A One-pot Procedure for Ring Enlargement of α-Chloromethyl *N*-Containing Heterocycles

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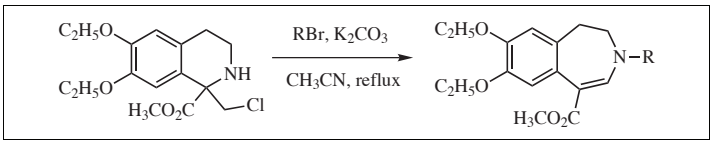

A simple one-pot procedure for ring enlargement of α-chloromethyl *N*-containing heterocycles has been developed. By reaction of chloromethyl tetrahydroisoquinoline and its thieno analog with benzyl or allyl bromide under basic conditions, ring expansion and *N*-substitution were achieved simultaneously. The key to the transformation was proposed to involve the formation of aziridinium salt and subsequent bond breaking between the nitrogen and tertiary carbon atoms.

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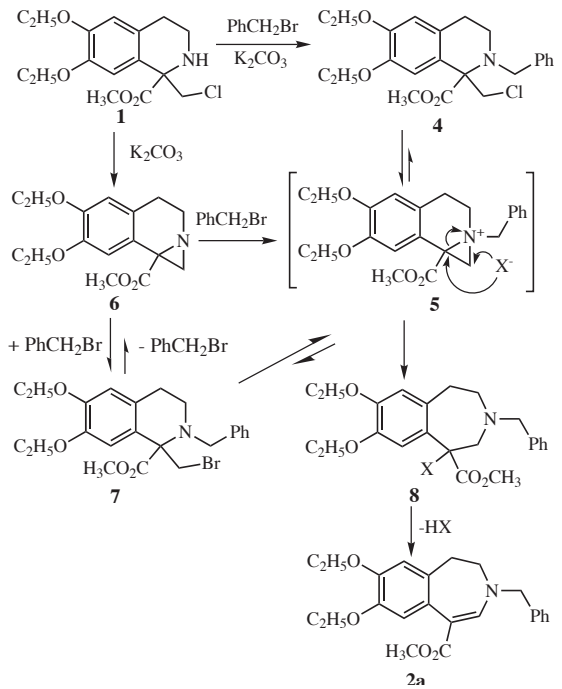
Ring expansion reactions *via* aziridinium or aziridine intermediates to larger nitrogen-containing heterocycles are commonly employed in organic synthesis [1]. For example, Kuehne *et al.* synthesized an indoloazepine from chloromethyl tetrahydro-β-carboline [2]. And 2-substituted-3-benzazepines have been prepared through aziridine intermediates [3]. In addition, several reports on the synthesis of piperidine or azepane derivatives *via* similar ring expansion of 2-halomethyl pyrrolidine or piperidines were reported in the literature [4]. However, the desired ring-expansion products were often contaminated by non-ring-expansion byproducts, and these reactions usually required stepwise reactions, *i.e* *N*-substitution of aziridines followed by ring expansion. In this paper, we described a simple one-pot procedure for both ring expansion and *N*-substitution by the reaction of chloromethyl tetrahydroisoquinoline and its thieno analog with benzyl or allyl bromide.

This one-pot approach is depicted in Scheme 1. Treatment of compound **1**, obtained by a modified procedure reported by Kuehne *et al.* [2], with benzyl or allyl bromide and anhydrous potassium carbonate in refluxing acetonitrile afforded *N*-benzyl or *N*-allyl-3-benzazepines **2a** and **2b** respectively in good yields. Compounds **2a** (R = Bn) and **2b** (R = allyl) were readily reduced with sodium cyanoborodyride in glacial acetic acid to their saturated derivatives **3a** and **3b** in 98% and 85% yields respectively.

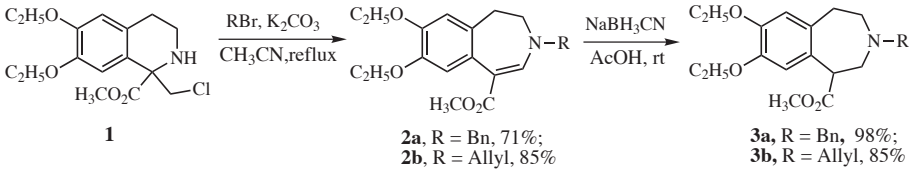
The conversion of compound **1** to benzazepine **2** could be rationalized by a series of chemical transformations shown in Scheme 2. On the one hand, *N*-alkylation of 1-chloromethyl- tetrahydroisoquinoline **1** in presence of potassium carbonate and benzyl bromide led to *N*-benzyl-

Scheme 2



tetrahydroisoquinoline **4** (observed by LC-MS(ESI):

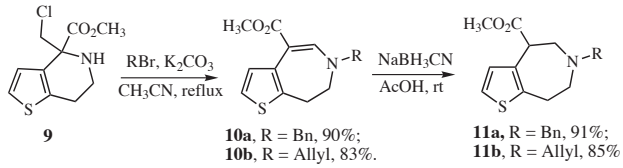
Scheme 1



418.4 $[M+H]^+$) which subsequently underwent intramolecular alkylation to give aziridinium salt **5** (X=Cl). On the other hand, intramolecular alkylation of compound **1** gave aziridine **6** which reacted with benzyl bromide to yield aziridinium salt **5** (X=Br). Aziridinium salt **5** could be attacked by a nucleophile either at the methylene to go back to the precursor **4** or **7**, or at the tertiary carbon to result in ring-expansion intermediate **8** (X=Cl or Br). Intermediate **8** lost HX in the basic condition to yield product **2a**. Apparently these analyses are consistent with a precedent of ring expansion from five to six membered nitrogen-containing compounds by Cossy J. *et al.* [5].

The above convenient one-pot method was easily applied to the synthesis of thienoazepine derivatives as depicted in Scheme 3. Chloromethyl tetrahydrothienopyridine **9** could be readily converted to compound **10** in good yields with benzyl bromide or allyl bromide in the presence of potassium carbonate in refluxing acetonitrile. The *N*-benzyl or *N*-allyl thienoazepines **10a** and **10b** were further reduced with sodium cyanoborohydride in acetic acid to give compounds **11a** (R = Bn) or **11b** (R = Allyl) in 91% and 85% yields respectively.

Scheme 3



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10a, R = Bn, 90%;
10b, R = Allyl, 83%.

11a, R = Bn, 91%;
11b, R = Allyl, 85%

In summary, the present paper revealed a simple one-pot ring expansion methodology which could be useful for the synthesis of 3-benzazepine and thieno[2,3-*d*]azepine derivatives. The key step of the reaction was proposed to be through the formation of an aziridinium salt intermediate by neighboring group participation. This strategy may be readily applied to the synthesis of similar azepine analogs.

EXPERIMENTAL

The starting compound **1** and **9** were prepared by a modified procedure reported by Kuehne *et al.* [2]. Melting points were taken on XT5 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 (300 and 75 MHz respectively) spectrometer. Chemical shifts were expressed in ppm relative to TMS or the residual signal of deuterated solvent. The mass spectra were recorded on Agilent 1100 LC-MS and electrospray ionization (ESI) was used.

General Procedure for Synthesis of Compounds (**1**) and (**9**).

A solution of 2-(3,4-diethoxyphenyl)ethanamine hydrochloride or 2-(thiophen-3-yl)ethanamine hydrochloride (3 mmol) and methyl chloropyruvate (0.82 g, 6 mmol) in glacial acetic acid (15 mL) was heated for 2 days at 80 ºC with stirring under nitrogen. After cooling, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (20 mL) and extracted with 10% hydrochloride (3×10 mL). The combined extracts were treated with concentrated ammonium hydroxide and extracted with ethyl acetate (3×10 mL). The organic phase were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the crude products. Purification by silica gel column chromatography (petroleum ether/ethyl acetate 5:1, v/v) provides **1** and **9** in 33% and 26% yields respectively.

Methyl 1-(chloromethyl)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (**1**).

White powder, mp 70-71 ºC. ^{1}H nmr (deuteriochloroform): δ 7.07 (s, 1H, Aromatic H), 6.61 (s, 1H, Aromatic H), 4.32 (d, ^{2}J = 10.8 Hz, 1H, 1-ClCH$_2$), 4.10-4.33 (m, 4H, 2 x *CH*$_2$CH$_3$), 3.79 (s, 3H, CH$_3$), 3.68 (d, ^{2}J = 10.5 Hz, 1H, 1-ClCH$_2$), 3.32-3.24 (m, 1H, 3-H), 3.18-3.12 (m, 1H, 3-H), 2.87-2.78 (m, 1H, 4-H), 2.73-2.65 (m, 1H, 4-H), 1.46-1.41 (m, 6H, 2 x CH$_2$*CH*$_3$); ^{13}C nmr (deuteriochloroform): δ 173.22, 148.98, 147.03, 129.54, 123.83, 113.82, 112.78, 65.19, 64.85, 64.55, 53.13, 52.37, 39.98, 29.48, 15.01; ms : *m/z* 328.1$[M+H]^+$, 330.1 $[M+(2+H)]^+$.

Methyl 4-(chloromethyl)-4,5,6,7-tetrahydrothieno [3,2-*c*] pyridine-4-carboxylate (**9**).

Colorless oil. ^{1}H nmr (deuteriochloroform): δ 7.11 (d, ^{3}J = 5.4 Hz, 1H, thieno H), 7.08 (d, ^{3}J = 5.4 Hz, 1H, thieno H), 4.28 (d, ^{2}J = 10.5 Hz, 1H, 4-ClCH$_2$), 3.80 (s, 3H, CH$_3$), 3.67 (d, ^{2}J = 10.5 Hz, 1H, 4-ClCH$_2$), 3.33-3.24 (m, 2H, 7-CH$_2$), 3.08-2.90 (m, 1H, 6-H), 2.95-2.76 (m, 1H, 6-H); ^{13}C nmr (deuteriochloroform): δ 172.17, 138.53, 130.46, 125.79, 122.90, 64.96, 53.18, 51.61, 40.80, 25.74; ms: *m/z* 246.0$[M+H]^+$, 248.0 $[M+(2+H)]^+$

General Procedure for the Synthesis of Compounds (**2**).

A mixture of 1-chloromethyl tetrahydroisoquinoline **1** (163.5 mg, 0.5 mmol), alkyl halogen (0.6 mmol) and anhydrous potassium carbonate (83 mg. 0.6 mmol) in dry acetonitrile (5 mL) was heated to reflux until completion. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude product. Purification was performed by flash chromatography on silica gel column.

(*E*)-Methyl 3-benzyl-7,8-diethoxy-4,5-dihydro-3*H*-benzo[d]azepine-1-carboxylate (**2a**).

This compound was prepared from compound **1** and benzyl bromide as white powder, mp 119-120 ºC, yield 71%. ^{1}H nmr (deuteriochloroform): δ 7.92 (s, 1H, 2-H), 7.37-7.22 (m, 6H, Aromatic H), 6.47 (s, 1H, Aromatic H), 4.42 (s, 2H, PhCH$_2$), 4.13-4.03 (m, 4H, 2 x *CH*$_2$CH$_3$), 3.77 (s, 3H, CH$_3$), 3.43-3.40 (m, 2H, 4-CH$_2$), 2.89-2.87 (m, 2H, 5-CH$_2$), 1.46-1.38 (m, 6H, 2 x CH$_2$*CH*$_3$); ^{13}C nmr (deuteriochloroform): δ 170.29, 147.34, 146.83, 146.62, 136.81, 132.76, 129.08, 128.15, 127.64, 127.58, 116.48, 114.05, 98.00, 64.99, 64.80, 63.72, 54.46, 51.39, 35.49, 15.18, 15.11; ms: *m/z* 382.2 $[M+H]^+$.

Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.24; H, 7.13; N, 3.86.

(*E*)-Methyl 3-allyl-7,8-diethoxy-4,5-dihydro-3*H*-benzo[*d*]azepine-1-carboxylate (**2b**).

This compound was prepared from compound **1** and allyl bromide as white powder, mp 67-68 ºC, yield 85%. ^{1}H nmr (deuteriochloroform): δ 7.71 (s, 1H, 2-H), 7.22 (s, 1H, Aromatic H), 6.51 (s, 1H, Aromatic H), 5.84-5.75 (m, 1H, *CH*=CH$_2$),

5.24-5.18 (m, 2H, CH=CH_2), 4.12-4.03 (m, 4H, 2 x CH_2CH_3), 3.81 (d, ^{3}J = 5.7 Hz, 2H, CH_2), 3.75 (s, 3H, CH_3), 3.49-3.46 (m, 2H, 4-CH_2), 2.91-2.88 (m, 2H, 5-CH_2), 1.45-1.39 (m, 6H, 2 x CH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 169.89, 146.67, 146.46, 146.25, 133.06, 132.34, 127.31, 118.21, 115.97, 113.63, 97.52, 64.65, 64.43, 61.99, 54.35, 51.05, 35.18, 14.88, 14.78; ms: *m/z* 332.2 $[M+H]^+$.

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.06; H, 7.64; N, 4.12.

General Procedure for the Synthesis of Compounds (**3**).

To a solution of the unsaturated benzazepine **2a** or **2b** (0.81 mmol) in glacial acetic acid (10 mL) was added in portions sodium cyanoborohydride (133 mg, 2.1 mmol). After stirring for 30 minutes at room temperature (tlc showed completion of the reaction), 5 drops of concentrated hydrochloride acid was added and stirred until gas evolution ceased. The reaction mixture was concentrated *in vacuo* to yield a syrup which was placed into 10 mL ice water and treated with ammonium hydroxide and extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with brine (3 × 10 mL), dried over anhydrous magnesium sulfate, concentrated under vacuum and purified by flash chromatography on silica gel column (petroleum ether/ethyl acetate 5:1, v/v) to give product **3a** or **3b**.

Methyl 3-benzyl-7,8-diethoxy-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine-1-carboxylate (**3a**).

This compound was prepared by reduction of **2a** as white solid, mp 70-72 ºC, yield 98%.^{1}H nmr (deuteriochloroform): δ 7.32-7.25 (m, 5H, Aromatic H), 6.65 (s, 1H, Aromatic H), 6.53 (s, 1H, Aromatic H), 4.10-3.99 (m, 4H, 2 x CH_2CH_3), 3.75 (d, ^{3}J = 6.0 Hz, 1H, 1-H), 3.71 (s, 3H, CH_3), 3.65 (d, ^{2}J = 13.5 Hz, 1H, $PhCH_2$), 3.58 (d, ^{2}J = 13.2 Hz, 1H, $PhCH_2$), 3.31 (dd, ^{2}J = 12.3 Hz, ^{3}J = 6.0 Hz, 1H, 2-H), 3.16-3.07 (m, 1H, 4-H), 2.83 (dd, ^{2}J = 12.3 Hz, ^{3}J = 6.9 Hz, 1H, 2-H), 2.66-2.57 (m, 2H, 5-CH_2), 2.36 (t, ^{3}J = 11.1 Hz, 1H, 4-H), 1.46-1.37 (m, 6H, 2 x CH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 173.17, 147.69, 146.60, 139.13, 134.99, 130.88, 129.19, 128.35, 127.26, 116.41, 116.37, 65.16, 64.85, 64.34, 58.24, 55.96, 53.04, 51.94, 36.97, 15.24; ms: m/z 384.2 $[M+H]^+$.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.08; H, 7.63; N, 3.75.

Methyl 3-allyl-7,8-diethoxy-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine-1-carboxylate (**3b**).

This compound was prepared by reduction of **2b** as colorless syrup, yield 85%. ^{1}H nmr (deuteriochloroform): δ 6.66 (s, 1H, Aromatic H), 6.54 (s, 1H, Aromatic H), 5.90-5.79 (m, 1H, CH=CH_2), 5.20-5.12 (m, 2H, CH=CH_2), 4.11-4.00 (m, 4H, 2× CH_3CH_2), 3.79 (d, ^{3}J = 6.3 Hz, 1H, 1-H), 3.74 (s, 3H, CH_3), 3.28-3.13 (m, 2H, 2-H), 3.09-3.01 (m, 2H, CH_2), 2.80-2.65 (m, 2H, 4-CH_2), 2.60-2.40 (m, 2H, 5-CH_2), 1.41 (q, J = 6.9 Hz, 6H, 2× CH_3CH_2); ^{13}C nmr (deuterio- chloroform): δ 173.06, 147.36, 146.35, 135.64, 134.51, 130.75, 117.35, 116.04, 115.80, 64.88, 64.58, 62.81, 57.28, 55.76, 52.43, 51.73, 36.59, 14.91; ms: m/z 334.2 $[M+H]^+$.

(*E*)-Methyl 6-benzyl-7,8-dihydro-6*H*-thieno[3,2-*d*]azepine-4-carboxylate (**10a**).

This compound was prepared from compound **9** and benzyl bromide following the general procedure for the synthesis of compounds **2**. White powder, mp 105-106 ºC, yield 90%. ^{1}H nmr (deuteriochloroform): δ 7.89 (s, 1H, 5-H), 7.46 (d, ^{3}J = 5.7 Hz, 1H, thieno H), 7.36-7.30 (m, 3H, Aromatic H), 7.26-7.23 (m, 2H, Aromatic H), 6.96 (d, ^{3}J = 5.4 Hz, 1H, thieno H), 4.46 (s, 2H, $PhCH_2$), 3.78 (s, 3H, CH_3), 3.41-3.38 (m, 2H, 7-CH_2), 3.03-2.99 (m, 2H, 8-CH_2); ^{13}C nmr (deuteriochloroform): δ169.47, 146.95, 136.24, 134.41, 133.08, 130.51, 128.81, 127.97, 127.37, 120.26, 95.32, 64.33, 52.28, 51.15, 30.14; ms: *m/z* 300.1 $[M+H]^+$.

Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.49; H, 5.91; N, 4.57.

(*E*)-Methyl 6-allyl-7,8-dihydro-6*H*-thieno[3,2-*d*]azepine-4-carboxylate (**10b**).

This compound was prepared from compound **9** and allyl bromide following the general procedure for the synthesis of compounds **2**. Colorless syrup, yield 83%; ^{1}H nmr (deuteriochloroform): δ 7.67 (s, 1H, 5-H), 7.43 (d, ^{3}J = 5.4 Hz, 1H, thieno H), 6.95 (d, ^{3}J = 5.4 Hz, 1H, thieno H), 5.86-5.75 (m, 1H, CH=CH_2), 5.26-5.20 (m, 1H, CH=CH_2), 3.86 (d, ^{3}J = 6.0 Hz, 2H, CH_2), 3.75 (s, 3H, CH_3), 3.46-3.43 (m, 2H, 7-CH_2), 3.08-3.05 (m, 2H, 8-CH_2); ^{13}C nmr (deuteriochloroform): δ 169.41, 146.52, 134.25, 133.14, 132.95, 130.46, 120.24, 118.42, 95.22, 62.98, 52.40, 51.08, 30.22; ms: *m/z* 250.1 $[M+H]^+$.

Methyl 6-benzyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine-4-carboxylate (**11a**).

This compound was prepared by reduction of compound **10a** following the procedure for the synthesis compound **3**. Colorless syrup, yield 91%;^{1}H nmr (deuteriochloroform): δ 7.33-7.24 (m, 5H, Aromatic H), 6.93 (d, ^{3}J = 5.1 Hz, 1H, thieno H), 6.71 (d, ^{3}J = 5.1 Hz, 1H, thieno H), 3.90 (dd, ^{3}J = 6.0 Hz, ^{3}J = 1.5Hz, 1H, 4-H), 3.69 (s, 2H, $PhCH_2$), 3.68 (s, 3H, CH_3), 3.37 (dd, ^{2}J = 12.9 Hz, ^{3}J = 5.7 Hz, 1H, 4-H), 3.14-3.04 (m, 1H, 5-H), 2.96-2.79 (m, 2H, 7-H), 2.70 (d, ^{2}J = 12.6 Hz, 1H, 8-H), 2.48 (t, ^{3}J = 11.1 Hz, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 172.38, 140.23, 138.95, 135.90, 129.68, 128.79, 128.14, 127.01, 120.67, 64.09, 58.27, 55.41, 51.77, 47.44, 29.93; ms: *m/z* 302.1 $[M+H]^+$.

Methyl 6-allyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine-4-carboxylate (**11b**).

This compound was prepared by reduction of compound **10b** following the procedure for the synthesis of compound **3**. Colorless syrup, yield 85%; ^{1}H nmr (deuteriochloroform): δ 6.94 (d, ^{3}J = 5.1 Hz, 1H, thieno H), 6.71 (d, ^{3}J = 5.4 Hz, 1H, thieno H), 5.91-5.82 (m, 1H, CH=CH_2), 5.22-5.16 (m, 2H, CH=CH_2), 3.94 (s, 1H, 4-H), 3.73 (s, 3H, -CH_3), 3.35-3.29 (m, 1H, 5-H), 3.24-3.18 (m, 2H, -CH_2), 3.11-3.02 (m, 1H, 5-H), 2.92-2.89 (m, 2H, 7-CH_2), 2.72-2.58 (m, 2H, 8-CH_2); ^{13}C nmr (deuteriochloroform): δ 172.48, 135.91, 135.06, 129.47, 120.77, 117.87, 109.72, 62.84, 57.34, 55.48, 51.85, 47.06, 29.60; ms: *m/z* 252.1 $[M+H]^+$.

Acknowledgment.

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