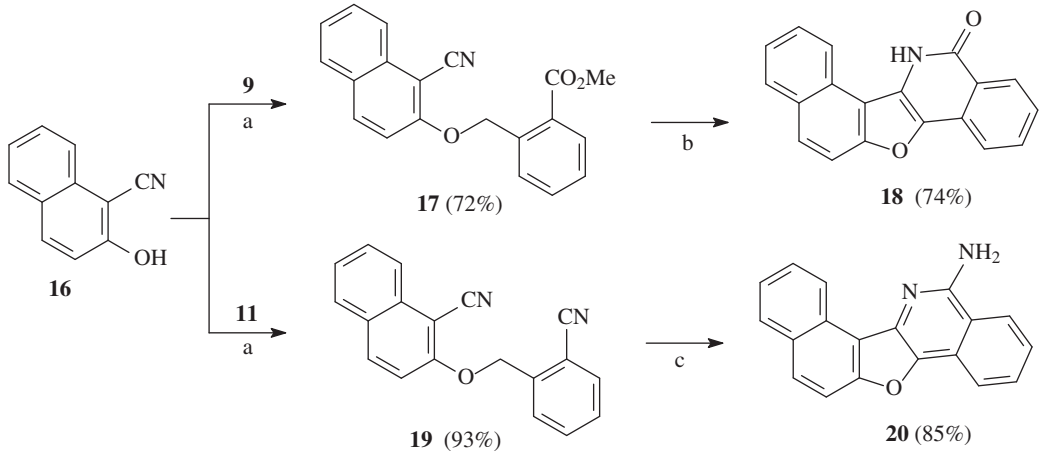
To a solution of **10a–c** or **17** (3 mmol) in DMF (3 ml) was added ^{t}BuOK (0.5 g, 4.5 mmol). The mixture was stirred at 40 °C for 30 min and then poured into a mixture of H_2O (30 ml) and AcOH (0.5 ml). The resulting crystals were filtered, washed with H_2O, dried, and recrystallized from an appropriate solvent.

1.2.1. Compound 1a

Yield 80%, mp 304–305 °C (DMF–MeOH) [Lit.[3] 310 °C (EtOH)]. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.39 (t, J = 7.3 Hz, 1H, H-8), 7.48 (t, J = 8.1 Hz, 1H, H-9), 7.60 (t, J = 7.3 Hz, 1H, H-2), 7.72 (d, J = 8.1 Hz, 1H, H-10), 7.88 (t, J = 7.3 Hz, 1H, H-3), 8.02 (m, 2H, H-1, H-7), 8.33 (d, J = 8.1 Hz, 1H, H-4), 12.33 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 112.64, 119.69, 120.05, 120.33, 122.17, 124.02, 124.83, 127.44, 127.58, 128.17, 129.07, 133.95, 135.93, 154.73, 161.89. IR (KBr) ν: 1652, 1640, 1604, 1588, 1548, 1456, 1352, 1324, 1208, 1060, 860, 764, 740 cm^{-1}. Anal. Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found: C, 76.66; H, 3.74; N, 5.83.

1.3. General procedure for the synthesis of compounds 12a–c and 19

To a stirred solution of **7a–c** or **16** (4 mmol) and 2-(chloromethyl)benzonitrile[9] (**11**) (0.6 g, 4 mmol) in DMF (4 ml) was added dry K_2CO_3 (1.1 g, 8 mmol). The mixture was stirred at 50–55 °C for 40 min, poured into H_2O (30 ml), and extracted with $CHCl_3$ (15 ml × 3). The extract was washed with H_2O (20 ml × 2) and



Scheme 6. Reagents and conditions: (a) 2 equiv K_2CO_3, DMF, 50–55 °C, 40 min; (b) 1.5 equiv ^{t}BuOK, DMF, 40 °C, 30 min; (c) 1 equiv ^{t}BuOK, DMF, 40 °C.

dried over Na_2SO_4. The solvent was evaporated in vacuo and the product crystallized from an appropriate solvent.

1.3.1. Compound 12a

Yield 84%, mp 130–131 °C ($CHCl_3$–hexane). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.10 (s, 2H, OCH_2), 7.15 (t, J = 8.1 Hz, 1H, ArH), 7.40 (d, J = 8.1 Hz, 1H, ArH), 7.61(td, J_1 = 8.1 Hz, J_2 = 2.2 Hz, 1H, ArH), 7.71 (t, J = 7.3 Hz, 1H, ArH), 7.76 (m, 3H, ArH), 7.94 (d, J = 7.3 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6) δ 68.34, 113.36, 116.05, 121.72, 129.42, 133.33, 133.49, 133.80, 135.09, 138.94, 159.43. IR (KBr) ν: 3072, 2224, 1596, 1496, 1444, 1260, 1036, 760, 752 cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 76.78; H, 4.22; N, 12.07.

1.4. General procedure for the synthesis of compounds 13a–c and 20

To a stirred solution of **12a–c** or **19** (3 mmol) in DMF (3 ml) was added ^{t}BuOK (0.337 g, 3 mmol). The mixture was stirred at 40 °C for 30 min and then poured into H_2O (30 ml). The resulting crystals were filtered, dried in air, and recrystallized from an appropriate solvent.

1.4.1. Compound 13a

Yield 82%, mp 214–215 °C (DMF–MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.89 (s, 2H, NH_2), 7.39 (t, J = 7.3 Hz, 1H, H-8), 7.49 (t, J = 7.3 Hz, 1H, H-9), 7.60 (t, J = 7.3 Hz, 1H, H-2), 7.74 (d, J = 7.3 Hz, 1H, H-10), 7.85 (t, J = 7.3 Hz, 1H, H-3), 7.95 (d, J = 6.6 Hz, 1H, H-7), 8.16 (d, J = 7.3 Hz, 1H, H-1), 8.38 (d, J = 8.1 Hz, 1H, H-4). ^{13}C NMR (75 MHz, DMSO-d_6) δ 112.05, 117.30, 119.36, 119.65, 123.07, 124.34, 125.02, 125.53, 125.77, 126.49, 130.93, 133.04, 138.71, 155.34, 155.58; IR (KBr) ν: 3308, 3226, 3176, 3060, 1636, 1568, 1420, 1212, 748 cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 77.08; H, 4.17; N, 11.80.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.080.

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