Beckmann Rearrangement of Adamantanone Oxime

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Adamantanone oxime underwent Beckmann rearrangement with thionyl chloride as the promoter to produce 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one in 85% yield. An investigation of reaction variables provided optimum reaction conditions and mechanistic information.

Recent reports on the Beckmann rearrangement of adamantanone oxime (*1*) have prompted us to publish our results in this area (*1, 5, 6, 8, 9*). This paper describes an alternative, high-yield synthesis for the rearranged product, plus a treatment of the mechanism.

4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one (2) was obtained from 1 by a simple procedure in 84–86% yield (2 + 2·HCl) with thionyl chloride as catalyst. A prior report (*1*) does not rate thionyl chloride at the same high level of preference. In recent disclosures, 2 was formed in 23–35% yield via the Schmidt reaction (*1, 9*), in 52–57% yield with polyphosphoric acid (*1, 5, 6*), in 65% yield with polyphosphate ester (*8*), and in 82% yield with phosphorus pentachloride (*5*).

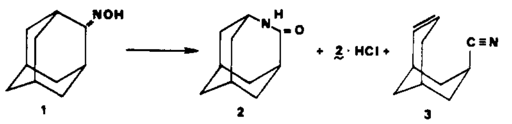
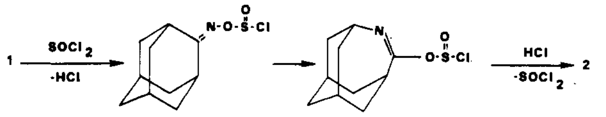
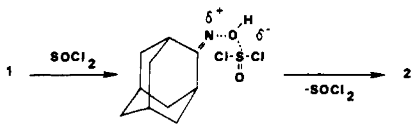


Table I summarizes the data for rearrangement under various conditions, usually in the presence of thionyl chloride. Best yields (2 + 2·HCl) were realized with a 2–4 molar ratio of thionyl chloride to 1 in ether at 0° C. The reaction was found to proceed in 63% yield with a catalytic amount of thionyl chloride ($SOCl_2$ to 1 = 0.2–1), and a 12-fold excess of promoter also provided less than the optimum quantity of 2 (72%). When appreciable amounts of thionyl chloride were used, the product was predominantly in the form of 2·HCl. Further investigation revealed that interaction of thionyl chloride with 2 afforded 2·HCl (52%). These observations nicely account for the paucity of 2·HCl when lower levels of thionyl chloride are employed. The yield of 2·HCl was not significantly altered under anhydrous conditions. Structure 2 was readily converted to 2·HCl (*1, 6, 9*) on exposure to hydrochloric acid; various amides are known to furnish stable protonated species (*4*). Under our conditions, a by-product (*1, 5, 8*), bicyclo[3.3.1]non-6-ene-3-carbonitrile, structure 3, present in 2–5% yield, was separated from 2 during recrystallization.

These experiments, as well as additional ones, provided information concerning the mechanistic features. When either hydrogen chloride or sulfur dioxide was used in conjunction with thionyl chloride, no yield enhancement was observed. The absence of a mass action effect suggests that these gases are not involved in the reaction pathway. With either of these two additives alone, rearrangement failed to occur; 1 was recovered quantitatively. Two plausible reaction pathways are illustrated.





Equation 2 is analogous to known cases which proceed in the absence of acid catalysis (*2*). The generated hydrogen chloride serves to regenerate the catalyst from lactam precursor. Path 3 which depicts thionyl chloride as a Lewis acid promoter has precedent in the prior literature (*3*). Both schemes can be used to accommodate formation of the "second order" Beckmann product, 3 (*1, 5, 8*).

Table I. Adamantanone Oxime and Thionyl Chloride

Catalyst	General procedure	Molar ratio $SOCl_2/1$	Temp, ° C	Solvent	Yield, % 2	 2·HCl	 Total
$SOCl_2$	A	4	0	Et_2O	24	60	84
$SOCl_2$	A[a]	4	0	Et_2O	36	50	86
$SOCl_2$	B[a]	4	0	Et_2O	22	63	85
$SOCl_2$	B[a]	0.2	0	Et_2O	56	7	63
$SOCl_2$	A	2	0	Et_2O	46	40	86
$SOCl_2$	A	12	0	Et_2O	12	60	72
$SOCl_2$	A	4	35	Et_2O	41	42	83
$SOCl_2$	A	4	0	CH_2Cl_2	27	52	79
$SOCl_2$	A	4	77	CCl_4	30	44	74
$SOCl_2$ + HCl	A	4	0	Et_2O	44	38	82
$SOCl_2$ + SO_2	A	4	0	Et_2O	40	38	78
$BzSO_2Cl$ + pyridine	...	...	...	...	...	...	<40

[a] Anhydrous.

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EXPERIMENTAL

Melting points, uncorrected, were determined with a Thomas-Hoover melting point apparatus. Infrared spectra were obtained with a Beckman IR-8 spectrophotometer, and nuclear magnetic resonance (nmr) spectra with a Varian HA-100 spectrometer in $CDCl_3$ with $Si(CH_3)_4$ as internal standard (*m* = multiplet). Gas-liquid chromatography analyses were obtained with a Varian Aerograph 1800 gas chromatograph, 10 ft × 0.25 in., 10% SE-30 on Chromosorb W (45–60 mesh), 170°C, He (120 ml/min). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Anhydrous experiments were performed in oven-dried glassware (110°C) with ether distilled from lithium aluminum hydride and distilled thionyl chloride. Adamantanone was obtained from Aldrich Chemical Co.

Adamantanone Oxime, 1. A literature method was used (3-hr reflux) with adamantanone (*10*). Recrystallization of crude 1 from ethanol–water afforded white needles (95%): mp 165–166°C; lit. mp 164–165.5°C (*8*).

4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one, 2. *General Procedure A*. A solution of 8.65 ml (0.120 mol) of thionyl chloride in 30 ml of anhydrous ether was added dropwise with agitation and cooling in an ice bath over a period of 0.5 hr to a solution of 5 grams (0.03 mole) of 1 in 60 ml of anhydrous ether. The mixture was stirred for an additional 1.5 hr at the same temperature, and then solvent was removed by evaporation. The white solid was treated with 150 ml of ice water and extracted with two 75-ml portions of benzene. The aqueous fraction was made caustic with 100 ml of 10% sodium hydroxide solution and extracted with three 50-ml portions of methylene chloride. Removal of the solvent from the dried mixture afforded 3 grams (60%) of the desired lactam. The solvent from the dried benzene fraction was removed and the solid on recrystallization from ether–pentene yielded an additional 1.2 grams (24%) of 2. The combined yield was 4.2 grams (84%): mp 308–309°C; lit. mp 304–311°C (*6*), mp 298–300°C (*8*). Gas-liquid chromatographic analysis revealed that the product was greater than 99% pure. The nmr spectrum displayed three broad absorptions at δ 7.82 ($\underline{H}$N), 3.31 ($\underline{H}$C—N), 2.65 ($\underline{H}$C—C=O), and a complex multiplet at 2.06–1.72 (12 C$\underline{H}$). Contrary to an earlier report (*8*), the absorption at δ 7.82 was assigned to the $\underline{H}$N—C proton by D_2O exchange. The infrared spectrum of 2 was identical to that obtained by previous workers (*8*).

The ether–pentane mother liquor was shown to contain a small amount of 2 and several other products, one of which was collected by gas-liquid chromatography and identified as 3: mp 170–171°C (dec); ν_{CCl_4} cm^{-1} 2240 (C≡N) and 3033 (C=C—$\underline{H}$); nmr δ 5.8–5.9 (m, 2H, C$\underline{H}$=C$\underline{H}$), 3.0 ($\underline{H}$C—C≡N), 2.6–1.4 (m, C$\underline{H}$); lit mp, 176.5–181.5°C (dec) (*5*), ν_{KBr} cm^{-1} 2230 (C≡N), 3020 (C=C$\underline{H}$); nmr δ 6.20–5.74 (m, 2H, C$\underline{H}$=C$\underline{H}$), 2.96 ($\underline{H}$C—C≡N) and 2.66–1.40 (m, C$\underline{H}$).

General Procedure B. Procedure A was modified in the work-up. After completion of the ether–thionyl chloride addition and subsequent stirring, the ether-insoluble 2·HCl was removed by filtration and washed with ether. The free lactam, liberated by treatment with 100 ml of 10% sodium hydroxide solution, was extracted with methylene chloride. Solvent removal from the dried solution afforded 3.15 grams (63%) of pure 2 (gas-liquid chromatographic analysis). The ether solution was concentrated, treated with 50 ml of ice water, and dried by rotary evaporation (water bath). The residue was recrystallized from ether–pentane giving 1.1 grams (22%) of 2. The combined yield of 2 was 85%.

4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one Hydrochloride (2·HCl). The aqueous portion of the reaction mixture from Procedure A gave a white salt upon evaporation, which is identical to that obtained by filtration in Procedure B. The infrared spectrum showed the following absorption: ν_{KBr} cm^{-1} 2900, 2150 (broad) (*4*), 1650 [—C(=O)—N]; [lit., ν_{KBr} cm^{-1} 2600-2000 and 1655 (*9*)].

Anal. Calcd for $C_{10}H_{16}ClNO$: C, 59.55; H, 7.99; Cl, 17.58; N, 6.95; O, 7.93. Found: C, 59.54; H, 7.94; Cl, 17.65; N, 6.94; O, 8.07.

2·HCl, identical in all respects to that derived from the Beckmann rearrangement of 1, was isolated (52%) after treatment of 2 with thionyl chloride as in Procedure A. The remainder of 2 was isolated unchanged. After neutralization of 2·HCl and isolation of 2, the combined recovery was 99.5%.

Treatment of 2 (1.65 grams) with 50 ml of concd hydrochloric acid for 10 min with stirring afforded 1.82 grams of 2·HCl (91%) after work-up.

Reaction of Adamantanone Oxime, 1, with Benzenesulfonyl Chloride–Pyridine. A published procedure was used, with benzenesulfonyl chloride in place of *p*-toluenesulfonyl chloride (*7*). Since 2 comprised only 60% of the crude product (3.3 grams) (gas-liquid chromatographic analysis), purification was not attempted.

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