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Microwave-Induced Bismuth Nitrate-Catalyzed Michael Reaction of 3-Amino β-Lactams with Enones

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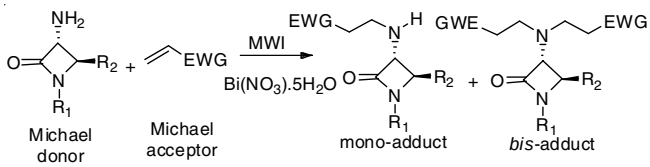
Microwave-induced bismuth nitrate-catalyzed reaction of 3-amino β-lactams with unsaturated ketones is performed in order to obtain substituted amino β-lactams. Amino β-lactams were obtained through the strategy of [2+2] ketene-imine cycloaddition followed by deprotection of phthalimido β-lactams with ethylene diamine.

Keywords: Microwave, Amino β-lactam, Bismuth nitrate, Catalysis, Michael reaction.

INTRODUCTION

Aza-Michael addition reaction is an important tool for the formation of C-N bond between nitrogen atom of donor and carbon atom of the acceptor molecules. This is a conjugate addition of nitrogen nucleophile to an α,β-unsaturated carbonyl compound. This is an important reaction to accesses diverse medicinally privileged molecules like antibiotics, anticancer and biomimetic molecules of oligomer of β-amino acids and peptides [1,2]. α-Amino β-lactams systems with *cis*-configuration are present in numerous monocyclic and bicyclic antibiotics [3]. Similar structures with antibacterial *trans*-configuration are also known [4]. *trans* α-Amino β-lactam is active against cancer cell lines *in vitro* [5,6], whereas *cis* β-lactams with anticancer activities are also reported in the literature [7]. β-Lactams are served as the key molecules for the synthesis of numerous other compounds including natural products, alkaloids, amino sugars and amino acids [8,9]. Reactions at 3-amino center of β-lactam ring is necessary to functionalize them. In this paper, a simple microwave-induced bismuth nitrate-catalyzed Michael reaction of 3-amino β-lactams with α,β-unsaturated ketone is described.

3-Amino β-lactams as donor react with electron deficient carbonyl compounds known as Michael acceptors lead to the formation of corresponding mono aza and *bis*-aza-adducts under microwave irradiation (**Scheme-I**). Despite progress in β-lactam research [10], no paper is published which describe functionalization of 3-amino group present in β-lactam ring through a catalytic Michael reaction [11,12]. In continuation of our efforts to explore the catalytic properties of bismuth nitrate in the synthesis of numerous organic molecules of biological interests, we report here a simple and environmentally benign procedure to obtain mono and *bis*-aza-substituted β-lactams under microwave condition in excellent yield. In previous study, aza Michael reaction of diverse aliphatic and aromatic amines to unsaturated enones *via* bismuth nitrate-catalyzed reactions is reported [13].



Scheme-I: Bismuth nitrate catalyzed aza-Michael mono and bi-addition under microwave condition

We extended the scope of this reaction using amino β-llactam. Our methodology of bismuth nitrate catalyzed aza-Michael reaction of enone was very simple and highly efficient.

This method had solved the difficulties of using of stoichiometric amount of Lewis acid catalysts. Most of the Lewis acid catalysts are moisture sensitive and corrosive in nature and not benign to environment [14]. The use of strong acids for this reaction also increased the chances of polymerization of acid-sensitive vinyl ketone, nitrile and ester.

EXPERIMENTAL

General procedure for the synthesis of Michael products: To amino β-lactam (1 mmol) was added ketone (2 mmol) in THF (0.2 mL) and bismuth nitrate pentahydrate (2.10 g, 10 mol%). The mixture was irradiated in an automated microwave oven at 50 ºC for a short period of time (Table-1). After the reaction, dichloromethane was added to the reaction mixture, it was washed with Na_2CO_3 solution (10 %, 2 mL), brine (2 mL), dried with sodium sulfate and the solvent was evaporated. The crude product was purified over silica gel using ethyl acetate and *n*-hexane (30: 70) as the solvents.

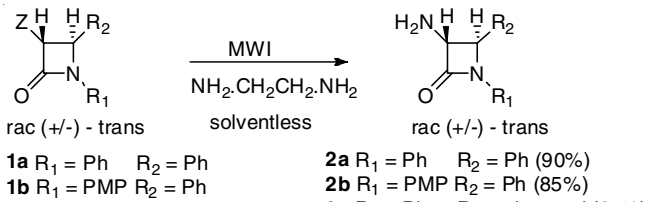
TABLE-1
AZA-MICHAEL REACTION OF *rac*-α-3-AMINO β-LACTAMS (**2a-d**) WITH METHYL VINYL KETONE (**3**)

Entry	Amine (**2**)		Yield[a] **4:5** (%)	T (°C)	Time[b] (min)
	R	R_1			
1	Ph	Ph (**2a**)	50:50	50	2
2	PMP	Ph (**2b**)	60:40	50	4
3	Ph	Cinnamyl (**2c**)	80:20	50	6
4	PMP	Cinnamyl (**2d**)	90:10	50	6

[a]Yield of pure isolated mono-and *bis*-adducts **4** and **5**; [b]Heating time
PMP = *para*-methoxy phenyl

RESULTS AND DISCUSSION

The starting compound for Michael reaction was *rac*-3-amino β-lactams (**1a-d**). Synthesis of α-amino β-lactams (**2a-d**) was achieved by a de-protection of an α-phthalimido group in β-lactam (**1a-d**) by ethylene diamine and other reagents in excellent yield under microwave irradiation [15-17] (**Scheme-II**).



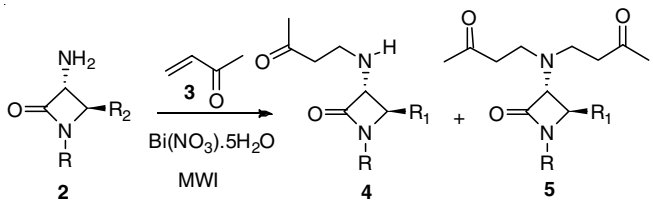
Scheme-II: Mild and efficient ethylenediiamine mediated deprotection of *N*-phthalimido group. A facile synthesis of (±) *rac-trans*-3-amino β-lactam

This de-protection reaction was performed in solvent or without solvents. The reaction protocols were involved in treatment of *N*-phthalimido-β-lactam (**1a-d**) with 1.0 M solution of ethylene diamine in THF under the exposure of automated microwave reactor for 2-5 min at elevated temperature. The *rac*-3-amino β-lactams (**2a-d**) was obtained in good to excellent yield.

α-Phthalimido β-lactams (**1a-d**) were obtained by Staudinger [2+2] ketene-imine cycloaddition reaction. The ketene derived from either *N*-phthalimido acetyl chloride or *N*-phthalimido acetic acid/triethylamine or Mukiyama reagent as an acid activator. The stereochemical outcome of β-lactam formation was greatly depending on the mode of addition of base to acid chloride or acid chloride to base. In addition, de-protection of α-phthalimido-β-lactams to α-amino β-lactams was also investigated [18].

Numerous substituted β-lactams (α-acetoxy, α-hydroxy, α-amido, α-unsubstituted, α-tosylate, α-sulfonamide, α-alkoxy, α-ether, α-benzyl ether, α-halo, α-carboxylate, α-amino, α-tosylate, α-mesylate) were prepared and tested against a variety of cancer cell lines. A few of them were also evaluated *in vitro* at the US National Cancer Institute against a panel of 60 cancer cell lines in 2001-2002 Diverse pyrrole-substituted β-lactams were prepared through 3-amino β-lactams [19].

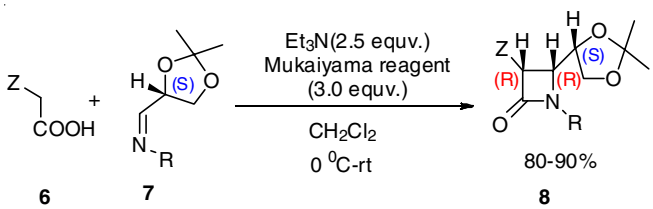
Aza-Michael addition of 3-amino-β-lactams with enones was performed. In this context, racemic *trans*-3-amino-α-lactam (**2**) was reacted with methyl vinyl ketone (**3**) (**Scheme-III**) in the presence of catalytic amounts of $Bi(NO_3)_3{\cdot}5H_2O$ in THF as the solvent under microwave condition. The reaction mixture was allowed to irradiate for 2-6 min at ambient temperature in an automated microwave reactor. The reactions proceed smoothly and the products (**4a-d**) were obtained along with substantial amount of *bis*-aza-adduct (**5a-d**) in good yield (Table-1).



Scheme-III: Aza-Michael rection under microwave condition

Regardless of reaction time, catalyst loading and molar ratio of acceptor, mono-aza adduct **4** was not formed selectively. The crude products formed were purified by column chromatography (Table-1).

The method was then extended to optically active 3-amino β-lactams **8**. Enantiopure α-3-amino β-lactams **8** were obtained by reported method [20]. The chiral induction was achieved by the imine component **7** by a reaction with *N*-phthalimido acetic acid **6** in presence of Mukiyama reagent as an acid activator under basic conditions (**Scheme-IV**).



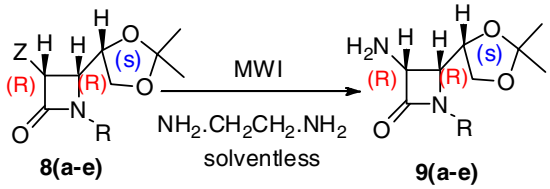
Scheme-IV: Asymetric staudinger [2+2] ketene-imine cyloaddition reaction

TABLE-2
AZA-MICHAEL ADDITION REACTION OF ENANTIOPURE 3-AMINO-β-LACTAM (**9a-e**) WITH METHYL VINYL KETONE (**3**)

Entry	3-Amino (*cis*)-β-lactam	Temp. (°C)	Catalyst (mmol)	Heating time (min)	Solvent	Yield[a] **8:9** (%)
1	**9a** R = Ph	25	1.0	3	Tetrahydrofuran	80:20
2	**9b** R = PMP	25	1.0	4	Tetrahydrofuran	90:10
3	**9c** R = 4-Me.C_6H_4	25	1.5	5	Dichloroethane	85:15
4	**9d** R = 4-Cl.C_6H_4	35	1.5	6	Dichloroethane	80:20
5	**9e** R = 4-F.C_6H_4	35	1.5	7	Dichloroethane	80:20

[a]Isolated yield of 10 and 11.

The excellent stereochemical selectivity was observed and the reaction yield compound **8** (3*R*,4*R*) as the major products in all instances. The *N*-phthalimido group in compound **8** was then de-protected by using reported protocol [20] to get free chiral 3-amino β-lactams (**9a-e**) in excellent yields (**Scheme-V**).



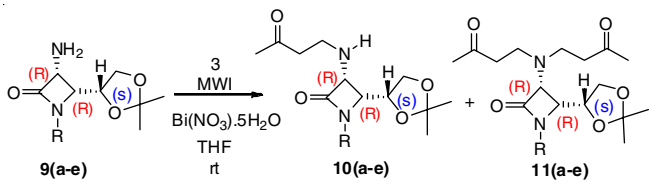
Z = *N*-phthalimido(-NtPh)

N-phthalimido β-lactam(**8**) (R)	T (^{0}C)	Time (min)	Yield[a] (%)
8a R = Ph	25	5	80
8b R = 4-OMe.C_6H_4	25	6	90
8c R = 4-Me.C_6H_4	25	6	90
8d R = 4-Cl.C_6H_4	40	8	75
8e R = 4-F.C_6H_4	40	8	75

a: isolated yield of **9(a-e)**

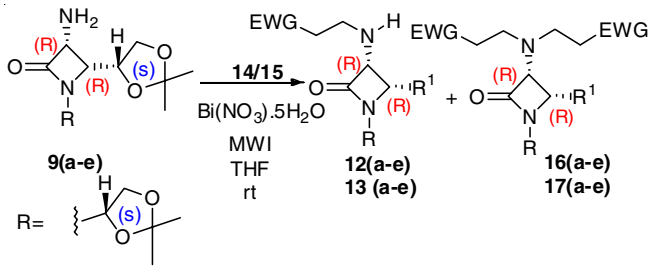
Scheme-V: Deprotection of *N*-phthalimido group under microwave irradiation

3-Amino-β-lactams (**9a-e**) were subjected to react with methyl vinyl ketone (**3**) under microwave condition with catalytic amount of bismuth nitrate in moist THF for 3-5 min. All the reaction are smooth with excellent yields (**Scheme-VI**, Table-2). Aza-Michael addition reaction with chiral β-lactam amines (**9a-e**) produced better selective to mono aza-adduct **10a-e** over the bis-adduct **11a-e**. The better selectivity was obtained with β-lactam that has *p*-methoxyphenyl group at N-1 position (entry 2, Table-2). It seemed electron withdrawing groups at nitrogen lowers the selectivity of product formation (entry 4 and 5, Table-2).



Scheme-VI: Bismuth nitrate catalysed Aza-Michael reaction of methy vinyl ketone with β-lactam amine under microwave condition

After the realization of successful aza-Michael reaction of methyl vinyl ketone with various racemic and enantiopure β-lactams, next focus was to explore the scope of present methodology with other Michael accepter (**Scheme-VII**, Table-3). The electro-withdrawing group in aromatic ring took longer time to complete the reaction. Tetrahydrofuran and dichloroethane were the good choice of solvent system for this reaction. The catalyst used 1.0-1.5 mmol and the reaction mixture irradiated for 2-10 min in automated microwave reactor.



Scheme-VII: Aza-Michael reaction of nitrile and ester under microwave condition

TABLE-3
DIFFERENT MICHAEL ACCEPTER WITH β-LACTAM AMINE

Entry	Acceptor (**14/15**)	β-Lactam amine	Yield[a] (%) (**12/13:16/17**)
1	CN (**14**)	**9a**	**12a** + **16a** (85:15)
2	**14**	**9b**	**12b** + **16b** (90:10)
3	**14**	**9c**	**12c** + **16c** (85:15)
4	**14**	**9d**	**12d** + **16d** (75:25)
5	**14**	**9e**	**12e** + **16e** (80:20)
6	CO_2Me (**15**)	**9a**	**13a** + **17a** (85:15)
7	**15**	**9b**	**13b** + **17b** (90:10)
8	**15**	**9c**	**13c** + **17c** (85:15)
9	**15**	**9d**	**13d** + **17d** (75:25)
10	**15**	**9e**	**13e** + **17e** (80:20)

[a]Isolaled yield

Other bismuth salts were not effective in pursuing Michael reaction of 3-amino β-lactams. For example, bismuth chloride, bismuth iodide and bismuth chloride was partially successful (about 20 % yield of the products). Because of the sensitivity of β-lactam ring, the use of stronger acids in catalytic amounts or higher amounts caused considerable difficulties in performing Michael reaction as described herein. Indeed, HCl, $SnCl_4$, $BF_3{\cdot}Et_2O$, $AlCl_3$, Et_2AlCl_2 were not as effective as bismuth nitrate pentahydrate. It is important to mention that the reactions tolerated moisture and did not require inert atmosphere. The coordination of vacant *d*-orbital of bismuth with lone pair of oxygen of ketone and ester facilitated a nucleophilic attack by amino group of β-lactam ring.

The reaction required approximately 10 mol % of bismuth nitrate. It was not necessary to use much solvent in this reaction. For 1 mmol of β-lactam, 0.2 mL of solvent was proved to be fine. Present protocol is very efficient high yielding reaction with diverse Michael acceptors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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