# FIRST SYNTHESIS OF 4-IMIDAZOLIDINONE

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Abstract ——— First synthesis of 4-imidazolidinone has been achieved via Beckmann rearrangement of 1-alkoxycarbonylazetidin-3-one oxime sulfonates with alumina, followed by removal of the alkoxycarbonyl groups.

Although the chemistry and biochemistry of azetidin-2-ones have been extensively investigated with regard to various β-lactam antibiotics, little is known about the chemistry of azetidin-3-ones.[1] In connection with the chemistry of azetidin-3-ones, we began a program using the aza-ring expansion of azetidin-3-ones to design unsubstituted 4-imidazolidinone (7), which has not previously been prepared. This compound would serve as a nucleus for the preparation of derivatives of potential pharmacological interest. Some 4-imidazolidinones possessing biological activities have been reported.[2] We now wish to report the synthetic method of 7 by Beckmann rearrangement of 1-alkoxycarbonylazetidin-3-one oxime sulfonates, followed by removal of the alkoxycarbonyl groups.

The synthetic route to 7 was shown in Chart 1. First, we examined the possibility of converting 4a having a relatively stable ethoxycarbonyl group into 6a. Treatment of 1 with excess ethyl chloroformate in refluxing benzene afforded 1-ethoxycarbonylazetidin-3-one (2a), mp 42-43°C, in a quantitative yield. Reaction of 2a with hydroxylamine hydrochloride in the presence of sodium acetate in aqueous ethanol gave the oxime (3a), mp 83-84°C (98%). Tosylation (TsCl, NaH, $Et_2O$, $N_2$) of 3a gave the tosylate (4a), mp 106-107°C (57%), and mesylation (MsCl, $Et_3N$, $CH_2Cl_2$) of 3a afforded the mesylate (5a), mp 81-82°C (80%). All attempts to effect the Beckmann rearrangement of 4a and 5a by standard reagents such as polyphosphoric acid, sulfuric acid, and formic acid were unsuccessful. These results demonstrated that 4a and 5a are very unstable under acidic conditions to give the hydrolyzed products, along with other complicated products. Therefore, we

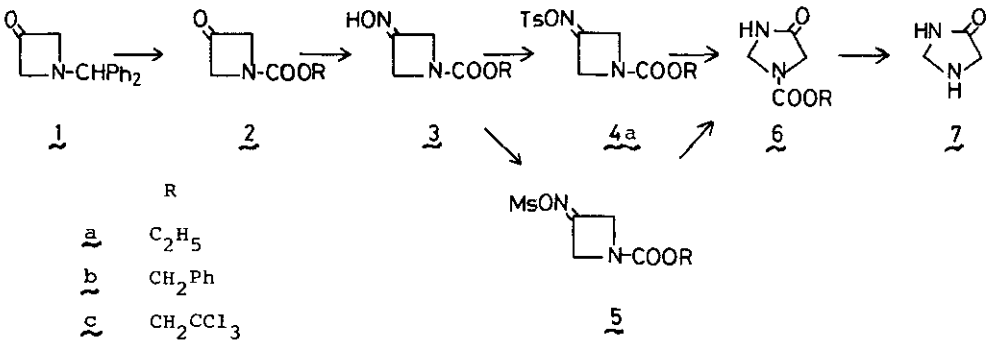


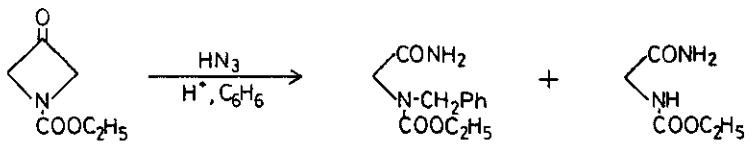

Chart 1

surveyed to examine the mild procedure of Craig and Naik[3] which had been shown to give good yields of the rearrangement product by using neutral alumina and to cause no isomerisation of the oxime during the reaction. We found that both neutral[4a,b] and basic[4c] alumina could effect the rearrangement of 4a and 5a to furnish the formation of the desired product (6a) in good yields. To our best knowledge, this is a first example of ring enlargement of azetidin-3-ones by Beckmann rearrangement. Thus, to a solution of 5a (0.16 g, 0.64 mmol) in benzene (10 ml) was adsorbed on a column of basic alumina (20 g). The column was eluted with ethyl acetate. The resulting solution was concentrated to give the rearrangement product, 6a, mp 133-134°C (91%). The spectral and elemental analytical data of 6a are in agreement with the value expected from the structure, as shown in Table I and II. The imidazolidinone (6a) was also obtained from 4a in 67% yield by using of neutral alumina.

Next, in order to obtain the unsubstituted compound (7), we examined the preparation of other 1-alkoxycarbonylazetidin-3-ones in which the alkoxycarbonyl groups could be deprotected under mild conditions. Thus, 1-benzyloxycarbonylazetidin-3-one (2b) was obtained as an oil in 82% yield by the reaction of 1 with benzyl chloroformate. Oximation of 2b gave the oxime (3b), mp 112-113°C (86%), and the mesylation of 3b afforded 5b, mp 101-102°C (68%). Similarly, we obtained 1-trichloroethoxycarbonylazetidin-3-one (2c), mp 55-56°C, its oxime (3c), mp 81-82°C, and the mesylate (5c) as an oil in good yields, respectively. Beckmann rearrangement of 5b and 5c in the same way as described above for the conversion of 5a into 6a gave 6b, mp 167-168°C, and 6c, mp 184-185°C, in 67 and 60% yields, respectively. Hydrogenolysis of 6b over 10% Pd on charcoal gave 7 as a pale yellow oil in 95% yield. On the other hand, 6c was treated with zinc powder and

acetic acid at room temperature for 70 h to afford the AcOH salt (8) of 7, mp 185-186°C (dec.) in a quantitative yield. The structure of 7 was established on the basis of this ir, nmr, and mass spectral data and elemental analytical data of 8 (Table I and II).

Finally, in order to obtain 7 by an alternative approach, we examined the Schmidt reaction of 2 as an example. Treatment of a benzene solution of 2 with hydrazoic acid in concentrated sulfuric acid at 10-15°C afforded no cyclic products, but gave amides, 9[5] and 10[6], in 25 and 22% yields, respectively, as shown in Chart 2. From the formation of 9, it was thought that the fragmentation might be facilitated by the preferentially formation of stable iminium ion ( $\overset{+}{>}N=CH_2 \longleftrightarrow >N-CH_2^+$ ).




2a 9 10

Chart 2

Table I. IR, NMR, and MS Spectral Data for 6a, 6b, 6c, and 7

| Compound | IR (KBr) $cm^{-1}$ | NMR (solvent) $\delta$ | MS (m/e) |
|---|---|---|---|
| 6a | 3200, 1705 1680, 1130 | ($CDCl_3$): 1.24 (3H, t, J=7Hz, $CH_2\underline{CH}_3$), 3.78 (2H, s, $COC\underline{H}_2$), 4.04 (2H, q, J=7Hz, $C\underline{H}_2CH_3$), 4.66 (2H, s, $NC\underline{H}_2N$), 7.66 (1H, br s, N$\underline{H}$CO) | 158 ($M^+$) |
| 6b | 3200, 1710 1680, 1120 | (DMSO-$d_6$): 3.85 (2H, s, $COC\underline{H}_2$), 4.75 (2H, s, $NC\underline{H}_2N$), 5.21 (2H, s, $C\underline{H}_2Ph$), 7.50 (5H, s, arom. H), 8.74 (1H, br s, N$\underline{H}$CO) | 220 ($M^+$) |
| 6c | 3200, 1725 1700, 1675 1120 | (DMSO-$d_6$): 3.90 (2H, s, $COC\underline{H}_2$), 4.81 (2H, s, $NC\underline{H}_2N$), 5.01 (2H, s, $C\underline{H}_2CCl_3$), 8.88 (1H, br s, N$\underline{H}$CO) | 261 ($M^+$) |
| 7 | 3400, 3240 1695, 1685 | (DMSO-$d_6$): 3.07 (2H, s, $COC\underline{H}_2$), 4.18 (2H, s, $NC\underline{H}_2N$), 4.28 (1H, s, $CH_2N\underline{H}CH_2$), 8.14 (1H, br s, N$\underline{H}$CO) | 86 ($M^+$) |

Table II. Elemental Analytical Data for 6a, 6b, 6c, and 8

| Compound | Formula | C (%) | | H (%) | | N (%) | |
|---|---|---|---|---|---|---|---|
| | | Calcd | Found | Calcd | Found | Calcd | Found |
| 6a | $C_6H_{10}N_2O_3$ | 45.57 | 45.67 | 6.37 | 6.40 | 17.71 | 17.75 |
| 6b | $C_{11}H_{12}N_2O_3$ | 59.99 | 60.05 | 5.49 | 5.51 | 12.72 | 12.66 |
| 6c | $C_6H_7N_2O_3Cl_3$ | 27.57 | 27.62 | 2.70 | 2.65 | 10.71 | 10.75 |
| 8 | $C_5H_{10}N_2O_3$ | 34.30 | 34.35 | 2.88 | 2.95 | 22.22 | 21.95 |

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5. 9 : a colorless powder, mp 99-100°C. IR (KBr) $cm^{-1}$: 3500, 3420, 1710, 1680. NMR (DMSO-$d_6$) $\delta$: 1.23 (3H, t, J=7Hz, $OCH_2\underline{CH_3}$), 3.82 (2H, s, $NC\underline{H_2}Ph$), 4.20 (2H, q, J=7Hz, $OC\underline{H_2}CH_3$), 4.48 (2H, s, $COC\underline{H_2}N$), 6.10 (2H, br s, $CON\underline{H_2}$), 7.30 (5H, s, arom. H). Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.93; H, 6.85; N, 11.93.
6. 10 : a colorless powder, mp 93-95°C. IR (KBr) $cm^{-1}$: 3380, 3325, 1687, 1659. NMR (DMSO-$d_6$) $\delta$: 1.22 (3H, t, J=7Hz, $OCH_2\underline{CH_3}$), 3.60 (2H, d, $NHC\underline{H_2}$), 4.07 (2H, q, J=7Hz, $OC\underline{H_2}CH_3$), 7.0-7.5 (3H, m, CONH, $CON\underline{H_2}$). Anal. Calcd for $C_5H_{10}N_2O_3$: C, 41.09; H, 6.90; N, 19.17. Found: C, 40.89; H, 6.93; N, 18.99.


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