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Stereocontrol of β-Lactam Formation Using Microwave Irradiation[1]

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ABSTRACT: *Formation of β-lactams by the reaction of an acid chloride, a Schiff base and a tertiary amine seems to involve multiple pathways some of which are very fast at higher temperatures. When β-1actam formation is conducted in open vessels in unmodified domestic microwave ovens, high level irradiation leads to preferential formation of trans β-1actams in several cases when the Schiff base is derived from an aryl aldehyde rather than glyceraldehyde acetonide.*

The discovery of penicillin and cephalosporin focused the attention of synthetic chemists on cis α-amido β-lactams. Interest turned to trans β-lactams also when thienamycin and several other antibiotics were found to belong to the trans family. In recent years we[2] have shown that cis and trans α-hydroxy-β-lactams are valuable synthons for a variety of natural products such as β-lactam antibiotics, amino sugars, amino acids, alkaloids, etc. The synthesis of α-hydroxy-β-lactams is now the center of much attention because the side chain of the antitumor drug taxol[3] can be derived from compounds of this type.

We[4] have described a 3-step method for preparing optically pure trans 3-hydroxy-2-azetidinones from readily available optically active cis α-hydroxy-β-lactam derivatives. The key step is an efficient S_N2 reaction between the tosylate (or mesylate) of the hydroxy group and sodium acetate in DMF or DMSO solution. We wish to report here a convenient direct approach to some trans 3-hydroxy-2-azetidinone derivatives using **M**icrowave-induced **O**rganic **R**eaction **E**nhancement (**MORE**) chemistry techniques.[5,6]

In an earlier publication we[7] have reported the rapid and efficient preparation of various substituted β-lactams (Scheme) and their transformations using **MORE** chemistry techniques. The stereochemistry (cis and/or trans) of the β-lactams **4** and **5** formed in the microwave oven with irradiation for a short period of time (1-2 min) at low power setting was about the same as obtained by the traditional method. Further studies have now shown that it may be possible to control in some cases the steric course of β-1actam formation by using high level irradiation in a domestic microwave oven.

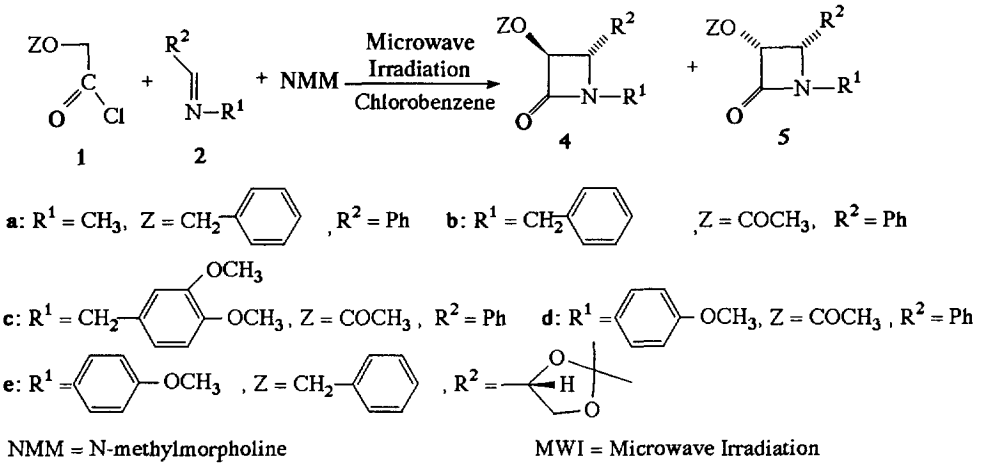
For a study of the effect of microwave irradiation on the formation of α-hydroxy-β-1actam derivatives we selected several Schiff bases (**2**) and the high boiling tertiary amine N-methylmorpholine (**3**) in place of lower boiling triethylamine. Chlorobenzene (b.p. 132°C) was chosen as the reaction medium in place of toluene which absorbs microwave energy only poorly. The approximate temperature of the reaction (110-120°C) was determined by using a thermometer after the microwave irradiation was

stopped. A beaker of water was placed next to the reaction vessel in the microwave oven as a "heat sink" for better control of the amount of microwave energy entering reaction mixtures of small size (1-5g).[5]

Preliminary observations on the preparation of α-benzyloxy-β-lactams from benzyloxyacetyl chloride (**1a**), **2a**, and N-methylmorpholine (**3**) showed the formation of varying amounts of cis and trans β-lactams (**4a**, **5a**). A systematic study was undertaken and the data shown in Table were collected. It was found that cis β-lactam (**5a**) formation was favored by lower level of microwave irradiation. At about 112°C final reaction temperature, there was more of the trans compound **4a** than the cis isomer **5a**.

When the reaction of the same acid chloride (**1a**) with a Schiff base (**2e**) derived from D-glyceraldehyde acetonide was conducted under MORE chemistry conditions, only the cis β-lactam (**5e**) was obtained both at low and high power settings. This is in clear contrast with the observation made on **2a** (see above), **2b**, **2c** and **2d** (see below).

SCHEME



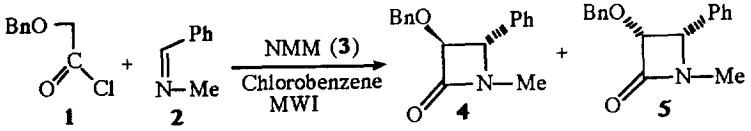
We (**8**) studied the β-lactam forming reaction when the Schiff base is derived from an aromatic aldehyde and an aryl alkyl amine as in (**2b**) and (**2c**). When the condensation was conducted in the traditional manner at 0°C by the "normal addition" sequence, only the cis β-lactam was formed. However, if the "inverse addition" technique was used, 30% cis and 70% trans β-lactams were obtained under the same conditions.

When this reaction was conducted in a microwave oven using chlorobenzene (preheated to about 110°C) as the reaction medium, the ratio of trans to cis β-lactam was 90 : 10 irrespective of the sequence of addition (i.e., "normal addition" or "inverse addition"). When the cis β-lactam **5c** was heated with N-methylmorpholine in chlorobenzene solution, there was no isomerization to the thermodynamically more stable trans β-lactam **4c**.

A compound of particular interest is the cis β-lactam **5d** (and its trans isomer **4d**) which can serve as intermediates for the side chain of taxol and its analogs such as Taxotere. When this reaction was conducted under microwave irradiation for 5 min, the ratio of the trans to cis isomer was 95 : 5.

In a recent paper Endo and Droghini[9] have reported the preparation of the racemic form of the trans β-lactam **(4d)** by the slow addition (1 h for 61.5 g amine) of triethylamine to a refluxing solution of the Schiff base and the acid chloride in toluene solution. This trans β-lactam **(4d)** is an intermediate for 2/-epi-taxol .

TABLE



NMM=N-methlmorpholine

Formation of β-Lactams (4) and (5) under Microwave Irradiation:

Time[a]	Power[b]	Temp.[c],°C	Ratio[d] of trans/cis
1 min	low	69	16:84
2 min	low	75	20:80
4 min	low	94	45:55
5 min	low	96	45:55
4 min	high	112	55:45

a : Time of irradiation in min of the reaction mixture. b : Power level of the microwave oven used for the reaction. Experiments were conducted in beakers in a domestic microwave oven (G. E. Model, maximum power, 1KW). c : Temperature of the reaction mixture observed after the microwave irradiation was stopped. d : Determined by ^{1}H NMR spectroscopy after extraction of the reaction mixture.

On the basis of the observations described above, it appears that the cyclization reaction involves multiple pathways[8] some of which are highly accelerated by microwave irradiation (and/or higher temperature). Further studies are in progress for explaining the difference in the steric course of reaction when the Schiff base is derived from an aliphatic aldehyde. In the mean time MORE chemistry techniques can be employed for the cost-effective and rapid synthesis of several types of trans α-hydroxy-β-lactam derivatives. In these times of budgetary restrictions, it is very convenient to be able to conduct stereocontrolled reactions in simple vessels without the need for the standard organic chemistry laboratory paraphernalia (such as, reflux condensers, ground glass equipment, stirrers, water separators, etc.).

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6. In previous publications[5] we have described simplified techniques of "Microwave-induced Organic Reaction Enhancement" (MORE) chemistry that are suitable for a variety of preparative reactions on small (a few mg) to medium size scale (several hundred grams). These reactions are conducted in a few minutes with complete safety in open glass vessels (beakers or Erlenmeyer flasks) at ordinary pressure in domestic microwave ovens. The strategy is to heat rapidly the reactants with a limited amount of solvent to an appropriately high temperature with only minimal vaporization.
An important element for successful operation is the selection of an efficient microwave energy transfer agent (for example, N,N-dimethylformamide, b.p. 153°C; ethylene glycol, b.p. 196°C; tetrachloroethylene, 121°C; chlorobenzene, b.p. 132°C; 1,4-dichlorobenzene, b.p. 173°C) as a high boiling reaction medium. Hydrocarbon solvents such as hexane, benzene and toluene are unsuitable as they absorb microwave energy poorly.

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8. In our early studies on β-lactam formation by the reaction of an acid chloride (or equivalent) with an imine in presence of triethylamine, we[10] had noted that the steric course of the reaction depended on several factors including the sequence of addition of the reagents. In the "acid chloride last" (or, "normal addition") method , the reaction was usually conducted in methylene chloride solution by the dropwise addition of azidoacetyl chloride (or other substituted acetyl chlorides) to a mixture of a Schiff base and an excess of triethylamine. This technique favored the formation of a cis β-lactam at room temperature or under reflux in methylene chloride solution. At 0°C or lower temperatures, cis β-lactams were almost the exclusive product in some cases.
In the "triethylamine last" (or, "inverse addition") method, an excess of triethylamine was added dropwise to a mixture of equimolar quantities of a Schiff base and an acid chloride in methylene chloride solution. This procedure favored the formation of the trans β-lactam.
The cis/trans ratio was determined very conveniently from a study of the ^{1}H NMR spectra of the crude reaction mixture.

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