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FACILE PREPARATION OF CARBAPENEM SYNTHONS VIA MICROWAVE-INDUCED RAPID REACTION ‡

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‡ Dedicated to Professor Derek H. R. Barton on the occasion of his 75th birthday.

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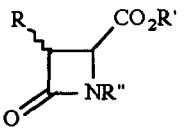
Abstract: A simplified and stereocontrolled synthesis of α-vinyl and α-alkyl β-lactams has been achieved in open vessels under microwave irradiation in unmodified domestic microwave ovens. These compounds - prepared in the course of a few minutes for each reaction step (including catalytic transfer hydrogenation) - are convenient synthons for various cis and trans carbapenems.

In recent publications [2] we have demonstrated that a variety of organic synthetic reactions can be conducted rapidly and safely in open glass vessels at ambient pressure [3] in domestic microwave ovens. The simplified techniques for "Microwave-induced Organic Reaction Enhancement" (MORE) chemistry that we have developed are highly cost-effective since reflux condensers, stirrers, water separators, ground glass equipment and other expensive items are not used for conducting reactions. Key factors for the success of these techniques are the selection of a proper microwave energy transfer medium as the solvent [4] and the control of the energy input.[5] The strategy is to heat rapidly the reactants with a limited amount of solvent to an appropriately high temperature with only minimal vaporization. For the reaction medium a solvent is chosen with a high dielectric constant for ensuring efficient absorption of microwave energy and a rapid rise in reaction temperature [6] ; a solvent with a high enough boiling point is employed such that the desired reaction temperature is at least 20-30 °C lower than the boiling point of the reaction mixture. It has been reported [7] that superheating of liquids is common under microwave irradiation.

There is a growing concern about environmental pollution caused during the manufacture of chemicals. As a result, "environmentally benign chemical synthesis and processing" are attracting serious attention. In this context the MORE chemistry techniques provide an important advantage over traditional methods since only limited amounts of solvents - enough to dissolve most of the reactants at higher temperatures - are required.

Carbapenem antibiotics, in particular thienamycin, have received considerable attention from many academic and industrial synthetic groups.[8] Unlike penicillins and cephalosporins, these compounds are characterized by alkyl side chains in place of amido side chains; also, they represent both cis and trans β-lactam structures. We wish to report a convenient approach to known β-lactam intermediates [9,10] of type **1** and demonstrate that all the synthetic steps can be conducted rapidly and economically by employing MORE chemistry techniques.

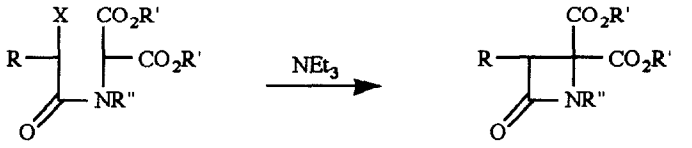


R = alkyl or alkenyl
R'= alkyl or H
R"= aryl, arylalkyl or H

1

Simplified Stereocontrol

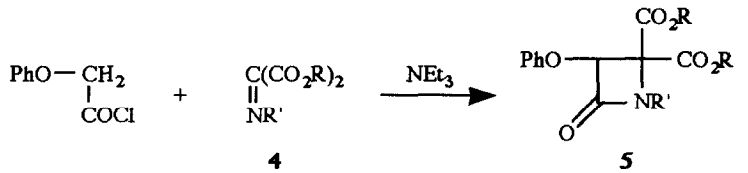
More than 40 years ago one of us had developed an efficient synthesis [11,12] of 4,4-dicarboxy-2-azetidinone derivatives (**3**) in nearly quantitative yield that involved a room temperature reaction between an α-haloacetamidomalonate (e. g., **2a**) and a mild base such as triethylamine. For β-lactams of type **3** the question of cis and trans isomers does not arise.



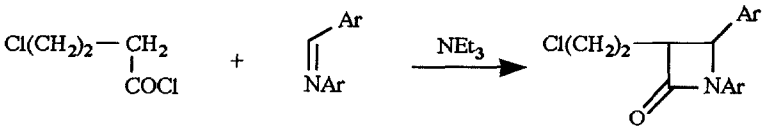
2 (a) R = H, X = Cl
(b) R = $BrCH_2CH_2$, X = Br

3 (a) R = H
(b) R = $BrCH_2CH_2$

Later, we [13] prepared compounds of type **3** (e.g., **5**) by using the acid chloride-imine reaction leading to **5** from the imine **4**. This reaction, however, produces α-alkyl β-lactams (e. g., **6**) in poor yield [14].

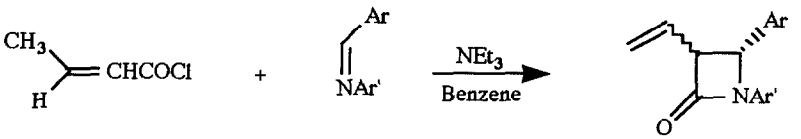


4 **5**



6

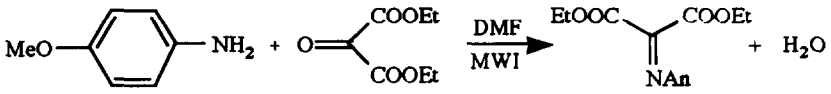
In 1971 we [15] discovered a convenient synthesis of α-vinyl β-lactams (e.g., **9**) by the reaction of an α,β-unsaturated acid chloride **7** with a Schiff base **8** and triethylamine. Only moderate yields of the β-lactams were obtained after several hours of heating under reflux in benzene solution, also the stereochemistry of the products was not predictable. [16]



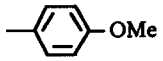
7 **8** **9**

Our present work combines useful aspects of the above synthetic approaches and provides complete stereocontrol of the target β-lactam. Furthermore, we have avoided the use of benzene [17] as the solvent because hydrocarbons absorb microwave energy very poorly. We have selected N,N-dimethylformamide (DMF), a good solvent of high boiling point (153 °C) and high dielectric constant (ε=36.7) that is miscible with water, as microwave energy transfer medium and solvent for a series of three synthetic steps.

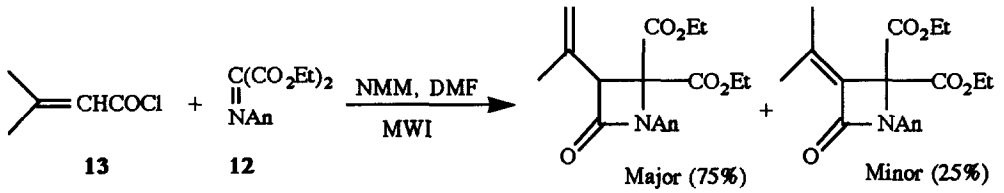
In the first step, commercially available diethyl ketomalonate **11** was allowed to condense with p-anisidine **10** to form the imino compound **12**. On a few gram scale, this reaction was 80% complete in about 6-7 min when conducted in DMF solution in a domestic microwave oven. The water formed in the reaction was retained by DMF (perhaps with partial loss to the atmosphere as the reaction temperature was about 125-135 °C).



10 **11** **12**

MWI = Microwave Irradiation An = 

The second step was the reaction of **12** with β,β-dimethylacryloyl chloride **13** and N-methylmorpholine (NMM) [18] to form a mixture of two isomeric β-lactams (**14** and **15**) in 60% yield which did not have to be separated.



13 **12** Major (75%) Minor (25%)

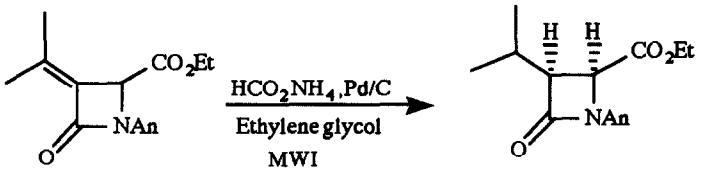
14 **15**

Following the method of Krapcho [19], elimination of one of the ester groups of the malonate derivatives **14** and **15** was attempted as the third step under the influence of sodium chloride in dimethylsulfoxide. The product was a single β-lactam **16** (50%) with the double bond conjugated with the β-lactam carbonyl.

14 and **15** **16**

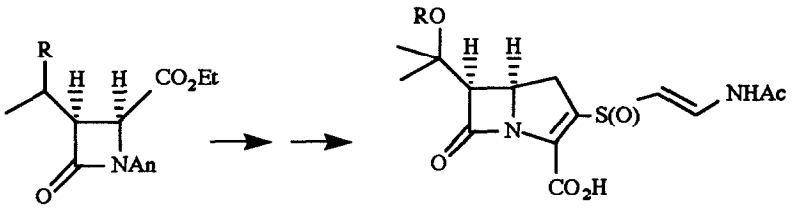
We have been able to conduct the Schiff base formation and β-lactam synthesis as a one pot reaction under microwave irradation and isolated **14** and **15** in about 60% yield [20] from **11**. The deesterification step was conducted in DMF solution with lithium chloride instead of the usual Krapcho conditions (DMSO - sodium chloride).

We [21] have shown earlier that MORE chemistry techniques are specially suitable for catalytic transfer hydrogenation. Using ethylene glycol (b.p. 196 °C) as the microwave energy transfer medium and ammonium formate as the hydrogen source in the presence of 10% Pd/C catalyst, β-lactam **16** was quantitatively reduced (at about 130 °C) to a single product **17**, a cis β-lactam.



16 **17**

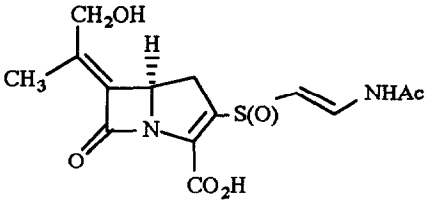
By an analogous set of reactions we have prepared **18** [22] by substituting crotonyl chloride for β,β-dimethylacryloyl chloride in the reaction with the imine **12**.



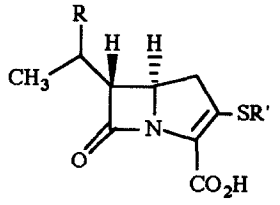
17 R = Me
18 R = H

19 Carpetimycin A: R = H
Carpetimycin B: R = SO_3H

It is known [23] that a 4-carboethoxy group in an N-substituted 2-azetidinone can be reduced by lithium borohydride to a primary alcohol group without cleavage of the β-lactam ring. Thus, cis carbapenems of the type of carpetimycin **19** are accessible via **17** and **18**. [24]



Asparenomycin



PS-5: R = H, R'= CH_2CH_2NHAc
PS-6: R = CH_3, R'= CH=CHNHAc

β-Lactams **16**, **17** and **18** had been prepared by us previously by traditional chemistry starting with the Schiff base derived from glyoxalate esters and p-anisidine.[9] These compounds have been shown by earlier workers [9,10] to be convenient intermediates for asparenomycin, PS-5 and PS-6.

In summary, microwave irradiation in simple glass vessels in unmodified [25] commercial microwave ovens can accelerate highly the formation of useful β-lactam synthons notwithstanding the fact that the nature of specific activation (if any) of organic reactions by microwaves is not yet understood.[26]

ACKNOWLEDGEMENT: This research was supported by Stevens Institute of Technology and the Howard Hughes Medical Institute (through a grant to our Chemical Biology Education Enhancement Program). We wish to thank Raza Naqvi, Keiko Tabei and Gregori Morriello[27] for technical assistance.

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3. Organic reactions in a microwave oven have been performed under a variety of conditions in different laboratories. Use of sealed tubes and capped teflon vessels result in high pressures and some explosions have been reported.
4. We have found that solvents (b.p.°C) such as 1,2-dichloroethane(83°C); dioxane(101°C) chlorobenzene(132°C); N,N-dimethylformamide(153°C); diglyme(162°C); 1,2-dichlorobenzene(180°C); ethylene glycol(196°C); 1,2,4-trichlorobenzene(214°C); formamide(216°C); triglyme(216°C) are efficient microwave energy transfer agents.
5. To control microwave energy input we have found it useful to place a beaker of water (heat sink) or other high boiling solvent near the reaction vessel. This absorbs a suitable portion of the microwave energy. This technique allows one to carry out reactions even on a small scale.
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14. Unpublished work from this laboratory.
15 Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167.
16. Zamboni, R.; Just, G. *Can. J. Chem.* **1979**, *57*, 1945; also see Ref. 9.
17. Under OSHA rules, benzene is in disfavor as a reaction medium, because of its possible carcinogenic properties.
18. Higher boiling base instead of NEt_3.
19. Krapcho, A. P. *Synthesis* **1982**, 805 and references cited therein.
20. The first step, Schiff base formation, proceeds in better than 80% yield.
21. It is suggested that hydrogenation reactions be carried out on a small scale using 100-200 mg of the catalyst and allow a longer reaction time for completion of hydrogenation. This step has the potential to generate free hydrogen and produce a fire hazard if the catalyst is added too rapidly to the reaction mixture.
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