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Microwave-Assisted Rapid Synthesis of α-Amino-β-Lactams[1]

Ajay K. Bose, M. Jayaraman, A. Okawa, S. S. Bari, E. W. Robb and M. S. Manhas*

McLean Chemical Sciences Center,
Stevens Institute of Technology, Hoboken, NJ 07030, USA

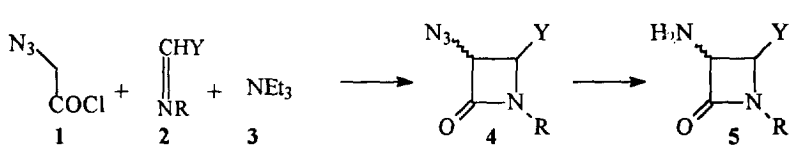
Dedicated to Prof. Charles C. Price

Abstract: A rapid and convenient approach to α-amino-β-lactams has been developed using the tetrachlorophthalimido group as a masked amino substituent. Reaction between glycine and tetrachlorophthalic anhydride in DMF for about 90 sec in a domestic microwave oven led to an imidoacetic acid in high yield; the corresponding acid chloride reacted with Schiff bases to provide mixtures of trans and cis β-lactams. Nearly exclusive formation of trans β-lactams could be achieved in some cases in a few minutes by conducting β-lactam formation under strong microwave irradiation. Facile conversion to α-amino-β-lactams was realized in 5-10 minutes via solventless reaction of these α-amino-β-lactams with ethylenediamine at room temperature. Copyright © 1996 Elsevier Science Ltd

Antibiotics belonging to the families of penicillins, cephalosporins, cephamycins, nocardicins and monobactams have in common an α-amino-β-lactam moiety.[2] Diversely substituted 3-amino-2-azetidinones can serve as synthons for such antibiotics as well as, amino sugars, alkaloids, and other natural products.[3]

A method[4] (**Scheme 1**) that we devised in 1966 is still in wide use in industrial and academic laboratories for preparing monocyclic and fused α-amino-β-lactams. It involves the formation of 3-azido-2-azetidinones (**4**) by the reaction of azidoacetyl chloride (or equivalent) (**1**) with an imino compound **2** and a base **3**. The stereochemistry of the β-lactam **4** can be mostly cis or a mixture of trans and cis depending on the sequence of addition of the reagents and the nature of substitution on the imino group in **2**.[4,5] The azido group is reduced to an amino group by various reagents to form α-amino-β-lactams **5**. The drawback of this method is the hazardous nature of azidoacetyl chloride - especially for large scale synthesis.

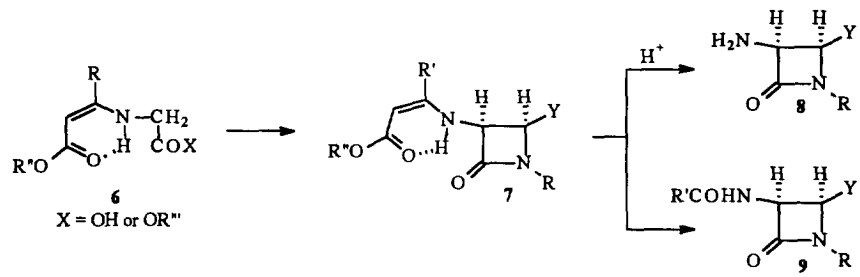
Scheme 1



1 2 3 4 5

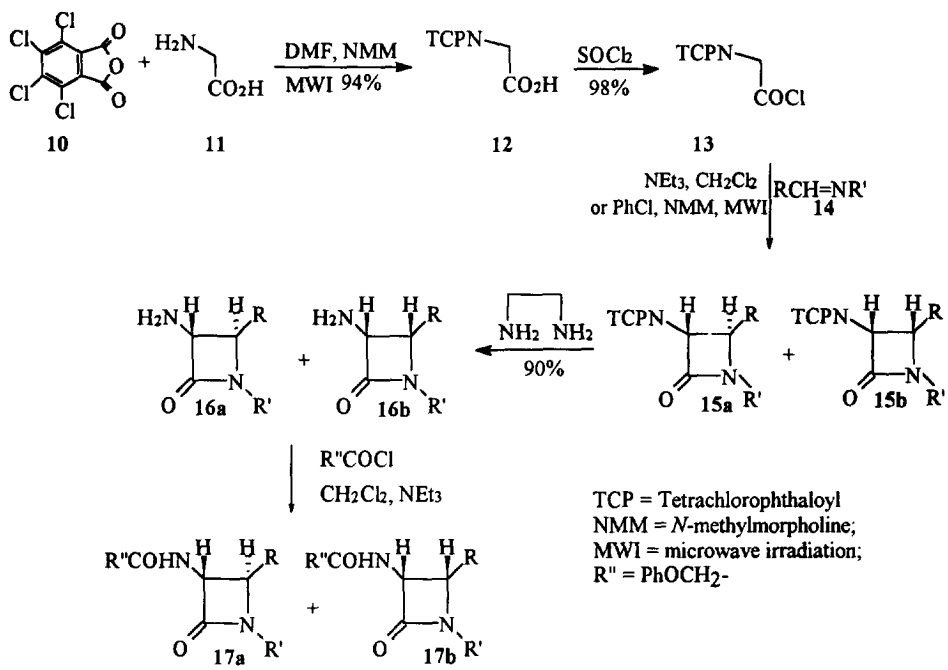
A nonhazardous method that we[6] developed involves the use of an enamine **6** prepared from glycine and a β-keto ester (**Scheme 2**). Following the formation of a cis β-lactam **7** the protective group can be removed under the influence of a mild acid to provide an α-amino-β-lactam **8**. On the other hand, oxidation of the side chain in (**7**) leads directly to a cis α-amido-β-lactam **9**.[7]

Scheme 2



We wish to describe now a rapid and convenient approach to α-amino-β-lactams[8] using tetrachlorophthalimidoacetic acid[11] as an intermediate. Our approach involves the use of Microwave-assisted Organic Reaction Enhancement (M.O.R.E) chemistry techniques developed in our laboratory.[13]

Scheme 3



Tetrachlorophthaloyl glycine (**12**) was prepared in 94% yield in 90 sec in a domestic microwave oven by using a modification of a large scale phthaloylation procedure developed by Bose, Greer and Price[14a,b] and a microwave-assisted variation[14c] developed in our laboratory. We have also carried out this protection of glycine (**11**) on a molar scale (350 g scale) of commercially available tetrachlorophthalic anhydride (**10**) and found that the tetrachlorophthaloyl (TCP) protected glycine **12** could be isolated in more than 90% yield after 8 min of irradiation followed by crystallization of the product from methanol. Treatment of this acid **12** with thionyl chloride in refluxing chlorobenzene for 4h provided the acid chloride **13** in quantitative yield.

Reaction of **13** with different imines in methylene chloride in the presence of triethylamine (conventional procedure) provided the TCP-protected α-amino-β-lactams **15a** & **15b** in moderate yields with varying *cis/trans* ratio. Treatment of the acid chloride **13** with imines **14** in chlorobenzene in the presence of *N*-methylmorpholine under microwave irradiation provided the corresponding TCP-protected β-lactams **15a** & **15b** in very good yield in 3-5 minutes.

High level of *trans* selectivity was observed when the reaction was carried out under microwave irradiation. However, under classical conditions the product was often a mixture of *cis/trans* isomers. It was also observed that the temperature at which the acid chloride was added is crucial for the stereoselectivity. The imine solution in chlorobenzene with *N*-methylmorpholine was initially irradiated for 1 min so as to reach a temperature of about 100 °C, then the acid chloride was quickly added and the mixture was further irradiated for 3 min at low power level (power level 3). Upon cooling the reaction mixture and adding n-hexane, the product that crystallized out was filtered off and washed with water to remove the hydrochloride salt and vacuum dried. The yield and *cis/trans* ratio are reported in **Table 1**. Surprisingly, in the case of 4-styryl-2-azetidinone only the *cis*-β-lactam was isolated even under a high level of microwave irradiation.

Table 1. Synthesis of β-Lactams 15a & 15b

No	R	R'	Yield (%)[a]	(15a:15b) (MWI)	(15a:15b) (classical)
1	Ph	PMP	83 (57)	100:0	55:45
2	PMP	PMP	98 (52)	100:0	10:90
3	Sty	PMP	99 (77)	0:100	0:100
4	Fu	PMP	90 (53)	100:0	20:80
5	Ph	Bn	83	80:20	-

a: Yields in parenthesis indicate the isolated yield of β-lactams obtained by the classical procedure
PMP = *p*-methoxyphenyl; Sty = styryl; Fu = furyl; Bn = benzyl

Deprotection of **15** was conveniently carried out by treating the TCP-protected β-lactam with a slight excess of ethylene diamine at room temperature in the absence of any solvent. In a typical procedure the TCP-protected β-lactam and 3 equivalents of ethylene diamine were mixed well with a pestle in a mortar and the reaction mixture was kept at room temperature. After the completion of the reaction (TLC disappearance of starting material) in about 5 minutes, water was added to dissolve the excess amine and then chloroform was added. The mixture was filtered off, the solids washed with chloroform and the chloroform fraction separated, dried (Na_2SO_4) and evaporated to get the corresponding 3-amino-β-lactams (**16a** & **16b**) in good yield. These samples of α-amino-β-lactams (**16**) were treated with phenoxyacetyl chloride in the presence of triethylamine to obtain the corresponding α-phenoxyacetamido-β-lactams (**17**) in quantitative yield[15].

In summary, we have developed a convenient and rapid procedure for the synthesis of α-amino-β-lactams using domestic microwave ovens for a few minutes. Several of these 3-amino-2-azetidinones and corresponding amides are known intermediates for β-lactam antibiotics. Further elaboration of this methodology and studies on the stereoselectivity of β-lactam formation under various conditions are currently in progress in our laboratories.

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