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Convenient Synthesis of 2-Benzazepines via Radical Cyclization

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Abstract: Synthesis of 2-benzazepines was readily achieved via 7-endo radical cyclization of *N*-*o*-bromobenzylitaconamides or *N*-*o*-bromobenzylmethacrylamides which were prepared in two steps from commercially available benzaldehydes, amines, and α,*β*-unsaturated acids.

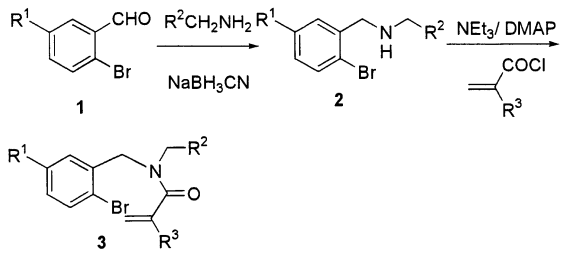
Integrins are recognized as pivotal proteins that play a key role in cell−cell adhesion, signaling, and apotosis.[1] Due to their biological importance, searching for a novel antagonist of integrins has been of interest to medicinal chemists because it is a promising candidate for a new drug. RGD sequence is the most well-known peptide sequence that interacts with $\alpha_v\beta_3$ integrin and acts as its antagonist. Recently, it has been reported that 2-benzazepine derivatives work as a non-peptide mimic for the RGD sequence,[2] and their binding site has been investigated with use of trifluoromethyl-substituted 2-benzazepines.[3] So far, however, the preparation of 2-benzazepines requires relatively long synthetic steps, and so development of a shorter, more efficient preparation has been desired.[2] Elaboration of medium-sized heterocyclic rings sometimes poses a challenging problem in organic synthesis.[4] Radical cyclization has been used as a powerful method for the preparation of carbocyclic or heterocyclic compounds.[5] In this paper, we report a convenient three-step synthesis of 2-benzazepine derivatives from commercially available aromatic aldehydes, amines, and α,*β*-unsaturated acids. The key reaction of the present procedure is a 7-endo-mode radical cyclization to α,*β*-unsaturated amides.[6] A multigram scale of preparation was also accomplished through this method.

TABLE 1. Preparation of Precursors 3

entry	R^1	R^2	**2**	yield[a] (%)	R^3	**3**	yield[a] (%)
1	MeO	CF_3	**2a**	87	CH_2CO_2Et	**3a**	77
2	MeO	CF_3	**2a**	87	Me	**3b**	81
3	MeO	CF_3	**2a**	87	H	**3c**	84
4	MeO	Ph	**2b**	83	CH_2CO_2Me	**3d**	78
5	MeO	Ph	**2b**	83	Me	**3e**	80
6	MeO	C_3H_7	**2c**	77	CH_2CO_2Me	**3f**	79
7	H	CF_3	**2d**	84	CH_2CO_2Me	**3g**	80
8	H	CF_3	**2d**	84	Me	**3h**	79
9	H	CF_3	**2d**	84	H	**3i**	75

[a] Isolated yield.

SCHEME 1



Preparation of cyclization precursors **3** was carried out through the reductive amination and subsequent acylation reaction with acyl halide (Scheme 1).[7] The results are summarized in Table 1. α,*β*-Unsaturated amides **3** were prepared in good yields.

Conversion of **3a** into 2-benzazepine **4a** was attempted. Initially, **3a** was exposed under the standard Heck reaction conditions,[8] but no 2-benzazepine **4a** was observed in the reaction mixture.[6d,e] Treatment of **3a** with Bu_3SnH, on the other hand, induced a 7-endo radical cyclization to give the desired **4a** along with small amounts of reduced product (Scheme 2). The results are summarized in Table 2.

A mixture of Bu_3SnH, AIBN, and **3a** in toluene at 110 °C gave **4a** in 39% yield (Table 2, entry 1). The slow-addition technique improved the yield of **4a** to 47% (Table 2, entry 2). The reaction performed at 0 °C with photoinitiation decreased the yield of **4a**; this might be due to

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TABLE 2. Optimization of Radical Cyclization of 3a

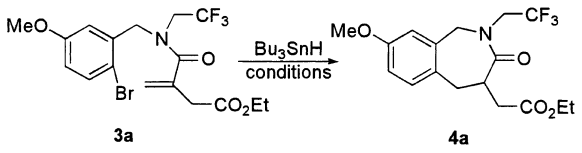
entry	solvent	conditions	time (h)	**4a**, yield (%)
1	toluene	110 °C	8	39
2	toluene	slow addition for 4 h, 80 °C	27	47
3	toluene	slow addition for 4 h, *hν*, 0 °C	13	32
4	benzene	slow addition for 6 h, 80 °C	15	57

TABLE 3. Radical Cyclization for Various Precursors 3

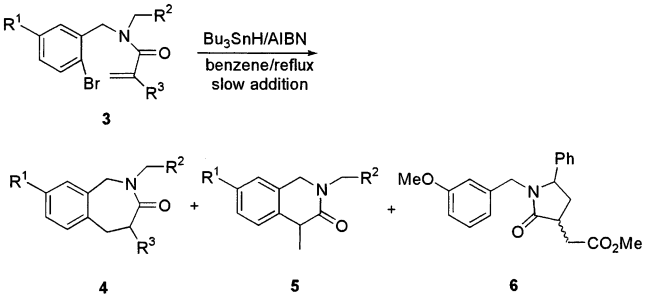
entry	**3**	R^1	R^2	R^3	**4**	yield[a] (%)	**5**	yield[a] (%)
1	**3a**	MeO	CF_3	CH_2CO_2Et	**4a**	57	**5a**	0
2	**3b**	MeO	CF_3	Me	**4b**	48	**5b**	0
3	**3c**	MeO	CF_3	H	**4c**	0	**5c**	50
4	**3d**	MeO	Ph	CH_2CO_2Me	**4d**	18	**5d**	0
5	**3e**	MeO	Ph	Me	**4e**	28	**5e**	0
6	**3f**	MeO	C_3H_7	CH_2CO_2Me	**4f**	56	**5f**	0
7	**3g**	H	CF_3	CH_2CO_2Me	**4g**	64	**5g**	0
8	**3h**	H	CF_3	Me	**4h**	49	**5h**	0
9	**3i**	H	CF_3	H	**4i**	0	**5i**	51

[a] Isolated yield.

SCHEME 2



SCHEME 3

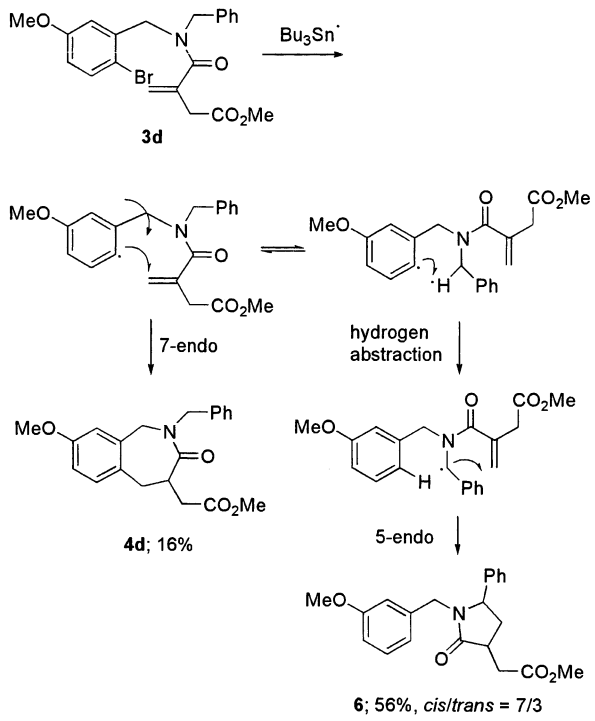


the restriction of the rotation between the C−N bond in the tertiary amide (Table 2, entry 3). Finally the best yield of **4a** was obtained in the reaction carried out in benzene with the slow-addition technique (Table 2, entry 4). This procedure was useful in the multigram scale of the preparation of **4a** (see the Experimental Section).

With these optimized conditions in hand, radical cyclization with various **3** was examined (Scheme 3). The results are summarized in Table 3.

Treatment of itaconamide **3a** and methacrylamide **3b** with Bu_3SnH produced 2-benzazepine **4a** and **4b** in good yields (Table 3, entries 1 and 2), while exposure of acrylamide **3c** under the same conditions resulted in 6-exo cyclization to give **5c** exclusively (Table 3, entry 3). In both cases, the formation of a small amount of reduced produced product was observed. Other unsaturated amides **3** showed similar results; itaconamides and methacrylamides preferred 7-endo cyclization to selectively give 2-benzazepine **4** (Table 3, entries 4−8), whereas acrylamides gave only 2*H*-isoquinolin-3-one **5** (Table 3, entry 9). This change of the cyclization selectivity depended on the presence or absence of R^3 substituent.

SCHEME 4



7-Endo cyclization occurred when some alkyl group occupied the R^3 position, while the absence of the substituent at R^3 exclusively caused 6-exo cyclization to produce **5**.

Treatment of benzyl amide **3d** with Bu_3SnH resulted in a poor yield of 2-benzazepine **4d** along with the formation of side product **6** that was isolated in a 56% yield. The structural elucidation based on NMR data revealed that compound **6** contained a 2-pyrrolidone structure. Compound **6** consisted of a pair of diastereomers whose ratio was about 7:3.[9] The formation of **6** from **3d** suggested that the 1,5-hydrogen transfer competed with the desired 7-endo cyclization reaction. A plausible reaction mechanism is depicted in Scheme 4.

First, the tributyltin radical abstracts the bromine atom attached to the benzene ring to generate an aryl radical. If the radical directly attacks the *β*-carbon of the unsaturated amide unit, 2-benzazepine **4d** is formed. The aryl radical, however, is reactive enough to abstract the benzylic hydrogen in the benzyl amide unit to give a benzyl radical,[10] which then attacks the *β*-carbon of the amide in the 5-endo mode and 2-pyrrolidine **6** is formed.[11] Considering the present product ratio, the 7-endo mode cyclization should be much slower than the abstraction of benzylic hydrogen.

(9) The NOE experiments for the major-**6** indicated the two substituents in the 2-pyrrolidone ring occupied a cis configuration because 2.3% signal enhancement between H3 and H5 was observed.

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In conclusion, the present procedure provides a convenient method to construct a 2-benzazepine ring which is of interest as a Gly-Asp mimic in the RGD sequence. It should be mentioned that the procedure could be applied in a multigram scale and 2-benzazepine **4a** was prepared in up to 5 g in a short time. As all of the starting materials were either commercially available or ready to be prepared, the present method will provide a convenient method to prepare these heterocyclic compounds.

Experimental Section

Preparation of [8-Methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-yl]acetic Acid Ethyl Ester (4a). General Procedure. A solution of Bu_3SnH (11.6 mL, 42.75 mmol) and AIBN (0.87 g, 5.27 mmol) in benzene (100 mL) was added to a solution of **3a** (11.34 g, 25.87 mmol) in benzene (40 mL) at refluxing temperature over 6 h. The resulting reaction mixture was allowed to stir at the same temperature for an additional 9 h. Benzene was removed in vacuo, and the crude residue was passed through flash chromatography (hexane then hexanes−ethyl acetate) to give **4a** in 57% yield (5.28 g):[12] white solid; mp 91 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.1 Hz), 2.45 (dd, 1 H, J = 5.6, 16.8 Hz), 2.90−3.06 (m, 3 H), 3.79 (s, 3 H), 3.83−4.00 (m, 3 H), 4.15 (q, 2 H, J = 6.9 Hz), 4.02−4.20 (m, 1 H), 5.34 (d, 1 H, J = 16.5 Hz), 6.61 (d, 1 H, J = 2.3 Hz), 6.79 (dd, 1 H, J = 2.6, 8.6 Hz), 7.034 (d, 1 H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.6, 34.9, 37.3, 48.1 (q, J = 34.2 Hz), 53.6, 55.5, 61.1, 114.0, 114.8, 125.5 (q, J = 280 Hz), 128.4, 132.2, 134.5, 158.0, 172.6, 175.3. Anal. Calcd for $C_{17}H_{20}F_3NO_4$: C, 56.82; H, 5.61; N, 3.90. Found: C, 56.78; H, 5.61; N, 3.88.

Radical cyclization for other **3** was performed in a similar manner.

8-Methoxy-4-methyl-2-(2,2,2-trifluoroethyl)-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (4b): mp 94 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3 H, J = 6.6 Hz), 2.84 (dd, 1 H, J = 6.9, 17.2 Hz), 3.00 (dd, 1 H, J = 4.3, 17.2 Hz), 3.43 (m, 1 H), 3.79 (s, 3 H), 3.83−3.99 (m, 1 H), 3.96 (d, 1 H, J = 16.9 Hz), 4.27 (qd, 1 H, J = 9.2, 15.8 Hz), 5.24 (d, 1 H, J = 16.8 Hz), 6.61 (d, 1 H, J = 2.3 Hz), 6.79 (dd, 1 H, J = 2.3, 8.2 Hz), 7.03 (d, 1 H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 17.5, 34.8, 37.0, 47.5 (q, J = 34.8 Hz), 53.0, 55.3, 113.4, 114.2, 124.4 (q, J = 279.9 Hz), 128. 6, 131.6, 134.1, 157.4, 176.4. Anal. Calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88. Found: C, 58.69; H, 5.68; N, 4.88.

7-Methoxy-4-methyl-2-(2,2,2-trifluoroethyl)-1,4-dihydro-2*H*-isoquinolin-3-one (5c): mp 77 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3 H, J = 7.3 Hz), 3.56 (q, 1 H, J = 7.3 Hz), 3.80 (s, 3 H), 4.09 (qd, 1 H, J = 9.2, 14.8 Hz), 4.21 (qd, 1 H, J = 9.2, 15.2 Hz), 4.48 (d, 1 H, J = 15.5 Hz), 4.61 (d, 1 H, J = 15.5 Hz), 6.73 (d, 1 H, J = 2.3 Hz), 6.86 (dd, 1 H, J = 2.6, 8.6 Hz), 7.14 (d, 1 H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 16.7, 40.7, 47.19, 47.4 (q, J = 34.2 Hz), 51.5, 55.3, 110.7, 113.5, 124.4 (q, J = 282.0 Hz), 127.0, 129.2, 132.0, 158.4, 173.3. Anal. Calcd for $C_{13}H_{14}F_3NO_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.09; H, 5.20; N, 5.10.

(2-Benzyl-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo-[*c*]azepin-4-yl)acetic acid methyl ester (4d): mp 93 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (dd, 1 H, J = 5.3,16.8 Hz), 2.94 (dd, 1 H, J = 7.1, 8.2 Hz), 3.08 (dd, 1 H, J = 8.6, 16.8 Hz), 2.88−3.12 (m, 1 H), 3.72 (s, 3 H), 3.73 (s, 3 H). 3.76 (d, 1 H, J = 14.5 Hz), 3.80−3.90 (m, 1 H), 4.33 (d, 1 H, J = 14.8 Hz), 5.01 (d, 1 H, J = 14.9 Hz), 5.11 (d, 1 H, J = 16.5 Hz), 6.37 (d, 1 H, J = 2.3 Hz), 6.74 (dd, 1 H, J = 2.6, 8.6 Hz), 7.01 (d, 1 H, J = 8.6 Hz), 7.18−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 34.6, 36.7, 37.0, 50.4, 51.3, 51.7, 55.2, 113.3, 114.0, 127.3, 127.9, 128.3, 128.5, 131.5, 135.0, 137.1, 157.3, 172.9, 173.9.

[1-(3-Methoxybenzyl)-2-oxo-5-phenylpyrrolidin-3-yl]acetic acid methyl ester (6): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.70 (td, 1 H, J = 9.6, 13.8 Hz), 2.57 (dd, 1 H, J = 8.9, 16.5 Hz), 2.69 (td, 1 H, J = 6.9, 12.5 Hz), 2.87−2.95 (m, 1 H), 3.02 (dd, 1 H, J = 4.0, 16.4 Hz), 3.47 (d, 1 H, J = 14.2 Hz), 3.70 (s, 3 H), 3.73 (s, 3 H), 4.33 (dd, 1 H, J = 7.2, 9.2 Hz), 5.02 (d, 1 H, J = 14.5 Hz), 6.53 (d, 1 H, J = 2.0 Hz), 6.58 (d, 1 H, J = 7.6 Hz), 6.79 (dd, 1 H, J = 2.3, 7.9 Hz), 7.12−7.19 (m, 3 H), 7.32−7.40 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 35.3, 36.2, 38.7, 44.5, 51.8, 55.2, 60.0, 113.2, 113.9, 120.9, 127.4, 128.3, 129.0, 129.5, 137.7, 140.1, 159.7, 172.3, 175.5.

2-Benzyl-8-methoxy-4-methyl-1,2,4,5-tetrahydrobenzo-[*c*]azepin-3-one (4e): mp 88 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3 H, J = 6.3 Hz), 2.88 (dd, 1 H, J = 12.5, 16.8 Hz), 3.00 (dd, 1 H, J = 4.9, 16.8 Hz), 3.42 (m, 1 H, J = 6.3 Hz), 3.71 (s, 3 H), 3.76 (d, 1 H, J = 16.5 Hz), 4.33 (d, 1 H, J = 14.8 Hz), 4.98 (d, 2 H, J = 15.2 Hz), 6.36 (d, 1 H, J = 2.6 Hz), 6.74 (dd, 1 H, J = 2.3, 8.6 Hz), 7.01 (d, 1 H, J = 8.6 Hz), 7.19−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.2, 35.5, 37.7, 50.9, 51.7, 55.7, 113.6, 114.4, 127.8, 128.9, 129.8, 131.9, 135.6, 138.0, 157.6, 176.2.

(2-Butyl-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo-[*c*]azepin-4-yl)acetic acid methyl ester (4f): mp 69 °C; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H, J = 7.3 Hz), 1.20 (m, 2 H, J = 7.3 Hz), 1.43 (m, 2 H, J = 7.3 Hz), 2.40 (dd, 1 H, J = 5.4, 16.8 Hz), 2.87 (dd, 1 H, J = 13.2, 16.8 Hz), 3.00 (dd, 1 H, J = 8.3, 16.5 Hz), 2.81−3.05 (m, 1 H), 3.40 (m, 1 H, J = 7.3 Hz), 3.51 (m, 1 H, J = 7.3 Hz), 3.70 (s, 3 H), 3.79 (s, 3 H), 3.82 (d, 1 H, J = 17.5 Hz), 5.21 (d, 1 H, J = 16.5 Hz), 6.62 (d, 1 H, J = 2.6 Hz), 6.76 (dd, 1 H, J = 2.6, 8.2 Hz), 7.01 (d, 1 H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.9, 30.3, 34.7, 36.6, 37.0, 47.7, 51.6, 52.3, 55.3, 113.0, 114.1, 128.5, 131.6, 135.6, 157.5, 173.0, 173.5.

[3-Oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-yl]acetic acid methyl ester (4g): mp 89 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (dd, 1 H, J = 5.3, 16.9 Hz), 2.91−3.12 (m, 3 H), 3.71 (s, 3 H), 3.80−4.20 (m, 4 H), 5.38 (d, 1 H, J = 16.5 Hz), 7.07−7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 35.2, 36.4, 36.7, 47.5 (q, J = 32.9 Hz), 51.8, 53.0, 124.2 (q, J = 280.8 Hz), 126.2, 128.2, 128.9, 130.6, 133.0, 136.1, 172.5, 174.7. Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.12; N, 4.44. Found: C, 57.18; H, 5.14; N, 4.48.

4-Methyl-2-(2,2,2-trifluoroethyl)-1,2,4,5-tetrahydrobenzo[*c*]azepin-3-one (4h): ^{1}H NMR ($CDCl_3$) δ 1.29 (d, 3 H, J = 6.3 Hz), 2.93 (dd, 1 H, J = 12.9, 17.5 Hz), 3.08 (dd, 1 H, J = 4.6, 17.5 Hz), 3.47 (m, 1 H, J = 6.3 Hz), 3.88 (qd, 1 H, J = 8.9, 15.1 Hz), 4.02 (d, 1 H, J = 16.8 Hz), 4.26 (qd, 1 H, J = 8.9, 15.2 Hz), 5.27 (d, 1 H, J = 16.5 Hz), 7.05−7.34 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 17.4, 34.6, 37.8, 47.4 (q, J = 34.3 Hz), 52.9, 124.4 (q, J = 279.6 Hz), 125.9, 128.1, 128.8, 130.5, 133.1, 137.0, 176.3. Anal. Calcd for $C_{13}H_{14}F_3NO$: C, 60.70; H, 5.49; N, 5.44. Found: C, 60.44; H, 5.54; N, 5.40.

4-Methyl-2-(2,2,2-trifluoroethyl)-1,4-dihydro-2*H*-isoquinolin-3-one (5i): ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3 H, J = 7.6 Hz), 3.62 (q, 1 H, J = 7.3 Hz), 4.10 (qd, 1 H, J = 8.9, 15.2 Hz), 4.23 (qd, 1 H, J = 8.9, 15.2 Hz), 4.53 (d, 1 H, J = 15.2 Hz), 4.65 (d, 1 H, J = 15.2 Hz), 7.18−7.36 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.3, 41.4, 47.4 (q, J = 33.0 Hz), 51.4, 124.4 (q, J = 280.8 Hz), 125.0, 125.8, 126.6, 128.1, 130.9, 137.1, 173.1.

Supporting Information Available: Experimental procedures for the preparation of compounds **2** and **3**, and spectroscopic charts for compounds **2a**−**d**, **3a**, **4d**−**f**, **5i**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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