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An efficient preparation of *N*-alkyl-2-benzazepine derivatives and investigation of their biological activity

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ABSTRACT

N-Alkyl-2-benzazepine derivatives are readily prepared through N-alkylation of secondary 2-benzazepines that are constructed via 7-endo selective cyclization of radical cyclization of *N*-boc-*N*-(2-bromo-5-methoxyphenylmethyl) methacrylamides. The structure and activity relationship of these derivatives are examined.

Benzazepines, containing seven-membered aza-heterocyclic ring fusing aromatic unit, are of interest due to their biological activity that would be expected as a potential drug candidate.[1] For example, this heterocyclic nucleus was applied in a part of peptide mimic of RGD motif, which was a well-known antagonist of integrin that engaged cell adhesion and signal transduction.[2] Recently, we found that 2-benzazepines structure showed an activity that promoted not only the epithelial cell migration in vitro but also the skin wound healing in vivo. This is a remarkable activity of 2-benzazepines promising new potential drug candidate.[3] Preparation of this structure used to require long steps.[2] 2-Benazepines are readily prepared through a unique 7-endo selective cyclization of aryl radical.[4] To investigate structure and activity relationship of these compounds, we need to develop a quick method to derivatize 2-benzazepines. In this Letter, we disclose a convenient derivatization of benzazepines through the preparation of secondary 2-benzaepienes and subsequent N-alkylation. The biological activity of these compounds is also reported.

Our strategy for the derivatization is based on the preparation of secondary 2-benzazepines **1** and following N-alkylation. To prepare compound **1**, a dummy substituent should be introduced before cyclization because any kind of cyclization from secondary amides should be reluctant to undergo due to dominant *s-trans* conformation of the amide unit. The dummy substituent should be readily introduced and removed in good yield under mild conditions. We chose *N*-carbamate derivatives such as *N*-boc as the suitable dummy substituents for this preparation.

Preparation of **1** was carried out straightly from commercial available 2-bromo-5-methoxybenzoic acid **2**. The acid was reduced to corresponding benzyl alcohol then converted into azide **3** in 89% yield through chloride. Reductive treatment of azide **3** with Raney-Ni gave primary benzyl amine which underwent acylation reaction with methacroyl chloride to give unsaturated amide **4** in 59% yield. *N*-protection of **4** with $(boc)_2O$ or $ClCO_2Me$ under standard conditions smoothly afforded precursor **5a** and **5b** in good yield (Scheme 1).

The radical cyclization of **5** was carried out under standard radical reaction conditions. Treatment of **5a** and **5b** with Bu_3SnH with syringe pump technique resulted in the smooth conversion to desired **6a** and **6b** in 29% and 44%, respectively. Although the yield was moderate, the cyclization took place very selective because no regioisomeric product of **6** was observed in the reaction pot. This is a great advantage in the preparation because the radical cyclization from *N*-alkyl amides always contained small amounts of side products such as 6-exo products which was hard to be removed through usual chromatographic treatment.[4] The 7-endo selectivity might be enhanced by the presence of carbamate group such as *N*-boc. Compound **6** was readily purified by recrystallization so the present method was much advantageous to prepare

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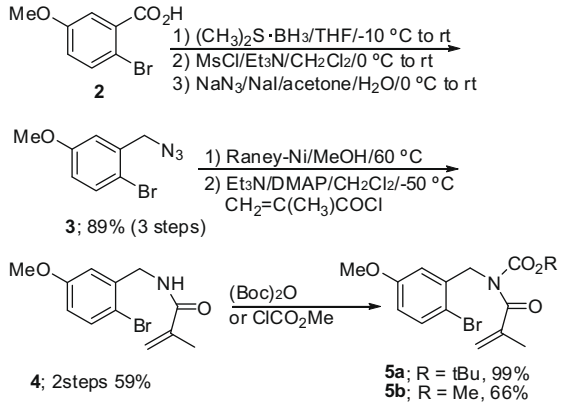


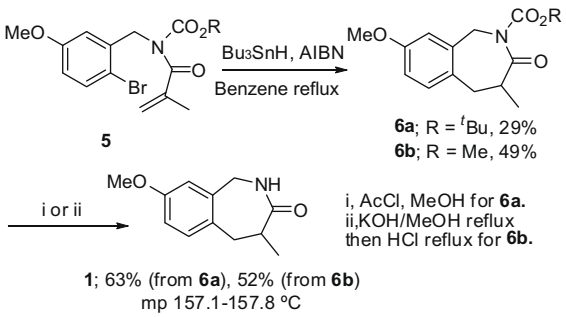
Scheme 1. Preparation of precursor **5** of 7-endo selective radical cyclization.

2-benzazepines in pure form. The *N*-boc group in **6a** was then removed by treatment with acidic media to give secondary benzazepine **1** in 63% yield. Basic treatment of **6b** followed by acidic treatment resulted in the removal of methoxycarbonyl group, giving **1** in 52% yield. The present preparation could be carried out in multi-gram scale so the present method was useful for quick derivatization of 2-benzazepine derivatives (Scheme 2).

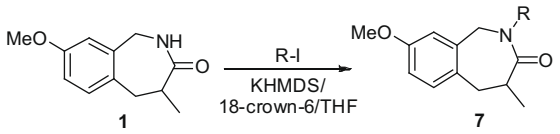
N-Alkylation of **1** was examined under various conditions. Finally we found that use of KHMDS in the presence of 18-crown-6 achieved efficient alkylation and desired *N*-alkyl-2-benzazepines **7** were prepared in good yield (Scheme 3). Use of wet 18-crown-6 spoiled the yield of **7** in a moderate level. Use of primary iodide progressed the reaction smoothly to give **7** in good yield. For example, MeI and EtI served as a good alkylating agent for **1** to give **7a** and **7b** in 81% and 87% yield, respectively (entries 1 and 2). Use of benzyl bromide was also good result (entry 9). On the other hand, use of secondary iodide, isopropyl iodide, gave **7g** in trace amounts (entry 7). Sterically demanding primary alkyl iodide also gave sluggish results (entry 8). The results are summarized in Table 1.[5]

With 2-benzazepine derivatives in hand, a biological activity of 2-benzazepine derivatives was evaluated using in vitro wound healing assay (scratch assay) with human skin epithelial HaCat cells.[3] The results were shown in Figure 1. Compounds **1**, **7a** and **7b** significantly promoted the migration of HaCat cells as fibronectin (positive control), whereas **7c**, **7d**, **7e**, **7g** and **7i** had no effect on it. A side chain at *N*-2 position was thus important for this biological activity of 2-benzazepine derivatives. The steric size between methyl and ethyl seems optimal at this side chain position, and longer alkyl chain than propyl group at *N*-2 position spoiled the biological activity.

In conclusion, we have developed a new preparation of 2-benzazepine derivatives from *N*-boc acrylamide. The present method



Scheme 2. 7-Endo selective radical cyclization of **5** and preparation of **1**.



Scheme 3. N-Alkylation and derivatization of **1**.

Table 1
Alkylation of amide **1**

Entry	R–I	7	Yield[a] (%)	Mp (°C)
1	Me	**7a**	81	75.5–76.0
2	Et	**7b**	87	105.8–106.2
3	Pr	**7c**	72	63.5–64.5
4	Bu	**7d**	71	61.8–62.3
5	C_5H_{11}	**7e**	79	68.8–69.3
6	C_6H_{13}	**7f**	58	36.8–37.4
7	^{i}Pr	**7g**	Trace	n.d.
8	^{i}Bu	**7h**	8	n.d.
9	Bn[b]	**7i**	84	104.9–105.4

[a] Isolated yields.
[b] Benzyl bromide was used.

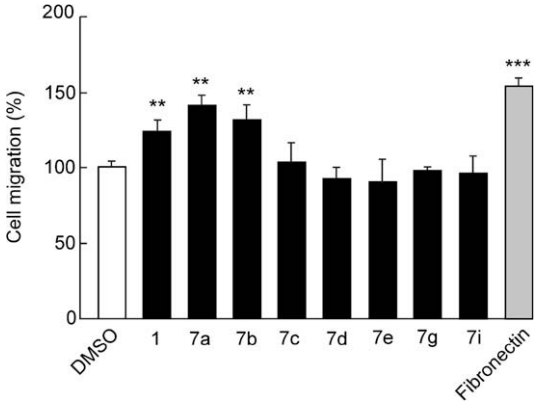


Figure 1. A biological activity of 2-benzazepine derivatives. The effects of the compounds on the migration of human skin epithelial HaCat cells were examined at 30 μM using in vitro wound healing assay (scratch assay). Fibronectin (100 nM) was used as positive control. Data were means ± S.E.M. of six independent determinations. **<0.01, ***<0.001 versus DMSO (Student's *t*-test).

is suitable for quick derivatization at *N*-2 side chain. Prepared derivatives were examined for SAR studies of their biological activity and *N*-side chain significantly affected the promotion activity for cell migration, in which methyl substituent at *N*-2 position showed the best activity. Further investigation on this system is now underway in our group.

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5. *Physical data for 2-benzazepines*; **1**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 1H), 6.79 (dd, J = 2.6, 8.3 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 3.99 (dd, J = 6.7, 16.0 Hz, 1H), 3.79 (s, 3H), 3.13 (ddd, J = 4.4, 6.8, 11.1 Hz, 1H), 2.97–2.88 (m, 2H), 1.26 (d, J = 6.7 Hz, 5H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 178.7, 157.8, 136.9, 131.4, 129.9, 113.7, 113.1, 55.3, 45.8, 36.4, 36.2, 17.5. HRMS (EI$^+$ M) m/z 205.1102. Calcd for $C_{12}H_{15}NO_2$ 205.1103.**7a**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.04 (d, J = 8.4 Hz, 1H), 6.78 (dd, J = 2.7, 8.5 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 5.18 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H), 3.76 (d, J = 13.8 Hz, 1H), 3.45–3.30 (m, 1H), 3.05 (s, 3H), 2.90 (m, 2H), 1.27 (d, J = 6.8 Hz, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.9, 157.5, 135.2, 131.8, 129.6, 114.3, 113.2, 55.3, 54.1, 37.1, 35.2, 34.8, 17.6. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.95; H, 7.69; N, 6.39. Compound **7b**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.02 (d, J = 8.4 Hz, 1H), 6.82 – 6.70 (m, 1H), 6.62 (d, J = 2.8 Hz, 1H), 5.10 (d, J = 16.4 Hz, 1H), 3.81 (d, J = 16.4 Hz, 1H), 3.79 (s, 3H), 3.52 (q, J = 7.2 Hz, 2H), 3.41–3.24 (m, 1H), 2.86 (d, J = 12.5 Hz, 2H), 1.24 (d, J = 6.5 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.3, 157.5, 136.0, 131.8, 129.7, 114.0, 113.0, 55.3, 52.0, 42.7, 37.2, 34.9, 17.5, 13.5. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.99; H, 8.32; N, 5.99. Compound **7c**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.02 (d, J = 8.4 Hz, 1H), 6.83–6.68 (m, 1H), 6.61 (d, J = 2.7 Hz, 1H), 5.12 (d, J = 16.6 Hz, 1H), 3.80 (d, J = 16.6 Hz, 1H), 3.79 (s, 3H), 3.48 (m, 1H), 3.43 – 3.25 (m, 1H), 3.00 – 2.73 (m, 2H), 1.48 (dd, J = 7.5, 15.0 Hz, 2H), 1.24 (d, J = 6.5 Hz, 3H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.5, 157.5, 135.9, 131.6, 129.5, 114.0, 113.0, 55.2, 52.4, 49.5, 37.2, 34.8, 21.4, 17.4, 11.0. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.71; H, 8.71; N, 5.66. Compound **7d**; H NMR (270 MHz, $CDCl_3$) δ 7.00 (d, J = 8.4 Hz, 1H), 6.75 (dd, J = 2.7, 8.4 Hz, 1H), 6.61 (s, 1H), 5.09 (d, J = 16.4 Hz, 1H), 3.80 (d, J = 16.3 Hz, 1H), 3.77 (s, 3H), 3.43 (m, 3H), 3.03–2.70 (m, 2H), 1.42 (dd, J = 7.1, 14.4 Hz, 2H), 1.29–1.15 (m, 5H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.5, 157.6, 136.0, 131.7, 129.7, 114.1, 113.0, 55.3, 52.4, 47.7, 37.3, 35.0, 30.4, 19.9, 17.5, 13.7. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.14; H, 8.88; N, 5.33. Compound **7e**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.02 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 5.11 (d, J = 16.4 Hz, 1H), 3.80 (d, J = 9.6 Hz, 1H), 3.78 (s, 3H), 3.60–3.24 (m, 3H), 3.03–2.74 (m, 2H), 1.52–1.39 (m, 3H), 1.24 (d, J = 6.5 Hz, 7H), 0.80 (t, J = 7.0 Hz, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.3, 157.5, 135.9, 131.5, 129.5, 113.9, 113.0, 55.2, 52.3, 47.8, 37.1, 34.8, 28.7, 27.8, 22.1, 17.4, 13.7. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.01; H, 9.18; N, 4.94. Compound **7f**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.01 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 2.6 Hz, 2H), 5.11 (d, J = 16.3 Hz, 1H), 3.80 (d, J = 16.3 Hz, 1H), 3.78 (s, 3H), 3.41 (m, 3H), 2.86 (m, 2H), 1.45 (m, 2H), 1.35–1.08 (m, 9H), 0.81 (t, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.5, 157.5, 136.0, 131.6, 129.6, 114.0, 113.0, 55.3, 52.4, 47.9, 37.2, 34.9, 31.4, 28.2, 26.3, 22.3, 17.5, 13.8. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.34; H, 9.72; N, 4.69. Compound **7i**; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.41 – 7.14 (m, 5H), 7.02 (d, J = 8.4 Hz, 1H), 6.74 (dd, J = 2.6, 8.4 Hz, 1H), 6.37 (d, J = 2.7 Hz, 1H), 4.99 (d, J = 14.9 Hz, 2H), 4.33 (d, J = 14.8 Hz, 1H), 3.77 (d, J = 16.5 Hz, 1H), 3.72 (s, 3H), 3.42 – 3.34 (m, 1H), 2.95 (m, 2H), 1.31 (d, J = 6.5 Hz, 3H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 175.7, 157.3, 137.6, 135.3, 131.4, 129.3, 128.4, 128.4, 128.1, 128.1, 127.3, 113.9, 113.2, 55.1, 51.1, 50.3, 37.1, 34.9, 17.5. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.11; H, 7.32; N, 4.63.