Convenient Synthesis of 2-Benzazepines via Radical Cyclization

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Supporting Information

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Experimental

General

All ¹H and ¹³C NMR spectra were measured in CDCl₃ or DMSO-d₆ and recorded on JEOL EX-270 (270 MHz for H and 67.5 MHz for C) spectrometer. All the reactions were performed under nitrogen atmosphere unless otherwise mentioned. Solvents used in the reaction described here were dried over appropriate drying agents (K for THF, Na for ether, benzene and toluene, and CaH₂ for all other solvents) and distilled under nitrogen before use. Bu₃SnH was purchased from TCI, which were used without further purification.

Preparation of N-(2-Bromo-5-methoxybenzyl)-2,2,2-trifluoroethylamine [2a].

General Procedure: To a mixture of 2-bromo-5-methoxybenzaldehyde (3.26 g, 15.2 mmol) and 2,2,2-trifluoroethylamine (1.40 mL, 17.6 mmol) in methanol (20 mL) at 0°C was added NaBH₃CN (1.70 g, 27.1 mmol) and acetic acid (1.00 mL, 18.9 mmol). The

reaction mixture was allowed to stir at ambient temperature for 7 h. After removal of methanol in vacuo, water (50 mL) was added to the residue and the resulting biphasic mixture was extracted with ether (3 x 30 mL). Combined organic phase was dried over Na₂SO₄. After filtration and evaporation of organic solvent, the crude product was purified through flash chromatography (hexane then hexane-ethyl acetate) to give **2a** in 87% yield (3.94 g). Colorless oil. ¹H-NMR (CDCl₃) δ 1.87 (s, 1 H), 3.18 (q, 2 H, *J* = 9.4 Hz), 3.79 (s, 3 H), 3.93 (s, 2 H), 6.70 (dd, 1 H, *J* = 3.3, 8.6 Hz), 6.97 (d, 1 H, *J* = 3.0 Hz), 7.43 (d, 1 H, *J* = 8.9 Hz). ¹³C-NMR (CDCl₃) δ 49.5 (q, *J* = 31.8 Hz), 52.9, 55.3, 113.8, 114.4, 115.7, 125.5 (q, *J* = 279 Hz), 133.4, 139.0, 159.0.

Other amines **2** were prepared in a similar manner.

N-Benzyl (2-bromo-5-methoxybenzyl)amine [2b]: ¹H-NMR (CDCl₃) δ 2.04 (s, 1 H), 3.79 (s, 3 H), 3.81 (s, 2 H), 3.84 (s, 2 H), 6.69 (dd, 1 H, *J* = 3.0, 8.6 Hz), 6.99 (d, 1 H, *J* = 3.0 Hz), 7.27-7.44 (m, 6 H). ¹³C-NMR (CDCl₃) δ 52.9, 53.0, 55.3, 114.1, 115.7, 126.9, 128.1, 128.3, 133.1, 139.9, 140.0, 158.9.

N-(2-Bromo-5-methoxybenzyl)-butylamine [2c]: ¹H-NMR (CDCl₃) δ 0.92 (t, 3 H, *J* = 7.3 Hz), 1.32-1.41 (m, 2 H), 1.46-1.55 (m, 2 H), 1.61 (s, 1 H), 2.63 (t, 2 H, *J* = 7.1 Hz), 3.79 (s, 3 H), 3.81 (s, 2 H), 6.67 (dd, 1 H, *J* = 3.3, 8.6 Hz), 6.97 (d, 1 H, *J* = 3.0 Hz), 7.41 (d, 1 H, *J* = 8.9 Hz). ¹³C-NMR (CDCl₃) δ 13.9, 20.3, 32.1, 48.8, 53.8, 55.2, 113.9, 114.0, 115.6, 133.0, 140.3, 158.8.

N-(2-Bromobenzyl)-2,2,2-trifluoroethylamine [2d]: ¹H-NMR (CDCl₃) δ 1.83 (br, 1 H), 3.18 (q, 2 H, *J* = 9.2 Hz), 3.98 (s, 2 H), 7.12-7.58 (m, 4H). ¹³C-NMR (CDCl₃) δ 49.4 (q, *J* = 31.7 Hz), 52.9, 123.8, 125.5 (q, *J* = 279.5 Hz), 127.5, 128.9, 130.1, 132.9, 138.0.

Preparation of

N-(2-Bromo-5-methoxybenzyl)2-methylene-N-(2,2,2-trifluoroethyl)-succinylamide-4-ethyl ester [3a]. General Procedure: To a solution of **2a** (2.88 g, 17.7 mmol), Et₃N

(2.50 mL, 17.7 mmol) and DMAP (0.1 g) in CH₂Cl₂ (25 mL) was added (monoethyl)itaconoyl chloride, prepared from monoethyl itaconate (2.80 g, 17.7 mmol) and SOCl₂ (1.48 mL, 20.4 mmol), at -50°C. The reaction mixture was allowed to warm to room temperature for 12 h. HCl(aq) (1 M, 30 mL) was added to the reaction mixture and the resulting solution was extracted with CH₂Cl₂ (3 x 40 mL). The organic phase was combined, washed with NaHCO₃ (50 mL) and dried over Na₂SO₄. After filtration and evaporation of organic solvent, the crude product was purified through flash chromatography (hexane then hexane-ethyl acetate) to give **3a** in 77% yield (3.26 g). Colorless oil. ¹H-NMR (CDCl₃) δ 1.26 (t, 3 H, *J* = 7.1 Hz), 3.49 (s, 2 H), 3.77 (s, 3 H), 4.14 (q, 2 H, *J* = 7.2 Hz), 4.09-4.18 (m, 2 H), 4.91 (br, 2 H), 5.45 (m, 2 H), 6.72 (d, 1 H, *J* = 8.6 Hz), 6.80 (d, 1 H, *J* = 2.6 Hz), 7.46 (d, 1 H, *J* = 8.6 Hz). ¹³C-NMR (CDCl₃) δ 14.0, 39.9, 48.8, 53.2, 55.4, 61.1, 113.2, 114.0, 114.6, 120.2, 124.3 (q, *J* = 280.8 Hz), 133.5, 135.6, 135.8, 159.4, 170.4, 172.3.

Other amides **3** were prepared in a similar manner.

***N*-(2-Bromo-5-methoxybenzyl)-2-methyl-*N*-(2,2,2-trifluoroethyl)acrylamide [3b]:**

¹H-NMR (CDCl₃) δ 2.00(s, 3 H), 3.78(s, 3 H), 4.02(q, 2 H, *J* = 8.9 Hz), 4.80(s, 2 H), 5.16 (s, 1 H), 5.29 (s, 1 H), 6.70-6.77 (m, 1 H), 6.74 (dd, 1 H, *J* = 3.0, 8.9 Hz), 7.47(d, 1 H, *J* = 8.9 Hz). ¹³C-NMR (CDCl₃) δ 20.3, 48.3, 52.6, 55.4, 113.4, 114.7, 114.9, 116.9, 124.3 (q, *J* = 280 Hz), 134.0, 135.8, 139.3, 159.3, 173.6. Anal. calc. for C₁₄H₁₅BrF₃NO₂: C, 45.92; H, 4.13; N, 3.83. Found: C, 45.64; H, 4.00; N, 3.71.

***N*-(2-Bromo-5-methoxybenzyl)-*N*-(2,2,2-trifluoroethyl)acrylamide [3c]:** ¹H-NMR

(DMSO-d₆) δ 3.43 (s, 2 H), 3.80 (s, 3 H), 4.43 (q, 1 H, *J* = 9.6 Hz), 4.62 (q, 1 H, *J* = 8.9 Hz), 4.71 (s, 1 H), 4.86 (s, 1 H), 5.87 (dd, 1 H, *J* = 10.7, 24.4 Hz), 6.36 (dd, 1 H, *J* = 2.3, 16.5 Hz), 6.57-6.65 (m, 2 H), 6.92-7.10 (m, 1 H), 7.63 (t, 1 H, *J* = 8.9 Hz). ¹³C-NMR (CDCl₃) δ 46.7 (q, *J* = 32.0 Hz), 52.5, 55.4, 112.3, 113.6, 114.4, 126.2, 128.2 (q, *J* = 272.8 Hz), 130.7, 133.9, 135.7, 159.5, 167.6. Anal. calc. for C₁₃H₁₃BrF₃NO₂: C, 44.34;

H, 3.72; N, 3.98. Found: C, 44.08; H, 3.81; N, 3.99.

***N*-(2-Bromo-5-methoxybenzyl)2-methylene-*N*-benzylsuccinylamide-4-methyl ester**

[3d]: $^1\text{H-NMR}$ (CDCl_3) δ 3.54 (s, 2 H), 3.68 (m, 3 H), 3.78 (s, 3 H), 4.68-80 (m, 4 H), 5.29-5.39 (m, 2 H), 6.70(br, 1 H), 6.88(d, 1 H, $J = 3.0$ Hz), 7.22-7.65 (m, 6 H).

$^{13}\text{C-NMR}$ (CDCl_3) δ 40.1, 48.1, 52.0, 55.5, 113.8, 114.2, 114.5, 118.7, 126.6, 127.4, 128.3, 128.7, 133.3, 133.7, 136.5, 159.4, 171.7 (2C). Anal. calc. for $\text{C}_{21}\text{H}_{22}\text{BrNO}_4$: C, 58.34; H, 5.13; N, 3.24. Found: C, 58.09; H, 5.07; N, 3.28.

***N*-(2-Bromo-5-methoxybenzyl)-2-methyl-*N*-benzylacrylamide [3e]: $^1\text{H-NMR}$**

(DMSO-d_6) δ 1.91 (s, 3 H), 3.72 (s, 3 H), 4.47 (br, 2 H), 4.58 (br, 2 H), 5.08 (br, 1 H), 5.21 (br, 1 H), 6.65 (d, 1 H, $J = 3.0$ Hz), 6.85 (dd, 1 H, $J = 3.0, 8.6$ Hz), 7.19-7.38 (m, 5 H), 7.50 (d, 1 H, $J = 8.6$ Hz). $^{13}\text{C-NMR}$ (DMSO-d_6) δ 20.3, 51.2 (m), 55.3, 113.9, 112.0, 114.6, 115.1, 127.3, 128.6, 133.4, 136.6, 136.9, 140.0, 158.9, 172.2. Anal. calc. for $\text{C}_{19}\text{H}_{20}\text{BrNO}_2$: C, 60.97; H, 5.39; N, 3.74. Found: C, 60.70; H, 5.28; N, 3.68.

***N*-(2-Bromo-5-methoxybenzyl)2-methylene-*N*-butylsuccinylamide-4-methyl ester**

[3f]: $^1\text{H-NMR}$ (DMSO-d_6 , 80 $^\circ\text{C}$) δ 0.93 (t, 3 H, $J = 7.3$ Hz), 1.33 (m, 2 H), 1.60 (m, 2 H), 3.38-3.43 (m, 2 H), 3.46 (s, 2 H), 3.69 (s, 3 H), 3.84 (s, 3 H), 4.68 (s, 2 H), 5.35 (s, 1 H), 5.50 (s, 1 H), 6.87-6.93 (m, 3 H), 7.59 (d, 2 H, $J = 8.6$ Hz). $^{13}\text{C-NMR}$ (CDCl_3) δ 13.6, 19.9, 28.6 and 30.5 (rotamer, 1 C), 39.7, 45.5 and 47.3 (rotamer, 1 C), 47.8 and 52.4 (rotamer, 1 C), 51.6, 55.3, 112.6, 113.8, 114.3, 118.0, 133.0, 133.3, 137.0, 159.2, 171.0, 171.1. Anal. calc. for $\text{C}_{18}\text{H}_{24}\text{BrNO}_4$: C, 54.28; H, 6.07; N, 3.52. Found: C, 54.58; H, 6.06; N, 3.46.

***N*-(2-Bromobenzyl)2-methylene-*N*-(2,2,2-trifluoroethyl)-succinylamide-4-methyl ester [3g]: $^1\text{H-NMR}$**

(DMSO-d_6 , 60 $^\circ\text{C}$) δ 3.37 (s, 2 H), 3.60 (s, 3 H), 4.26 (q, 2 H, $J = 9.2$ Hz), 4.78 (s, 2 H), 5.33 (s, 1 H), 5.51 (s, 1 H), 7.21-7.28 (m, 2 H), 7.42 (t, 1 H, $J = 7.3$ Hz), 7.64 (d, 1 H, $J = 8.0$ Hz). $^{13}\text{C-NMR}$ (CDCl_3) δ 39.7, 45.1 (m), 50.8 (m), 52.1, 120.2, 123.1, 124.3 (q, $J = 280.9$ Hz), 128.0, 128.6, 133.3, 134.7, 135.8, 171.0, 172.2. Anal. calc. for $\text{C}_{15}\text{H}_{15}\text{BrF}_3\text{NO}_3$: C, 45.70; H, 3.84; N, 3.55. Found: C, 45.77; H, 3.85; N,

3.49.

***N*-(2-Bromobenzyl)-2-methyl-*N*-(2,2,2-trifluoroethyl)acrylamide [3h]:** $^1\text{H-NMR}$ (CDCl_3) δ 1.98 (s, 3 H), 4.01 (q, 2 H, $J = 8.9$ Hz), 4.85 (s, 2 H), 5.15 (s, 1 H), 5.28 (s, 1 H), 7.17-7.36 (m, 3 H), 7.60 (dd, 1 H, $J = 1.0, 7.9$ Hz). $^{13}\text{C-NMR}$ (CDCl_3) δ 20.2, 44.7 (m), 52.9 (m), 116.8, 124.3 (q, $J = 282.0$ Hz), 127.8, 129.5, 133.4, 134.7, 139.3, 173.6. Anal. calc. for $\text{C}_{13}\text{H}_{13}\text{BrF}_3\text{NO}$: C, 46.45; H, 3.90; N, 4.17. Found: C, 46.71; H, 4.00; N, 4.12.

***N*-(2-Bromobenzyl)-*N*-(2,2,2-trifluoroethyl)acrylamide [3i]:** $^1\text{H-NMR}$ (DMSO-d_6) δ 4.34 (q, 1 H, $J = 9.4$ Hz), 4.53 (q, 1 H, $J = 8.9$ Hz), 4.69 (s, 1 H), 4.84 (s, 1 H), 5.73 (d, 1 H for rotamer A, $J = 9.2$ Hz), 5.83 (d, 1 H for rotamer B, $J = 9.2$ Hz), 6.27 (dd, 1 H, $J = 2.3, 16.5$ Hz), 6.55 (dd, 1 H, $J = 10.2, 16.5$ Hz), 6.93-7.68 (m, 4 H). $^{13}\text{C-NMR}$ (CDCl_3) δ 46.4 (q, $J = 34.2$ Hz), 52.4, 126.2, 127.8, 128.4 (q, $J = 276.3$ Hz), 129.4, 130.5, 133.2, 167.5. Anal. calc. for $\text{C}_{12}\text{H}_{11}\text{BrF}_3\text{NO}$: C, 44.74; H, 3.44; N, 4.35. Found: C, 44.69; H, 3.47; N, 4.29.

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 OPERATOR :

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BF 0.16 Hz
RGAIN 16
OPERATOR :

C:\Inetpub\ftproot\kamimura\yt02025-13c.gxd

YT02025-13C

DEFILE
COMNT
DATIM
OBNUC
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POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
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EXREF
BF
RGAIN

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BCM

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2b

05-JUN-02 16:39:49
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POINT 5800.0 Hz
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RGAIN 16
OPERATOR :

S11

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PW1 3.9 us
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OPERATOR :

22-OCT-01 09:22:32

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OBNUC 1H

EXMOD NON

OFR

OBSET

OBFIN

POINT

FREQU

SCANS

ACQTM

PD

PW1

IRNUC 1H

CTEMP

SLVNT CDCL3

EXREF

BF

RGAIN 21

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112.00 KHz
5800.0 Hz
32768
5405.4 Hz
16
3.031 sec
3.969 sec
5.2 us

21.0 C
0.00 ppm
0.16 Hz

YT01056-1B

2d

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34.045

1.000

35.556

87.132

[illegible]

20-NOV-01 06:59:55

DFILE Q1H

OBNUC 1H

EXMOD NON

OFR

OBSET

OBFIN

POINT

FREQU

SCANS

ACQTM

PD

PW1

IRNUC 1H

CTEMP

SLVNT CDCL3

EXREF

BF

RGAIN 17

OPERATOR :

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5405.4 Hz
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0.16 Hz

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PPM

03-NOV-01 19:05:44

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OBNUC 13C

EXMOD BCM

OFR

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22.6 c

77.00 ppm

1.50 Hz

29

OPERATOR :

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OBSET 112.00 kHz
OBFIN 5800.0 Hz
POINT 32768
FREQU 5405.4 Hz
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PD 3.969 sec
PW1 5.2 us
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BF 0.16 Hz
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OPERATOR :

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 PW1 3.9 us
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 BF 1.50 Hz
 RGAIN 29
 OPERATOR :

04-JUL-02 00:37:41

DFILE Q1H

OBNUC 1H

EXMOD NON

OFPR

OBSET

OBFIN

POINT

FREQU

SCANS

ACQTM

PD

PW1

IRNUC 1H

CTEMP

SLVNT CDCL3

EXREF

BF

RGAIN 16

OPERATOR :

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112.00 kHz
5800.0 Hz
32768
5405.4 Hz
16
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3.969 sec
5.2 us

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0.00 ppm
0.17 Hz

YT02033A-ALL

01-AUG-02 10:35:23

DFILE QIH

ORNUC 1H

EXMOD NON

OFR 270.05 MHz

OBSET 112.00 kHz

OBFIN 5800.0 Hz

POINT 32768

FREQU 5405.4 Hz

SCANS 16

ACQTM 3.031 sec

PD 3.969 sec

PW1 5.2 us

IRNUC 1H

CTEMP 26.3 c

SLVNT CDCL3

EXREF 0.00 ppm

BF 0.15 Hz

RGAIN 17

OPERATOR :

YT02034

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1.003 →
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1.000 →
0.087 →

S22

19-JUL-02 15:36:57

OFIL Q1H

OBNUC 1H

EXMOD NON

OFR

OBSET

OBFIN

POINT

FREQ

SCANS

ACQTM

PD

PW1

IRNUC 1H

CTEMP

SLVNT CDCL3

EXREF

BF

RGAIN 18

OPERATOR :

5f

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PPM

25-SEP-02 23:50:23

DFILE Q1H

OBNUC 1H

EXMOD NON

OFR

270.05 MHz

112.00 kHz

5800.0 Hz

32768

5405.4 Hz

16

3.031 sec

3.969 sec

5.2 us

IRNUC 1H

23.5 C

SLVNT CDCL3

EXREF

0.00 ppm

BF

0.17 Hz

RGAIN 20

OPERATOR :

YT02038C-CH

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0.343 →
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1.006 →
1.082 →

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 CTEMP 24.8 c
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 EXREF 77.00 ppm
 BF 1.50 Hz
 RGAIN 29
 OPERATOR :