

# Synthesis of 7-azabicyclo[2.2.1]heptane derivatives via bridgehead radicals

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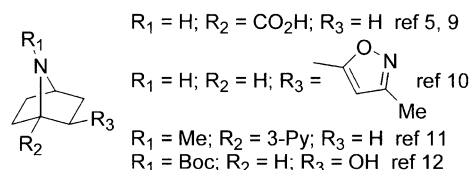
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**Abstract**—This report shows the versatility and synthetic potential of 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (Ahc) to obtain several bridgehead 1-substituted-7-azabicyclo[2.2.1]heptane derivatives, including halogen derivatives, via bridgehead radical reactions, proving the existence of the bridgehead radical in 7-azabicyclo[2.2.1]heptane systems. Moreover, we have obtained the interesting compound *N*-benzoyl-7-azabicyclo[2.2.1]heptane, a precursor of epibatidine. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

The reaction of *O*-acyl thiohydroxamates (Barton esters) to give free-radicals was achieved in 1983 by the Barton group<sup>1</sup> and has many useful modifications. This type of chemistry has developed as an important source of radicals for decarboxylations, decarboxylative halogenations or to trap them with double bonds.<sup>2</sup> There are some examples of  $\alpha$ -amino-substituted radicals generated from oxidative decarboxylation of  $\alpha$ -amino acids<sup>3</sup> as well as of bridgehead radicals from carboxylic acids.<sup>4</sup> However, there are very few examples including both aspects, the bridgehead  $\alpha$ -amino-substituted radicals. Moreover, there are few reactions in which these  $\alpha$ -amino-substituted radicals generated from oxidative decarboxylation of  $\alpha$ -amino acids are captured with halogens to afford  $\alpha$ -haloamino-derivatives -*N,X*-acetals-. To the best of our knowledge, this fact is only possible in special situations as the generation of 2-haloaziridinyl derivatives.<sup>3</sup>

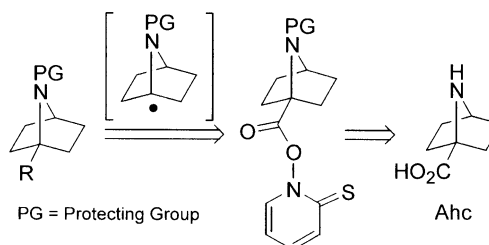
In this context, Rapoport and co-workers used the Barton procedure to achieve the decarboxylation of a quaternary and bridgehead amino acid (1*S*,4*R*)-*N*-(benzyloxycarbonyl)-7-azabicyclo[2.2.1]heptan-3-one-1-carboxylic acid, in a formal synthesis of epibatidine.<sup>5</sup> The interest in this 7-azabicyclo[2.2.1]heptane system as important biomolecular substructure is due to its presence in the epibatidine skeleton (Fig. 1). Because of this, the synthesis of different 7-azabicyclo[2.2.1]heptane derivatives has been the subject of numerous synthetic studies.<sup>6</sup> In addition, the 7-aza-



**Figure 1.** Several 7-azabicyclo[2.2.1]heptane derivatives.

bicyclo[2.2.1]heptane-1-carboxylic acid (Ahc) is particularly interesting, since it can be regarded as a conformationally constrained proline. In fact, it has been introduced in two biomolecules as a proline analogue.<sup>7,8</sup> In the structure block, we show several related structures that have been already synthesized.<sup>9–12</sup>

In the course of our investigations, we have developed a new and versatile method to obtain the Ahc.<sup>9</sup> Now, our goal is to obtain different 1-substituted-7-azabicyclo[2.2.1]heptane derivatives, including halogen derivatives due to the difficulty of its synthesis, via bridgehead radical carbon and starting from the Barton ester of Ahc. A retrosynthesis of these compounds is shown in Scheme 1.



**Scheme 1.** Retrosynthetic analysis of 1-substituted-7-azabicyclo[2.2.1]heptane systems.

**Keywords:** bicyclic heterocyclic compounds; radicals and radical reactions; amino acids and derivatives; halogenation; X-ray crystal structures.

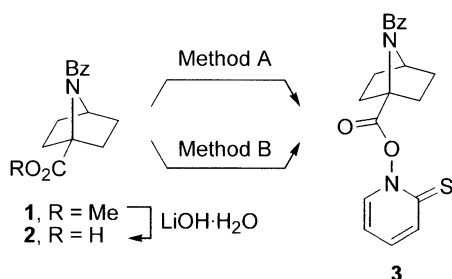
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## 2. Results and discussion

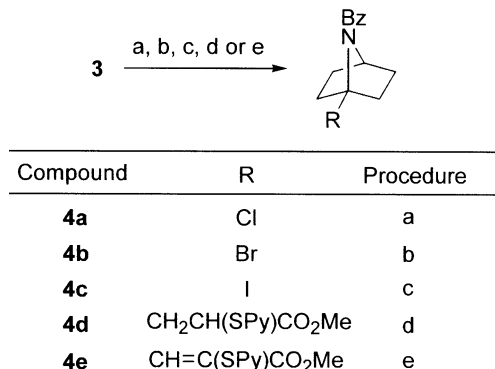
### 2.1. Synthesis of 1-substituted-7-azabicyclo[2.2.1]heptane derivatives

Our starting material was compound **1**, an intermediate obtained in the synthesis of Ahc.<sup>9</sup> From this compound and by treatment with LiOH·H<sub>2</sub>O in methanol, acid **2** was obtained in a good yield. The *O*-acyl thiohydroxamate can be prepared by reaction of *N*-hydroxypyridine-2-thione with an activated acyl derivative from acid **2** or using coupling reagents. First, we tried the use of *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) combined with diisopropylethylamine (DIEA), a very useful procedure for hindered amino acids synthesis,<sup>13</sup> and we achieved a satisfactory yield of the yellow ester **3**, which was purified through a flash chromatography. Nevertheless, the coupling of the acid chloride of **2** (obtained by treatment of **2** with oxalyl chloride) with *N*-hydroxypyridine-2-thione in the presence of TEA gave ester **3** in a better and excellent yield and was used for the next reaction without any further purification (Scheme 2).

The chlorination of **3** was then carried out using neat tetrachloromethane as solvent and reagent. The mixture was irradiated with a 200 W tungsten lamp and after stirring for 6 h, the solvent was evaporated and the residue was purified by chromatography to obtain **4a** in a 23% yield. The bromo was introduced using neat bromotrichloromethane to give an 85% yield of **4b**. Finally, to get the iodo derivative we used dichloromethane as a solvent and



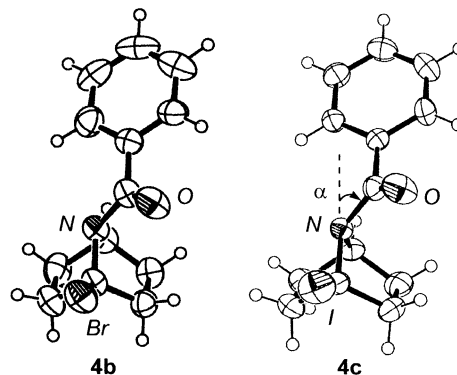
**Scheme 2.** Method A: BOPCl, DIEA, CH<sub>2</sub>Cl<sub>2</sub>, *N*-hydroxypyridine 2-thione, rt, 16 h. Method B: (a) Oxalyl chloride, dichloroethane, DMF, rt, 3 h; (b) TEA, THF, *N*-hydroxypyridine-2-thione, rt, 1 h.



**Scheme 3.** (a) CCl<sub>4</sub>, 200 W, 6 h, 23%. (b) BrCCl<sub>3</sub>, 200 W, 6 h, 85%. (c) CF<sub>3</sub>CH<sub>2</sub>I, CH<sub>2</sub>Cl<sub>2</sub>, 200 W, 6 h, 37%. (d) CH<sub>2</sub>=CHCO<sub>2</sub>Me, toluene, reflux, 59%. (e) CH≡CCO<sub>2</sub>Me, toluene, reflux, 62%.

1,1,1-trifluoro-2-iodoethane<sup>4</sup> to give a 37% yield of **4c** (Scheme 3). In order to explore the capability of Barton ester **3** to generate C–C bonds, we tried its reaction with methyl acrylate, as terminal olefin.<sup>14</sup> The reaction was carried out in toluene at reflux to give 59% of methyl ester compound **4d**. Moreover, we also created a double carbon–carbon bond by the reaction of ester **3** with propynoic acid methyl ester, in the same conditions described earlier, to produce a 62% yield of **4e** (Scheme 3).

In the case of **4b** and **4c**, we could obtain two single crystals and it was possible to determine by X-ray diffraction the defined structures and the non-planarity of the amide structures. The planarity of amide nitrogen can be represented by two angle parameters, the summation of the three valence angles around the nitrogen ( $\theta=360^\circ$ ) and the out-of-plane angle of the *N*-substituents ( $\alpha=0^\circ$ ). The single crystal structures of **4b** and **4c** (Fig. 2) revealed significant pyramidalization of the amide nitrogen:  $\theta=335.8, 330.0^\circ$  and  $\alpha=41.4, 37.0^\circ$ , respectively, as referenced for other *N*-acyl-7-azabicyclo[2.2.1]heptane systems.<sup>15,16</sup>



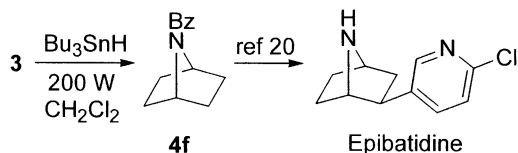
**Figure 2.** ORTEP diagrams for **4b** and **4c**.

The amide bond is the crucial linkage in the structures of proteins and the isomerization between planar *cis* and *trans* amide conformations is essential for protein folding and for many other processes.<sup>17</sup> This isomerization probably involves a transition state with a pyramidal nitrogen. In this sense, the knowledge of new compounds, which present distorted amides, will help to understand the isomerization process of amides. Therefore and taking into account that the pyramidal nitrogen of amides plays an important role in the chemical and biological processes<sup>17</sup> and it is still an exceptional phenomenon due to the few examples reported, the structures of **4b** and **4c** reported here constitute additional examples of the intrinsic pyramidal nitrogen of *N*-acyl-7-azabicyclo[2.2.1]heptanes, suggested by Ohwada.<sup>15,16</sup>

### 2.2. Formal synthesis of epibatidine

Since the isolation of epibatidine,<sup>18</sup> *N*-benzoyl-7-azabicyclo[2.2.1]heptane (**4f**) and its derivatives have attracted the attention of the chemists in the last years. Recently, both Hassner,<sup>19</sup> from a monoprotected 1,4-cyclohexanedione, and Olivo,<sup>20</sup> from *trans*-4-aminocyclohexanol, have reported the synthesis of several *N*-alkyl-7-

azabicyclo[2.2.1]heptane systems. We could obtain **4f** by simple decarboxylation of thiohydroxamic ester **3**, using tributyltin hydride ( $\text{Bu}_3\text{SnH}$ ) as a source of hydrogen radical. As the epibatidine has been obtained from **4f** by microbial oxidation,<sup>21</sup> we can therefore consider the synthesis of **4f** as a formal synthesis of epibatidine (Scheme 4).



Scheme 4. Synthesis of epibatidine from Barton ester **3** via **4f**.

### 3. Conclusion

We have showed the versatility and synthetic potential of the azabicyclo **1** to obtain several bridgehead 1-substituted compounds, including halogen derivatives, via radical reactions, proving the existence of the bridgehead radical in 7-azabicyclo[2.2.1]heptane systems. Moreover, we have obtained the interesting compound **4f**, a precursor of epibatidine. In future, we wish to extend this methodology to other azabicycles and to use the halogen derivatives to try some coupling reactions.

## 4. Experimental

### 4.1. General

Melting points are uncorrected. All the manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. The chemical reagents were purchased from Aldrich Chemical Co. Analytical TLC was performed using Polychrom SI F<sub>254</sub> plates. Column chromatography was performed using Kieselgel 60 (230–400 mesh). Organic solutions were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and, when necessary, concentrated under reduced pressure using a rotary evaporator.  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) of IR spectra are given for the main absorption bands. NMR spectra were recorded at 300 MHz ( $^1\text{H}$ ) and at 75 MHz ( $^{13}\text{C}$ ) and are reported in ppm downfield from TMS. Mass spectra were obtained by electrospray ionization (ESI).

**4.1.1. N-Benzoyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid (2).** Compound **1** (760 mg, 2.93 mmol) was dissolved in a mixture of  $\text{MeOH}/\text{H}_2\text{O}$  3:2 (50 mL) and  $\text{LiOH}\cdot\text{H}_2\text{O}$  (1.23 g, 29.30 mmol) was added. The reaction was stirred at rt for 48 h and the solvent was then evaporated in vacuo. The residue was diluted with  $\text{H}_2\text{O}$  (30 mL) and washed with dichloromethane (2×20 mL). The aqueous phase was acidified with a 2N HCl solution and extracted with dichloromethane (2×20 mL). The organic layer was dried, filtered and evaporated to give 711 mg of a residue corresponding to compound **2**, which was used in the following step without purification (99%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.44–1.56 (m, 2H),

1.75–1.94 (m, 4H), 2.23–2.36 (m, 2H), 4.20 (t, 1H,  $J=4.2$  Hz), 7.30–7.50 (m, 3H), 7.55–7.65 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.9, 32.3, 62.3, 68.1, 128.2, 128.4, 131.4, 134.2, 172.2, 173.1.

**4.1.2. N-Benzoyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid 2-thioxo-2H-pyridin-1-yl ester (3).** Method A. BOPCl (115 mg, 0.45 mmol) and DIEA (0.26 mL, 1.48 mmol) were added into a mixture of *N*-hydroxypyridine-2-thione (50 mg, 0.45 mmol) and carboxylic acid **2** (92 mg, 0.37 mmol) in dichloromethane at 0°C with protection against light. The reaction was stirred at rt for 16 h and the solvent was then evaporated and the residue purified by flash column chromatography using hexane/ethyl acetate 1:1, with protection against light, to obtain a yellow compound, which was used in the following step without further purification. Method B. To a suspension of acid **2** (93 mg, 0.38 mmol) in dichloroethane (6 mL), DMF (3  $\mu\text{L}$ , 0.129 mmol) and oxalyl chloride (84  $\mu\text{L}$ , 0.95 mmol) were added. The mixture was stirred for 3 h at rt and evaporated. The residue was dissolved, in the dark, in THF (5 mL) and cooled to 0°C, *N*-hydroxypyridine-2-thione (89 mg, 0.80 mmol) and TEA (116  $\mu\text{L}$ , 0.84 mmol) in THF (4 mL) were then added. The mixture was stirred for 1 h at rt and filtered. The residue was washed with cooled THF and the solvent was evaporated with protection against the light to obtain a yellow compound, which was used in the following step without purification.

**4.1.3. N-Benzoyl-1-chloro-7-azabicyclo[2.2.1]heptane (4a).** The yellow solid **3** (starting from 0.37 mmol of **2**, Method A) was dissolved in tetrachloromethane and irradiated with a 200 W tungsten lamp at rt for 6 h. The solvent was eliminated and the residue purified by column chromatography using hexane/ethyl acetate 8:2 to give 20 mg of **4a** as a white solid (23% yield). Mp 155–158°C. IR ( $\text{CH}_2\text{Cl}_2$ ,  $\text{cm}^{-1}$ ): 1718.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.52–1.67 (m, 2H), 1.98–2.15 (m, 4H), 2.30–2.39 (m, 2H), 4.21 (t, 1H,  $J=4.5$  Hz), 7.36–7.52 (m, 3H), 7.65–7.73 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.9, 38.7, 59.7, 81.8, 128.2, 128.6, 131.4, 135.6, 173.2. ESI+ ( $m/z$ )=236 (3), 238 (1). Anal. Calcd for  $\text{C}_{13}\text{H}_{14}\text{ClNO}$ : C, 66.24; H, 5.99; N, 5.94. Found: C, 66.15; H, 6.07; N, 5.82.

**4.1.4. N-Benzoyl-1-bromo-7-azabicyclo[2.2.1]heptane (4b).** The yellow solid **3** (starting from 0.59 mmol of **2**, Method B) was dissolved in bromotrichloromethane and irradiated with a 200 W tungsten lamp at rt for 6 h. The solvent was eliminated and the residue purified by column chromatography using hexane/ethyl acetate 9:1 to give 117 mg of **4b** as a white solid (85% yield). Mp 56–58°C. IR ( $\text{CH}_2\text{Cl}_2$ ,  $\text{cm}^{-1}$ ): 1665.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.45–1.57 (m, 2H), 1.90–2.17 (m, 4H), 2.38–2.51 (m, 2H), 4.06 (t, 1H,  $J=5.1$  Hz), 7.35–7.53 (m, 3H), 7.67–7.75 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  30.9, 40.0, 59.9, 70.9, 128.3, 128.8, 131.6, 135.5, 173.4. ESI+ ( $m/z$ )=280 (1), 282 (1). Anal. Calcd for  $\text{C}_{13}\text{H}_{14}\text{BrNO}$ : C, 55.73; H, 5.04; N, 5.00. Found: C, 55.91; H, 5.16; N, 5.12.

**4.1.5. N-Benzoyl-1-iodo-7-azabicyclo[2.2.1]heptane (4c).** The yellow solid **3** (starting from 0.40 mmol of **2**, Method B) was dissolved in dichloromethane and 1,1,1-trifluoro-2-iodoethane (1.77 g, 4.49 mmol) was added and the mixture

was then irradiated with a 200 W tungsten lamp at rt for 6 h. The solvent was eliminated and the residue purified by column chromatography using hexane/ethyl acetate 7:3 to give 49 mg of **4c** as a white solid (37% yield). Mp 85–87°C. IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1660. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39–1.51 (m, 2H), 1.84–1.96 (m, 2H), 2.03–2.15 (m, 2H), 2.45–2.57 (m, 2H), 3.81 (t, 1H, *J*=5.4 Hz), 7.35–7.53 (m, 3H), 7.67–7.74 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 32.1, 42.7, 43.0, 58.6, 128.2, 128.8, 131.6, 135.3, 173.3. ESI+ (*m/z*)=328. Anal. Calcd for C<sub>13</sub>H<sub>14</sub>INO: C, 44.73; H, 4.31; N, 4.28. Found: C, 44.98; H, 4.46; N, 4.12.

**4.1.6. 3-(*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)-2-(2-pyridylthio)-propionic acid methyl ester (4d).** The yellow solid **3** (starting from 0.60 mmol of **2**, Method B) was dissolved in degassed and dry toluene and methyl acrylate (0.54 mL, 6.00 mmol) was added. Then, the mixture was heated at reflux for 15 h. The solvent was eliminated and the residue purified by column chromatography using hexane/ethyl acetate 6:4 to give 140 mg of **4d** as a yellow oil (59% yield). IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1734, 1634. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.40–1.48 (m, 2H), 1.62–2.05 (m, 6H), 2.96 (dd, 1H, *J*=6.0, 14.7 Hz), 3.31 (dd, 1H, *J*=8.1, 14.7 Hz), 3.70 (s, 3H), 4.02–4.06 (m, 1H), 4.78 (t, 1H, *J*=7.2 Hz), 6.94–7.02 (m, 1H), 7.16–7.23 (m, 1H), 7.31–7.55 (m, 6H), 8.37–8.42 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 29.8, 33.7, 34.3, 36.5, 43.6, 52.5, 61.0, 67.7, 119.9, 122.3, 127.6, 128.1, 130.3, 136.1, 137.2, 149.3, 157.0, 171.1, 173.3. ESI+ (*m/z*)=397. Anal. Calcd for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>S: C, 66.64; H, 6.10; N, 7.07; S, 8.09. Found: C, 66.91; H, 6.26; N, 7.12; S, 8.21.

**4.1.7. 3-(*N*-Benzoyl-7-azabicyclo[2.2.1]hept-1-yl)-2-(2-pyridylthio)-acrylic acid methyl ester (4e).** The yellow solid **3** (starting from 0.61 mmol of **2**, Method B) was dissolved in degassed and dry toluene and propionic acid methyl ester (0.56 mL, 6.10 mmol) was added. Then, the mixture was heated at reflux for 6 h. The solvent was eliminated and the residue purified by column chromatography using hexane/ethyl acetate 7:3 to give 140 mg of **4e** as a white oil (62% yield). IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1723, 1644. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.48–1.60 (m, 2H), 1.80–1.92 (m, 3H), 2.03–2.32 (m, 3H), 3.66 (s, 3H), 4.10–4.17 (m, 1H), 6.93–7.01 (m, 1H), 7.26–7.49 (m, 5H), 7.52–7.67 (m, 3H), 8.35–8.40 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 30.4, 33.0, 52.3, 61.2, 67.9, 119.9, 120.2, 121.4, 128.2, 128.3, 131.2, 135.6, 136.6, 148.8, 149.3, 159.6, 167.2, 172.9. ESI+ (*m/z*)=395. Anal. Calcd for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S: C, 66.98; H, 5.62; N, 7.10; S, 8.13. Found: C, 66.91; H, 5.76; N, 7.22; S, 8.21.

**4.1.8. *N*-Benzoyl-7-azabicyclo[2.2.1]heptane (4f).** The yellow solid **3** (starting from 0.38 mmol of **2**, Method B) was dissolved in THF and Bu<sub>3</sub>SnH (204 μL, 0.76 mmol) was added. Then, the mixture was irradiated with a 200 W tungsten lamp at rt for 6 h. The solvent was eliminated and the residue purified by column chromatography using hexane/ethyl acetate 6:4 to give 47 mg of **4f** as a white solid (61% yield). Mp 73–76°C. IR (CH<sub>2</sub>Cl<sub>2</sub>, cm<sup>-1</sup>): 1624. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.34–1.55 (m, 4H), 1.70–2.00 (m, 4H), 4.09–4.13 (m, 1H), 4.72–4.76 (m, 1H), 7.32–7.45 (m, 3H), 7.50–7.57 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 28.7, 30.4, 53.6, 58.7, 127.6, 128.2, 130.3, 136.2, 168.6. ESI+ (*m/z*)=202.

Anal. Calcd for C<sub>13</sub>H<sub>15</sub>NO: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.25; H, 7.37; N, 6.82.

## 4.2. X-Ray structure analysis

Crystals of **4b** and **4c** were obtained by slow evaporation from a mixture of hexane/dichloromethane.

**4.2.1. Crystal data of 4b.** C<sub>13</sub>H<sub>14</sub>BrNO, *M<sub>w</sub>*=280.26, colourless crystal of 0.4×0.35×0.25 mm<sup>3</sup>, *T*=293 K, triclinic, space group *P*  $\bar{1}$ , *Z*=4, *a*=9.7401(2) Å, *b*=11.4344(3) Å, *c*=12.0738(3) Å, *V*=1232.16(5) Å<sup>3</sup>, *d<sub>calc</sub>*=1.510 g cm<sup>-3</sup>, *F*(000)=568, λ=0.71070 Å (Mo Kα), μ=3.315 mm<sup>-1</sup>, Nonius kappa CCD diffractometer, θ range 2.49–27.48°, 5606 collected reflections, 5606 unique, full-matrix least-squares (SHELXL97<sup>22</sup>), *R*<sub>1</sub>=0.0567, *wR*<sub>2</sub>=0.0966, (*R*<sub>1</sub>=0.1130, *wR*<sub>2</sub>=0.1078 all data), goodness of fit=1.529, residual electron density between 0.571 and -0.634 e Å<sup>-3</sup>. Hydrogen atoms fitted at theoretical positions.

**4.2.2. Crystal data of 4c.** C<sub>13</sub>H<sub>14</sub>INO, *M<sub>w</sub>*=327.15, colourless crystal of 0.67×0.25×0.25 mm<sup>3</sup>, *T*=293 K, orthorhombic, space group *P*, *b*, *c*, *a*, *Z*=8, *a*=9.1770(2) Å, *b*=13.5170(3) Å, *c*=20.2600(5) Å, *V*=2513.16(5) Å<sup>3</sup>, *d<sub>calc</sub>*=1.729 g cm<sup>-3</sup>, *F*(000)=1280, λ=0.71070 Å (Mo Kα), μ=2.528 mm<sup>-1</sup>, Nonius kappa CCD diffractometer, θ range 2.86–27.47°, 2868 collected reflections, 2868 unique, full-matrix least-squares (SHELXL97<sup>22</sup>), *R*<sub>1</sub>=0.0436, *wR*<sub>2</sub>=0.0969, (*R*<sub>1</sub>=0.0687, *wR*<sub>2</sub>=0.1077 all data), goodness of fit=1.397, residual electron density between 0.409 and -1.714 e Å<sup>-3</sup>. Hydrogen atoms fitted at theoretical positions.

## 5. Supplementary material

Further details on the crystal structures **4b** and **4c** are available on request from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, UK on quoting the depository numbers CCDC 173438 and 173439, respectively.

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