Annelation of Imines to β-Lactams at Low Temperatures[1]

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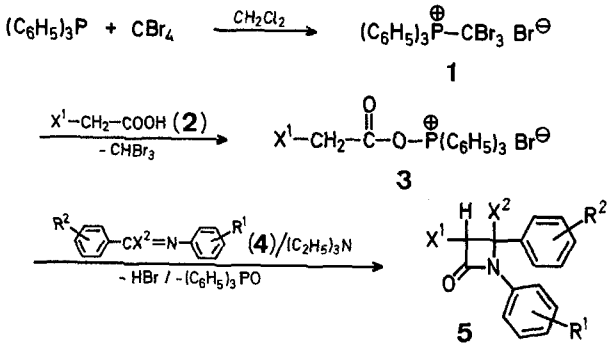
Multisubstituted β-lactams are often sensitive to various reagents. Therefore, we have been interested in exploring methods for β-lactam formation that operate under mild conditions. We report here that the reaction of an imine (**4**) with an appropriately substituted acetic acid (**2**) and triethylamine in presence of triphenylphosphine and carbon tetrabromide[2] at very low temperatures (near −78°) gives β-lactams in 30–85% yield.

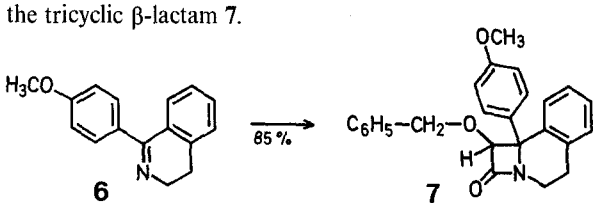
For maximum yields of β-lactams (**5**) via this reaction, the optimum reaction temperature was found to be about −78°. Reaction temperatures of 25° or higher either fail to provide the cyclic product or the yields are drastically reduced. Furthermore, the yields of the β-lactams were significantly curtailed when carbon tetrachloride was substituted for carbon tetrabromide.

Mechanistically, the reaction may be conceived as proceeding through the intermediate formation of an active ester (**3**) from the acid **2** and the *in situ* generated phosphonium salt **1**. The active ester **3** then reacts with the Schiff base **4** in the presence of triethylamine to yield the cyclic product **5**.

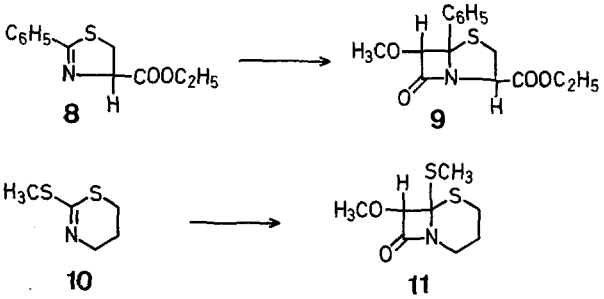


The stereochemistry of the monocyclic β-lactams (**5**) listed in Table 1 was derived from their ^{1}H-N.M.R. spectra. The C-3 and C-4 protons appear as two doublets in the region $\delta = 5$–6 ppm. The coupling constant $J \approx 2$ Hz has been considered to indicate that these protons are *trans* to each other whereas a value of $J \approx 5$ Hz has been considered to be indicative of their *cis* configurations[3]. The ^{1}H-N.M.R. of the crude product **5** shows the formation of a single isomer only. On the basis of the available data, however, it is not possible to predict the steric course of these reactions.

The reaction works equally well when a Schiff base is replaced by a cyclic imine, such as a dihydroisoquinoline. Thus, the reaction of 1-(4-methoxyphenyl)-3,4-dihydroisoquinoline (**6**)[4] with benzyloxyacetic acid and triethylamine in the presence of triphenylphosphine and carbon tetrabromide gives the tricyclic β-lactam **7**.



Our new method of β-lactam synthesis appears to be generally applicable. Thus, treatment of the 4,5-dihydro-1,3-thiazole **8**[5] and the 5,6-dihydro-4*H*-1,3-thiazine **10**[6] with methoxyacetic acid under the above-mentioned conditions affords 3-ethoxycarbonyl-6-methoxy-5-phenylpenam[5] (**9**) and 7-methoxy-6-methylthiocepham[7] (**11**), respectively.



Certain structural features in the acid component in this reaction appear to have a noticeable effect on the yield of the product. Cyanoacetic acid and *N*-benzoylglycine failed to provide the corresponding substituted monocyclic or polycyclic β-lactams. In all cases in which any one of these acids were employed, the Schiff bases or the imine components were recovered unchanged even when the reactions were carried out under a variety of experimental conditions. The yield of β-lactam **5j** (Table 1) from (benzylthio)-acetic acid (**2**, $X^1 = C_6H_5—CH_2—S—$) and *N*-(4-methoxybenzylidene)-4-methylaniline (**4**, $R^1 = 4\text{-}CH_3$, $R^2 = X^2 = H$) is low (30%). As is expected on the basis of our previous work, the thio group at C-3 is exclusively *trans*[8,9] to the substituent at C-4 in this product.

In view of the continued interest in α-amino- and α-acylamino-β-lactams, we studied the scope of the present method for producing such lactams. The reaction of azidoacetic acid under a variety of conditions and even in the presence of excess triphenylphosphine did not afford 3-azido-2-oxoazetidines; on the other hand, the reaction of phthalimidoacetic acid gave the corresponding *trans*-β-lactams in good yield. Recently, the conversion of α-phthalimido-β-lactams into α-amino-β-lactams under mild conditions has been reported[10].

Table 1. β-Lactams (**5**) from Substituted Acetic Acids (**2**) and *N*-Benzylidenanilines (**4**)

5	R^1	R^2	X^1	X^2	Yield [%]	m.p.	Configuration	Brutto formula[a]
a	4-CH_3	4-OCH_3	C_6H_5—CH_2—O—	H	80	159–160°[b]	*cis*	
b	4-CH_3	H	C_6H_5—CH_2—O—	H	85	195–196°	*cis*	$C_{23}H_{21}NO_3$ (359.4)
c	H	H	C_6H_5—O—	H	50	190–192°[c]	*trans*	
d	4-CH_3	4-OCH_3	H_3C—O—	H	85	114–115°[d]	*cis*	
e	4-CH_3	4-OCH_3	C_6H_5—O—	H	70	148°	*cis*	$C_{23}H_{21}NO_3$ (359.4)
f	4-OCH_3	4-OCH_3	Pi[e]	H	80	192–194°	*trans*	$C_{25}H_{20}N_2O_5$ (428.4)
g	4-OCH_3	H	Pi[e]	H	85	190–191°	*trans*	$C_{24}H_{18}N_2O_4$ (398.4)
h	4-CH_3	4-NO_2	Pi[e]	H	70	218–220°	*trans*	$C_{24}H_{17}N_3O_5$ (427.4)
i	4-CH_3	4-OCH_3	C_6H_5—CH_2—O—CO—NH—	H	50	177–178°[f]	*cis*	
j	4-CH_3	4-OCH_3	C_6H_5—CH_2—S—	H	30	113–114°[g]	*trans*	
k	H	H	H_3C—O—	—S—CH_3	65	114°[h]	—	

[a] The elemental analyses showed the following maximum deviations from the calculated values: C, ±0.34; H, ±0.16; N, ±0.22.
[b] Ref.[4], m.p. 159–160°.
[c] Ref.[12], m.p. 190–192°.
[d] Ref.[4], m.p. 114–115°.
[e] Pi = 
[f] Ref.[11], m.p. 177–178°.
[g] Ref.[9], m.p. 118–119°.
[h] Ref.[9], m.p. 126°.

Table 2. Spectroscopic Data for β-Lactams **5**

5	I.R. (nujol) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (DMSO/$CDCl_3$) δ [ppm]
a	—	
b	1760	3.7 (s, 3H); 4.25 (q, 2H, J = 12 Hz); 5.15 (d, 1H, J = 6 Hz); 5.45 (d, 1H, J = 6 Hz); 6.8–7.45 (b, 14H)
c	—	
d	—	
e	1755	($CHCl_3$): 2.3 (s, 3H); 3.8 (s, 3H); 4.55 (d, 1H, J = 6 Hz); 5.45 (d, 1H, J = 6 Hz); 6.7–7.5 (b, 13H).
f	1760, 1720	3.75 (s, 3H); 3.8 (s, 3H); 5.25 (d, 1H, J = 2 Hz); 5.45 (d, 1H, J = 2 Hz); 6.8–7.6 (b, 12H).
g	1760, 1720	3.75 (s, 3H); 5.25 (d, 1H, J = 2 Hz); 5.42 (d, 1H, J = 2 Hz); 6.7–7.85 (b, 13H)
h	1755, 1720	2.3 (s, 3H); 5.3 (d, 1H, J = 2 Hz); 6.0 (d, 1H, J = 2 Hz); 7.2–8.2 (b, 12H)
i	—	
j	—	
k	—	

The one step formation of α-acylamino-β-lactams described by us[11] earlier could be successfully carried out under the new reaction conditions. Thus, with *N*-benzyloxycarbonylglycine the *cis*-β-lactam **5i**[11] was obtained in 50% yield.

All melting points are uncorrected. The I.R. were recorded on a Perkin-Elmer Infracord spectrophotometer using a thin film of Nujol mull, and the N.M.R. spectra were taken on Perkin-Elmer R-12 B and Varian A-60 A instruments. The microanalyses were performed at the central Drug Research Institute, Lucknow, India.

Preparation of β-Lactams (5); General Procedure:
A mixture of the *N*-benzylidenaniline **4** (0.01 mol), triethylamine (4.05 g, 0.04 mol), the substituted acetic acid **2** (0.02 mol), and triphenylphosphine (5.25 g, 0.02 mol) in dichloromethane (200 ml) is stirred under a nitrogen atmosphere at −78° while a solution of carbon tetrabromide (6.633 g, 0.02 mol) in dichloromethane (50 ml) is added dropwise. Stirring is continued at −78° for 1 h and then at room temperature overnight. The resultant mixture is washed with 5% aqueous sodium carbonate and water and is column-chromatographed on Florisil using dichloromethane/hexane (1:1) as eluent. The solvent is evaporated from the eluate and the residue is recrystallized from dichloromethane/hexane.

1-Benzyloxy-9b-(4-methoxyphenyl)-2-oxo-1,2,4,5-tetrahydro-9bH-azeto[2,1-a]isoquinoline (**7**) is obtained under similar conditions from 1-(4-methoxyphenyl)-3,4-dihydroisoquinoline (**6**) and benzyloxyacetic acid; yield: 85%; m.p. 128–130°.

$C_{25}H_{23}NO_3$	calc.	C 77.90	H 6.01	N 3.63
(385.5)	found	77.80	5.68	3.38

I.R. (Nujol): ν_{max} = 1755 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.62 (m, 2H); 3.0 (m, 2H); 3.82 (s, 3H); 4.5 (s, 2H); 4.9 (s, 1H); 6.8–7.3 ppm (b, 13H).

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