A CONVENIENT SYNTHESIS OF MONOCYCLIC β-LACTAMS

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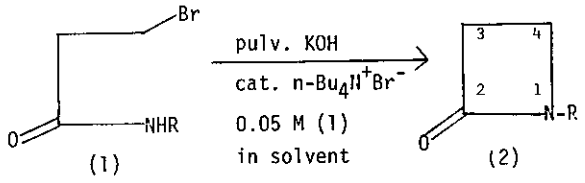
Abstract: The intramolecular N-alkylation of β-bromopropionamide (1) under phase transfer conditions gave monocyclic β-lactams (2) in high yields.

Synthesis of 2-azetidinones, the basic structure unit of the β-lactam antibiotic, is attractive to organic chemists as a synthetic target. Formation of these four-membered rings has been approached from nearly every conceivable way.[1] In continuation of our work on N-alkylation of lactams under phase-transfer conditions,[2] we now report a facile synthesis of β-lactams by the formation of N-C_4 bond, which mimics the proposed biosynthesis,[3] by cyclization of β-bromopropionamides (1), readily available from coupling of β-bromopropionylchrolide with amines,[4] in solid-liquid system.[5]



R= A. C_6H_5 B. p-$MeOC_6H_4$ C. p-ClC_6H_4
D. p-$O_2NC_6H_4$ E. α-naphtyl
F. $C_6H_5CH_2$ G. p-$MeOC_6H_4CH_2$
H. $C_6H_5CH(COOMe)$ I. $C_6H_5CH_2CH_2$
J. cyclohexyl K. n-propyl

A typical procedure for the formation of β-lactams is as follows. To a suspension of pulverlized KOH (5.5 mmol) and n-$Bu_4N^+Br^-$ (1 mmol) in 50 ml of dry CH_2Cl_2 at room temperature was added a solution containing N-3-bromopropionyl-2-phenylglycine methyl ester (1H) (5 mmol) in 50 ml of dry CH_2Cl_2 over 6 hr with stirring. After completion of the addition, the reaction mixture was stirred for 30 min. The precipitate was filtered off and then washed with CH_2Cl_2. After removal of the combined solvent, the residue was purified by column chromatography on silica gel (CH_2Cl_2-MeOH) (50:1) to give the desired β-lactam (2H) in 83 % yield. The spectral data [ν c=o (neat) 1735 and 1725 cm^{-1}; δ($CDCl_3$) 2.83-3.27 (3H, m), 3.67 (1H, t, J=3.5 Hz), 3.83 (3H, s, COOMe), 5.67 (1H, s, CHCOOMe), 7.45 (5H, s, ArH); m/e 219 (M^+)] and elemental analysis (molecular formura $C_{12}H_{13}NO_3$) supported this assignment.

Table

Compd.[a]	mp (°C)[b]	Yield (%)	IR ν c=o (cm^{-1})[c]
(2A)	79-81	94	1730
(2B)	104-5	92	1725
(2C)[d]	137-9	94	1730
(2D)[d]	162-4	81	1745
(2E)[d]	52-3	91	1740
(2F)	oil	86	1740
(2G)[d]	oil	85	1745
(2H)	oil	83	1735
(2I)[e]	oil	83 (50)[f]	1740
(2J)[e]	oil	63 (74)[f]	1730
(2K)	oil	67 (94)[f]	1745

a) All new compounds gave satisfactory elemental analyses.

b) The oil compounds were purified by chromatography, because the distilation resulted in partial decomposition of β-lactams.

c) (2A-E) (nujol), (2F-K) (neat).

d) The solvent (CH_2Cl_2: CH_3CN) (19:1) was used.

e) The acrylamides of by-products were obtained in 14% and 6% yields.

f) The THF was used as a solvent.

The results are summarized in Table. The cyclization of amides (1) to the β-lactams (2) was dependent on the concentration of the solution, the addition rate of amides to the base and the solvent. Both the high concentration over 0.05 M and the rapid addition of the amides resulted in low yields of β-lactams, along with the formation of substantial amounts of N-alkyl acrylamides. With regard to the solvent employed, the β-lactams (2A-I) could be prepared in good yields by using CH_2Cl_2, however, the use of THF for their cyclization caused complication. On the other hand, the use of THF was favoured over that of CH_2Cl_2 for cyclization of (1J) and (1K). In paticular, this reaction proceed at room temperature, the procedure is simple, straightforward, and easy to work up, the formation of by-products was scarcely caused, and the desired products were obtained in high yields. In conclusion, this procedure under phase transfer conditions is more convenient for N-alkyl monocyclic β-lactams syntheses.[1,6,7,8] In addition, the β-lactams thus readily obtained have high reactivities (Fries rearrangement,[9]

C-C bond formation at C_3-position,[10] azidation at C_3-position,[11] oxidation at C_4-position,[12] and so on[13]). Therefore, they would be served as potential synthetic intermediates as well as those of natural products containing the β-lactam ring.[11]

References and Notes

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4. Compounds (1) were obtained in satisfactory yields (70-90%). The details of preparation will be described in full papers.

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