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Unexpected formation of novel oxazolidine and tetrahydrooxazine derivatives by condensation of 2-(hydroxymethy) or 2-(2-hydroxyethyl) piperidine, and ketones

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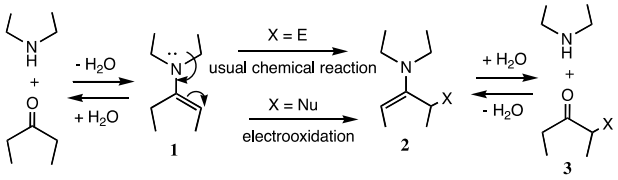
Several novel oxazolidine and tetrahydrooxazine derivatives, which possess a spiro carbon, were unexpectedly obtained during our attempts to prepare enamines that possess a hydroxy group by condensation between a piperidine alcohol and a ketone in the presence of an acidic catalyst. The reaction times under reflux conditions were significantly influenced by the structure of the starting substrates.

Key words: Enamine, Oxazolidine, Tetrahydrooxazine, Spiro carbon, Three ring compounds.

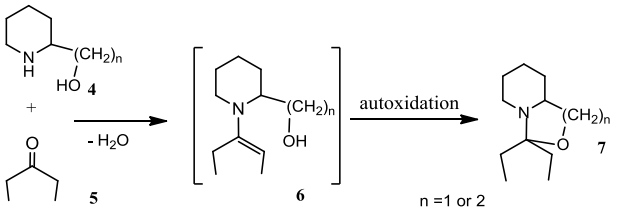
INTRODUCTION

As shown in Scheme 1, enamine **1** is often utilized as a precursor for the preparation of α-substituted ketone **3**. In such reactions, electrophiles (E) such as alkyl or acyl halides attacks **1** at the β-position of the nitrogen atom to give substituted enamine **2** (X=E), which readily undergoes hydrolytic cleavage to yield **3** (X=E) [1, 2].



Scheme 1. Preparation of α-substituted ketone via enamine

In contrast, Shono et al. [3] and Chiba et al. [4] have previously reported that **1** can instead be attacked by a nucleophile (Nu), such as a methoxide ion or organic anions derived from β-dicarbonyl compounds, via electrooxidation to give **2** (X=Nu), which then hydrolyzes to **3** (X=Nu). Consequently, we were naturally interest in the electrooxidative behavior of enamines, such as compound **6** that possess a hydroxyl group. We attempt to prepare **6** by refluxing a mixture of **4** and **5** in toluene in the presence of catalytic amount of an acidic catalyst. However the reaction resulted in unexpected formation of three ring compounds, probably via autoxidation by ambient oxygen in the open dehydration apparatus. [5]



Scheme 2. Unexpected formation of three rings compound **7.**

EXPERIMENTAL

The oxazolidine (**7**, n=1) and tetrahydrooxazine (**7**, n=2) derivatives were prepared as follow: in a 200-mL round bottomed flask equipped with a water trap condenser was added hydroxy piperidine **4** (50 mmol), symmetrical ketone **5 (**55 mmol), and *p*-toluenesulfonic acid (PTSA 0.1 g) in toluene (50 mL). The reaction mixture was refluxed until water was completely removed using the water trap (Table 1). After removal of the toluene under vacuum, the resulting residue was purified by distillation under reduced pressure. Structures of the isolated products were confirmed by IR and NMR and High resolution mass spectra. Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. NMR spectra were obtained on a JEOL JNM-ECX 400 spectrometer. High resolution mass spectra were measured on a JEOL JMS-100GCV gas chromatography time-of-flight mass spectrometer.

- compound **7a**. Colorless viscous oily liquid, bp : 108–110ºC/19 mmHg. R_f : 0.90(Silica gel TLC, Et_2O). IR (neat) : 2934, 2861, 2805, 1463, 1441, 1347, 1153, 1144, 1079, 1032 cm^{-1}. ^1H

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NMR ($CDCl_3$) :δ= 0.84(t, J= 12Hz, 3H), 0.90(t, J=12Hz, 3H), 1.1–1.2(m, 2H), 1.3–1.8(m, 8H), 2.4–2.5(m, 1H), 2.7–2.8(m, 2H), 3.3–3.4(m, 1H), 3.9–4.0(m, 1H). ^{13}C NMR ($CDCl_3$) :δ= 7.30(CH_3), 8.85(CH_3), 23.89(CH_2), 25.88(CH_2), 27.15(CH_2), 27.89(CH_2), 28.45(CH_2), 44.67(CH_2), 58.57(CH), 71.62(CH_2), 96.86(C). MS m/z (relative intensity, %) : 183(2) [M^+], 156(14), 155(33), 154(100), 98(48), 70(10), 57(17), 56(14), 41(18), 29(15). HRMS : m/z calcd. for $C_{11}H_{21}NO$: 183.1623 ;found : 183.1614[M^+].

- compound **7b**. Colorless viscous oily liquid, bp : 143–145˚C/45 mmHg. R_f : 0.56(Silica gel TLC, Et_2O). IR (neat) : 2935, 2867, 2798, 1440, 1323, 1280, 1226, 1141, 1057, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.2–1.4(m, 2H), 1.5–1.9(m, 11H), 2.2-2.3 (m, 1H), 2.5–2.7(m, 1H), 2.8-2.9(m, 1H), 3.4-3.5(m, 2H), 3.8–4.0(m, 1H). ^{13}C NMR ($CDCl_3$) :δ= 23.01(CH_2), 23.25(CH_2), 24.48(CH_2), 25.29(CH_2), 27.78(CH_2), 29.55(CH_2), 35.35(CH_2), 45.35(CH_2), 59.87(CH), 69.31(CH_2), 105.58(C). MS m/z (relative intensity, %) : 181(20) [M^+], 153(36), 152(100), 139(21), 98(33), 97(36), 82(28), 57(25), 55(28), 41(25). HRMS : m/z calcd. for $C_{11}H_{19}NO$: 181.1467 ;found : 181.1470[M^+].

- compound **7c**. [6, 7] Slightly yellowish viscous oily liquid, bp : 143-145˚C/19 mmHg. R_f : 0.23 (Silica gel TLC, Et_2O). IR (neat) : 2933, 2858, 2796, 1442, 1373, 1244, 1229, 1200, 1123, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.1–1.2(m, 1H), 1.3–1.4(m, 2H), 1.5–1.8(m, 10H), 1.9–2.3(m, 4H), 2.7–3.0(m, 2H), 3.7–3.8(m, 2H). ^{13}C NMR ($CDCl_3$) :δ=22.39(CH_2), 23.59(CH_2), 24.83(CH_2), 26.26(CH_2), 26.68(CH_2), 28.70(CH_2), 32.88(CH_2), 38.73(CH_2), 45.16(CH_2), 53.55(CH_2), 60.65(CH), 100.10(C). MS m/z (relative intensity, %) : 195(41) [M^+], 166(100), 151(55), 150(72), 138(64), 122(86), 84(54), 83(57), 55(51), 41(52). HRMS : m/z calcd. for $C_{12}H_{21}NO$: 195.1623 ; found : 195.1648[M^+].

- compound **7d**. Colorless viscous oily liquid, bp : 132–134ºC/16 mmHg. R_f : 0.85(Silica gel TLC, Et_2O). IR (neat) : 2933, 2860, 2804, 1448, 1365, 1291, 1203, 1155, 1130, 1037 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.0-1.3(m, 4H), 1.4–1.9(m, 12H), 2.2-2.4(m, 1H), 2.6–2.9(m, 2H), 3.3–3.5(m, 1H), 3.8–4.0(m, 1H). ^{13}C NMR ($CDCl_3$) :δ=22.86(CH_2), 23.77(CH_2), 23.83(CH_2), 25.73(CH_2), 25.81(CH_2), 28.14(CH_2), 29.93(CH_2), 35.78(CH_2), 45.43(CH_2), 58.72(CH), 70.08(CH_2), 94.93(C). MS m/z (relative intensity, %) : 195(26) [M^+], 166(17), 153(35), 152(100), 139(25), 98(26), 96(23), 82(18), 55(21), 41(23). HRMS : m/z calcd. for $C_{12}H_{21}NO$:195.1623 ;found : 195.1638[M^+].

- compound **7e**. [6, 7] Slightly yellowish viscous oily liquid, bp : 153–155ºC/19 mmHg. R_f : 0.47(Silica gel TLC, Et_2O). IR (neat) : 2932, 2857, 2796, 1445, 1375, 1289, 1258, 1227, 1117, 1084 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.0–1.2(m, 1H), 1.2–1.4(m, 4H), 1.4–1.8(m, 12H), 2.1–2.2(m, 1H), 2.2-2.3(m, 1H), 2.6–2.8(m, 1H), 2.9–3.0(m, 1H), 3.6-3.8(m, 2H). ^{13}C NMR ($CDCl_3$) :δ= 21.84(CH_2), 22.41(CH_2), 22.66(CH_2), 23.72(CH_2), 26.10(CH_2), 26.74(CH_2), 31.85(CH_2), 34.24(CH_2), 36.10(CH_2), 45.84(CH_2), 52.04(CH_2), 58.80(CH), 87.39(C). MS m/z (relative intensity, %) : 209(20) [M^+], 166(70), 165(49), 164(34), 138(29), 123(34), 122(100), 82(36), 55(36), 41(35). HRMS : m/z calcd. for $C_{13}H_{23}NO$: 209.1780 ;found : 209.1764[M^+].

- compound **7f**. Colorless viscous oily liquid, bp : 125-127˚C/2 mmHg. R_f : 0.87(Silica gel TLC, Et_2O), IR (neat) : 2938, 2865, 2804, 1442, 1365, 1289, 1203, 1154, 1130, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 0.86(s, 9H, 3 × CH_3), 0.8–1.0(m, 2H), 1.1-1.8(m, 13H), 2.2–2.3(m, 1H), 2.7–2.8(m, 1H), 2.8-2.9(m, 1H), 3.3–3.4(m, 1H), 3.9–4.0(m, 1H). ^{13}C NMR ($CDCl_3$) :δ= 23.64(CH_2), 23.82(CH_2), 24.58(CH_2), 25.70(CH_2), 27.71(CH_3), 28.13(CH_2), 29.82(CH_2), 32.39(C), 35.93(CH_2), 45.45(CH_2), 47.82(CH), 58.87(CH), 70.12(CH_2), 94.23(C). MS m/z (relative intensity, %) : 251 (14) [M^+], 236(18), 194(38), 153(40), 152(100), 139(29), 98(28), 97(28), 55(25), 41(25). HRMS : m/z calcd. for $C_{16}H_{29}NO$: 251.2249 ;found : 251.2260[M^+].

- compound **7g**. Colorless viscous oily liquid, bp : 150-152˚C/19 mmHg. R_f : 0.96(Silica gel TLC, Et_2O), IR (neat): 2931, 2857, 2799, 1455, 1441, 1275, 1221, 1126, 1074, 1032 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.1–1.3(m, 2H), 1.3-1.9(m, 16H), 2.2-2.3(m, 1H), 2.5–2.6(m, 1H), 2.9-3.0(m, 1H), 3.3-3.4(m, 1H), 3.8-3.9(m, 1H). ^{13}C NMR ($CDCl_3$) :δ= 22.86(CH_2), 23.29(CH_2), 23.72(CH_2), 25.71(CH_2), 27.88(CH_2), 30.08(CH_2), 30.75(CH_2), 32.82(CH_2), 40.55(CH_2), 45.14(CH_2), 58.54(CH), 69.91(CH_2), 98.21(C). MS m/z (relative intensity, %) : 209(24) [M^+], 166(37), 153(36), 152(100), 139(30), 98(27), 97(28), 82(21), 55(27), 41(25). HRMS : m/z calcd. for $C_{13}H_{23}NO$:209.1780 ;found : 209.1792[M^+].

- compound **7h**. Colorless viscous oily liquid, bp : 162–164ºC/17 mmHg. R_f : 0.72(Silica gel TLC, Ethyl ether), IR (neat) :2930, 2854, 2800, 1443, 1278, 1195, 1142, 1124, 1075, 1037 cm^{-1}. ^{1}H NMR ($CDCl_3$)δ= 1.1–1.3(m, 2H), 1.4–1.9(m, 18H), 2.2-2.3(m, 1H), 2.6–2.7(m, 1H), 2.9-3.1(m, 1H), 3.3-3.4(m, 1H), 3.8-3.9(m, 1H). ^{13}C NMR

($CDCl_3$) :δ= 22.15(CH_2), 22.64(CH_2), 23.78(CH_2), 24.80(CH_2), 25.92(CH_2), 27.65(CH_2), 28.16(CH_2), 28.70(CH_2), 29.47(CH_2), 36.83(CH_2), 45.91(CH_2), 59.15(CH), 70.11(CH_2), 97.08(C). MS m/z (relative intensity, %) : 223(23) [M^+], 194(26), 192(26), 166(32), 153(45), 152(100), 139(87), 98(44), 97(59), 55(34). HRMS : m/z calcd. for $C_{14}H_{25}NO$:223.1936 ;found : 223.1933[M^+].

RESULTS AND DISCUSSION

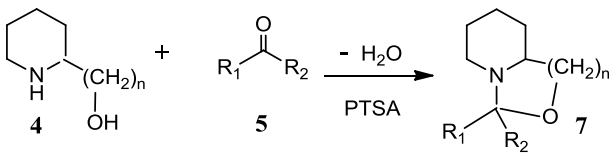
Beginning of the study, we examined preparation of **6** by refluxing 2-(hydroxymethy) piperidine (**4d**, n=1) (Entry 4 in Table 1) or 2-(2-hydroxyethyl) piperidine (**4e**, n=2) (Entry 5), and several symmetrical ketones (**5a**–**h)**. Although after theoretical amount of water could be removed from the reaction mixture, unexpected oxazolidine (**7d**, n=1**)** and tetrahydrooxazine (**7e**, n=2**)** derivatives were formed dominantly via a probable formation of the corresponding **6** (n=1 or 2) as the intermediates in good yield.

Interestingly, to the best of our knowledge, there are only very few reports regarding the preparation of compound type **7**, and most of the unique products consisting of three condensed rings obtained here are novel compounds. [6–11]

Table 1. Formation of oxazolidine and tetrahydrooxazine derivatives [a)]

Entry	**4**, **5**, **7**	n	R_1	R_2	r. time (h)	Yield of **7** (%) [b)]
1	a	1	Et	Et	70	75
2	b	1	-(CH_2)$_4$-		2	93
3	c	2	-(CH_2)$_4$-		3	95
4	d	1	-(CH_2)$_5$-		2	88
5	e	2	-(CH_2)$_5$-		26	87
6	f	1	-(CH_2)$_2$CH(*t*-Bu)(CH_2)$_2$-		7	95
7	g	1	-(CH_2)$_6$-		7	85
8	h	1	-(CH_2)$_7$-		9	64

[a)] **4**: 50 mmol, **5** : 55 mmol, PTSA : 0.1 g. Refluxing in toluene : 50 mL.
[b)] Isolated yields.



Scheme 3.

Table 1 shows relationship among the type of piperidine **4**, ketone **5**, reaction time, and the yields of the corresponding cyclic compound **7**. Refluxing times (see experimental section) required to complete the reaction were significantly depended on the structure of not only **4** but also **5** moiety. For example cyclopentanone **5b** (Entry 2), **5c** (Entry 3) and cyclohexanone **5d** (Entry 4) react readily with **4** (n=1 and 2) to give the corresponding cyclic compounds **7b**, **7c** and **7d** in high yields (88~95%), however much more long reaction times were needed in the cases of 3-pentanone **5a** (Entry 1, 70h) and cyclohexanone **5e** (Entry 5, 26h). Long refluxing time decreased the yield of **7h** (r. time 20hr, 55%) in the case of Entry 8. Further investigations of reactivity between **4** and **5**, and into the stereo-specificity of the products are currently underway in our laboratories.

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НЕОЧАКВАНО ОБРАЗУВАНЕ НА НОВИ ПРОИЗВОДНИ НА ОКСАЗОЛИДИН И ТЕТРАХИДРООКСАЗИН ПРИ КОНДЕНЗАЦИЯ НА 2-(ХИДРОКСИМЕТИЛ) ИЛИ 2- (2-ХИДРОКСИЕТИЛ) ПИПЕРИДИН И КЕТОНИ

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(Резюме)

Няколко нови производни на оксазолидин и тетрахидрооксазин, притежаващи спиро-въглерод, бяха получени неочаквано при опитите да се получат енамини, които притежават хидроксилна група, при кондензация на пиперидинов алкохол и кетон в присъствието на киселинен катализатор. Реакционните времена при нагряване с обратен хладник се влияят значително от структурата на изходните субстрати.