Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2383-2388, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

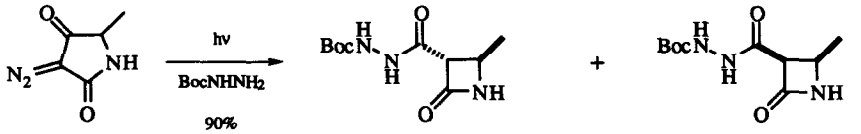
Photochemically Mediated Ring Contraction of Pyrazolidin-3-ones to β–Lactams

James D. White* and Steven G. Toske

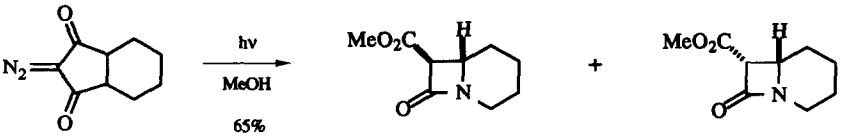
Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

(*Received* 1 *April* 1993)

Synthetic routes to β-lactams have conventionally followed either a one-bond cyclization or two-bond cycloaddition strategy.[1] Virtually all possible variations of these two constructions have been realized[2] and several, notably N-C_4 cyclization[3] and chlorosulfonylisocyanate cycloaddition,[4] have adapted well to the synthesis of therapeutically important β-lactam antibiotics. In contrast, ring contraction approaches to 2-azetidinones have received relatively little attention and none has been applied to the synthesis of a clinically useful β-lactam.

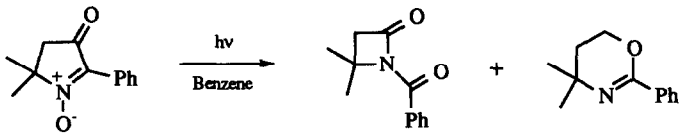


1 **2** **3**



4 **5** **6**

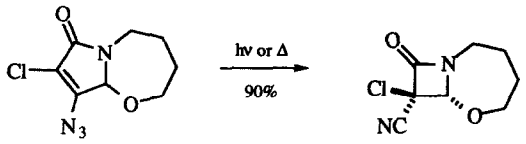
Among the earliest reports of a successful ring contraction to yield an azetidinone is that of Lowe,[5] who effected photolytic Wolff rearrangement of diazopyrrolidinedione **1** in the presence of a hydrazine derivative to give a mixture of stereoisomeric β-lactams, **2** and **3**. Analogous Wolff rearrangement of **4** in methanol was found by Stork to afford a mixture of bicyclic β-lactams **5** and **6**.[6]



7 **8** **9**

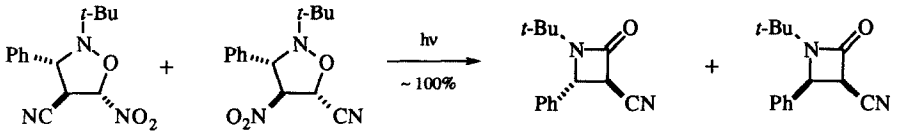
The pyrroline oxide **7** undergoes photochemically induced ring contraction to give β-lactam **8** accompanied by the oxazinone **9**.[7] In a study of the reactivity of 4-azido-2-pyrrolinones, eg **10**, Moore found

that these systems undergo both photolytic and thermal contraction with complete stereoselectivity to yield α-cyanoazetidinones **11**.[8]

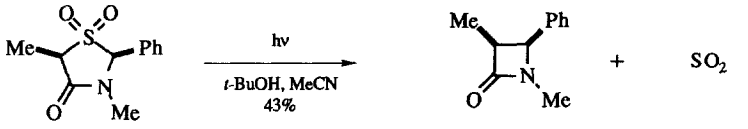


10 **11**

Nitro substituted oxazolidines such as **12** and **13**, the products of dipolar cycloaddition of a nitrone, are reported to give β-lactams **14** and **15** on photolysis.[9] Ring contraction of 1,1-dioxo-4-thiazolidinones such as **16** occurs via photochemically mediated extrusion of sulfur dioxide to afford a β-lactam **17** in modest yield and with relatively low stereoselectivity.[10]

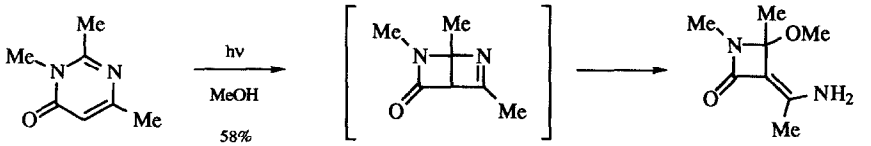


12 **13** **14** **15**



16 **17**

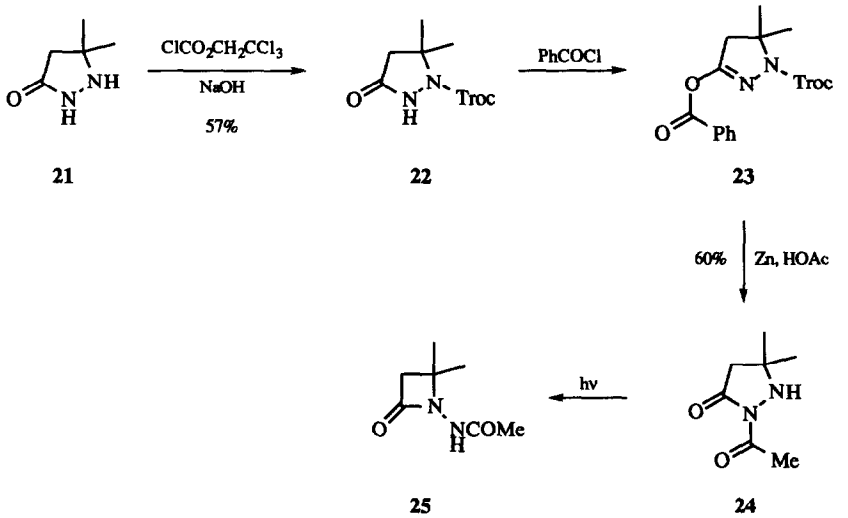
A single example of contraction of a six-membered cycle to a β-lactam is known in which photolysis of the 4-pyrimidone **18** was found to yield the azetidinone **20**, presumably via the bicyclic lactam **19**.[11]



18 **19** **20**

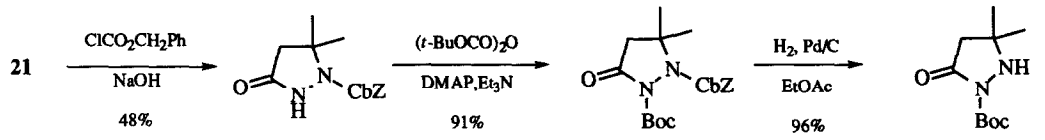
A brief report by Ege in 1968 that N-phenylpyrazolidin-3-one **21** undergoes a photochemical reaction leading to N-aminoazetidinone **22**[12] was an important prelude to the attempts to employ five-membered heterocycles as precursors of β-lactams. Although a more comprehensive account of Ege's novel ring contraction appeared subsequently[13] and attempts were made to develop the scope of this azetidinone synthesis,[14,15] results were generally disappointing from the perspective of a practical route to β-lactam antibiotics. A valuable contribution made by Johnson,[14] however, was the recognition that an acyl substituent at N2 of the pyrazolidinone significantly improved the efficiency of the ring contraction. Since it was not possible to introduce this acyl group without first blocking N1, Johnson devised a protection-deprotection sequence

employing the 2,2,2-trichloroethoxycarbonyl (Troc) group. Thus, the pyrazolidinone **21** was first protected as **22** which, upon benzoylation, afforded **23**. Treatment of this compound with zinc and acetic acid effected both acetylation of N2 (via rearrangement of a presumed ortho ester derivative) and removal of the Troc group to give **24**. The latter was then photolyzed to yield β-lactam **25**.



21 **22** **23** **25** **24**

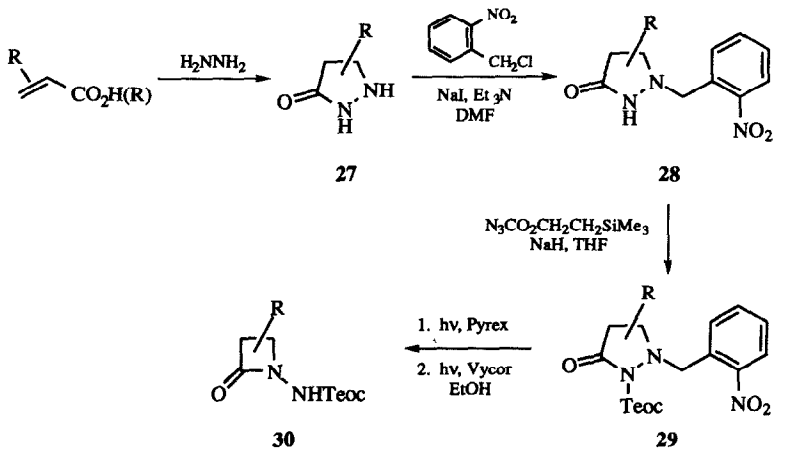
A general route to β-lactams based on the foregoing chemistry requires a means for removal of the nitrogen substituent after ring contraction – a potentially troublesome step with a species such as **25**. Our initial plan for solving this problem envisioned the Boc substituted pyrazolidinone **26** as the azetidinone precursor and, in fact, **26** was prepared in good yield from **21** by using Cbz as the removable protecting group at N1. However, a much more attractive solution offered itself in the form of the trimethylsilylethoxycarbonyl (Teoc) substituent at N2 in combination with a *photoremovable* blocking group at N1 of the pyrazolidinone. *o*-Nitrobenzyl was selected for the latter since its cleavage could be effected in a tandem, one-flask photochemical process which led directly to an azetidinone.



26

The general method for ring contraction of pyrazolidin-3-ones to β-lactams which we eventually adopted is presented in Scheme I.[16] Pyrazolidinones **27** are easily prepared by the addition of hydrazine hydrate to either an αβ-unsaturated carboxylic acid[17] or the corresponding ester,[18] and they undergo clean N1 alkylation with *o*-nitrobenzyl chloride in the presence of sodium iodide. Subsequent treatment of **28** with 2-(trimethylsilyl)ethyl azidoformate under Carpino's conditions[19] provides the substrate **29** for photochemical ring contraction. This latter reaction was accomplished by means of a two-stage process in which irradiation was first conducted through a Pyrex filter (to remove the *o*-nitrobenzyl protection) and then through a Vycor filter. The choice of

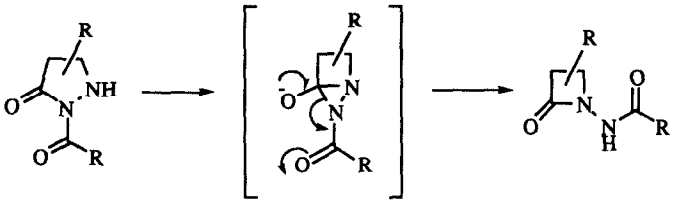
conditions for this sequence of transformations was based on the knowledge that no pyrazolidinone ring contraction, which requires that N1 be unsubstituted, occurs at $\lambda > 250$ nm.



27 28 29 30

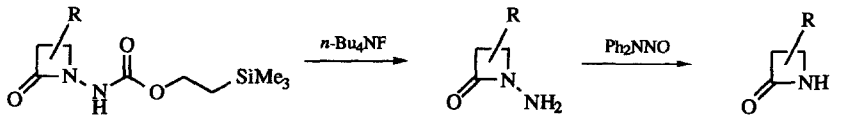
Scheme I

A plausible mechanism for the ring contraction step was originally proposed by Johnson[14] and invokes the highly strained bicyclic diazirine **31** which collapses to the azetidinone by a hetero variant of a retro aldol fission.



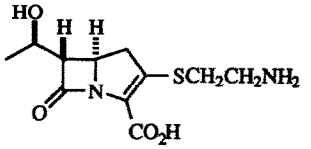
31

Cleavage of the Teoc group from **30** with fluoride affords N-aminoazetidin-2-ones **32**, substances which are of interest in their own right as antibacterial agents.[20] More generally, it was found that the amine substituent can be removed from **32** in a mild nitrosative deamination with diphenylnitrosamine to furnish the parent lactam **33**.[21]

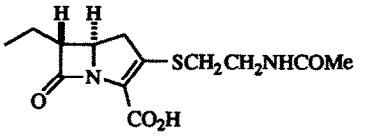


30 **32** **33**

Many applications of this photochemically mediated contraction of a pyrazolidinone to an azetidinone can be envisioned in the context of β-lactam synthesis. Particular interest in our laboratory has centered on cis substituted monobactams and carbapenems, substances which are not easily accessible by conventional methods of synthesis[22] and which are stereoisomeric with the important naturally occurring penems such as thienamycin (**34**) and PS-5 (**35**).

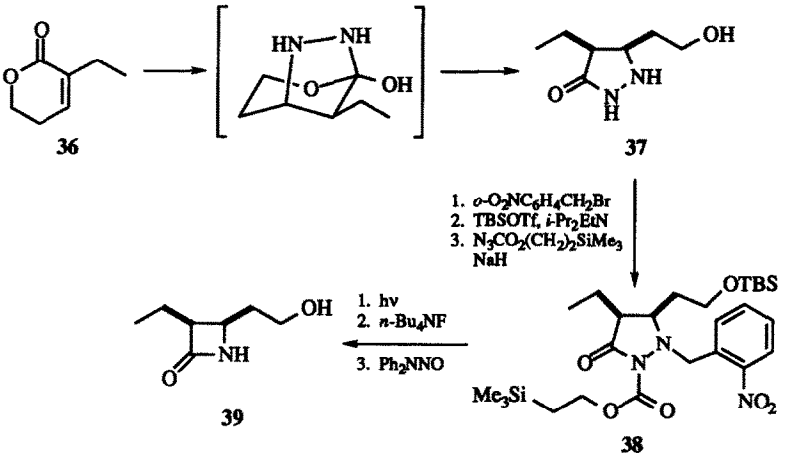


34



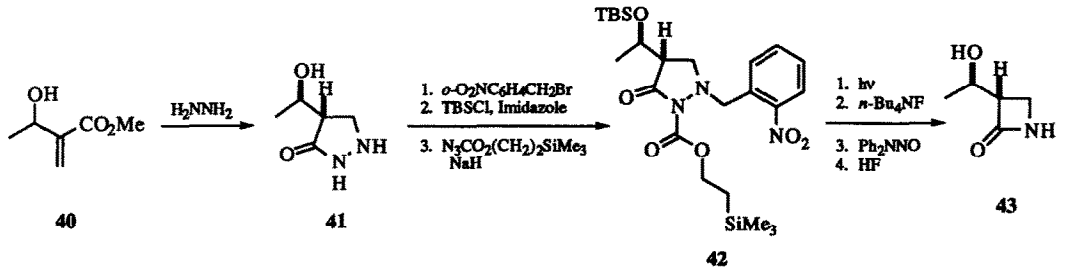
35

A route to the cis monocyclic lactam **39** possessing the PS-5 side-chain is illustrated in Scheme II beginning from δ-lactone **36**.[23] Condensation of **36** with hydrazine yielded **37** which was then protected at the hydroxyl group and both nitrogens. Irradiation of **38** afforded an azetidinone in which cis configuration had been retained, and subsequent treatment with fluoride (which removed both TBS and Teoc groups), followed by deamination, gave β-lactam **39**. The latter can be isomerized to the more stable trans subsituted azetidinone which has previously been taken to (+)-PS-5 (**35**).[24]



Scheme II

A further application of the pyrazolidinone-azetidinone contraction is illustrated in Scheme III, which leads to a β-lactam **43** bearing the hydroxyethyl side-chain of **34**. The pyrazolidinone **41**,[25] obtained with its stereoisomer from the acrylate derivative **40**,[26] was converted to the photolysis precursor **42** in the usual manner. Ring contraction, followed by removal of the protecting groups and deamination, yielded **43**.



Scheme III

The ease of access to substituted pyrazolidin-3-ones, coupled with the simplicity and convenience of their photochemical contraction, makes this an attactive route to a wide variety of azetidin-2-ones. Future studies aimed at more precise stereocontrol and other improvements can be expected to broaden the scope of this β-lactam synthesis.

Acknowledgement. This work was assisted financially by National Science Foundation grant CHE-9015466.

References

1. Thomas, R.C. in *Recent Progress in the Chemical Synthesis of Antibiotics*, Lukacs, G.; Ohno, M., Eds.; Springer-Verlag: Berlin, Germany, 1990, pp 533-564.
2. Morin, R.B.; Gorman, M., Eds. *Chemistry and Biology of β-Lactam Antibiotics*, Academic: New York, 1982, vol 2.
3. Miller, M.*J. Acc. Chem. Res.* **1986**, *19*, 49.
4. Palomo, C. in *Recent Progress in the Chemical Synthesis of Antibiotics*, Lukacs, G.; Ohno, M., Eds.; Springer-Verlag: Berlin, Germany, 1990, pp 568-573.
5. Lowe, G.; Ridley, D. *J. Chem. Soc., Perkin Trans 1* **1973**, 2024.
6. Stork, G.; Szajewski, R.P. *J. Am. Chem. Soc.* **1974**, *96*, 5787.
7. St. Clair Black, D.; Boscacci, A.B. *J. Chem. Soc., Chem Commun.* **1974**, 129.
8. Moore, H.W.; Hernandez, Jr., L.; Kunert, D.M.; Mercer, F.; Sing, A. *J. Am. Chem. Soc.* **1981**, *103*, 1769.
9. Padwa, A.; Koehler, K.F.; Rodriguez, A. *J. Am. Chem. Soc.* **1981**, *103*, 4974.
10. Johnson, M.R.; Fazio, M.J.; Ward, D.L.; Sousa, L.R. *J. Org. Chem.* **1983**, *48*, 494.
11. Hirokami, S.; Hirai, Y.; Nagata, M.; Yamazaki, T.; Date, T. *J. Org. Chem.* **1979**, *44*, 2083.
12. Ege, S.N. *J. Chem. Soc., Chem Commun.* **1968**, 759.
13. Ege, S.N. *J. Chem. Soc. C* **1969**, 2624.
14. (a) Johnson, P.Y.; Hatch, III, C.E. *J. Org. Chem.* **1975**, *40*, 909. (b) Johnson, P.Y.; Hatch, III, C.E. *J. Org. Chem.* **1975**, *40*, 3502.
15. Ege, S.N.; Butler, W.M.; Bergers, A.; Biesman, B.S.; Boerma, J.E.; Corondan, V.I.; Locke, K.D.; Meschinchi, S.; Ponas, S.H.; Spitzer, T.D. *J. Chem. Soc., Perkin Trans 1* **1983**, 1111.
16. Perri, S.T.; Slater, S.C.; Toske, S.G.; White, J.D. *J. Org. Chem.* **1990**, *55*, 6037.
17. Rabini, T.; Vita, G. *J. Org. Chem.* **1965**, *30*, 2486.
18. Stetter, H.; Findeinsen, K. *Chem. Ber.* **1965**, *98*, 3228.
19. Carpino, L.A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem Commun.* **1978**, 358.
20. Curran, W.V.; Lenhard, R.H. *J. Med. Chem.* **1989**, *32*, 1749.
21. White, J.D.; Perri, S.T.; Toske, S.G. *Tetrahedron Lett.* **1992**, *33*, 433.
22. Bateson, J.H.; Hickling, R.I.; Smale, T.C.; Southgate, R. *J. Chem. Soc., Perkin Trans 1* **1990**, 1793.
23. White, J.D.; Toske, S.G. *Tetrahedron Lett.* **1993**, *34*, 207.
24. Favara, D.; Omodei-Salè, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, *23*, 3105.
25. Jungheim, L.N. *Tetrahedron Lett.* **1989**, *30*, 1889.
26. Hoffmann, H.M.R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849.