A practical synthesis of 1-cyano-4,5-dimethoxybenzocyclobutene

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A practical synthesis of 1-cyano-4,5-dimethoxybenzocyclobutene, the key intermediate of Ivabradine, was developed in four or five steps using two different routes. 2-Bromo-4,5-dimethoxyhydrocinnamonitrile was produced via the condensation of 2-bromo-4,5-dimethoxybenzaldehyde with acetonitrile or cyanoacetic acid and reduction by $NaBH_4$. Cyclisation gave 1-cyano-4,5-dimethoxybenzocyclobutene. Overall yields of the routes A and B were 30% and 37% respectively. Route B is a short and simple route, permitting the synthesis of 1-cyano-4,5-dimethoxybenzocyclobutene on a large scale.

Keywords: ivabradine, 1-cyano-4,5-dimethoxybenzocyclobutene, condensation, reduction

Angina pectoris is very common in the elderly. Ivabradine (**1**) (Procoralan, Servier) is a potent bradycardic agent which has been approved for the treatment of ischaemic heart disease, congestive heart failure and angina pectoris.[1,2] It is the first representative of a new class of selective agents for reducing heart rate which inhibit the I_f current in the sinoatrial node.[3,4] 1-Cyano-4,5-dimethoxybenzocyclobutene **2** is a key intermediate in the synthesis of Ivabradine (Fig. 1).

The first synthetic route to **2**, reported in 1972 by Paull,[5] involved three steps from 3,4-dimethoxycinnamonitrile by hydrogenation, bromination and ring closing reaction. In 1973, Kametani[6] also published a four-step procedure from 2-bromo-4,5-dimethoxybenzaldehyde **4** by the condensation with cyanoacetic acid, reduction, decarboxylation, and ring closing reaction.[6] In 1982, Schiess and coworkers reported[7] the formation of substituted benzocyclobutanes by flash vacuum pyrolysis using 2-methyl-4,5-dimethoxybenzaldehyde as the starting material. However, these methods required harsh conditions that lead to lower yields and were expensive.

Recently, our research group has been interested in developing a large-scale preparation of 1-cyano-4,5-dimethoxybenzocyclobutene **2**. We now present two synthetic routes, A and B, as shown in Fig. 2 starting from 3,4-dimethoxybenzaldehyde **3.**

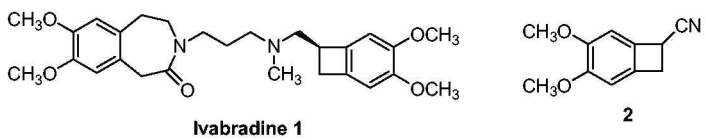
In route A, the procedure described by Kametani in 1973,[5] was used with some modification. The starting compound, 3,4-dimethoxybenzaldehyde **3** was brominated with bromine according to the procedure of Charlton[8] at 50 °C to afford 2-bromo-4,5-dimethoxybenzaldehyde **4** in 87% yield. Without purification, compound **4** was directly condensed with cyanoacetic acid in xylene using the Dean–Stark reaction setup to provide 3-(2-bromo-4,5-dimethoxyphenyl)-2-cyanoacrylic acid **5** in 64% yield. 3-(2-Bromo-4,5-dimethoxyphenyl)-2-cyanopropionic acid **6** was obtained by reduction of the cyanoacrylic acid **5** with $NaBH_4$. The determining step in this procedure was the condensation of benzaldehyde **4** with cyanoacetic acid. Because of the long reaction time, there was a possibility of forming impurities in the starting material **4**. At this stage, we used a higher boiling solvent xylene instead of toluene to make sure this reaction was complete. Subsequently decarboxylation of **6** in dimethylacetamide produced hydrocinnamonitrile **8** in 51% yield for two steps. Finally ring closing reaction,[8] the target molecule **2** was obtained in 74% yield and 98% purity assessed by high-performance liquid chromatography (HPLC). In this procedure, the decarboxylation of compound **5** yielded compound **7** which was also used in route B. This has the disadvantage of being a longer route and it is highly expensive. Thus the alternative route B was developed in our laboratories.

Route B began by condensing **4** with acetonitrile in the presence of sodium hydroxide under reflux to provide cinnamonitrile **7** in good yield. The cinnamonitrile **7** has the (*E*)-configuration as demonstrated by coupling constants (J = 16.4 Hz) for the signals of the two vinylic protons at δ = 5.68 ppm and 7.66 ppm. Attempts to carry out the reduction reaction with $NaBH_4$ and Lewis acids did not give satisfactory results. Compound **7** was then reduced with $NaBH_4$ in a mixture of pyridine and methanol, to give **8** by in 82% yield.[9] After the ring closure reaction, **2** was obtained as a colourless powder. The highlight of this method lies on the condensation between acetonitrile and aldehyde **4**, and on its reduction by $NaBH_4$ in the system of pyridine and methanol. Product **2** was isolated in 37% overall yield and 98% HPLC purity by this synthetic route.

In conclusion, a practical synthesis of 1-cyano-4,5-dimethoxybenzocyclobutene, the key intermediate of Ivabradine, was developed in four or five sequences steps using two different routes. The 2-bromo-4,5-dimethoxyhydrocinnamonitrile fragment could be produced successfully via the condensation of 2-bromo-4,5-dimethoxybenzaldehyde with acetonitrile and reduction by $NaBH_4$ in a mixture of pyridine and methanol. A ring closure reaction gave 1-cyano-4,5-dimethoxybenzocyclobutene. We found that route B was more efficient than route A for the synthesis of compound **2,** as it involves shorter reaction times and gives a better overall yield. Although the early decarboxylation in route A gives higher yields compared to the reaction performing the decarboxylation at a later step, it is still inferior to the route B. Route B involves easy to handle chemicals and can be carried out on the kilogram scale.

Experimental

All chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Melting points were determined with a RY-1 apparatus, and were uncorrected.



Ivabradine 1 **2**

Fig. 1 The structures of Ivabradine **1** and its intermediate **2.**

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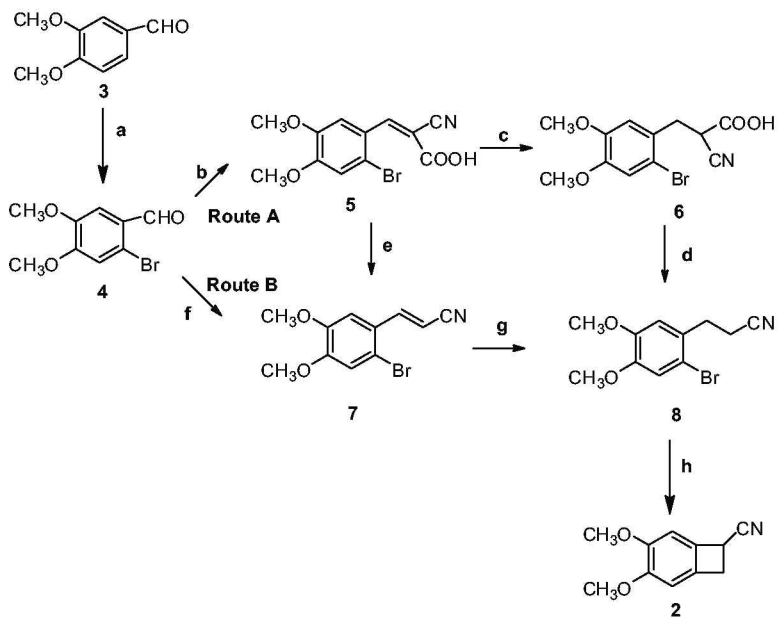

Fig. 2 Reagents and conditions: (a) Br_2/CH_3COOH, 50 °C, 6 h; (b) Cyanoacetic acid/Ammonium acetate/Xylene/Pyridine, reflux, 12 h; (c) $NaBH_4/NaHCO_3$, r.t., 12 h; (d) dimethylacetamide, 170 °C, 2 h; (e) dimethylacetamide, 170 °C, 2 h; (f) $CH_3CN/NaOH$, reflux, 8 h; (g) $NaBH_4$/Pyridine/CH_3OH, reflux, 2 h; (h) $NaNH_2$/liquid NH_3, –45 °C, 2 h.

IR spectra were determined as KBr pellets on a Shimadzu model 470 spectrometer. ^1H NMR spectra were recorded using a Bruker AV 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6 with tetramethylsilane as the internal standard. The mass spectra were recorded on Shimadzu QP 2010 system. Elemental analyses were performed on a Vario EL III elemental analyser. All the products except for compound **7** were known compounds and the data (m.p., ^1H NMR) accord with that reported in the literature.

2-bromo-4,5-dimethoxybenzaldehyde (**4**): Bromine (30.8 mL, 0.6 mol) was added dropwise with stirring at room temperature over 30 min to a solution of 3,4-dimethoxybenzaldehyde (**3**, 100.0 g, 0.60 mol) in acetic acid (400 mL). The reaction mixture was stirred at 50 °C for 6 h. After cooling to room temperature, water (500 mL) was added, the precipitate was filtered, and the excess bromine was washed away with water several times. The product was dried under vacuum to give the crude product **4** as white solid. This product was used directly in the next step. Crude yield 126.6 g (87%); m.p. 151–152 °C (lit.[8]: m.p. 148–150 °C).

3-(2-Bromo-4,5-dimethoxyphenyl)-2-cyanoacrylic acid (**5**): Ammonium acetate (41.6g, 0.54 mol) was added in portions to a solution of 2-bromo-4,5-dimethoxybenzaldehyde **4** (122.0 g, 0.50 mol) and cyanoacetic acid (46.8 g, 0.55 mol) in xylene (500 mL) and pyridine (100 mL) at room temperature. This reaction mixture was then heated under reflux for 12 h using a Dean and Stark apparatus. After the calculated amount of water had separated, the mixture was cooled and acidified with 10% HCl. Yellow crystals separated out slowly, and were collected, Recrystallisation from EtOH to give the title compound **5** as pale yellow needles. Yield 89.0 g (64%); m.p. 266–268 °C (lit.[6]: m.p. 272–272.5 °C).

3-(2-Bromo-4,5-dimethoxyphenyl)-2-cyanopropionic acid (**6**): 3-(2-Bromo-4,5-dimethoxyphenyl)-2-cyanoacrylic acid **7** (120.0 g, 0.38 mol) was added to a saturated $NaHCO_3$ solution (800 mL) at room temperature. Then sodium borohydride (28.9 g, 0.76 mol) was added in small portions, producing effervescence and the stirring was continued for 4 h. Acidification with 10% HCl solution produced white crystals. The precipitate was collected to give the title product **6** as colourless crystals. Yield 86.4 g (72%); m.p. 165–167 °C (lit.[6]: m.p. 166–168 °C). IR (cm^{-1}): 2228 (CN). ^1H NMR: δ 3.16–3.28 (m,2H), 3.74 (s, 3H), 3.77 (s, 3H), 4.28 (t, 1H, J = 8.4 Hz), 7.08 (s, 1H), 7.14 (s, 1H), 13.84 (brs, 1H).

2-Bromo-4,5-dimethoxycinnamonitrile (**7**)

Route A procedure: A suspension of cyanoacrylic acid **5** (150.0 g, 0.48 mol) in dimethylacetamide (500 mL), was heated at 170 °C. Evolution of CO_2 ceased after 30 min. The reaction mixture was poured into water (500 mL) and set aside overnight. The crystals which separated were collected, washed with water, and recrystallised from ethanol to obtain colourless crystals of **7**. Yield 91.8 g (71%). m.p. 147–148 °C.

Route B procedure: 2-Bromo-4,5-dimethoxybenzaldehyde **4** (200.0 g, 0.82 mol) was dissolved in acetonitrile (800 mL) and heated to reflux. Then sodium hydroxide (39.3 g, 0.98 mol) was added in batches, and the reaction mixture was refluxed for 8 h. After the solvent was removed *in vacuo*, the residue was diluted with water (800 mL), and the product was extracted with ethyl acetate (600 mL × 3). The organic layer was washed with water (300 mL × 2), and dried over $MgSO_4$. The solvent was removed under vacuum, followed by recrystallisation of the residue from EtOH to give compound **7**. Yield 156.0 g (71%). m.p. 147–148 °C. IR (cm^{-1}): 2230 (CN), 1612 (C=C). ^1H NMR: δ 3.84 (s, 6H), 5.68 (d, 1H, J = 16.4 Hz), 6.88 (s, 1H), 7.00 (s, 1H), 7.66 (d, 1H, J = 16.4 Hz). MS (EI, *m/z*): 267/269 (M^+, 100/98), 252, 224, 145, 130, 117, 102, 75. Anal. Calcd. for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.02; H, 3.98; N, 4.99%.

2-Bromo-4,5-dimethoxyhydrocinnamonitrile (**8**)

Route A procedure: A suspension of 3-(2-bromo-4,5-dimethoxyphenyl)-2-cyanopropionic acid **6** (120.0 g, 0.38 mol) in dimethylacetamide (500 mL) was heated at 170 °C for 2 h. The evolution of the calculated amount of CO_2 ceased after 30 min. The reaction mixture was poured into water (500 mL), and set aside overnight. The crystals which separated were collected, washed with water, and recrystallised from ethanol to obtain a white powder **8**. Yield 83.9 g (81.4%). m.p. 76–78 °C (lit.[6]: m.p. 79–80 °C). Purity by HPLC: 96.5%.

Route B procedure: 2-Bromo-4,5-dimethoxycinnamonitrile **7** (80.0 g, 0.30 mol) was dissolved in a mixture of methanol (320 mL) and pyridine(80 mL). $NaBH_4$ (22.8 g, 0.60 mol) was added in small portions. The reaction mixture was refluxed for 2 h. When the reaction was complete it was cooled to room temperature, and 10% HCl solution was added to acidify the reaction mixture. The product was extracted with ethyl acetate (150 mL × 3), and the organic layer separated and washed with water (120 ml × 2), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was recrystallised from EtOH to provide **8** as white crystals. Yield 65.7 g (81%); m.p. 75–77 °C (lit.[6]: m.p.79–80 °C). IR (cm^{-1}): 2239 (CN). ^1H NMR: δ 2.57 (t, 2H, J = 7.3 Hz), 2.93 (t, 2H, J = 7.3 Hz), 3.78 (s, 3H), 3.79 (s, 3H), 6.73 (s, 1H), 6.94 (s, 1H); Purity by HPLC: 97.5%.

1-Cyano-4,5-dimethoxybenzocyclobutene (**2**): $NaNH_2$ (39.0 g, 1.0 mol) was added in portions to a solution of hydrocinnamonitrile **8** (224.0 g, 0.83 mol) in liquid ammonia at –45 °C, and the reaction mixture was stirred at –45 °C for 2 h. After evaporation of the excess NH_3, NH_4Cl (20.0 g) and water (1000 mL) were added in portions. After standing at room temperature, greyish crystals separated and were collected and recrystallised with ethanol to give the title compound **2** as a colourless powder. Yield 116.5 g (74%); m.p. 79–81 °C (lit.[5]: m.p. 83–84 °C). IR (cm^{-1}): 2232 (CN). ^1H NMR:δ3.31–3.35 (m,1H), 3.52–3.57 (m, 1H), 3.73 (s, 6H), 4.45 (t, 1H, J = 7.6 Hz), 6.86 (s, 1H), 6.96 (s, 1H). MS (EI, *m/z*): 189 (M^+, 100), 174, 146, 116, 91, 76. Purity by HPLC: 98.2%.

The authors are grateful to Mr Junzhi Luo at Shanghai utopharm Co. Ltd. for providing necessary support.

Received 3 May 2009; accepted 27 May 2009
Paper 09/0561 *doi: 10.3184/030823409X4655259*
Published online: 14 July 2009

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