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Facile synthesis of 7–10 membered rings by intramolecular condensation using dialkylcarbonate as solvent

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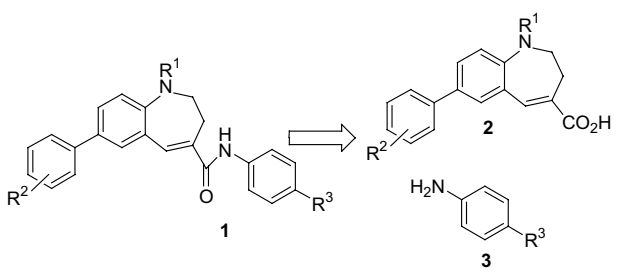
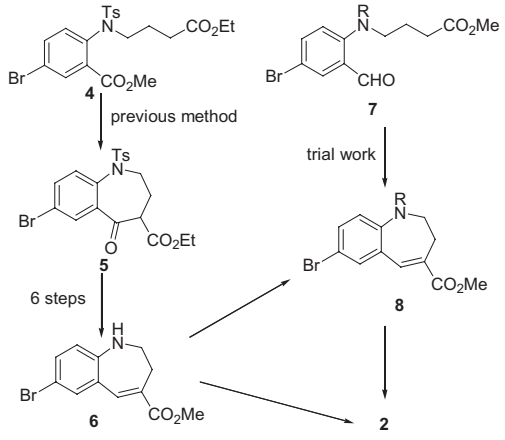
Abstract—A convenient large-scalable synthesis of 1-benzazepines **19** as an important intermediate of CCR5 antagonist, oral HIV-1 therapy, was established. The anilination of *o*-halogenobenzaldehyde **9** with alkylamino-acid **16** gave *o*-formylaniline-acid **17**. Compound **17** was esterified followed by the improved reaction using the combination of alcoholate and dialkyl carbonate in one-pot, to easily produce **19**. Namely, these new processes afforded the desired product **19** in only two steps from the starting materials, as compared with the previous 10 steps. Moreover, these convenient methodologies were applied to other heterocycles to give 8–10 membered rings, such as 1-benzazocine, 1-benzazonine, and 1-benzazecine.

In nature, there is a large amount of compounds containing the nitrogen atom, which shows the various biological activities. These compounds and modified products have popularly been utilized as a pharmacore for therapeutic drugs.[1] Therefore, it is very important to develop convenient synthesis of heterocyclic products for the timely supply of bulk for the patients. On the other hand, 1-alkyl-2,3-dihydro-1-benzazepines **1** have recently been found to be potent oral HIV-1 candidates, as CCR5 antagonists,[2–4] and these products were synthesized by the condensation of carboxylic acid **2** and aniline **3** (Scheme 1).[2] In medicinal synthesis,[2] β-oxo-ester **5** was converted to **6** followed by alkylation, arylation, or acylation, which was led to the important intermediate product **2** (Scheme 2). However, this approach involved several limitations from the standpoint of large-scale preparation, for example, multisteps (12 steps) and repeated tedious chromatographic methods. Hence, an efficient preparation of **1** on a large scale was required to support toxicological evaluation. For the preparation of 2,3-dihydro-1-benzazepines, most reported syntheses have had the same strategy, in that the Dieckmann type reaction was the key reaction. There have been few reports based on other generation



Scheme 1.



Scheme 2.

Keywords: Dialkylcarbonate; Intramolecular Claisen type reaction; 7–10 Membered ring; CCR5 antagonist.
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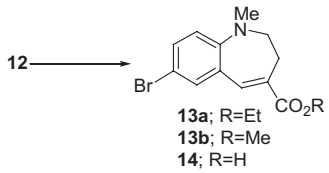
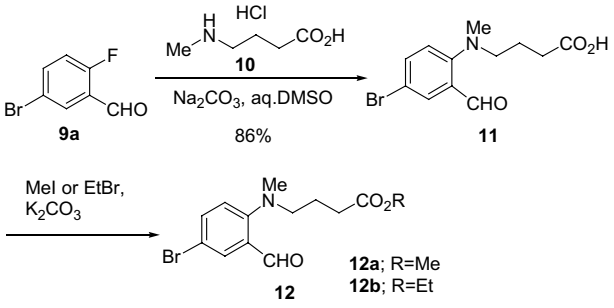
Table 1. Intramolecular condensation of **12** under various conditions[a]



Entry	12	Base	Solvent	Conditions	Yield (%)[d]
1	**12b**	NaOMe[b]	$(MeO)_2CO$	rt, 5.5 h	**13b**; 83
2	**12a**	NaOEt[c]	$(EtO)_2CO$	rt, 4 h	**13a**; 90
3	**12a**	NaOEt	EtOH	rt, 1 h, then reflux, 1 h	**13a**; 38, **14**; 11
4	**12a**	KOBu^t	THF	rt, 1 h	**13a**; 38, **14**; 31

[a] General procedure: A mixture of substrate and base (1.2 equiv) in solvent was stirred.
[b] NaOMe (28%) in MeOH was used.
[c] NaOEt (20%) in EtOH was used.
[d] NaOEt (20%) in EtOH was used.

(Scheme 5).[5] Our retro-synthetic analysis of **2** as the key intermediate compound is depicted in Scheme 2. We have previously reported the convenient synthesis of 2,3-dihydro-1-benzothiepin-4-carboxylate using the improved intramolecular Claisen type reaction of 4-(*o*-formylphenylthio)butyrate with alcoholate in dialkylcarbonate.[6] Therefore, **8** was recognized to be accessed by the treatment of 4-(*o*-formylphenylalkylamino)butyrate **7** under the reported conditions. In this paper, we announce the convenient and efficient synthesis of **8**, which led to **1**, and the synthesis of 8–10 membered rings having the possibility as the templates of new biological compounds.



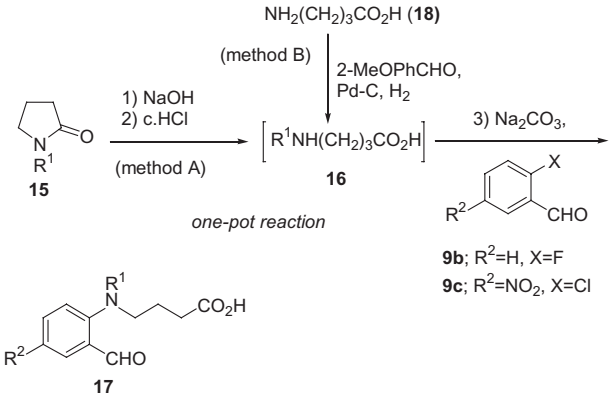
Scheme 3.

First, 4-(*N*-aryl-*N*-methylamino)butyric ester **12** was chosen as a model substrate and allowed to react with base in solvent (Table 1). Compound **12** was synthesized as shown in Scheme 3. Aryl halide **9a** was refluxed with 4-methylaminobutyric acid hydrochrolide **10** and Na_2CO_3 in aqueous DMSO to give acid **11** in 86% yield, although the use of DMF instead of aqueous DMSO as a solvent produced a large amount of 5-bromo-2-dimethylaminobenzaldehyde. When NaOH was used as a base, the main product was 5-bromo-salicylaldehyde. The treatment of **11** with MeI or EtBr led to ester **12**. The traditional conditions,[7] such as the treatment of **12a** with NaOEt in EtOH solution in EtOH as a solvent, provided a mixture of 1-benzazepine **13a** in 38% yield and hydrolyzed **14** in 11% yield (entry 3). Changing to THF as the solvent did not protect the hydrolysis (entry 4). Our conditions,[6] which we discovered in the synthesis of 2,3-dihydro-1-benzothiepines, were applied to this reaction. Namely, **12a** was reacted with 1.2 equiv of NaOEt in EtOH solution in diethyl carbonate instead of ether or alcohol as a solvent at room temperature for 4 h. Surprisingly, the reaction gave the desired **13a** in 90% yield, and did not detect **14** (entry 2), while the cyclization using *t*-butyl ester of **12** and *t*-BuOK gave 77% yield.[5] The use of dimethyl carbonate as a solvent in the case of **12b** also showed the preparation of **13b** in 83% yield. Moreover, the treatment of acid **11** was carried out with MeI and K_2CO_3 in DMF followed by cyclization with the combination of NaOMe in dimethylcarbonate in one-pot, to give **13b** in 86% yield.

Next, we explored the scope and limitation of the new protocol of 1-alkyl-2,3-dihydro-1-benzazepines. A variety of *o*-formylaniline-acids **17** as precursor were prepared by two methods, and the results are summarized in Table 2. One result was that *N*-alkylamide **15** [9] was hydrolyzed with aqueous NaOH, followed by the neutralization and anilination of *o*-halogenobenzaldehyde **9** in one-pot (method A). The hydrolysis of **15** gave 85–90% yield, as determined by ^{1}H NMR. The other result was that the reductive alkylation of 4-aminobutyric acid with 2-methoxybenzaldehyde catalyzed Pd–C under a hydrogen atmosphere led to alkylamino-acid **16**, which was anilinated with **9** in one-pot (only *N*-benzyl type, method B). The substrates having the bulky groups on the nitrogen atom gave lower yields than that having the straight alkyl group (entry 1 vs entries 2 and 3). The electron-withdrawing groups in **9** increased the yields (entry 6 vs entry 7).

The intramolecular condensations of **17** using new conditions were carried out (Table 3). In the Claisen type reactions of 1-benzazepines, the functional groups on the aromatic ring did not affect the yields of **19** (entry 6 vs entry 7). The yields were affected by the substituted groups on the nitrogen atom, and the reactions using substrates having the branched groups, such as isopropyl and cyclohexyl groups, gave lower yields (entry 1 vs entries 2 and 3). The treatment of **17e** having the benzyl type group smoothly proceeded the cyclization to give **19e** in 93% yield. The yield of cyclization using

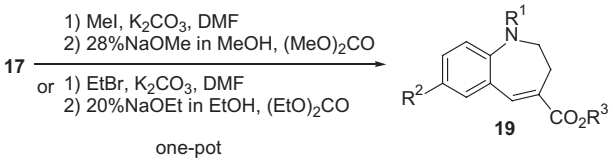
Table 2. Coupling reaction of **9** with **16** led from **15** or **18** in one-pot[a]



Entry	Substrates		Method	Product **17**	Yield (%)[c]
	16	**9**			
1	**16a**; R^1 = *n*-Bu	**9a**	A	**17a**; R^1 = *n*-Bu, R^2 = Br	84
2	**16b**; R^1 = *i*-Pr	**9a**	A	**17b**; R^1 = *i*-Pr, R^2 = Br	22
3	**16c**; R^1 = cyclohexyl	**9a**	A	**17c**; R^1 = cyclohexyl, R^2 = Br	3
4	**16d**; R^1 = allyl	**9a**	A	**17d**; R^1 = allyl, R^2 = Br	50
5	**16e**; R^1 = 2-$MeOC_6H_4CH_2$	**9a**	B	**17e**; R^1 = 2-$MeOC_6H_4CH_2$, R^2 = Br	70
6	**16f**; R^1 = Me[b]	**9b**	A	**17f**; R^1 = Me, R^2 = H	78
7	**16f**[b]	**9c**	A	**17g**; R^1 = Me, R^2 = NO_2	92

[a] See Ref. 8 for general procedures (methods A and B).
[b] Compound **10** was used as reagent.
[c] Isolated yield.

Table 3. Intramolecular condensation of **17**–**19** in one-pot

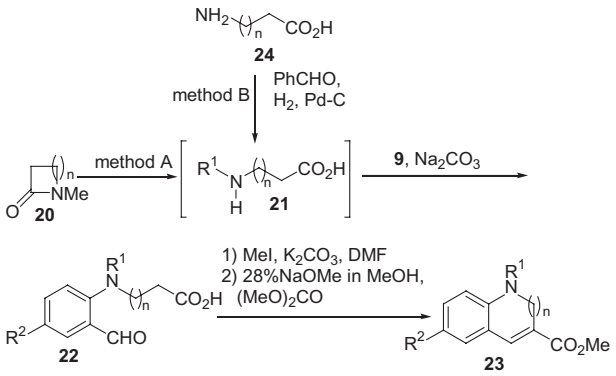


Entry	Substrate	Product **19**	Yield (%)[a]
1	**17a**	**19a**; R^1 = *n*-Bu, R^2 = Br, R^3 = Me	81
2	**17b**	**19b**; R^1 = *i*-Pr, R^2 = Br, R^3 = Et	74
3	**17c**	**19c**; R^1 = cyclohexyl, R^2 = Br, R^3 = Et	44
4	**17d**	**19d**; R^1 = allyl, R^2 = Br, R^3 = Me	73
5	**17e**	**19e**; R^1 = 2-$MeOC_6H_4CH_2$, R^2 = Br, R^3 = Et	93
6	**17f**	**19f**; R^1 = Me, R^2 = H, R^3 = Et	74
7	**17g**	**19g**; R^1 = Me, R^2 = NO_2, R^3 = Et	72

General procedure: To a suspension of **17** (1.0 g) K_2CO_3 (1.1 equiv) and DMF (3 mL) was added alkyl halide (1.2 equiv) and stirred for 2 h at room temperature. Subsequently, dialkylcarbonate (6 mL) and sodium alcoholate (2.4 equiv) were added, and stirred for 0.5 h at 50 °C in one-pot.
[a] Isolated yield.

the combination of alcoholate and dialkylcarbonate increased considerably, as compared with the case of 2,3-dihydro-1-benzothiepine (best yield was 71%).

Furthermore, the new methodologies for 1-benzazepines were applied to other heterocyclic compounds containing a nitrogen atom, 8–10 membered rings (Scheme 4 and Table 4). Acid **22** was synthesized by methods A and B. The treatments of **22a–d** using our conditions gave 1-benzazocines. The treatment of **22c** or **22d** was converted to **23c** or **23d** in 78% and 76% yields, respectively. Surprisingly, the combination of NaOMe and dimethylcarbonate as a reagent of condensation also provided 1-benzazonine **23e** or 1-benzazecine **23f**, although there has been no report of the synthesis of these heterocyclic compounds to the best of our knowledge. The structures of 1-benzazonine and 1-benzazecine were determined by ^1H and ^{13}C NMR to be single isomers, respectively, however, the accurate configurations were not clearly confirmed. Recently, the preparations of some nitrogen-containing cyclic compounds by ring-closing metathesis (RCM), such as benzazepine and benzazocine, have been reported.[10] However, it is difficult that RCM applies to a large-scale preparation



Scheme 4.

because of the requirement of low reaction concentration (0.002–0.01 M) and the use of expensive reagent. On the other hand, our preparation have predominancy from RCM in reaction concentration (ca. 1 M) with inexpensive reagents. Moreover, the productions having ester group have the possibility as pharmacores.

In conclusion, we have developed a facile and efficient synthesis of 1-benzazepines by the improved Claisen type reaction of 4-(*N*-alkylamino-*N*-aryl)butyric ester using the combination of alcoholate and dialkyl carbonate. These processes afforded the target products by only two steps from the starting materials. Moreover, these convenient methodologies were applied to other heterocycles to give 8–10 membered rings.

References and notes

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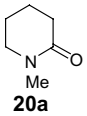
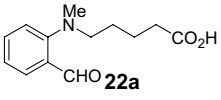
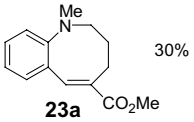
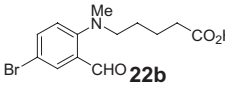
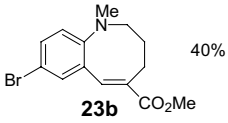
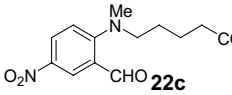
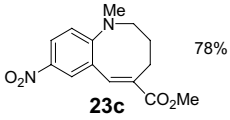
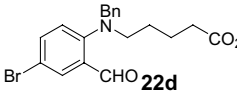
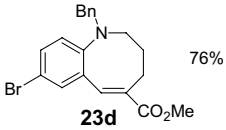
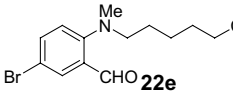
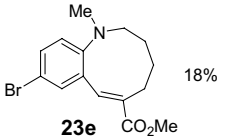
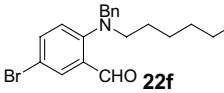
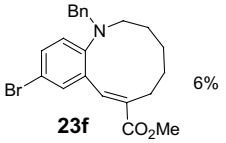
Table 4. Preparation of 8–10 membered ring

Entry	Substrates	Acid **22**, yield (%)[b]	8–10 Membered ring **23**, yield (%)[b]
1[a]	 , **9b** **20a**	 37% **22a**	 30% **23a**
2[a]	**20a**, **9a**	 58% **22b**	 40% **23b**
3	**20a**, **9c**	 93% **22c**	 78% **23c**
4[a]	$H_2N(CH_2)_4CO_2H$ (**24a**), **9a**	 61% **22d**	 76% **23d**
5[a]	 , **9a** **20b**	 80% **22e**	 18% **23e**
6	$H_2N(CH_2)_6CO_2H$ (**24b**), **9a**	 27% **22f**	 6% **23f**

See Ref. 8 for general procedures (methods A and B).
[a] The ester of **22** was isolated.
[b] Isolated yield.

Baba, M.; Fujino, M. *J. Med. Chem.* **2000**, *43*, 2049–2063; (c) Imamura, S.; Ishihara, Y.; Hattori, T.; Kurasawa, O.; Matsushita, Y.; Sugihara, Y.; Kanzaki, N.; Iizawa, Y.; Baba, M.; Hashiguchi, S. *Chem. Pharm. Bull.* **2004**, *52*(1), 63–73; (d) Lynch, C. L.; Hale, J. J.; Budhu, R. J.; Gentry, A. L.; Mills, S. G.; Chapman, K. T.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Cascieri, M. A.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hauzuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Schlief, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3001–3004; (e) Finke, P. E.; Oastes, B.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Carella, A.; Carver, G.; Holmes, K.; Danzeisen, R.; Hauzuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Schlief, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2475–2479; (f) Palani, A.; Shapiro, S.; Clader, J. W.; Greenlee, W. J.; Cox, K.; Strizki, J.; Endres, M.; Baroudy, B. M. *J. Med. Chem.* **2001**, *44*, 3339–3342; (g) Tagat, J. R.; Steensma, R. W.; McCombie, S. W.; Nazareno, D. V.; Lin, S.-I.; Neustandt, B. R.; Cox, K.; Xu, S.; Wojcik, L.; Murray, M. G.; Vantuno, N.; Baroudy, B. M.; Strizki, J. M. *J. Med. Chem.* **2001**, *44*, 3343–3346; (h) Maeda, K.; Yoshimura, K.; Shibayama, S.; Habashita, H.; Tada, H.; Sagawa, K.; Miyakawa, T.; Aoki, M.; Fukushima, D.; Mitsuya, M. *J. Biol. Chem.* **2001**, *276*, 35194–35200.

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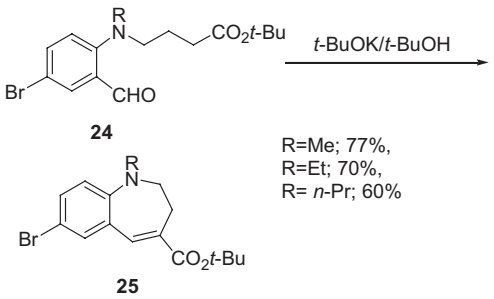
5. See Ref. 2. They reported three cases using some steps and expensive reagents, as shown in Scheme 5.



Scheme 5.

6. Ikemoto, T.; Ito, T.; Nishiguchi, A.; Tomimatsu, K. *Tetrahedron* **2004**, *60*, 10851–10857.
7. (a) Hatinguais, P.; Patoiseau, J. F.; Marcelon, G. EP67086; (b) Fuchs, P. L. *J. Am. Chem. Soc.* **1974**, *96*, 1607.
8. General procedure: The hydrolysis of *N*-alkylamide **15** or **20** (2 equiv) with 4 N NaOH solution for 8 h under the refluxing condition followed by the neutralization with concn HCl, which was refluxed with aryl halide **9** (1 equiv), Na_2CO_3 (4 equiv), and aqueous DMSO in one-pot (method A). The reductive-alkylation of **18** or **24** (2 equiv) with 2-methoxybenzaldehyde or benzaldehyde (2 equiv), 1 N NaOH (2 equiv), and a catalytic amount of Pd–C overnight at room temperature under the hydrogen atmosphere followed by the neutralization with concn HCl and concentration, which was refluxed with aryl halide **9** (1 equiv), Na_2CO_3 (4 equiv), and aqueous DMSO in one-pot (method B).
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