# **RSC Advances**



View Article Online

View Journal | View Issue

# PAPER

Check for updates

Cite this: RSC Adv., 2018, 8, 6146

# An efficient route to *N*-alkylated 3,4dihydroisoquinolinones with substituents at the 3position<sup>+</sup>

A facile synthetic procedure for the production of N-alkylated 3,4-dihydroisoguinolinone derivatives is

described. The desired products were obtained by N-alkylation of 3,3'-dimethyl-3,4-dihydroisoquinoline

Aoi Tazawa,<sup>ab</sup> Junki Ando,<sup>a</sup> Kohei Ishizawa,<sup>a</sup> Isao Azumaya,<sup>b</sup> \*<sup>b</sup> Hidemasa Hikawa <sup>b</sup> and Minoru Tanaka<sup>\*a</sup>

Received 25th December 2017 Accepted 31st January 2018

DOI: 10.1039/c7ra13627g

rsc.li/rsc-advances

# derivatives followed by oxidation of the resulting iminium salts. Reaction conditions for both steps were very mild and the desired cyclization products could be obtained in good yield. This strategy allows the generation of *N*-substituted 3,4-dihydroisoquinolinone derivatives with substituents at the 3-position.

# Introduction

3,4-Dihydroisoquinolinone **1** is an important member of the class containing a core structure found in compounds that exhibit biological and pharmacological properties, such as antinausea/vomiting,<sup>1</sup> antidiabetic,<sup>2,3</sup> and antiallergy/antiasthmatic<sup>4</sup> activities. Some examples of pharmacologically active compounds that include the dihydroisoquinolinone moiety are shown in Fig. 1. Its suitable size and moderate polarity as a pharmacophore make 3,4-dihydroisoquinolinone



 Fig.
 1
 Representative
 pharmacologically
 active

 dihydroisoquinolinones.

"Sohyaku Innovative Research Division, Mitsubishi Tanabe Pharma Corporation, 1000 Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-0033, Japan. E-mail: tanaka.

<sup>b</sup>Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi,

available.

See

DOI:

Chiba 274-8510, Japan. E-mail: isao.azumaya@phar.toho-u.ac.jp

† Electronic supplementary information (ESI)

a suitable scaffold that has been widely used in various drug candidates. For 3,4-dihydroisoquinolinone derivatives, the introduction of substituents at the 3-position generally improve their biostability<sup>5</sup> because the substituent prevents oxidation of the unsubstituted 3-position. Nevertheless, only a few methods for effective preparation of *N*-alkylated 3,4-dihydroisoquinolinone with substituents at the 3-position are available, most of which are related to the synthesis of *N*-methyl analogues.<sup>6</sup>

One of the simplest synthetic methods of the *N*-alkylated dihydroisoquinolinone skeleton is direct *N*-alkylation of *N*-unsubstituted dihydroisoquinolinone **A** (Scheme 1).<sup>7</sup> The *N*-alkylation reaction, however, often does not proceed in the case of substrates with some substituents at the 3-position. Another





Scheme 1 Retrosynthetic analysis of 3-substituted 3,4dihydroisoquinolinones.

minoru@mw.mt-pharma.co.jp

10.1039/c7ra13627g

#### Paper

method for preparing the skeleton involves benzylic oxidation of *N*-alkylated tetrahydroisoquinoline **B-1**.<sup>8</sup> However, this route cannot be applied to substrates in which another position can be easily oxidized. Using this approach, the precursor is easy to synthesize because the nitrogen atom of tetrahydroisoquinolines **B-2** is more nucleophilic than that of 3,4-dihydroisoquinolinones **A**. However, in the case of 3-substituted analogues, precursors **B-2** are not obtained *via* cyclization reactions of the corresponding phenethylamine derivatives **B-3**.<sup>9</sup>

Thus, we have focused on the oxidation reaction of *N*-alkylated iminium salts **C-1**. As previous reports are limited to 3unsubstituted analogues,<sup>10</sup> we examined whether this strategy was compatible with 3-substituted dihydroisoquinolinone derivatives. In the course of the reaction, *N*-alkylation proceeds *via* a less sterically hindered transition state when compared with that of direct *N*-alkylation of dihydroisoquinolinone **A**. Therefore, this method has an apparent advantage for *N*-alkylation of sterically hindered analogues. In this work, we developed an effective synthetic method of 3-substituted *N*-alkyldihydroisoquinolinone derivatives *via* iminium intermediates.

## **Results and discussion**

#### Preparation of 3,3-dimethyl-dihydroisoquinolinium salt

3,3-Dimethyl-3,4-dihydroisoquinoline **8**, was prepared by referring to a previously described procedure (Scheme 2).<sup>11</sup> Our synthesis began with commercially available 2-bromophenylacetic acid **2**, which was converted into an ester and reacted with methyl Grignard reagent to afford the tertiary alcohol **4**. Nucleophilic substitution of **4** with chloroacetonitrile followed by reaction with thiourea afforded the tertiary amine



Scheme 2 Reagents and conditions: (i) conc.  $H_2SO_4$  (5 mol%), MeOH, reflux: (ii) MeMgBr (2.5 equiv.), THF, 0 °C to rt, 98% (2 steps); (iii) ClCH<sub>2</sub>CN (2 equiv.), conc.  $H_2SO_4$  (1.3 equiv.), AcOH (3 equiv.), 0 °C to rt; (iv) thiourea (1.2 equiv.), EtOH–AcOH (5 : 1), 100 °C, quant (2 steps); (v) EtOCHO (2.0 M), 60 °C, 85%; (vi) (COCl)<sub>2</sub> (1.1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>; (vii) FeCl<sub>3</sub> (1.5 equiv.); (viii) MeOH–H<sub>2</sub>SO<sub>4</sub> (19 : 1), reflux, 89%.

 $6^{12}$  in high yield. Amidation of the tertiary amine 6 with ethyl formate under neat conditions produced the formamide 7 in 85% yield. Tandem cyclization of 7 using oxalyl chloride followed by iron(m) chloride afforded a tricyclic intermediate, which was pyrolyzed by MeOH-H<sub>2</sub>SO<sub>4</sub> to give 3,3-dimethyl-3,4-dihydroisoquinoline in 89% yield.

After obtaining 3,3-dimethyl-3,4-dihydroisoquinoline **8**, we examined the formation of isoquinolinium key precursors **9**. For the preparation of the 3,3-dimethyl-dihydroisoquinolinium salt **9** (Scheme 3), dihydroisoquinoline **8** was reacted with methyl bromoacetate (2 equiv.) in acetonitrile at 60 °C. After 6 h, the desired product **9** was produced and precipitated as a colorless powder. The obtained powder was sufficiently pure for use in the next reaction without further purification.

#### Synthesis of 3-substituted dihydroisoquinolinones

We next examined the oxidation of the 3,4-dihydroisoquinolinium salt 9. The reaction was first examined in the presence of hydrochloric acid and dimethyl sulfoxide with reference to a previously described procedure (Table 1, entry 1),<sup>10a</sup> but the desired product was not obtained. Next, we focused on optimizing the oxidation conditions. When 9 was reacted with *m*-chloroperoxybenzoic acid, dealkylation of 9 to dihydroisoquinoline 8 occurred predominantly (entry 2). Employing Dess-Martin periodinane as the oxidant, the reaction became messy and a complex product mixture that included 8 was obtained (entry 3). When oxone was employed as the oxidant, no reaction was observed (entry 4). However, when 9 was reacted with oxone in the presence of sodium bicarbonate, desired product 10 was obtained as the major product (entry 5). This suggested that basic conditions were preferable for 3-substituted dihydroisoquinolinones. As the yield was not satisfactory, further experiments were conducted. Treatment of 9 with potassium ferricyanide in the presence of potassium hydroxide gave the desired product as the hydrolyzed carboxylic acid 11 in 69% yield (entry 6).13 Dealkylated compound 8 was also obtained as a minor product.

We also examined the oxidation reaction of isoquinolinium salts, including those with other alkyl substituents on the nitrogen atom.<sup>14</sup> As expected, under optimal conditions, the desired dihydroisoquinolinones were obtained in high yields (Scheme 4). However, when dihydroisoquinolinium salt **16** was employed in the oxidation reaction, the desired product was obtained only in trace amounts, while dealkylated compound **8** was generated as the major product (Scheme 5). This was probably due to steric hindrance at the oxidation site.



Scheme 3 Alkylation of 3,3-dimethyl-3,4-dihydroisoquinoline.

Paper



Entry	$Conditions^a$	Yields (%)
1	Conc. HCl, DMSO (1:7)	N.R.
2	$mCPBA$ (1.5 equiv.), $CH_2Cl_2$	8: 88%
3	Dess-Martin periodinane (1.2 equiv.), CH <sub>2</sub> Cl <sub>2</sub>	Decomposed
4	Oxone (2 equiv.), MeCN/H <sub>2</sub> O (3 : 2)	N.R.
5	Oxone (2 equiv.), NaHCO <sub>3</sub> (2 equiv.), MeCN/H <sub>2</sub> O (3 : 2)	<b>10:</b> 39%
6	$K_3$ Fe(CN) <sub>6</sub> (6 equiv.), KOH (24 equiv.), dioxane/H <sub>2</sub> O (1 : 2)	<b>11:</b> 69%, <b>8:</b> 25%

<sup>a</sup> 3,3-dimethyl-3,4-dihydroisoquinolinium salt 9 (0.1 mmol), oxidants, and solvent (0.1 M) were reacted for 12 h at ambient temperature.



Scheme 4 Reagents and conditions: (i) Mel (10 equiv.), acetone, rt; (ii) BnBr (10 equiv.), toluene, 70 °C; (iii)  $K_3Fe(CN)_6$  (6 equiv.), KOH (24 equiv.), dioxane/H<sub>2</sub>O (1 : 2), rt.

#### Investigation of the reaction mechanism

We hypothesize that the mechanism of the reaction involves a hydroxide ion as an oxygen source and proceeds through a radical pathway, because hexacyanoferrate(m) is a typical oneelectron oxidizing agent.<sup>15</sup>



Scheme 5 Oxidation of a 3,3-dimethyl-3,4-dihydroisoquino-linium derivative.

To verify this hypothesis, we conducted the oxidation reaction of isoquinolinium salt 12 under a nitrogen atmosphere. As a result, the reaction proceeded smoothly and the desired product 13 was obtained in excellent yield (Scheme 6, eqn (1)), suggesting that atmospheric oxygen  $(O_2)$  was not the oxygen source. Next, we investigated the reaction of 12 with only potassium hydroxide solution to confirm that hydroxide ions were the oxygen source. The tetrahydroisoquinolinol intermediate 18 was determined by LC/MS and <sup>1</sup>H NMR analysis<sup>16</sup> of the crude mixture. Furthermore, when potassium ferricyanide was added to the solution of intermediate 18, generation of the desired product was detected (eqn (2)). When the reaction was conducted in the presence of a radical scavenger, the reaction mixture became messy and the desired product was not detected (eqn (3)). Based on these experimental results, we concluded that the oxidation reaction proceeded through a radical process via the tetrahydroisoquinolinol intermediate 18.



Scheme 6 Control experiments for investigating the mechanism.

We have developed a novel and efficient approach for the preparation of 3-substituted *N*-alkyl-3,4-dihydroisoquinolinones *via* the oxidation of iminium intermediates. Using this method, *N*alkyl-3,4-dihydroisoquinolinones bearing substituents at the 3position, which had not been obtained by *N*-alkylation of the amide nitrogen, could be obtained in moderate yield. We believe this method will contribute to the development of pharmacologically active compounds based on this skeleton. However, there is currently a limitation of the substituent patterns on the nitrogen atom such as a reactive methylene moiety, which we are currently trying to overcome by searching for various reaction conditions including oxidizing reagents.

## **Experimental**

#### General information

<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker 400 ULTRASHIELD PLUS. <sup>1</sup>H and <sup>13</sup>C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS,  $\delta$  scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on a PerkinElmer Spectrum One FT-IR Spectrometer using attenuated total reflection (ATR). Melting points (mp) were recorded on a BÜCHI Melting Point B-545. Mass spectra were provided at the DMPK Research Laboratory, Mitsubishi Tanabe Pharma Corporation.

*N*-(1-(2-Bromophenyl)-2-methylpropan-2-yl)formamide (7). In a flask, 1-(2-bromophenyl)-2-methylpropane-2-amine 613 (2.0 g, 8.77 mmol) and ethylformate (1.0 M, 8.77 mL) were placed and the mixture was stirred at 60 °C. The reaction proceeded very slowly. After 5 d, ethylformate (1.0 M, 8.77 mL) was added and stirred for another 5 d at 60 °C. The disappearance of the starting material was confirmed by LC/MS. The reaction mixture was concentrated in vacuo to afford N-(1-(2-bromophenyl)-2methylpropan-2-yl)formamide 7 (1.92 g, 7.49 mmol) in 85% yield. mp 63.6–63.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\rm H}$ : 8.11–8.01 (1H, m), 7.60–7.56 (1H, m), 7.29–7.08 (3H, m), 5.73–5.29 (1H, m), 3.29-3.03 (2H, m), 1.43-1.40 (6H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta_{\rm C}$ : 162.6, 160.8, 137.3, 135.9, 133.5, 133.1, 132.5, 132.4, 128.8, 128.2, 127.3, 127.1, 126.1, 126.0, 77.2, 76.8, 55.4, 54.0, 48.2, 43.6, 28.6, 27.4; IR (ATR cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 3293, 2970, 2858, 1659, 1540, 1466, 1382, 1258, 1017, 759, 705, 657; HRMS (ESI) [M + H]<sup>+</sup> calculated for C<sub>11</sub>H<sub>15</sub>BrNO: 256.03315, found: 256.03357.

**5-Bromo-2-(2-methoxy-2-oxoethyl)-3,3-dimethyl-3,4-dihydroisoquinolin-2-ium bromide (9).** Methyl bromoacetate (0.078 mL, 0.84 mmol, 1.0 equiv.) was added to a solution of 5-bromo-3,3-dimethyl-3,4-dihydroisoquinoline **8** (200 mg, 0.84 mmol) in acetonitrile (4.2 mL, 0.20 M). The resulting mixture was stirred for 6 h at 60 °C. As the reaction proceeded, a colorless powder precipitated. After the reaction, the precipitate was filtered and washed with ethyl acetate to afford methyl 5-bromo-2-(2-methoxy-2-oxoethyl)-3,3-dimethyl-3,4-dihydro-isoquinolin-2ium bromide **9** (195.4 mg, 0.50 mmol) in 60% yield. mp 182.7–182.8 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ<sub>H</sub>: 9.35 (1H, s), 8.20 (1H, dd, J = 7.7, 1.0 Hz), 7.97 (1H, dd, J = 7.7, 1.0 Hz), 7.59 (1H, dd, J = 7.7, 7.7 Hz), 5.19 (2H, s), 3.82 (3H, s), 3.35 (2H, s), 1.46 (6H, s); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ )  $\delta_C$ : 171.3, 167.7, 142.5, 136.6, 134.8, 130.7, 126.0, 124.1, 64.1, 64.1, 55.0, 53.8, 53.8, 23.7, 23.7; IR (ATR cm<sup>-1</sup>)  $v_{max}$ : 2925, 1748, 1644, 1417, 1223, 1198, 1129, 795, 693; HRMS (ESI) [M - Br]<sup>+</sup> calculated for C<sub>14</sub>H<sub>17</sub>BrNO<sub>2</sub>: 310.04372, found: 310.04402.

**5-Bromo-2,3,3-trimethyl-3,4-dihydroisoquinolin-2-ium iodide** (12). 5-Bromo-2,3,3-trimethyl-3,4-dihydroisoquinolin-2-ium iodide 12 was obtained following the same procedure described in detail for the preparation of isoquinolinium **9** from **8**. mp 182.5-182.6 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta_{\text{H}}$ : 9.24 (1H, s), 8.11 (1H, dd, *J* = 8.2, 1.0 Hz), 7.87 (1H, dd, *J* = 7.7, 1.0 Hz), 7.55 (1H, dd, *J* = 8.2, 7.7 Hz), 3.74 (3H, s), 3.28 (2H, s), 1.47 (6H, s); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta_{\text{C}}$ : 167.1, 141.2, 136.3, 133.5, 130.4, 126.5, 123.8, 62.6, 62.6, 42.7, 23.8, 23.8; IR (ATR cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2969, 1650, 1562, 1445, 1376, 1231, 1204, 1120, 901, 785, 700, 571; HRMS (ESI) [M – I<sup>-</sup>] calculated for C<sub>12</sub>H<sub>15</sub>BrN: 252.03824, found: 252.03869.

2-Benzyl-5-bromo-3,3-dimethyl-3,4-dihydroisoquinolin-2-ium bromide (14). 2-Benzyl-5-bromo-3,3-dimethyl-3,4-dihydroisoquinolin-2-ium 14 was obtained following the same procedure detailed for the preparation of isoquinolinium 9 from 8. mp 179.3–179.4 °C; <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta_{\rm H}$ : 9.39 (1H, s), 8.15 (1H, dd, J = 8.2, 1.0 Hz), 8.01 (1H, dd, J = 7.7, 1.0 Hz), 7.59– 7.42 (5H, m), 5.38 (2H, s), 3.32 (2H, s), 1.42 (6H, s); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ )  $\delta_{\rm C}$ : 168.6, 141.6, 136.6, 134.5, 133.5, 130.4, 129.6, 129.6, 129.4, 129.0, 129.0, 126.7, 123.7, 64.3, 64.3, 58.3, 24.6, 24.6; IR (ATR cm<sup>-1</sup>)  $\nu_{\rm max}$ : 3313, 2921, 1642, 1561, 1448, 1375, 1254, 1194, 1129, 955, 789, 761, 700, 692; HRMS (ESI) [M – Br<sup>-</sup>] calculated for C<sub>18</sub>H<sub>19</sub>BrN: 328.06954, found: 328.06984.

2-(5-Bromo-3,3-dimethyl-1-oxo-3,4-dihydroisoquinolin-2(1H)yl)acetic acid (11). Potassium hydroxide (8.0 M in water, 0.307 mL, 2.46 mmol, 24 equiv.) was added to a solution of potassium ferricyanide (137.7 mg, 0.614 mmol, 6.0 equiv.) in H<sub>2</sub>O (1.4 mL). After the reagent was dissolved, a solution of methyl 5-bromo-2-(2-methoxy-2-oxoethyl)-3,3-dimethyl-3,4-dihydro-isoquinolin-2ium bromide 9 (40.0 mg, 0.102 mmol) in dioxane (0.7 mL) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was washed with CHCl<sub>3</sub> and the aqueous layer acidified to pH 4 by adding a 1 M hydrochloric acid solution. The aqueous layer was extracted with CHCl<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford 2-(5-bromo-3,3dimethyl-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetic acid 11 (22 mg, 0.070 mmol) in 69% yield. mp 169.4–169.5 °C; <sup>1</sup>H NMR  $(400 \text{ MHz}, \text{CDCl}_3) \delta_{\text{H}}$ : 8.03 (1H, d, J = 7.7 Hz), 7.70 (1H, d, J = 8.2Hz), 7.22 (1H, dd, J = 8.2, 7.7 Hz), 5.16 (1H, brs), 4.30 (2H, s), 3.11 (2H, s), 1.36 (6H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta_{\rm C}$ : 172.7, 164.9, 136.3, 136.0, 129.7, 128.3, 127.7, 123.1, 56.7, 44.2, 42.0, 26.8, 26.8; IR (ATR cm<sup>-1</sup>)  $\nu_{\text{max}}$ : 2967, 1703, 1644, 1467, 1402, 1329, 1258, 1168, 1123, 915, 808, 752, 653; HRMS (ESI)  $[M + H]^{\dagger}$ calculated for C<sub>13</sub>H<sub>15</sub>BrNO<sub>3</sub>: 312.02298, found: 312.02296.

Methyl 2-(5-bromo-3,3-dimethyl-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (10). Sodium hydrogen carbonate (128.9 mg, 0.820 mmol, 4.0 equiv.) was added to a solution of Oxone® (943.2 mg, 0.820 mmol, 4.0 equiv.) in  $H_2O$  (2 mL). Then, a solution of methyl 5-bromo-2-(2-methoxy-2-oxoethyl)-3,3dimethyl-3,4-dihydroisoquinolin-2-ium bromide **9** (150 mg, 0.384 mmol) in acetonitrile (4.0 mL) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with water and CHCl<sub>3</sub>. The aqueous layer was extracted with CHCl<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography (hexane : EtOAc = 3 : 1) to give methyl 2-(5-bromo-3,3-dimethyl-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetate **10** (48.2 mg, 0.148 mmol) in 39% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\rm H}$ : 8.04 (1H, dd, J = 7.7, 1.5 Hz), 7.69 (1H, dd, J = 8.2, 1.0 Hz), 7.22 (1H, dd, J = 8.2, 7.7 Hz), 4.30 (2H, s), 3.76 (3H, s), 3.12 (2H, s), 1.35 (6H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta_{\rm C}$ : 170.4, 163.9, 136.1, 135.9, 130.1, 128.2, 127.7, 123.0, 56.2, 52.3, 43.4, 42.2, 26.9, 26.9; IR (ATR cm<sup>-1</sup>)  $\nu_{\rm max}$ : 2950, 1750, 1643, 1562, 1455, 1413, 1386, 1199, 1167, 1012, 970, 754, 653; HRMS (ESI) [M + H]<sup>+</sup> calculated for C<sub>14</sub>H<sub>17</sub>BrNO<sub>3</sub>: 326.03863, found: 326.03908.

**5-Bromo-2,3,3-trimethyl-3,4-dihydroisoquinolin-1**(2*H*)-one (13). 5-Bromo-2,3,3-trimethyl-3,4-dihydroisoquinolin-1(2*H*)-one 13 was obtained following the same procedure described in detail for the preparation of isoquinolinium 11 from 9. mp 91.5–91.6 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\rm H}$ : 8.06 (1H, dd, *J* = 7.7, 1.0 Hz), 7.66 (1H, dd, *J* = 8.2, 1.0 Hz), 7.21 (1H, dd, *J* = 8.2, 7.7 Hz), 3.09 (3H, s), 3.03 (2H, s), 1.33 (6H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta_{\rm C}$ : 163.7, 135.8, 135.4, 130.6, 128.1, 127.7, 122.9, 55.5, 41.9, 27.3, 26.3, 26.3; IR (ATR cm<sup>-1</sup>)  $\nu_{\rm max}$ : 2967, 1636, 1566, 1455, 1409, 1369, 1163, 1101, 1042, 800, 732; HRMS (ESI) [M + H]<sup>+</sup> calculated for C<sub>12</sub>H<sub>15</sub>BrNO: 268.03315, found: 268.03329.

2-Benzyl-5-bromo-3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)one (15). 2-Benzyl-5-bromo-3,3-dimethyl-3,4-dihydroisoquinolin-1(2*H*)-one 15 was obtained following the same procedure described in detail for the preparation of isoquinolinium 11 from 9. mp 133.3–133.4 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\rm H}$ : 8.13 (1H, dd, *J* = 7.7, 1.0 Hz), 7.69 (1H, dd, *J* = 8.2, 1.0 Hz), 7.33–7.20 (6H, m), 4.84 (2H, s), 3.06 (2H, s), 1.28 (6H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta_{\rm C}$ : 164.3, 139.5, 136.1, 135.7, 130.7, 128.5, 128.5, 128.2, 127.9, 127.1, 127.1, 126.8, 123.0, 56.7, 45.3, 42.7, 27.1, 27.1; IR (ATR cm<sup>-1</sup>)  $\nu_{\rm max}$ : 2975, 1624, 1561, 1454, 1403, 1356, 1287, 1197, 1120, 990, 800, 744, 698, 666; HRMS (ESI) [M + H]<sup>+</sup> calculated for C<sub>18</sub>H<sub>19</sub>BrNO: 344.06445, found: 344.06422.

### Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank the members of this team for stimulating discussions, in particular Dr Masayuki Watanabe, Mr Kazunari Shimooka and Ms Kaoru Marukawa. We also thank Ms Kaori Murakoshi and Ms Saori Tahara for technical support of LC-MS/ MS and FT-IR analysis. We thank Mr Iwao Takamuro for helpful advice. This research was supported by the Mitsubishi Tanabe Pharma Corporation.

## Notes and references

1 R. D. Clark, A. B. Miller, J. Berger, D. B. Repke, K. K. Weinhardt, B. A. Kowalczyk, R. M. Eglen,

- D. W. Bonhaus, C. H. Lee, A. D. Michael, W. L. Smith and E. H. Wong, *J. Med. Chem.*, 1993, **36**, 2645–2657.
- 2 E. Kutter, G. Griss, W. Grell and M. Kleemann, *US Pat.*, US1973/3708486, 1973.
- 3 M. S. Malamas, US Pat., US1992/5106978, 1992.
- 4 J. H. Van Duzer and D. M. Roland, EP Pat., EP0526402, 1993.
- 5 (a) Y. Lou, X. Han, A. Kuglstatter, R. K. Kondru,
  A. K. Sweeney, M. Soth, N. Dewdney, H. Zecic,
  J. P. Taygerly, K. Sarma, J. Hong, R. J. Hill, T. Gabriel,
  D. M. Goldstein and T. D. Owens, *J. Med. Chem.*, 2015, 58,
  512–516; (b) G. Szántó, A. Makó, I. Vágó, T. Hergert, I. Bata,
  B. Farkas, S. Kolok and M. Vastag, *Bioorg. Med. Chem. Lett.*,
  2016, 26, 3905–3912; (c) P. Qian, Y.-B. Zhang, Y.-F. Yang,
  W. Xu and X.-W. Yang, *Molecules*, 2017, 22, 214–232.
- 6 (a) D. M. Bailey and C. G. DeGrazia, J. Org. Chem., 1970, 35, 4088-4093; (b) D. M. Bailey and C. G. DeGrazia, Tetrahedron Lett., 1970, 9, 633-636; (c) W. Liu, Q. Yu, L. Hu, Z. Chen and J. Huang, Chem. Sci., 2015, 6, 5768-5772; (d) T. Miura, M. Morimoto, M. Yamauchi and M. Murakami, J. Org. Chem., 2010, 75, 5359-5362; (e) A. G. Schultz, T. J. Guzi, E. Larsson, R. Rahm, K. Thakkar and J. M. Bidlack, J. Org. Chem., 1998, 63, 7795-7804.
- 7 (a) M. J. Fisher, B. P. Gunn, S. Um and J. A. Jakubowski, *Tetrahedron Lett.*, 1997, 38, 5747-5750; (b) D. Zhou,
  J. L. Gross, A. B. Adedoyin, S. B. Aschmies, J. Brennan,
  M. Bowlby, L. Di, K. Kubek, B. J. Platt, Z. Wang, G. Zhang,
  N. Brandon, T. A. Comery and A. J. Robichaud, J. Med. Chem., 2012, 55, 2452-2468; (c) F. A. Davis and
  Y. W. Andemichael, Tetrahedron Lett., 1998, 39, 3099-3102; (d) J. M. Fevig, J. Feng, K. A. Rossi, K. J. Miller, G. Wu,
  C.-P. Hung, T. Ung, S. E. Malmstrom, G. Zhand,
  W. J. Keim, M. J. Cullen, K. W. Rohrbach, Q. Qu, J. Gan,
  M. A. Pelleymounter and J. A. Robl, *Bioorg. Med. Chem.* Lett., 2013, 23, 330-335.
- 8 (a) A. G. Schultz, T. J. Guzi, E. Larsson, R. Rahm, K. Thakkar and J. M. Bidlack, J. Org. Chem., 1998, 63, 7795-7804; (b)
  W.-J. Huang, O. V. Singh, C.-H. Chen, S.-Y. Chiou and S.-S. Lee, Helv. Chim. Acta, 2002, 85, 1069-1078; (c)
  A.-R. Song, J. Yu and C. Zhang, Synthesis, 2012, 22, 2903-2909; (d) M. Nakanishi and C. Bolm, Adv. Synth. Catal., 2007, 349, 861-864; (e) M. Ochiai, D. Kajishima and T. Sueda, Tetrahedron Lett., 1999, 40, 5541-5544; (f)
  D. Crich and V. Krishnamurthy, Tetrahedron, 2006, 62, 6830-6840.
- 9 When **6** was reacted with paraformaldehyde (100 wt%) and AcOH-H<sub>2</sub>SO<sub>4</sub> (0.8 M, 3:1) from ambient temperature to 80 °C to generate the tetrahydroisoquinoline, no reaction was observed.
- 10 (a) S. Ruchirawat, M. Chuankamnerdkarn and S. Thianpatanagul, *Tetrahedron Lett.*, 1984, 25, 3479–3480;
  (b) A. P. Venkov and S. M. Statkova-Abeghe, *Tetrahedron*, 1996, 52, 1451–1460; (c) B. Bechi, S. Herter, S. Mckenna, C. Riley, S. Leimkühler, N. J. Turner and A. J. Carnell, *Green Chem.*, 2014, 16, 4524–4529.
- 11 R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider and I. Shinkai, *J. Org. Chem.*, 1991, **56**, 6034–6038.

#### Paper

- 12 S. D. Brown and D. J. Matthews, US Pat., US2012/0252802, 2012.
- 13 (a) N. Itou and S. Sugasawa, *Tetrahedron*, 1957, 1, 45–48; (b)
   E. Dominguez, E. M. Marigorta, L. Carrillo and R. Fañanás, *Tetrahedron*, 1991, 47, 9253–9258.
- 14 A. G. Mikhailovskii, V. S. Shklyaev and E. V. Feshina, *Chem. Heterocycl. Compd.*, 1998, **34**, 211–215.
- 15 B. S. Thyagarajan, Chem. Rev., 1958, 58, 439-460.
- 16 In <sup>1</sup>H NMR analysis, we confirmed the disappearance of the iminium proton peak and detected the doublet peaks of the OH and O–CH–N moieties. See the ESI† for more details.