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Nitrosative Deamination of 1-Aminoazetidin-2-ones. An Entry to N-Unsubstituted β-Lactams

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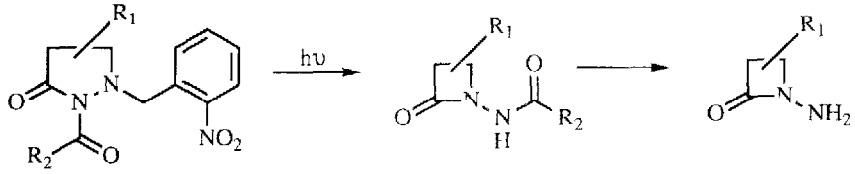
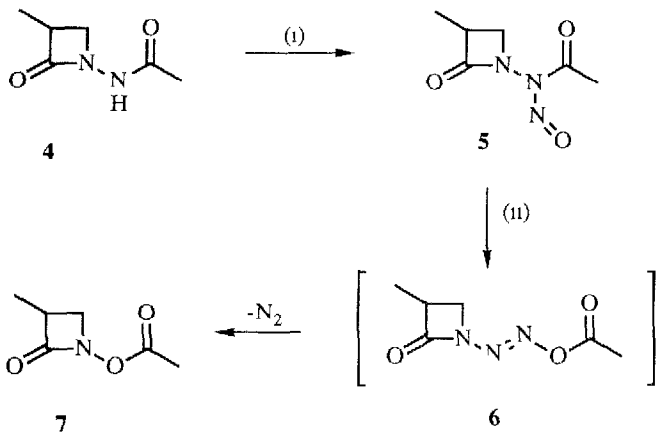
Abstract *Nitrosative deamination of 1-aminoazetidin-2-ones was carried out with diphenylnitrosamine to give the N-unsubstituted systems, thus completing a route to β-lactams by photochemical ring contraction of pyrazolidin-3-ones*

The valuable therapeutic properties of certain monocyclic β lactams (monobactams) as antibiotics[1] has prompted an extensive search for methods of synthesis of this class of structures [2] Towards this end, we recently reported a route to 1-aminoazetidin-2-ones by photochemical contraction of pyrazolidin-3-ones [3] This β-lactam synthesis, which extends previous studies on the photochemistry of pyrazolidinones by Ege[4] and by Johnson,[5] relies on the activating influence of an acyl substituent at N2 and a photoremovable protecting group (*o*-nitrobenzyl)[6] at N1 of the pyrazolidinone **1** The reaction leads to a N-acylaminoazetidinone **2** which can be converted to the amino derivative **3** [7] Completion of a general entry to N-unsubstituted β-lactams along these lines requires cleavage of the N-N bond of **2** or **3**, a transformation that poses difficulties in the presence of a relatively fragile ring We describe herein a simple solution to this problem



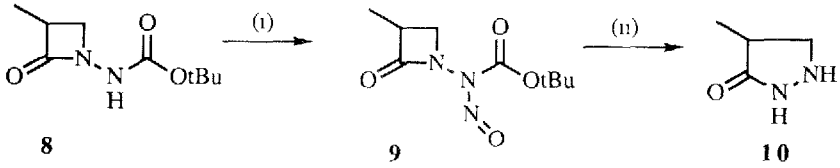
1 **2** **3**

N-Acetylamino derivatives of azetidin 2-ones (**2** R_2 = Me) were found to be inert to hydrogenolysis with Raney nickel and underwent decomposition with electron transfer reducing agents, eg samarium diiodide However, nitrosation of **4** proceeded in good yield to afford **5** This nitrosohydrazide was converted in refluxing chloroform to the N-acyloxyazetidinone **7** together with variable quantities of the denitrosated material **4** Hydroxamic acid derivative **7**, which shows a positive response to ferric chloride, presumably arises by N → O acyl rearrangement followed by extrusion of nitrogen from the intermediate diazotate **6** [8] Unfortunately, although this sequence provides access to the new and potentially interesting class of N-acyloxy β-lactams, no satisfactory method could be found for reducing **7** to the parent azetidinone [9]



Reagents (i) $NaNO_2$, HOAc, Ac_2O (77%) (ii) $CHCl_3$, Na_2CO_3, Δ (41%)

In the hope of circumventing this difficulty, Boc derivative **8** was reacted with sodium nitrite in acetic acid or with dinitrogen tetroxide to give the nitroso derivative **9** However, this urethane failed to undergo the acyl transfer reaction previously observed with acetyl derivative **5** and furnished instead the denitrosated product **8** accompanied by 4-methylpyrazolidin-3-one (**10**) The latter could originate from the N-aminoazetidinone via reversal of the ring contraction that yields the β-lactam, a process that has precedent in studies by Testa [10]

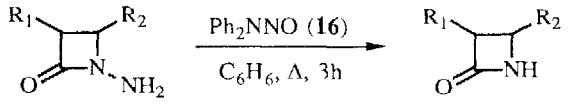


Reagents (i) $NaNO_2$, HOAc, Ac_2O (69%) or N_2O_4, NaOAc, $CHCl_3$ (36%)
(ii) $CHCl_3$, Δ (33%)

N-Aminoazetidinones **3** can be prepared without the complication of ring enlargement from 2-(trimethylsilyl)ethoxycarbonyl derivatives (**2**, R = $OCH_2CH_2SiMe_3$),[11] by removal of the carboxyl substituent with fluoride [12] Thus, 1-aminoazetidin-2-ones **11** - **15** were acquired in good yield,[3] and this enabled us to focus on a deamination protocol for these structures

Following a report by Rees and Storr[13] that deamination of 1-aminotriazines can be accomplished with diphenylnitrosamine (**16**), it was found that treatment of **11** - **15** with **16** resulted in their smooth conversion to the parent β-lactam The results are summarized in Table I Nitrosative deamination proceeds rapidly in benzene at reflux but more slowly in refluxing methanol Diphenylamine and (presumably) nitrous oxide are byproducts of the reaction, the former is readily separable from product lactam by crystallization or chromatography The azetidinoneacetic ester resulting from **15** has been employed as an intermediate for the synthesis of carbapenem antibiotics, including PS-5, PS-6, and thienamycin [14]

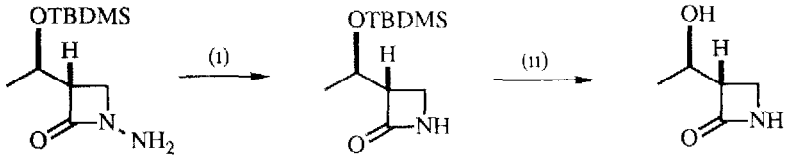
Table I Nitrosative Deamination of 1-Aminoazetidin-2-ones



Compound	Aminoazetidinone R_1	R_2	Yield of β-Lactam (%)
11	H	H	61
12	H	Me	51
13	Me	H	55
14[a]	Me	Me	67
15	H	CH_2CO_2Et	65

[a] Cis trans mixture (3 5 1), unchanged after deamination

The aminoazetidinone **17**,[3] prepared from the corresponding pyrazolidinone **12**,[15] was deaminated uneventfully with **16** to yield **18** The latter was deprotected with hydrofluoric acid to afford alcohol **19**, a hybrid β-lactam possessing the thienamycin side-chain configuration

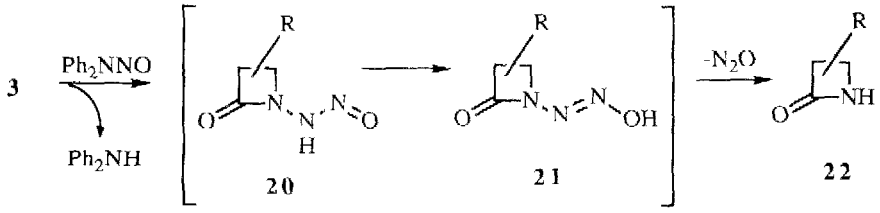


17 **18** **19**

Reagents (i) Ph_2NNO, C_6H_6, Δ, 3h (68%) or Ph_2NNO, MeOH, Δ, 19h (64%),
(ii) 5 % HF, MeCN (64%)

A plausible mechanism for the deamination of 1-aminoazetidin-2-ones (**3**) with **16** involves transnitrosation to yield **20** and diphenylamine In contrast to its acyl derivative **6**, the diazotate tautomer **21** does not extrude nitrogen but instead undergoes elimination of N_2O to give the β-lactam **22** Conventional nitrosation of N-aminoazetidinones with sodium nitrite or dinitrogen tetroxide failed to produce deaminated products

The nitrosative deamination described above completes a sequence that transforms readily prepared pyrazolidin-3-ones (from addition of hydrazine to α,β-unsaturated carboxylic acids[16] or their esters[17]) into β-lactams Application of this chemistry to the synthesis of useful antibiotic materials is under investigation



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