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

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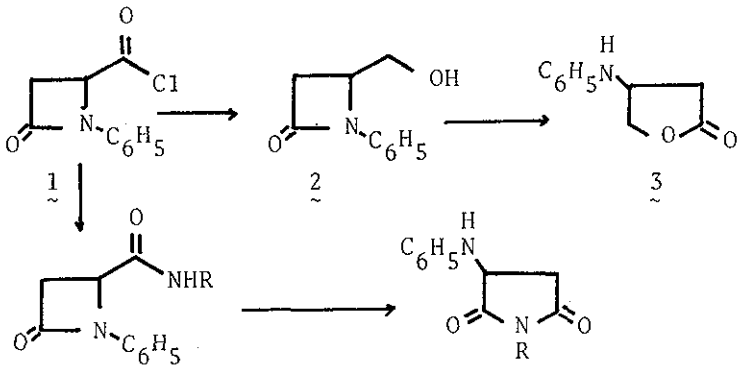
Treatment of 4-hydroxymethyl-1-phenylazetidin-2-one (2) with methanesulfonic acid at room temperature yielded 4-anilino-2-oxotetrahydrofuran (3). On heating 4-benzylcarbamoyl-1-phenylazetidin-2-one (4) in methanesulfonic acid, anilinosuccinimide (6) was obtained. N-Methyl analogue (7) was also obtained 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-dihydrocarbostyril (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-dihydrocarbostyril. We wish to report these results in this paper[3].

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 temperatute to give the anilinobutyrolactone (3) in 87 % yield, mp 98-99°C (MeOH-Et_2O) [ir (nujol): 1735 cm^{-1} ; nmr ($CDCl_3$) 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 anilinooctahydroindolizin-2-one, respectively. The amide (4), prepared from the acid chloride (1) and benzylamine, was heated in methanesulfonic aid at 100°C to give N-benzylanilinosuccinimide (6) in 83 % yield, mp 125-126°C [ir (nujol): 1670 cm^{-1} ; nmr ($CDCl_3$) 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-

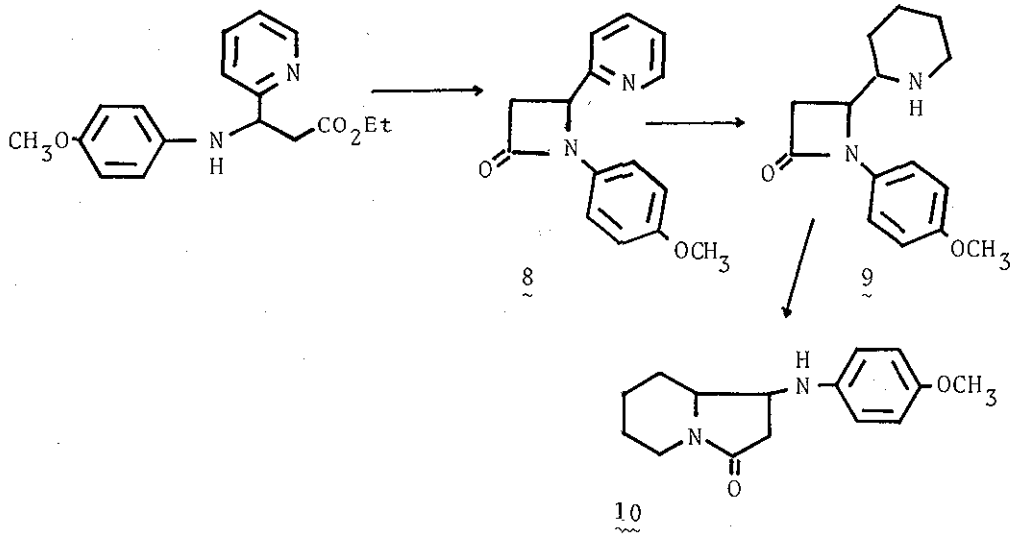
phenyl)-4-(2-pyridyl)azetidin-2-one (8) prepared by the usual method[5,6], over platinum oxide, afforded 1-(4-methoxyphenyl)-4-(2-piperidino)azetidin-2-one (9)[7] in 85 % yield. The azetidin-2-one (9) was heated in ethanol in the presence of sodium ethoxide to yield 4-(4-methoxyanilino)octahydroindolizin-2-one (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),



1 2 3

4: R=-$CH_2C_6H_5$
5: R=-CH_3

6: R=-$CH_2C_6H_5$
7: R=-CH_3



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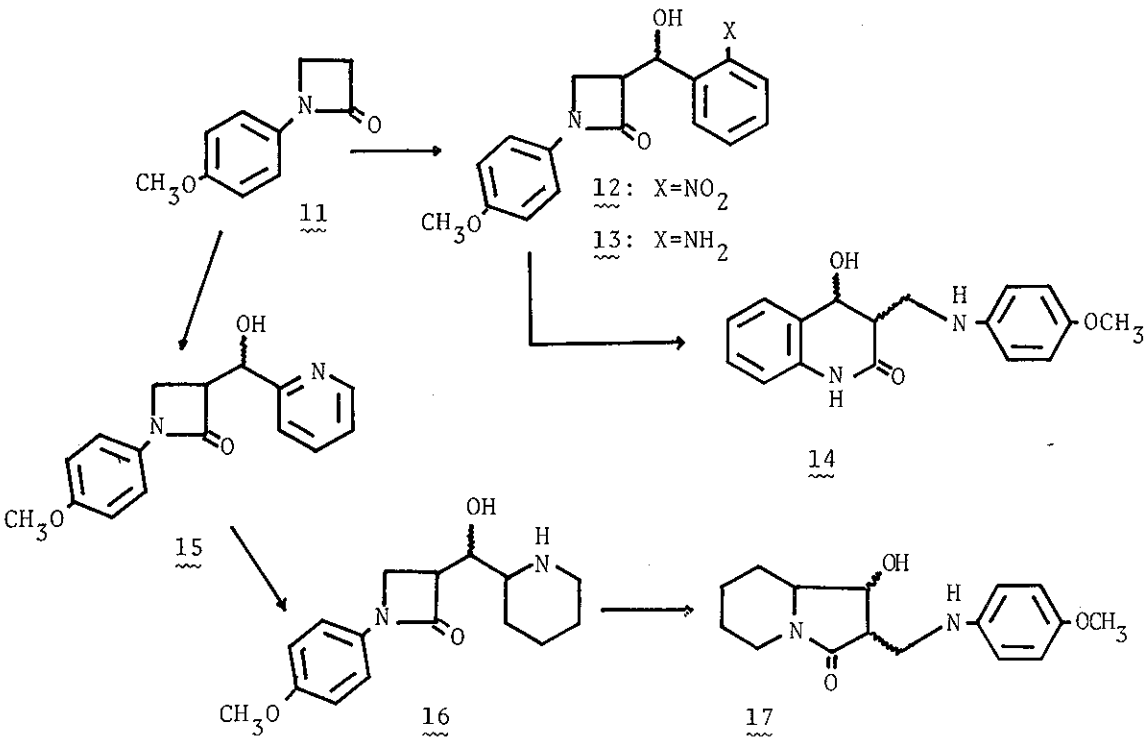
3.80 (3H, OCH_3), 6.55 (2H, d, J=9 Hz), 6.75 (2H, d, J=9 Hz)].

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 Durst[8]. 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 mixture[9]. 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-dihydrocarbostyril (14)[9], 186-189°C, in 85 % yield [ir (nujol): 1675 cm^{-1} ; nmr ($CDCl_3$) δ: 3.63 (3H, OCH_3), 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.



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7. The relative configuration at the 4- and 5-position was not determined.
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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.

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