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Facile synthesis of medium-sized cyclic amines based on Friedel–Crafts reaction via iminium cation by use of acetylene dicobalt complex

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Abstract—An intramolecular Friedel–Crafts reaction of *N*-methoxymethyl sulfoneamides **3e–j** containing an acetylene dicobalt moiety was found to proceed smoothly to afford eight- and nine-membered cyclic amines **4e–j** in high yields.

Nature abounds with compounds containing eight- or nine-membered cyclic amine as a prominent architectural feature and showing significant biological activities. Such compounds include buflavine,[1a] balasubramide,[1b] manzamines,[1c] moschamide,[1d] securamine A,[1e] neodihydrothebaine[1f] and rhazinilam (Fig. 1).[1g] Despite numerous advances in the field of synthetic organic chemistry, the development of general and efficient strategies for the construction of these ring systems remains as a significant challenge. Pictet–Spengler reaction, which is regarded as Friedel–Crafts (FC) reaction of iminium cation, is well known as an efficient method to prepare tetrahydroisoquinoline derivatives.[2] Such a method was also applicable to the construction of seven-membered cyclic amines.[3] However, there have been few reports on construction of eight- and nine-membered cyclic amines based on this method.[3f–h] We thus describe herein FC cyclization of *N*-methoxymethyl sulfoneamides **1** into eight-membered cyclic amines via iminium cations. The installation of an acetylene dicobalt moiety often makes the formation of a medium-sized cyclic compound easier since the moiety takes a bended conformation which looks like *cis*-olefin.[4] Furthermore, unlike *cis*-olefin, an acetylene dicobalt is stable to acid. Thus, we also report an intramolecular FC reaction of *N*-methoxymethyl sulfoneamides **3** with an acetylene dicobalt moiety (Fig. 2).

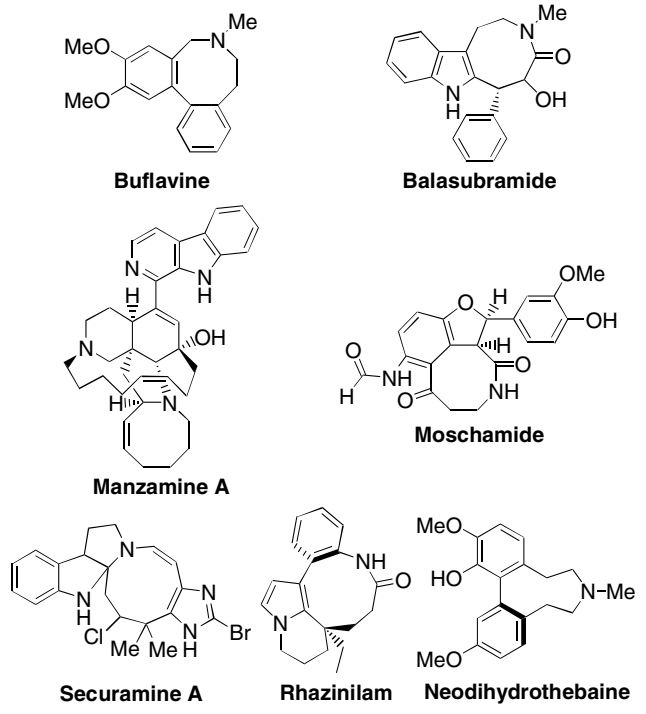

Figure 1. Natural products containing eight- or nine-membered cyclic amines.

N-Methoxymethyl sulfoneamide **1** was prepared as shown in Scheme 1. Sonogashira coupling of

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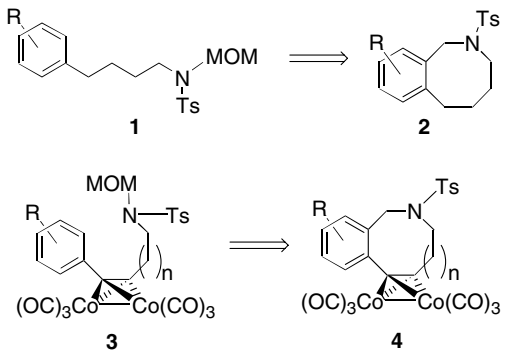
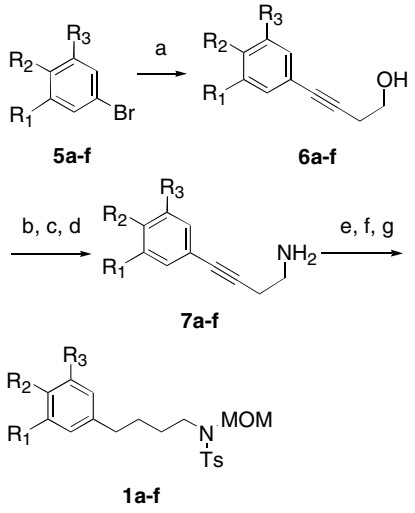


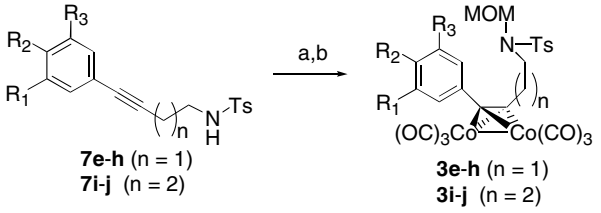
Figure 2.

bromobenzenes **5a**–**f** and 3-butyn-1-ol gave alcohols **6a**–**f**[5] in high yields.[6] Mesylation of **6a**–**f** followed by the sequence of substitution with sodium azide and reduction with Ph_3P afforded amines **7a**–**f**,[7] which were converted into *N*-methoxymethyl sulfoneamides **1a**–**f**[5] by tosylation and the subsequent catalytic hydrogenation and introduction of a MOM group.



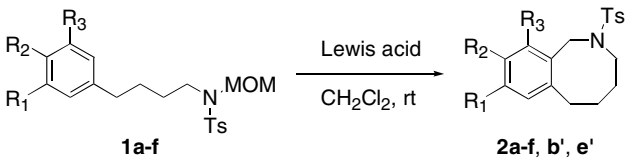
Scheme 1. Reagents and conditions: (a) 3-butyn-1-ol, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, 70 °C, 80–100%; (b) MsCl, Et_3N, CH_2Cl_2, rt, 87–98%; (c) NaN_3, DMF, 60 °C, 89–100%; (d) Ph_3P, THF, H_2O, 60 °C, 91–100%; (e) TsCl, DMAP, pyridine, rt, 78–100%; (f) 20% $Pd(OH)_2$–C, H_2, MeOH or AcOEt, rt, 91–100%; (g) MOMCl, NaH, THF, rt, 80–100%.

Table 1 summarizes the FC reaction of *N*-methoxymethyl sulfoneamide. Treatment of **1a** with 0.5 equiv of trimethylsilyltriflate (TMSOTf) at room temperature gave the eight-membered cyclic amine **2a**[5] in 58% yield after 29 h (Table 1, entry 1). The effect of an electron-releasing group on the reactivity was examined. The presence of a methyl group on a benzene ring increased the reaction rate. Sulfoneamides **1b**–**d** with one or two methyl groups on aromatic rings were converted into the corresponding cyclic amines in excellent yields within 10–30 min by treatment with TMSOTf (entries 2–4). In entry 2, both regioisomers **2b** and **2b′** were obtained. Surprisingly, introduction of a methoxyl group, which is a stronger electron-releasing group than a methyl group, caused the decomposition to lower the yield of the desired compounds **2e** and **2f** (entries 5 and 6). Also treatment of the isolated **2f** with TMSOTf gave the complex mixture. The decomposition of **2e** and **2f** by treatment with TMSOTf might be attributed to the fission of the C1-N2 bond, which is nearly parallel to the π-orbital of the benzene ring. Probably, methoxyl groups on the benzene ring should facilitate the bond cleavage. Since cyclic amines having a methoxyl group on the benzene ring were found to be instable to TMSOTf, which is a strong Lewis acid, we carried out the FC reaction of **1f** by using a mild Lewis acid. As a result, $La(OTf)_3$ promoted the cyclization of **1f** moderately to afford **2f** in 58% yield after 24 h.



Scheme 2. Reagents and conditions: (a) MOMCl, NaH, THF, rt, 97–100%; (b) $Co_2(CO)_8$, CH_2Cl_2, rt, 89–100%.

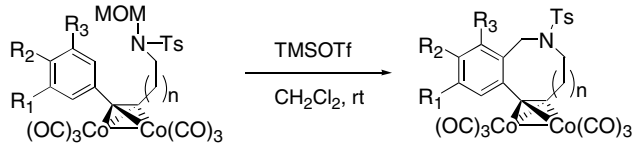
Table 1.



Entry	Substrates	R_1	R_2	R_3	Lewis acid	Time	Products	Yield (%)
1	**1a**	H	H	H	TMSOTf	29 h	**2a**	58
2	**1b**	Me	H	H	TMSOTf	30 min	**2b** + **2b′** ($R_1 = R_2 = H$, $R_3 = Me$)	94 (**2b**:**2b′** = 9:1)
3	**1c**	Me	H	Me	TMSOTf	10 min	**2c**	93
4	**1d**	Me	Me	H	TMSOTf	10 min	**2d**	94
5	**1e**	OMe	H	H	TMSOTf	10 min	**2e** + **2e′** ($R_1 = R_2 = H$, $R_3 = OMe$)	11 (**2e**:**2e′** = 9:1)
6	**1f**	OMe	H	OMe	TMSOTf	10 min	**2f**	2
7[a]	**1f**	OMe	H	OMe	$La(OTf)_3$	24 h	**2f**	58

[a] In entry 7, **1f** was also recovered in 14% yield.

Table 2.



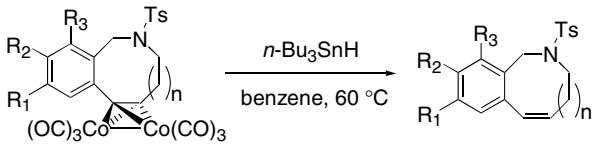
3e-i **4e-i, e', h'**

Entry	Substrates	R_1	R_2	R_3	*n*	Time (min)	Products	Yield (%)
1	**3e**	OMe	H	H	1	20	**4e** + **4e′** ($R_1 = R_2 = H$, $R_3 = OMe$)	86 (**4e**:**4e′** = 4:1)
2	**3f**	OMe	H	OMe	1	15	**4f**	95
3	**3g**	OMe	OMe	H	1	10	**4g**	88
4	**3h**	OMe	H	Me	1	10	**4h** + **4h′** ($R_1 = Me$, $R_2 = H$, $R_3 = OMe$)	81 (**4h**:**4h′** = 2:1)
5	**3i**	OMe	OMe	H	2	10	**4i**	84
6	**3j**	OMe	H	OMe	2	10	**4j**	81

Next, we carried out an intramolecular FC reaction of *N*-methoxymethyl sulfoneamides **3** with an acetylene dicobalt moiety. Compounds **3e–i**[5] were prepared by alkylation with methoxymethyl chloride followed by treatment of **7e–i**[5] with $Co_2(CO)_8$ (Scheme 2).

Interestingly, the presence of cobalt complexes was found to increase the stabilization of cyclic amine with methoxyl groups on the aromatic ring (Table 2). Treatment of **3e–h** with TMSOTf in CH_2Cl_2 afforded eight-membered cyclic amine **4e–h**[5] in high yields (Table 2, entries 1–4). The presence of dicobalt moiety in 2-benzazocines might prevent the C1–N2 bond from taking the orientation parallel to the π-orbital of the benzene ring. Also cyclization of **3i–j** proceeded smoothly to give the corresponding nine-membered cyclic amine **4i–j**[5] (entries 5 and 6). The dicobalt moieties of **4f–j** were successfully removed by reduction with *n*-Bu_3SnH to produce **8f–j**[5] in high yields (Scheme 3).[8]

In conclusion, an intramolecular Friedel–Crafts reaction of the iminium cation derived from *N*-methoxymethyl sulfoneamide was found to be an efficient method to generate eight-membered cyclic amines. A methyl group on a benzene ring was a good electron-releasing group to promote this reaction. However, the presence of a methoxyl group on a benzene ring resulted in decomposition of the corresponding cyclic amine. Introduction of a cobalt complex to the side chain of the substrates was found to suppress the decomposition. Further extension of these reactions is in progress.



4f	($R_1 = R_3 = OMe$, $R_2 = H$, n = 1)	**8f**	(80%)
4g	($R_1 = R_2 = OMe$, $R_3 = H$, n = 1)	**8g**	(74%)
4h	($R_1 = OMe$, $R_2 = H$, $R_3 = Me$, n = 1)	**8h**	(87%)
4i	($R_1 = R_3 = OMe$, $R_2 = H$, n = 2)	**8i**	(87%)
4j	($R_1 = R_2 = OMe$, $R_3 = H$, n = 2)	**8j**	(88%)

Scheme 3.

Acknowledgement

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5. All new compounds gave spectroscopic data in agreement with assigned structures. Representative data are shown below. Compound **4f**: IR (neat, cm^{-1}) 3450, 3024, 2056. SIMS-POSI *m*/*z* 657 (M^+), 573; HR-SIMS calcd for $C_{26}H_{21}Co_2NO_{10}S$: 656.9550, found: 656.9603. ^1H NMR (270 MHz): δ 7.72 (2H, d, $J = 8.2$ Hz), 7.27 (2H, d, $J = 8.2$ Hz), 6.77 (1H, d, $J = 2.3$ Hz), 6.42 (1H, d, $J = 2.3$ Hz), 4.30 (2H, s), 3.88 (3H, s), 3.82 (3H, s), 3.67 (2H, t, $J = 5.6$ Hz), 3.31 (2H, t, $J = 5.6$ Hz), 2.42 (3H, s). ^{13}C NMR (100 MHz): δ 199.46 (C × 6), 160.31 (C), 158.21 (C), 143.21 (C), 139.06 (C), 135.85 (C), 129.43 (CH × 2), 127.57 (CH × 2), 118.07 (C), 109.82 (CH), 98.79 (CH), 95.83 (C), 91.29 (C), 56.07 (CH_3), 55.23 (CH_3), 50.19 (CH_2), 43.32 (CH_2), 36.46 (CH_2), 21.49 (CH_3). Compound **8f** (white crystal): mp 132–134 °C (AcOEt). IR (KBr, cm^{-1}) 3448, 3014, 2936, 1319, 1158. EI-MS *m*/*z* 373 (M^+), 218, 190; HR-MS *m*/*z* calcd for $C_{20}H_{23}NO_4S$: 373.1348, found: 373.1343. ^1H NMR (400 MHz): δ 7.73 (2H, d, $J = 8.2$ Hz), 7.28 (2H, d, $J = 8.2$ Hz), 6.37 (1H, d, $J = 12.2$ Hz), 6.34 (1H, d, $J = 2.4$ Hz), 6.26 (1H, d, $J = 2.4$ Hz), 5.78 (1H, dt, $J = 12.2$, 5.9 Hz), 4.49 (2H, s), 3.79 (3H, s), 3.71 (3H, s), 3.34–3.28 (2H, m), 2.42 (3H, s), 2.34–2.27 (2H, m). ^{13}C NMR (100 MHz): δ 160.09 (C), 159.37 (C), 142.71 (C), 140.15 (C), 137.31 (C), 131.63 (CH), 129.34 (CH × 2), 127.87 (CH), 127.34 (CH × 2), 114.05 (C), 104.06 (CH), 97.60 (CH), 55.42 (CH_3), 55.27 (CH_3), 42.74 (CH_2), 42.08 (CH_2), 29.89 (CH_2), 21.47 (CH_3). Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.03; H, 6.21; N, 3.64.
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