

FORMATION OF SOME HETEROCYCLES THROUGH RING
TRANSFORMATION OF 1-ARYLAZETIDIN-2-ONES

Shinzo Kano^{*}, Tsutomu Ebata, Yoko Denta, Satoshi Hibino,
and Shiroshi Shibuya

Tokyo College of Pharmacy

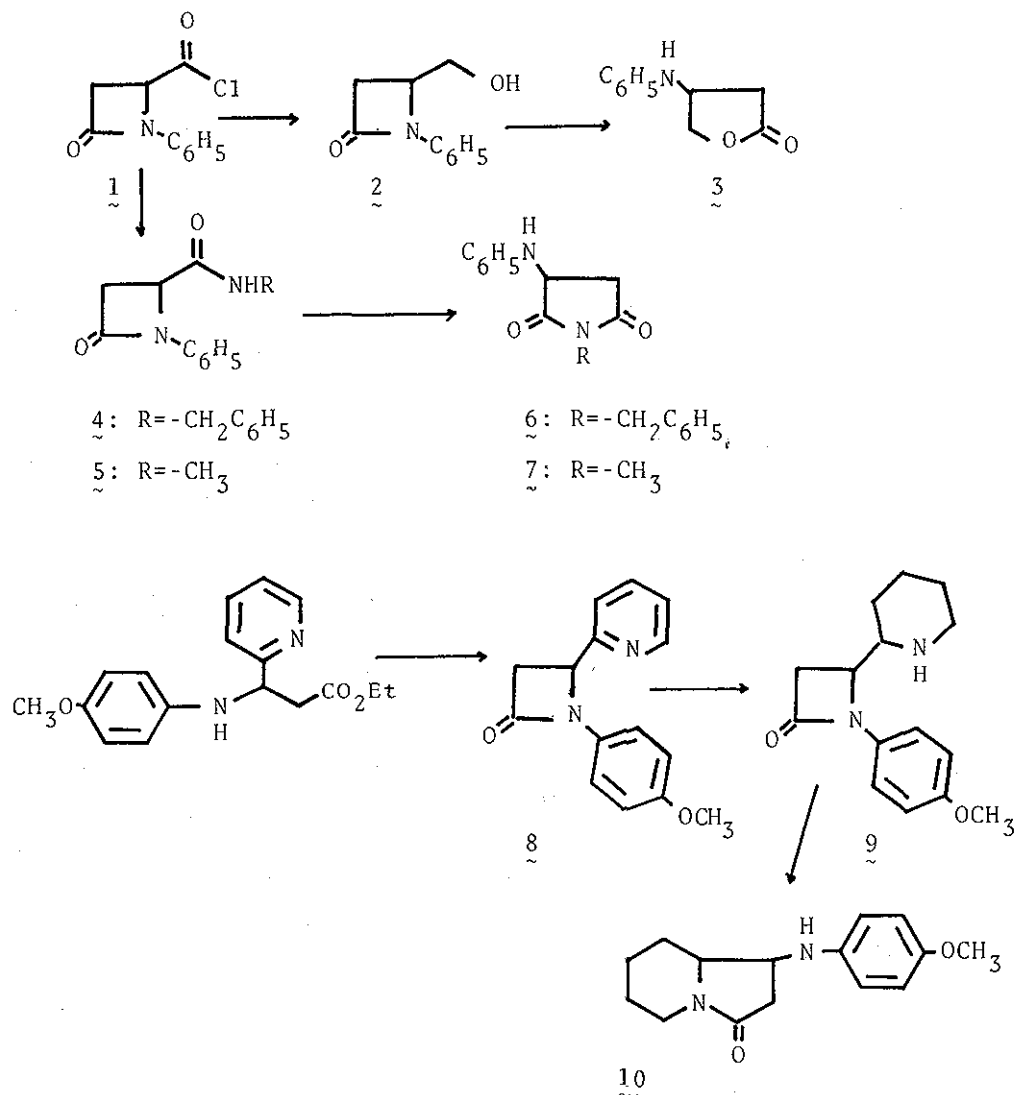
1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Treatment of 4-hydroxymethyl-1-phenylazetidin-2-one (2) with methanesulfonic acid at room temperature yielded 4-anilino-2-oxotetrahydrofuran (3). On heating 4-benzylcarbamoyl-1-phenylazetidin-2-one (4) in methanesulfonic acid, anilinosuccinimide (6) was obtained. N-Methyl analogue (7) was also obtained from 4-methylcarbamoyl-1-phenylazetidin-2-one (5). 4-(2-Piperidino)-1-(4-methoxyphenyl)azetidin-2-one (9) gave octahydro-4-(4-methoxyphenyl)indolizin-2-one (10) under base-catalyzed conditions. Furthermore, 3-(4-methoxyanilinomethyl)-4-hydroxy-3,4-dihydrocarbostyryl (14) was obtained by acid-catalyzed rearrangement of the corresponding 3-substituted 1-arylazetidin-2-one (13). 3-(4-methoxyanilino)-4-hydroxyoctahydroindolizin-2-one (17) was also obtained by the application of these nucleophilic cleavage of -N-CO- bond to the corresponding 1-arylazetidin-2-one (16).

It is known that some azetidin-2-ones show high chemical reactivity and are a potential synthon of -N-C-C-CO- moiety^{1,2}. We have explored the utility of substituted monocyclic azetidin-2-ones as a source for the preparation of different heterocycles. The easy cleavage of -N-CO- bond of azetidin-2-ones by the reaction with various kinds of nucleophiles led us to investigate the ring transformation of 1-arylazetidin-2-ones to lactone, succinimide, indolizine, and 3,4-dihydrocarbostyryl. We wish to report these results in this paper³.

Firstly, cleavage of -N-CO- bond by the nucleophilic attack of hydroxy group was applied for the preparation of butyrolactone. 4-Hydroxymethyl-1-phenylazetidin-2-one (2), prepared by the reduction of the acid chloride (1)⁴ with sodium borohydride in THF at -78°C, was treated with methanesulfonic acid in benzene solution at room temperature to give the anilinobutyrolactone (3) in 87 % yield, mp 98-99°C (MeOH-Et₂O) [ir (nujol): 1735 cm⁻¹; nmr (CDCl₃) δ: 2.43 (1H, d,d, J=18.5, 2.5 Hz), 2.86 (1H, d,d, J=18.5, 6 Hz), 4.30 (1H, m)]. Similar transformation was observed in the case of 4-carbamoyl-1-arylazetidin-2-one and 4-(2-piperidino)-1-arylazetidin-2-one to yield anilinosuccinimide and anilinoctahydroindolizin-2-one, respectively. The amide (4), prepared from the acid chloride (1) and benzylamine, was heated in methanesulfonic acid at 100°C to give N-benzylanilinosuccinimide (6) in 83 % yield, mp 125-126°C [ir (nujol): 1670 cm⁻¹; nmr (CDCl₃) δ: 2.62 (1H, d,d, J=18, 5 Hz), 3.28 (1H, d,d, J=18, 8 Hz), 4.62 (2H, s), 4.71 (1H, d,d, J=8, 5 Hz)]. The amide (5) was also converted to the N-methyl derivative (7), mp 122-123°C, in 90 % yield. Catalytic hydrogenation of 1-(4-methoxy-

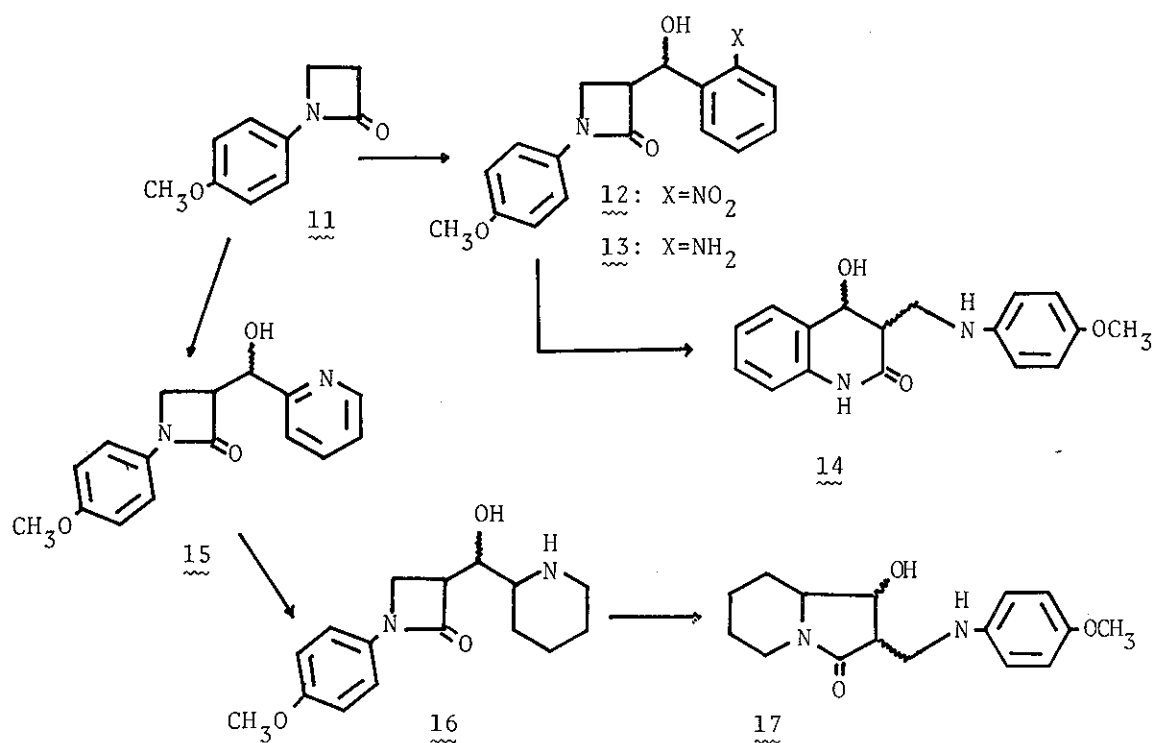
phenyl)-4-(2-pyridyl)azetidin-2-one (8) prepared by the usual method^{5,6}, over platinum oxide, afforded 1-(4-methoxyphenyl)-4-(2-piperidino)azetidin-2-one (9)⁷ in 85 % yield. The azetidin-2-one (9) was heated in ethanol in the presence of sodium ethoxide to yield 4-(4-methoxyanilino)octahydroindolizin-2-one (10)⁷, mp 99-101°C [ir (nujol): 1640 cm^{-1} ; nmr (CDCl_3) δ : 1.10-3.34 (10H, m), 4.10 (1H, m),



3.80 (3H, OCH₃), 6.55 (2H, d, $J=9$ Hz), 6.75 (2H, d, $J=9$ Hz)].

Secondly, the ring transformation of 3-substituted 1-arylazetidin-2-ones (13) and (16) was investigated. Introduction of the substituent to the 3-position of azetidin-2-ones was carried out by the method reported by Durst⁸. The addition of 1-(4-methoxyphenyl)-azetidin-2-one (11) to a solution of LDA (1.1 eq.) in THF at -78°C resulted in lithilation of 11. Quenching of this solution (after 2 min. at -78°C) with *o*-nitrobenzaldehyde afforded 3-(α -hydroxy-*o*-nitrobenzyl)-1-(4-methoxyphenyl)azetidin-2-one (12) in 55 % yield, mp 154-157°C, as a diastereoisomeric mixture⁹. Catalytic hydrogenation of 12 over 5 % Pd-C, followed by the treatment of the corresponding amino compound (13), mp 166-168°C, with three equimolar amounts of hydrochloric acid in ethanol under reflux to give a diastereoisomeric mixture of 4-methoxyanilinomethyl-4-hydroxy-3,4-dihydrocarbostyryl (14)⁹, 186-189°C, in 85 % yield [ir (nujol): 1675 cm⁻¹; nmr (CDCl₃) δ : 3.63 (3H, OCH₃), 5.47 (1H, m, 3-H), 6.55 (2H, d, $J=9$ Hz), 6.73 (2H, d, $J=9$ Hz)]. The 3-substituted 1-(4-methoxyphenyl)azetidin-2-one (15), prepared by lithilation of 11, followed by quenching with pyridin-2-aldehyde, was subjected to catalytic hydrogenation over platinum oxide in a mixture of ethanol and acetic acid. During the work-up of the product (16), ring transformation occurred easily to yield a diastereoisomeric mixture of 3-(4-methoxyanilinomethyl)-4-hydroxyoctahydroindolizin-2-one (17) in 75 % yield [oil, ir (liquid) 1650 cm⁻¹]].

Thus, ring transformation of substituted monocyclic azetidin-2-ones was found to offer useful method to yield some heterocycles.



REFERENCES

1. A. K. Mukerjee and A. K. Singh, Synthesis, 1975, 547.
2. M. S. Manhas, S. G. Amin, and A. K. Bose, Heterocycles, 5, 669. (1976).
3. Satisfactory microanalyses and spectroscopic data were obtained for all new compounds.
4. B. G. Chatterjee and P. N. Moza, J. Med. Chem., 9, 259 (1966).
5. R. W. Holley and A. D. Holley, J. Amer. Chem. Soc., 71, 2124 (1949).
6. R. W. Holley and A. D. Holley, J. Amer. Chem. Soc., 71, 2129 (1949).

7. The relative configuration at the 4- and 5-position was not determined.
8. T. Durst and M. J. Lebelle, Can. J. Chem., 50, 3196 (1972).
9. Although it showed a considerably sharp melting point and a single spot on tlc, its nmr spectrum indicated that it should be a mixture of diastereoisomers.

Received, 10th August, 1977