Pergamon

Tetrahedron Letters, Vol. 37, No. 48, pp. 8695-8698, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02039-4

Ring-expansion of an Aziridinone to a Hexahydrotriazine through the Agency of a Novel Rearrangement♦

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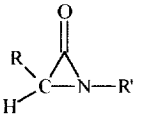
Abstract: Reaction of 1,3-di-*tert*-butylaziridinone (1a) and similar aziridinones with thiosemicarbazide affords, as one of the products, a compound devoid of sulfur, *viz.*, a substituted *N*-aminoimidazolidinone (3a) by selective cleavage of the acyl-nitrogen bond. Compound 3a undergoes a novel, acid-catalyzed rearrangement to a 3-imino-hexahydro-1,2,4-triazin-6-one (7a), which can also be obtained by treatment of 1a with hydrazine followed by BrCN, involving again selective cleavage of the acyl-nitrogen bond. Copyright © 1996 Elsevier Science Ltd

Interest in the synthetic uses of aziridinones (1) stems from the high degree of selectivity reported in their reactions with nucleophiles. Thus, it is said that protic nucleophiles (HZ) cause cleavage mainly or exclusively of the alkyl-nitrogen bond, whereas aprotic nucleophiles (Z^-) lead to products derived solely from scission of the acyl-nitrogen bond.[1] Such a simple rationale, reiterated in another review,[2] is incompatible with our earlier report[3] that magnesium iodide and magnesium methoxide afford products from diametrically opposite cleavages: the former cleaving exclusively the alkyl-nitrogen bond and the latter cleaving exclusively the acyl-nitrogen bond. The present manuscript provides another example of the dramatic reversal of the reported selectivity, this time by protic nucleophiles, as well as the first example of ring-expansion of an isolated aziridinone to a six-membered ring involving a novel rearrangement.



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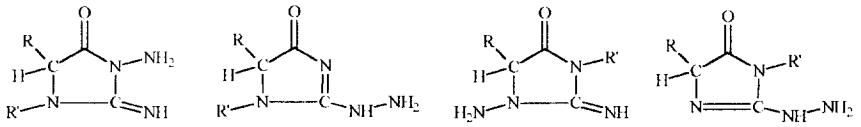
a. R = R′ = *tert*-Bu
b. R = 1-adamantyl, R′ = *tert*-Bu
c. R = *tert*-Bu, R′ = 1-adamantyl

Treatment of 1,3-di-*tert*-butylaziridinone (1a) with thiosemicarbazide (2) in boiling tetrahydrofuran for 24 hours, followed by chromatography on silica gel, affords two types of products. One of them, m.p. 129-130°C, is totally devoid of sulfur, whereas the other contains sulfur. Elemental analysis of the former product, obtained in yields up to 40%, corresponds to the formula $C_{11}H_{22}N_4O$, thus leading to a net combination of 1a and 2 by loss of H_2S. The following data suggested one possible structure for it to be a derivative of an imidazolidinone: ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9H), 1.40 (s, 9H), 3.55 (s, 1H), the rest of the signals (3H) being broad; ^{13}C NMR ($CDCl_3$) δ 26.7 (q), 28.7 (q), 36.6 (s), 57.8 (s), 65.1 (d), 158.5 (s), 172.4 (s); IR (KBr) 3430 (sh), 3309, 3273, 3169, 2968, 2927 (sh), 2872, 1732, 1672, 1630, 1337, 1252, 1084, 837 cm^{-1}; MS m/e 226 (M^+), 170 ($M^+ - C_4H_8$), 114 (100%, $M^+ - 2C_4H_8$). These data are compatible with structures 3a, 4a, 5a or 6a. The first two arise from acyl-nitrogen cleavage of 1a, and the last two are derived from alkyl-nitrogen cleavage.



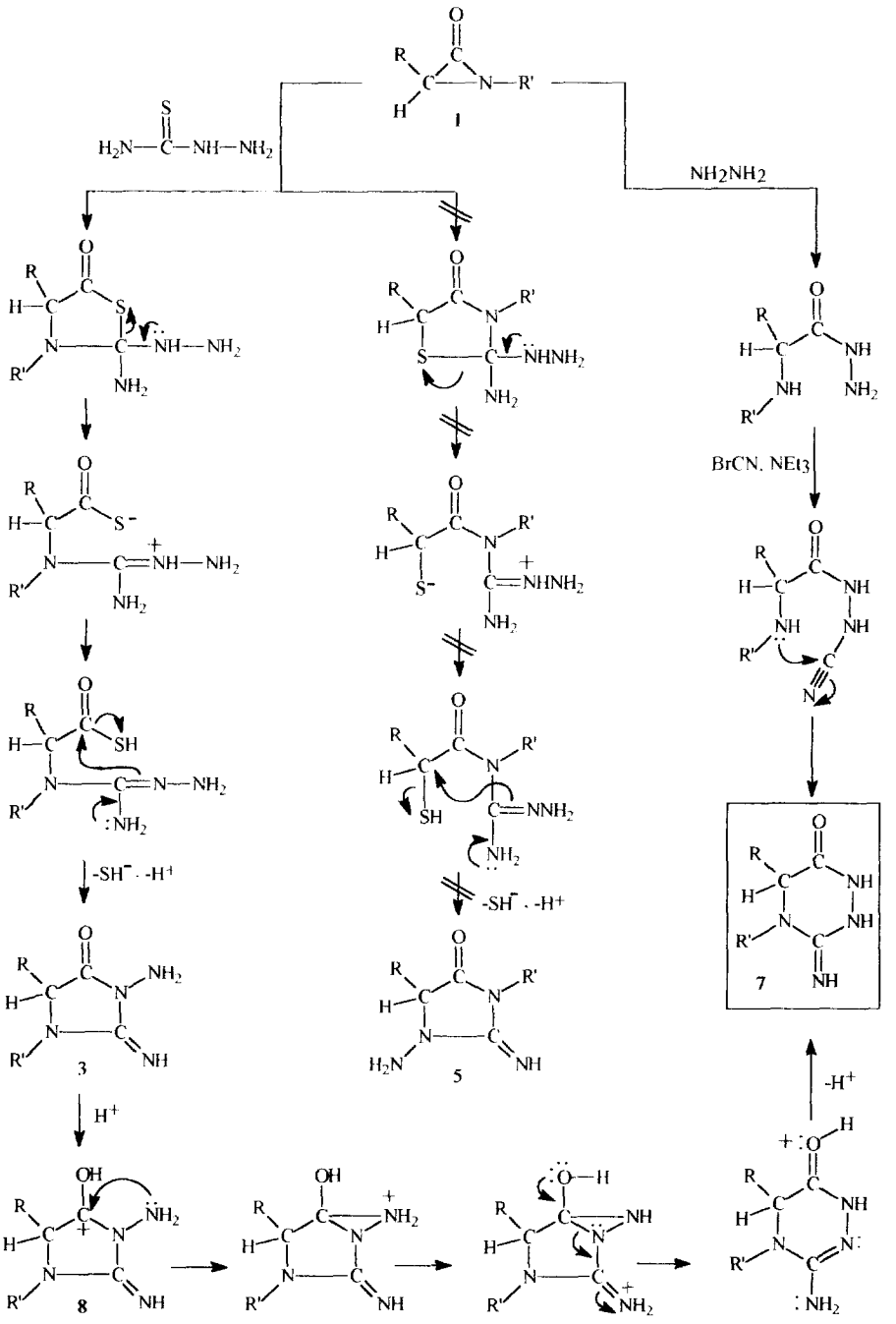
3 4 5 6

Compound **4a** is an acyliminoguanidine, whereas the rest are acylaminoguanidines. The uv spectrum at pH=12 of several examples of the former class of compounds (albeit without the -NH_2 group and the simple, less bulky alkyl groups) exhibits a λmax greater than 220 nm,[4,5] whereas the λmax of the latter class are invariably below 220 nm. Since the product from our reaction displays λmax at 216 nm under similar conditions, [λmax (EtOH) 214 nm (ε=9125), 246 (sh, ε=1900)nm], **4a** appears to be its least likely structure. A distinction among the remaining three structures became possible by the observation that it underwent rearrangement to an isomeric structure in the presence of acid (for example, 0.1N HCl or even exposure to $CDCl_3$ and air over several weeks) and by consideration of the relevant mechanism. This new compound, m.p. 218-219°C, exhibited the following spectral features: ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.01 (s, 9H), 3.56 (s, 1H), 4.85 (br); ^{13}C NMR ($CDCl_3$) δ 26.5 (q), 29.4 (q), 35.1 (s), 50.8 (s), 57.6 (d), 162.4 (s), 164.0 (s); IR (KBr) 3410 (sh), 3313, 3134, 2962, 2932 (sh), 2870, 1659, 1614, 1574, 1391, 1229; MS m/e 226 (M^+), 169 (M^+ - C_4H_9), 113 (100%, M^+-C_4H_9-C_4H_8); uv (EtOH) 224 nm (ε=6076), 208 (sh, ε=4830); at pH=12, 226 nm. Its structure **7a** was unequivocally determined by its synthesis from **1a** by reaction with hydrazine, followed by treatment with cyanogen bromide in the presence of triethylamine. A key feature to be established in this synthesis was the mode of ring-opening of **1a**. Based on a previous report cited above,[1] one would have expected alkyl-nitrogen cleavage by N_2H_4. However, we show that the bond cleaved is the acyl-nitrogen bond by comparison of the ^{1}H NMR spectra of the hitherto unreported products of the reaction of **1a** with related nitrogen nucleophiles (Table).

Table Product of the Reaction of **1a** with Nitrogen Nucleophiles

Nucleophile	M.P. °C	^{1}H NMR (in $CDCl_3$)	^{13}C NMR (in $CDCl_3$)
CH_3NH_2	170-171	δ 0.97(s, 9H), 1.03(s, 9H), 2.80 (d, 3H), 2.90(s, 1H), 7.25(br)	25.4(q), 27.4(q), 29.1(q), 33.6(s), 51.1(s), 65.9(d), 175.7(s)
NH_3	121-122	δ 1.00(s, 9H), 1.07(s, 9H), 2.88 (s, 1H), 1.26 (s, 1H), 4.72(br)	27.3(q), 29.0(q), 33.3(s), 51.0(s), 65.8(d), 178.5(s)
N_2H_4	71-73	δ 0.97(s, 9H), 1.03(s, 9H), 2.96 (s, 1H), 8.12(br)	27.3(q), 28.9(q), 33.7(s), 51.1(s), 65.1(d), 175.6(s)
$PhNHNH_2$	oil	δ 1.04(s, 9H), 1.09(s, 9H), 3.05 (s, 1H), 6.16(br), 6.86-6.90 (m), 7.20-7.26(m), 8.81(br)	27.4(q), 29.1(q), 33.9(s), 51.3(s), 65.4(d), 114.1(d), 121.1(d), 129.1(d of d), 129.5(s), 175.1(s)

The most convincing evidence is provided by the reaction of CH_3NH_2 with **1a** the product of which exhibits a doublet signal for the methyl group, indicating coupling to an amide-type hydrogen rather than an amine-type hydrogen. Although such a characteristic alkyl signal is not available for determining the course of the other reactions, the ^{1}H NMR spectra of the products of the reaction of **1a** with the other nucleophiles bear a strong resemblance to the spectrum of the product derived from CH_3NH_2 in that the chemical shifts of the two *tert*-butyl protons (a constant difference in δ of about 0.06 ppm)[6] and that of the *tertiary*-hydrogen attached to carbon (first three singlets listed for each nucleophile) are very similar, indicating a common feature of the structure |*t*-BuNH-CH(*t*-Bu)-C(=O)-N-|. This similarity of the ^{1}H NMR spectra is carried over also to the corresponding ^{13}C NMR spectra. Another feature of the above synthesis of **7a** to be determined was which nitrogen of the intermediate hydrazide undergoes reaction with BrCN. One would favor the primary amino nitrogen on account of its greater basicity, and this presumption was supported by the absence of a reaction between BrCN and the product from CH_3NH_2 under similar conditions.



Scheme

Consideration of the mechanism of the acid-catalyzed rearrangement resulting in the formation of **7a** indicates that its precursor, the product of the reaction of **1a** and **2**, is **3a**, since the other alternative structures **4a**, **5a** and **6a** cannot be envisaged to undergo ready rearrangement to **7a**. **3a** may be regarded as a modified creatinine, the end-product of nitrogen metabolism in vertebrates. Proposed mechanisms of the conversion of **1a** to **3a**, the rearrangement of **3a** to **7a**, and the independent synthesis of **7a** from **1a** *via* the hydrazide are depicted in the Scheme, which also explains why similar products derived from alkyl-nitrogen cleavage of **1a**, such as **5a**, are not observed. Formation of **5a** would require the expulsion of HS^- from an alkyl (neopentyl) carbon, which would be much slower than the observed expulsion of HS^- from an acyl carbon leading to **3a**. Although the rearrangement of **3a** to **7a** could also occur by initial protonation of the imino group rather than the carbonyl group followed by a similar ring-expansion involving the primary amino group, this pathway appears to be less likely because it would lead to a more stable guanidinium ion, which would not undergo ring expansion as readily as the carbocation **8a**.

There are two interesting aspects of the novel rearrangement of **3a** to **7a** reported here. First, it may be regarded as an acid-catalyzed version of the base-catalyzed Gabriel-Colman rearrangement,[7] which also leads to conversion of a five-membered heterocyclic system (a phthalimide) to a six-membered ring (an isoquinoline). Second, Brace[8] considered an acylamidine salt to be a new acylating agent, which he used for intermolecular acylation of an alcohol. The intermediate (**8**) can be regarded as an acylamidine salt (actually, an acylguanidine salt), which undergoes intramolecular acylation of an amino group in our reaction to ultimately afford **7**.

Since the reaction of **2** with other aziridinones (**1b** and **1c**) afforded similar results, one can conclude that this reaction constitutes a novel synthesis of a specifically-substituted imidazolidinone (**3**) and thence of a 3-imino-hexahydro-1,2,4-triazin-6-one (**7**) bearing corresponding substituents.[9]

REFERENCES AND NOTES

♦ The authors dedicate this manuscript to Prof. G.A. Russell on his 71st birthday and to the memory of Prof. R.B. Woodward.

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6. The close proximity of the signals for the two *tert*-butyl groups appears to be a convenient way of determining that the open-chain product from 1(a) and simple nucleophiles is derived from acyl-nitrogen cleavage. The difference in these two signals for the corresponding product from **1(a)** and methanol is δ 0.11 ppm.
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9. Sarel, S.; Greenberger, A. *J. Org. Chem.* **1958**, *23*, 330 reported the only other example of ring-expansion of an aziridinone to a six-membered ring, *viz.*, formation of a diketopiperazine from Ph-CHCl-$\overset{\overset{O}{\|}}{C}$-N$^-$-Ph *via* 1,3-diphenylaziridinone. However, the involvement of this aziridinone, which has never been isolated or even detected, is not obligatory: dimerization of the amide anion could account for the piperazinedione.

(*Received in USA* 19 *September* 1996; *revised* 4 *October* 1996; *accepted* 10 *October* 1996)