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MICROWAVE-INDUCED ORGANIC REACTION ENHANCEMENT CHEMISTRY. 4
CONVENIENT SYNTHESIS OF ENANTIOPURE α-HYDROXY-β-LACTAMS[1]

Bimal K. Banik, Maghar S. Manhas*, Zbignew Kaluza, Khaled J. Barakat and Ajay K. Bose
Department of Chemistry and Chemical Engineering
Stevens Institute of Technology, Hoboken, New Jersey 07030, U.S.A.

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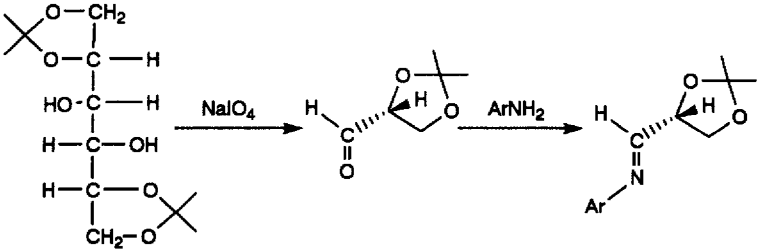
ABSTRACT: A convenient and rapid synthesis of enantiopure α-hydroxy-β-lactams using microwave-induced organic reaction enhancement chemistry has been developed. Reactions in domestic microwave ovens, which are very convenient and economical for small scale work in research or teaching laboratories, can also be conducted on a preparative scale of 100-500g in simple beakers or flasks

In the course of our studies on ß-lactams we have used optically active 3-hydroxy-2-azetidinones as versatile synthons for various natural products including amino sugars, higher sugars and several types of antibiotics.[3,4] We have prepared such α-substituted ß-lactams by the reaction of achiral acid chlorides with chiral imino compounds in presence of a base such as triethylamine. We have observed that the reaction of a Schiff base derived from an achiral aldehyde and a chiral amine usually gives a mixture of diastereomers [4] Independent work from two laboratories has shown that if the Schiff base be derived from a chiral aldehyde and an achiral amine, formation of α-amino ß-lactam derivatives is enantiospecific.[5] Since then we have shown that α-hydroxy ß-lactams can also be similarly prepared in an enantiospecific fashion.[6]

Schiff bases from D-glyceraldehyde acetonide prepared from D-mannitol are convenient starting materials. Although this aldehyde is commercially available, we find it more convenient as well as economical to start with D-mannitol diacetonide[7] (1) and conduct the next three reactions without the separation of intermediates. The first step is the oxidation of this 1,2-diol with sodium periodate following the method of Baer and Fischer[8a] with minor variations. The aqueous solution of the aldehyde (2) so obtained is utilized for condensation with an amine in 1,2-dichloroethane solution in a well-stirred two phase reaction mixture.[8b]



(1) (2) (3)

The Schiff base stays in the organic layer which is separated from the water layer after the reaction is over and dried (magnesium sulfate) carefully. This solution containing the Schiff base (3) is now ready for the ß-lactam forming reaction.

In previous publications we have reported techniques for the use of microwave irradiation for the safe and rapid conduct of a variety of organic reactions.[1,2] The key to the success of Microwave-induced Organic Reaction Enhancement (MORE) chemistry is the use of a solvent that absorbs microwave radiation efficiently and has a sufficiently high boiling point so as not to boil under the irradiation conditions used.[9a] Hydrocarbons solvent, such as benzene or tolulene, which are commonly used as reaction media in organic laboratories, are not suitable as they absorb microwave radiation very poorly.[9b] We have found some chlorinated hydrocarbons[9a] to be convenient for many reactions. We prefer ethylene glycol to lower boiling alcohols for certain types of reactions - for example, catalytic hydrogenation at elevated temperatures. For reactions that are usually conducted in ether or tetrahydrofuran, it is convenient to use dioxane, diglyme or triglyme as microwave energy trasfer agents. A variety of reactions (excluding those involving phosphorus oxychloride or phosphorus pentachloride such as the Bischler-Napieralski reaction[10]) are conveniently conducted in a microwave oven in N,N-dimethylformamide (or in formamide if reaction temperature of 180-190°C is desired) as the reaction medium. We have found it unnecessary to employ a large volume of the reaction medium while conducting reactions under microwave irradiation: a slurry at room temperature in many cases provided a clear solution during the rapid rise in temperature under microwave heating.

Kitchen microwave ovens produce 2450 MHz radiation at a rate that can be controlled to a moderate degree by an on-off cycle. For reactions on 5-10 g scale a "heat sink" is usually unnecessary since the on-off cycle provides adequate control. For finer control of the microwave energy input into small scale reaction mixtures, we find it convenient to place near the reaction vessel a "heat sink" - usually a beaker of water or dimethylformamide - which absorbs a suitable proportion of the microwave energy circulating in the cavity of the oven.

The ß-lactam forming reaction can be conducted under the traditional reaction conditions by adding triethylamine to the ethylene dichloride solution of (3) followed by an appropriate acid chloride (for example, benzyloxyacetyl chloride) and storing the reaction mixture at room temperature or lower for a few hours.[6] Alternatively, MORE chemistry conditions were followed by placing the reaction mixture in a large beaker or an Erlenmeyer flask with a loose cover for a top and a beaker of water by its side. Irradiation for 3 min under low energy setting heated the reaction mixture to near its boiling point but without much vaporization. Under these reaction conditions there was no need for a reflux condenser or a stirrer. After the usual work up[6] a *cis* ß-lactam[11] could be isolated in about 70% yield (see Table 1).

To obtain 3-hydroxy-2-azetidinones, the 3-benzyloxy-N-aryl-2-azetidinones were submitted to hydrogenolysis. Previously it has been shown that catalytic hydrogenation requiring special equipment can be replaced by transfer hydrogenation involving treatment with formic acid or a formate in presence of 10% Pd/C catalyst.[12,2] For such a reaction with ß-lactams, ethylene glycol is a convenient microwave energy transfer agent. On a small scale (about 1-5 g of ß-lactams), hydrogenolysis is usually complete in less than two minutes (Table 1). N-debenzylation of 1-benzyl-2-azetidinones does not occur under these conditions, but, 4-aryl-2-azetidinones undergo ring scission to provide acyclic amides.[2]

Typical experimental procedures are described below.

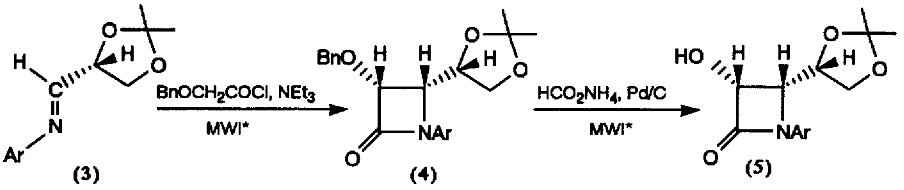
(a) *Schiff base formation:* Sodium periodate (20.31 g, 0.095 mol) was dissolved in 150 mL of water and cooled. 1,2:5,6-Di-O-isopropylidene-D-mannitol (1) (25 g, 0.095 mol) was added over a 10 min period with stirring. After an additional 30 min of stirring the reaction mixture was filtered to provide an aq. sol. of D-glyceraldehyde acetonide (2). To the cooled filtrate at 0-5°C was added a solution of an aromatic amine (0 19 mol) in 1,2-dichloroethane (150 mL). The mixture was stirred at room temperature for 2 h after which the organic layer was separated. The aq. layer was saturated with NaCl and extracted with dichloroethane (2x50 mL). The combined organic layer containing the Schiff base (3) was dried ($MgSO_4$).

(b) *β-Lactam formation under microwave irradiation:* To the above solution of the imine (37 mL) in a 500-mL Erlenmeyer flask was added sequentially 75 mmol of triethylamine and 47.5 mmol of benzyloxyacetyl chloride. The flask was capped with a glass funnel and placed in a microwave oven (G.E. model, 1,450 Watts). A 500 mL beaker containing 150 mL of water was placed in the oven next to the reaction flask to serve as a "heat sink." The mixture was irradiated for 3 min. After the usual work up, (4) was isolated.

(c) *Hydrogenation in a microwave oven:* To 10 mL of ethylene glycol were added ß-lactam 4 (2.72 mmol), ammonium formate (10.84 mmol) and 10% Pd/C (1g). This reaction mixture was irradiated in a microwave oven for 2 min at low power setting and then worked up after removing the catalyst by filtration.[13] The filtrate was diluted with 30 mL of water and then extracted with ethyl acetate (3x15 mL). Evaporation of the solvent from the organic layer gave (5) in about 90% yield.[14]

TABLE 1

Organic Reactions Under Microwave Irradiation



Entry	Ar	(4) mp, °C [yield, %]	(5) mp,°C [yield, %]
(a)	$C_6H_4OMe(p)$	120 [70]	200 [90]
(b)	$CH_2C_6H_5$	63 [75]	159 [90]
(c)	$C_6H_4Me(p)$	110 [70]	196 [88]
(d)	C_6H_5	118 [75]	212 [90]

*** Microwave irradiation for 2-5 min. at low power setting for about 10g of reaction mixture.**

MORE chemistry can be conducted on several hundred gram scale in about 10 min of irradiation in an unmodified kitchen microwave oven rated at about 1000 watts. The "one pot" preparation of an optically active Schiff base combined with the use of microwave irradiation for rapid cycloaddition and hydrgenolysis reactions reduces substantially the time required to obtain enantiopure ß-lactams. We have prepared 25 g of the optically active ß-lactam (4b) starting with mannitol diacetonide in just one day. This type of methodology should be particularly valuable for medium scale (100 g to 500 g) operations because of the simplicity of equipment and the need for small amounts of solvent.

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9. (a) We found the following solvents to be convenient microwave energy transfer agents (solvent, b.p.,°C): 1,2-dicholoroethane, 83°C; dioxane, 101°C; Chlorobenzene, 132°C; N,N-Dimethylformide, 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.
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11. All new compounds were characterized by satisfactory analytical and spectral data.
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13. The Pd/C catalyst, if separated by decantation, can be recycled a few times without appreciable loss of activity.
14. CAUTION.The Pd/C catalyst is a fine powder that is flammable. The hydrogenolysis step has the potential to generate free hydrogen and produce a hazard if the catalyst be added rapidly to the reaction mixture. It is advisable to use only small ammounts of catalyst (100-200 mg of 10% of Pd/C catalyst) and allow a longer reaction period (5-10 min instead of 2 min) for completion of hydrogenolysis.The catalyst should be placed first in the reaction vessel as a slurry with the glycol; the β-lactam and the ammonium formate should be added last. It is standard practice in our laboratories to place microwave ovens inside hoods. Many commercial microwave ovens are equipped with a timer such that heating can be started after the operator has moved away from the hood containing the microwave oven.
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