Synthesis of 1,2-Polymethyleneimidazoles Utilizing Intramolecular Ring Transformation

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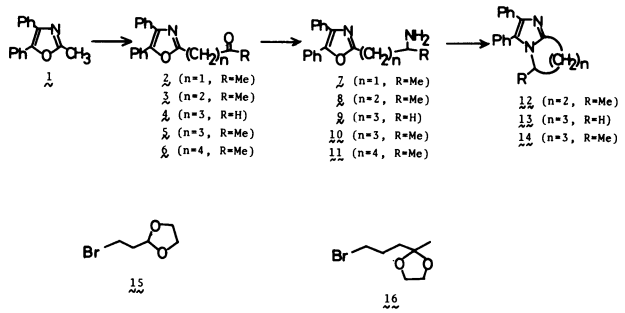
Synopsis. Among the intramolecular cyclodehydration of 2-(β-, δ-, and ε-aminoalkyl)oxazoles, 2-(δ-aminoalkyl)oxazoles afforded the desired 1,2-tetramethyleneimidazoles on pyrolysis, while 2-(β- and ε-aminoalkyl)oxazoles unchanged under the same conditions.

We have recently studied[1] an intramolecular cyclodehydration of 2-(γ-aminoalkyl)oxazole affording 1,2-trimethyleneimidazole (*i.e.*, **3**→**8**→**12**) based on the intramolecular ring transformation strategy.[2-4] To apply this method for the synthesis of other 1,2-polymethyleneimidazoles, it is significant to know the effects induced by the number of bridging atoms between an oxazole and an amino function. For this purpose, 2-(β-, δ-, and ε-aminoalkyl)oxazoles were prepared and their pyrolysis was studied.

2-Methyloxazole **1**[5] was lithiated with *n*-BuLi in THF at −78 °C[6] and acylated with ethyl acetate to give β-oxazolyl ketone **2** in 51% yield. The lithiated **1** afforded δ-oxazolyl aldehyde **4** in 65% yield on treatment with bromo acetal **15**[7] followed by hydrolysis of the coupled acetal. δ-Oxazolyl ketone **5** was prepared in 46% yield by the transformation of **4** *via* Grignard reaction followed by the oxidation of the resulting secondary alcohol with pyridinium chlorochromate (PCC). ε-Oxazolyl ketone **6** was similarly prepared in 45% yield from **1** and bromo acetal **16**[8] The carbonyl function of **2**, **4**, **5**, and **6** was indicated by strong absorptions at 1715, 1725, 1715, and 1715 cm^{-1} respectively and their structures were supported by the spectral and elemental analyses. The prepared ketones **2**, **5**, and **6** were reductively aminated to the corresponding amines **7**, **10**, and **11** respectively on treatment with $NaBH_3CN$ in the presence of ammonium acetate. This conversion was indicated by methyl doublets at δ 1.24 (J= 6.8 Hz) for **7**, 1.12 (*J*=6.8 Hz) for **10**, and 1.05 (*J*=6.8 Hz) for **11** and D_2O-exchangeable N–H signals at δ 1.80 for **7**, 1.90 for **10**, and 1.70 for **11** in the ^1H NMR spectra. Without further purification, δ-oxazolyl amine **10** was directly heated at 280 °C under reduced pressure (5 mmHg, 1 mmHg≈133.322 Pa) to give cyclodehydrated 1,2-tetramethyleneimidazole **14** in 50% overall yield from **5**. In the same manner as for δ-oxazolyl ketone **5**, δ-oxazolyl aldehyde **4** was successfully transformed to **13** in 29% overall yield. The structure of **13** was definitely confirmed by the spectral comparison with an authentic sample reported in the literature,[9] and with the spectral data for **13** in hand, that of **14** was readily determined; ring closure was verified by disappearance of D_2O-exchangeable N–H signal and the chemical shift of ring protons at δ 1.60—2.30 (4H, m, C-6 and C-7 H), 2.70—3.15 (2H, m, C-8 H), and 3.90—4.50 (1H, m, C-5 H). In contrast to the successful ring transformation of **9** and **10**, any attempted pyrolysis of 2-(β- and ε-aminoalkyl)oxazoles **7** and **11** resulted in the recovery of the starting material.

In summary, cyclodehydration of 2-(aminoalkyl)oxazoles was found to be effective for the synthesis of not only 1,2-trimethylene- but also tetramethyleneimidazole ring system. Further application could make this strategy quite capable of providing a number of different fused ring system of interest.



Experimental

Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO-IRA-1 spectrometer. ^1H NMR spectra were recorded on a JEOL C-60-HL spectrometer and chemical shifts are reported in ppm (δ) relative to Me_4Si as internal standard. Microanalyses were performed with Perkin-Elmer 240B elemental analyzer. Pyrolysis was carried out with a Sibata Glass Tube Oven GTO-250.

2-(2-Oxopropyl)-4,5-diphenyloxazole (2). To a solution of **1**[5] (2.0 g, 8.5 mmol) in dry THF (30 ml) was added a solution of *n*-BuLi in hexane (1.6 M, 6.3 ml, 10.2 mmol) dropwise over 15 min at −78 °C under the current of N_2. After the resulting deep orange-red suspension was stirred at −78 °C for additional 20 min, ethyl acetate (0.95 ml, 9.7 mmol) was added and the mixture was stirred at −78 °C for 30 min. The resulting mixture was then slowly warmed to room temperature and quenched with 30 ml of phosphate buffer (pH 7). The organic layer was extracted with $CHCl_3$ (3×20 ml). The combined $CHCl_3$ solution was washed 3 times with water, dried over $MgSO_4$, and concentrated to leave a yellow oil, which was chromatographed on a silica gel column (AcOEt/hexane 1:2) to give crude **2**. Further purification by recrystallization from ethanol gave 1.2 g (51%) of **2** as yellow crystals; mp 106—108 °C; IR (KBr) 3090, 2910, 1715, 1600, 1570, and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.30 (3H, s, CH_3), 3.97 (s, 2H, CH_2), and 7.20—7.80 (10H, m, Ar). Found: C, 77.70; H, 5.72; N, 5.05%. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05%.

2-(4-Oxobutyl)-4,5-diphenyloxazole (4). To a solution of the lithiated **1** (2.0 g, 8.5 mmol) prepared as above, **15**[7] (1.1 ml, 9.4 mmol) was added and the mixture was stirred at −78 °C for 30 min. The resulting mixture was then slowly warmed to room temperature and quenched with 30 ml of phosphate buffer (pH 7). The organic layer was extracted with $CHCl_3$ (3×30 ml). The combined $CHCl_3$

solution was washed 3 times with water, dried over $MgSO_4$, and concentrated to leave acetal as a yellow oil. A mixture of crude acetal and 0.5 M aqueous HCl (40 ml) was heated under reflux for 1 h. After cooling to room temperature, an orange oil was extracted with $CHCl_3$ (3×30 ml). The combined $CHCl_3$ solution was washed 3 times with water, dried over $MgSO_4$, and concentrated to leave an oil, which was chromatographed on s silica gel column (AcOEt/hexane 1:1) to afford 1.6 g (65%) of **4** as a yellow oil; IR (neat) 3045, 2940, 2810, 2710, 1725, 1600, 1570, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18 (2H, quintet, J=6.8 Hz, CH_2), 2.50—3.10 (4H, m, CH_2×2), 7.20—7.80 (m, 10H, Ar), and 9.78 (1H, t, J=1.2 Hz, CHO). Found: C, 78.24; H, 6.00; N, 4.78%. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81%.

2-(4-Oxopentyl)-4,5-diphenyloxazole (5). To a solution of methylmagnesium iodide in ether (6 ml) prepared from magnesium (70 mg, 2.9 mmol) and methyl iodide (0.18 ml, 2.9 mmol), was added a solution of **4** (640 mg, 2.2 mmol) in ether (4 ml) at room temperature. After stirring at room temperature for 1.5 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (20 ml) and extracted with ether (3×15 ml). The combined ether solution was dried over $MgSO_4$ and concentrated to leave crude alcohol as a yellow oil, which was dissolved in CH_2Cl_2 (4 ml). This solution was added to a solution of PCC (630 mg, 2.9 mmol) in CH_2Cl_2 (4 ml) and stirred at room temperature for 17 h. After removal of the solvent, the residue was extracted with ether (3×10 ml). Concentration of the combined ether solution and subsequent chromatography on a silica-gel column (Et_2O/hexane 1:1) gave 320 mg (48%) of **5** as a yellow oil; IR (neat) 3050, 2940, 1715, 1600, 1570, 1500, and 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18 (3H, s, CH_3), 2.45—3.08 (6H, m, 3×CH_2), and 7.20—7.80 (10H, m, Ar). Found: C, 78.56; H, 6.32; N, 4.53%. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59%.

2-(5-Oxohexyl)-4,5-diphenyloxazole (6). By the similar procedure to the preparation of **4**, ε-oxazolyl ketone **6** was prepared by the reaction of the lithiated **1** with bromoacetal **16**[8] at −78 °C, followed by hydrolysis of the resulting acetal with 0.5 M aqueous HCl. Purification was performed on a silica-gel column (Et_2O/hexane 1:1); yield 45; yellow oil; IR (neat) 3050, 2940, 1715, 1600, 1575, 1500, and 1445 cm^{-1}; ^1H NMR ($CDCL_3$) δ=1.50—3.00 (8H, m, 4×CH_2), 2.14 (3H, s, CH_3), and 7.20—7.80 (10H, m, Ar). Found: C, 78.86; H, 6.60; N, 4.63%. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39%.

2,3-Diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrdine (13). A solution of **4** (470 mg, 1.6 mmol), $NaBH_3CN$ (710 mg, 11.3 mmol), and ammonium acetate (1.2 g, 15.6 mmol) in dry methanol (16 ml) was heated under reflux for 3 h. The resulting mixture was acidified with concentrated aqueous HCl (pH 2) and then basified with 20% aqueous NaOH (pH 9). After extraction with $CHCl_3$ (3×15 ml), the combined organic layer was dried over $MgSO_4$. Removal of the solvent yielded crude amine **9** as a yellow oil, which was then heated at 280 °C under 5 mmHg for 20 min in a glass tube oven with a trap bulb heated at 200 °C. Tetrahydroimidazopyridine **13** was trapped as a yellow oil, which immediately solidified on cooling; 130 mg (29%); mp 140—142 °C (from AcOEt) (Lit,[9] 137—138 °C). Its spectral data are in good agreement with those reported in the literature.

5-Methyl-2,3-diphenyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (14). In the same way as above, **14** was obtained in 50% yield by the reductive amination of **5**, followed by pyrolysis of the crude 2-(δ-aminoalkyl)oxazole **10**. An analytical sample was obtained by chromatographic purification; mp 116—119 °C; IR (KBr) 3040, 2830, 1600, 1510, 1440, and 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.98 (3H, d, J=6.8 Hz, CH_3), 1.60—2.30 (4H, m, C-6 and C-7 H), 2.70—3.15 (2H, m, C-8 H), 3.90—4.50 (1H, m, C-5 H), and 7.10—7.60 (10H, m, Ar). Found: C, 83.51; H, 6.81; N, 9.68%. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71%.

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