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MICROWAVE-INDUCED STEREOSELECTIVE SYNTHESIS OF β-LACTAMS CONTAINING AROMATIC CARBOXYLIC ACIDS

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Abstract:
Microwave-induced cycloaddition of *N*-aromatic carboxy silylated aromatic imines produces *N*-aromatic carboxy silylated β-lactams. This reaction produces a mixture of *cis* and *trans N*-aromatic carboxy silylated β-lactams depending upon the nature of the acid chlorides. The silyl group is removed by a reaction in the presence of methanol to afford unique acids.

Key words:β-Lactams, Silyl Protection, Microwave, Stereoselectivity

Introduction:

Stereocontrolled synthesis of β-lactams is a major research goal. In general, cycloaddition of imines with acid chloride in the presence of a tertiary base produces β-lactams[1]. The stereochemistry of the β-lactams may vary from *cis* to *trans* or a mixture of both[2]. Direct synthesis of β-lactams with a free carboxy group at any part is difficult because imines are not possible to prepare from carbonyl compounds and primary amino acids. In this paper, microwave-induced facile synthesis of both *cis* and *trans* β-lactams is described with protected *N*-aromatic carboxy silyl β-lactams[3]. These are then transformed to their acids following standard method.

Results and Discussions:

Chemistry contributes significantly to the economic development of humans. Despite it faces significant societal and environmental challenges that need reexamination of traditional methods. To replace traditional method partly, microwave-induced chemical reactions are developed.

Higher activation energy organic reactions that are difficult or impossible to conduct with conventional heating (oil bath, steam bath, and mantle) are conducted successfully with microwave due to the facile energy transfer method. Heat goes from external source externally and passes through the reaction container and solvent when thermally-assisted reactions are performed. Due to the inefficient heat transfer process, many reactions prove inefficient. In

contrast, microwave-assisted reactions have a few advantages. Microwave heating consists of coupling, irradiation, and molecular heating. Microwave coupling indicates the propagation of microwave energy to a substance and this it gets instantaneous heating. Microwave heating is an energy propagation method to the reactants and solvents. This method increases the kinetic movement of the molecules. This is measured by quick energy transfer. Microwave irradiation is a non-ionizing radiation that exchanges energy of the system doing interaction with polar substrates. Moreover, the quick energy exchange from microwave to the reactants enhance the reaction rate.

4-Amino benzoic acid **1** was attempted to react with benzaldehyde **2a** first by refluxing in benzene solution. However no desired imine was formed. The carboxy group in **1** was protected with trimethyl silyl chloride in the presence of triethyl amine to afford **2**. The reaction of **2** with various aromatic aldehydes **3a-d** underwent smoothly at room temperature in the presence of molecular sieves to produce imines **4a-d**. CEM automated microwave-induced reaction of the imines **4a-d** with acetoxy acetyl chloride was performed using *N*-methylmorpholine as the tertiary base and dichloroethane as the solvent at 40^0C. Acetoxy acetylchloride produced higher percentage of the *trans* β-lactams **6a-d** than *cis* isomer **7a-d** (4:1). Interestingly, the same reaction with cooled reagents and at ice-cold conditions afforded the *cis* isomer **7a**. The silyl protecting group in **6a** and **7a** was removed by aqueous methanol/TBAF in THF to afford the *trans* and *cis*-*N*-arylcarboxy β-lactams **8** and **9** in excellent yield (Scheme 1 and Table 1).

Scheme 1:

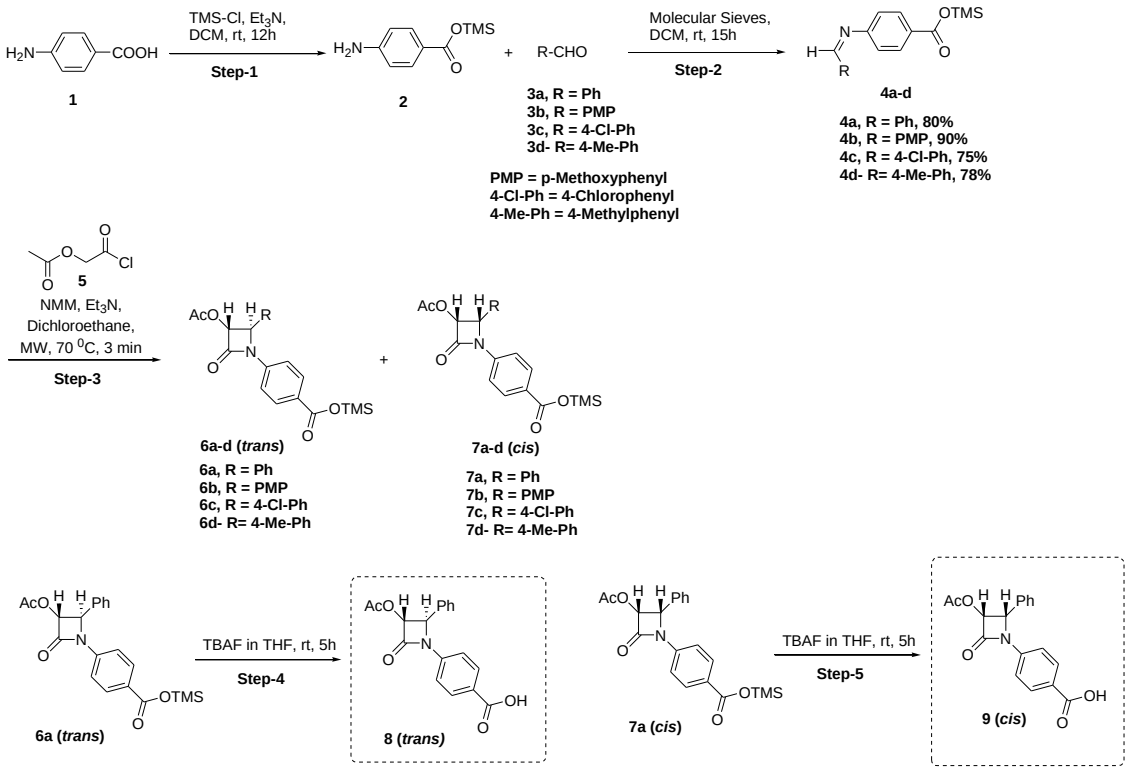

Table 1. Synthesis of β-lactams *trans* (**6a-d)** and *cis* (7**a-d)**

β-lactams **6** and **7**	**Aldehyde**[a]	**Acid Chloride**	Ratio of **6** and **7**[b]	Yield (%)[c]	Mp of **6** (˚C)[d]	Mp of **7** (˚C)[d]
a	-Ph	-OMe	78:22	90	231-232	82-83
b	-PMP	-OMe	80:20	87	111-112	72-73
c	-4-Cl-Ph	-OMe	83:17	86	247-248	191-192
d	-4-Me-Ph	-OMe	81:19	93	158-159	209-210

[a] PMP = *p*-Methoxyphenyl; 4-Cl-Ph = 4-Chlorophenyl; 4-Me-Ph = 4-Methylphenyl
[b] The ratio of the diastereomers **6** and **7** was determined by ^{1}H NMR.
[c] Isolated yields of the diastereomeric mixture of **6** and **7**.
[d] Pure diastereomers were obtained by flash column chromatography.

A typical experimental procedure is as follows. To a mixture of imine **4a** (1 mmol) in dichloroethane (2 mL) was added N-methylmorpholine (3 mmol) and acetoxyacetyl chloride **5** (1.3 mmol) in a small microwave reaction test tube. It was then irradiated at 70^{0C} for 3 min. After the reaction, water was added to the reaction mixture (5 mL) and it was then transferred to a separatory funnel. Lower layer was collected and it was then washed with dilute hydrochloric acid (10%, 5 mL), saturated aqueous sodium carbonate solution (5 mL), brine (5 mL) and then the organic part was dried with anhydrous sodium sulfate (3 gm). The crude product was filtered and solvent was evaporated in a rotavapor under reduced pressure. The ^{1}H NMR data of the crude materials indicates two products **6a** and **7a** were formed in a ratio of 78: 22. These compounds **6a** and **7a** can be crystallized from ethylacetate-hexane and Flash column chromatography.

Conclusions:

Despite the progress in β-lactams research, direct synthesis of carboxy-substituted molecules was not possible. These compounds are extremely versatile because of the presence of aromatic acid group in the β-lactam ring system. Due to the presence of the aromatic acid group, a number of chemical modifications can be performed and therefore, novel β-lactams can be created.

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References:

1. (a) Banik, B. K., Ed. "*Heterocyclic Scaffolds I. Top. Heterocycl. Chem., Springer*, **2010**, 22, 1-379; (b) Banik, B. K., Ed. "β-Lactams: Synthesis and Biological Evaluation", *Top. Heterocycl. Chem., Springer*, **2012,** 30, 1-226; (c) Banik, I.; Banik, B. K., "Microwave-Induced Chemical Manipulation of β-Lactam", *Springer*; **2012,** 88, 781-1007; (d) Banik, B. K., "Beta Lactams: Novel Synthetic Pathways and Applications", *Ed. Springer*, **2017,** 1-419; (e) Parvatkar, P. T.; Parameswaran, P. S.; Banik, B. K., "Solid Phase Synthesis of β-Lactams:

Results and Scope in Banik, B. K., *Beta Lactams: Novel Synthetic Pathways and Applications, Ed. Spinger*, **2017,** 253-284; (f) Basu, S.; Banik, B. K., "Beta Lactams as Clinically Active Molecules" in Banik, B. K., *Beta Lactams: Novel Synthetic Pathways and Applications, Ed. Springer*, **2017,** 285-310; (g) Banik, B. K., "Synthesis and Biological Studies of Novel β-Lactams", CRC Book, **2013**, 31-72.

2. (a) Banik, I.; Becker, F. F.; Banik, B. K., "Stereoselective Synthesis of β-Lactams with Polyaromaic Imines: Entry to New and Novel Anticancer Agents", *J. Med. Chem*., **2003**, 46, 12-15; (b) Banik, B. K.; Becker, F. F.; Banik, I., "Synthesis of Anticancer β-Lactams: Mechanism of Action", *Bioorg. Med. Chem*., **2004**, 12, 2523-2528; (c) Banik, B. K.; Banik, I.; Becker, F. F., "Stereocontrolled Synthesis of Anticancer β-Lactams via the Staudinger Reaction", *Bioorg. Med. Chem*., **2005**, 13, 3611-3622; (d) Banik, B. K.; Becker, F. F., "Selective Anticancer Activity of β-Lactams Derived from Polyaromatic Compound", *Mol. Med. Rep*., **2010**, 3, 315-316; (e) Banik, B. K.; Banik, I.; Becker, F. F., "Asymmetric Synthesis of Anticancer β-Lactams *via* Staudinger Reaction: Utilization of Chiral Ketene from Carbohydrate", *Eur. J. Med. Chem*., **2010**, 45, 846-848; (f) Banik, B. K.; Samajdar, S.; Becker, F. F., "Asymmetric Synthesis of Anticancer β-Lactams Via Staudinger Reaction", *Molecular Medicine Reports*, **2010**, 3, 319-321.

3. (a) Bose**,** A. K.; Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S., "Polyhydroxy Amino Acid derivatives via β-Lactams Using Enantiospecific Approaches and Microwave Techniques", *Tetrahedron*, **2000**, 56, 5603-5619; (b) Bandyopadhyay, D.; Cruz, J.; Banik, B. K., "Microwave-Induced Synthesis of 3-Pyrrole Substituted β-Lactams Via Bismuth Nitrate-Catalyzed Reactions", *Tetrahedron Symposium-in-Print*, **2012**, 68, 10686-10695.

4. (a) Montel, S. Bouyssi, D.; Balme,G. "An Efficient and General Microwave-Assisted Copper-Catalyzed Conia-Ene Reaction of Terminal and Internal Alkynes Tethered to a Wide Variety of Carbonucleophiles", *Adv Synth Catal*, 2010, 352, 2315- 2320; (b) Victoria, M. G.; Aranda, A. I.; Moreno, A.; Cossio, F. P.; Cozar, A. D.; Diaz-Ortiz, A.; Hoz, A.D.L.; Prieto, P. "Microwave-assisted Reactions of Nitroheterocycles with Dienes. Diels–Alder and Tandem Hetero Diels–Alder/[3, 3] Sigmatropic Shift, *Tetrahedron*, **2009,** 65, 5328-5336; (c) Declerck, V.; Martinez, J.; Lamaty, F. "Microwave-Assisted Copper-Catalyzed Heck Reaction in PEG Solvent", *Synlett* **2006**, 18 3029-3032.

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