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A convenient $CeCl_3 \cdot 7H_2O$/NaI-promoted synthesis of structurally novel and strained tricyclic β-lactams from hydrazines

Lal Dhar S. Yadav *, Vijai K. Rai

Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211 002, India

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ABSTRACT

A convenient synthetic protocol for structurally novel and strained highly derivatized tricyclic β-lactams has been developed. The synthesis involves $CeCl_3 \cdot 7H_2O$/NaI catalyzed addition–condensation of mercaptoacetic acid and *N*-aroyl-*N*′-arylidenehydrazines followed by intramolecular cyclodehydration to afford bicyclic 5*H*-thiazolo[4,3-*b*][1,3,4]-oxadiazoles, which on treatment with acid chlorides in the presence of triethylamine furnish highly derivatized tricyclic 3*H*-azetidino[2,1-*b*]-thiazolo[3,4-*d*][1,3,4]-oxadiazol-6-ones in 80–93% yields. The process presents an excellent illustration of Ce(III)-catalyzed C–C, C–N and C–S bond formation in a one-pot procedure.

β-Lactam antibiotics have occupied a central role in the fight against bacterial infections over the past several decades.[1] Bacterial resistance to β-lactam antibiotics by producing β-lactamase is a serious concern, which has motivated a growing interest in the synthesis of new types of β-lactams. An attractive strategy to overcome this problem consists of the co-administration of an antibiotic and suicide inhibitor[2] of the enzyme, which restores the activity of sensitive antibiotics by selectively inactivating β-lactamase. The easy opening of the β-lactam ring is a prerequisite for the design of new suicide inhibitors of β-lactamase.

Recently, tricyclic β-lactam antibiotics, generally referred to as trinems, have been the subject of considerable study owing to their broad spectrum of antibacterial activity, resistance to β-lactamase and stability to renal dehydropeptidases.[3] Amongst the most remarkable of these are GV104326 and GV143253A (Fig. 1). The ever-growing new applications of 2-azetidinones in fields such as enzyme inhibition[4] to the use of these products as starting materials to develop new synthetic methodologies[5] has triggered renewed interest in the construction of new polycyclic β-lactam systems in an attempt to move away from classical β-lactam antibiotic structures.[6] Thus, tricyclic β-lactams have become interesting targets for synthesis in modern synthetic organic chemistry.

Trivalent rare earth compounds[7] such as Ce(III) salts exhibit characteristic Lewis acid properties. After the pioneering work by

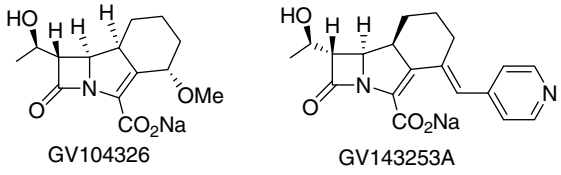

Figure 1.

Luche[8] and Imamoto,[9] numerous reactions and methodologies employing Ce(III) derivatives as key components have been developed.[10] Amongst these, commercially available $CeCl_3 \cdot 7H_2O$ has attracted much attention as a Lewis acid in organic synthesis due to its special attributes, which include water tolerance, non-toxicity and easy handling.[11] It has been reported that the Lewis acid character of $CeCl_3 \cdot 7H_2O$ increases very strongly in conjunction with an iodine source such as NaI.[12] The $CeCl_3 \cdot 7H_2O$/NaI system is active towards the cleavage of carbon–oxygen and silicon–oxygen bonds under neutral conditions,[13] and new reactions for nitrogen–carbon[14] and oxygen–carbon[15] bond formation promoted by this system have also been developed.

Along with various reports[16] on the synthesis of trinems, we have also described the synthesis of β-lactam antibiotics.[17] Most of these trinems have been prepared by annulation of 2-azetidinone with carbocyclic rings, whereas in the present study we have fused the 2-azetidinone motif with heterocyclic rings of biological potential. The continued interest of synthetic chemists in tricyclic

* Corresponding author. Tel.: +91 5322500652; fax: +91 5322460533.
E-mail address: ldsyadav@hotmail.com (L. D. S. Yadav).

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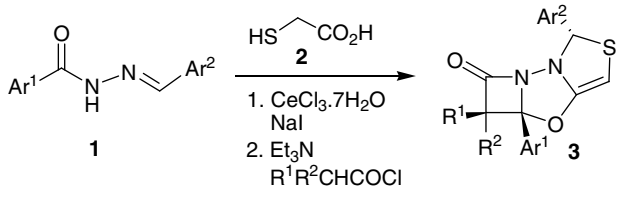
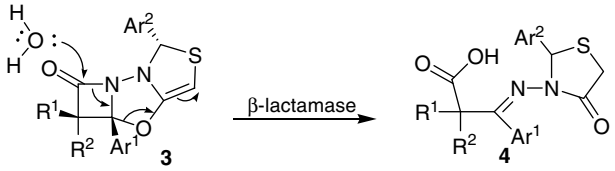
β-lactams and our ongoing efforts to develop new, one-pot heterocyclization processes,[18] especially for small rings,[17,19] prompted us to design and realize the annulation of 2-azetidinone with a biologically versatile thiazolo-oxadiazole framework, which is hitherto unreported and appears to offer an attractive scaffold for exploiting chemical diversity and generating a drug-like library to screen lead candidates. In the present Letter, we disclose the straightforward synthesis of trinem antibiotics, namely, highly derivatized 3*H*-azetidino[2,1-*b*]-thiazolo[3,4-*d*][1,3,4]-oxadiazol-6-ones **3** starting from *N*-aroyl-*N*′-arylidenehydrazines **1** (Scheme 1). A probable mechanism for the facile ring opening of strained tricyclic β-lactams **3**, which is a prerequisite for the design of new suicide inhibitors of β-lactamase, is shown in Scheme 2.

In our initial experimentation for the synthesis of compounds **6**, we used anhydrous $ZnCl_2$ as catalyst with reagents **1** and **2**; however, compounds **5**, rather than **6**, were isolated in 69–72% yields, which on further treatment with concd H_2SO_4 afforded thiazolo-1,3,4-oxadiazoles **6** in 57–64% yields (Scheme 3). In order to improve the yields and synthesize thiazolo-1,3,4-oxadiazoles **6** expeditiously from compounds **1** in a one-pot procedure, we examined various Lewis acid catalysts (Table 1). Amongst these, the best result was obtained with $CeCl_3{\cdot}7H_2O$/NaI (1:1) (Table 1, entry 4). This is in conformity with the earlier observation that the catalytic activity of $CeCl_3{\cdot}7H_2O$ increases dramatically in the presence of an iodide source, such as NaI,[12] owing to the formation of a complex which exhibits stronger Lewis acid character than $CeCl_3{\cdot}7H_2O$. We also tested the effect of solvents on the formation of **6a** and found that amongst MeOH, EtOH, 1,4-dioxane and THF, EtOH was the best solvent in terms of the yield.

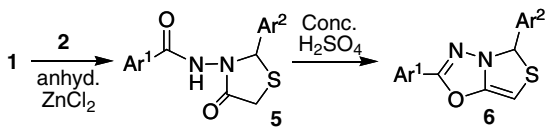


3	R^1	R^2	Ar^1	Ar^2	3	R^1	R^2	Ar^1	Ar^2
a	H	H	Ph	Ph	**g**	H	Cl	Ph	4-ClC_6H_4
b	H	H	4-$MeOC_6H_4$	Ph	**h**	H	Cl	4-$MeOC_6H_4$	4-ClC_6H_4
c	H	H	4-ClC_6H_4	Ph	**i**	H	Cl	4-ClC_6H_4	4-ClC_6H_4
d	H	Cl	Ph	Ph	**j**	Me	Cl	Ph	4-ClC_6H_4
e	H	Cl	4-$MeOC_6H_4$	Ph	**k**	Me	Cl	4-$MeOC_6H_4$	4-ClC_6H_4
f	H	Cl	4-ClC_6H_4	Ph	**l**	Me	Cl	4-ClC_6H_4	4-ClC_6H_4

Scheme 1. Formation of tricyclic β-lactams **3**.



Scheme 2. Probable mechanism for the ring opening of strained tricyclic β-lactams **3**.



5,6	Ar^1	Ar^2	5,6	Ar^1	Ar^2
a	Ph	Ph	**d**	Ph	4-ClC_6H_4
b	4-$MeOC_6H_4$	Ph	**e**	4-$MeOC_6H_4$	4-ClC_6H_4
c	4-ClC_6H_4	Ph	**f**	4-ClC_6H_4	4-ClC_6H_4

Scheme 3. Synthesis of compounds **6** from **1** using anhyd $ZnCl_2$.

Table 1
Optimization of the Lewis acid catalyst for the synthesis of **6a**

Entry	Catalyst[a]	Time[b] (h)	Yield[c,d] (%)
1	$Ce_2(SO_4)_3{\cdot}8H_2O$	10	29
2	$Ce_2(SO_4)_3{\cdot}8H_2O$/NaI (1:1)	9	71
3	$CeCl_3{\cdot}7H_2O$	8	51
4	$CeCl_3{\cdot}7H_2O$/NaI (1:1)	6	83
5	$Cu(OTf)_2$	8	17
6	$Zn(ClO_4)_2$	8	13

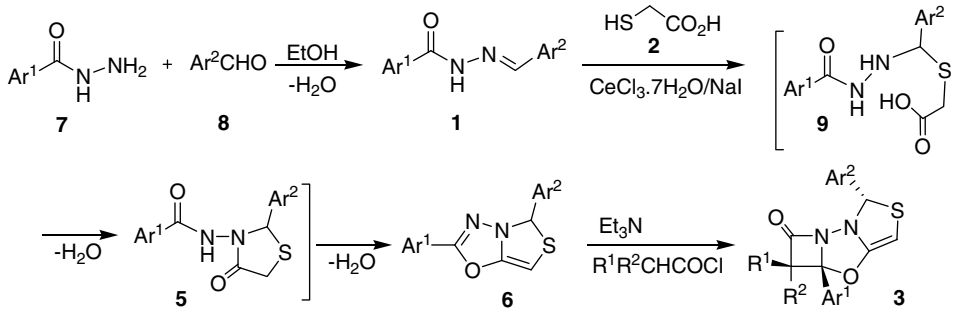
[a] Catalyst loading was 25 mol %.
[b] Time for completion of the reaction at 60 °C as indicated by TLC.
[c] Yield of isolated and purified product **6a**.
[d] For the experimental procedure, see Ref. 19.

The present optimized synthesis is accomplished by stirring a mixture of *N*-aroyl-*N*′-arylidenehydrazine **1**, mercaptoacetic acid **2** and $CeCl_3{\cdot}7H_2O$/NaI in ethanol with a few drops of water at 60 °C for 6–9 h to afford 5*H*-thiazolo[4,3-*b*][1,3,4]-oxadiazoles **6** in 79–85% yields.[19] Compounds **6** on stirring with an acid chloride and triethylamine in dioxane at room temperature for 4–6 h afforded the target β-lactams **3**[20] in 80–93% yields (Table 2). The $CeCl_3{\cdot}7H_2O$/NaI-catalyzed one-pot synthesis of compounds **6** from *N*-aroyl-*N*′-arylidenehydrazines **1** is postulated via intermediate formation of compounds **5** and **9** (Scheme 4). This conclusion is based on the observation that the representative intermediate compound **5a** could be isolated in 42% yield,[21] and that this could be converted into the corresponding thiazolo-1,3,4-oxadiazole **6a** in quantitative yield. The formation of trinems **3** was entirely diastereoselective. The relative stereochemistry of **3** was established by NOE experiments. For example, an 8.5% NOE was observed between 3-H and 7-H; 6.7% between 7-H and the Me of 4-$MeOC_6H_4$ at position 7a in the case of compound **3e**, whereas a 9.2% NOE was observed between 3-H and 7-Me; 7.9% between 7-Me and the Me of 4-$MeOC_6H_4$ at position 7a in the case of compound **3k** (Fig. 2). This indicates that 3-H, 7-H/Me and 4-$MeOC_6H_4$ at position 7a

Table 2
$CeCl_3{\cdot}7H_2O$/NaI-promoted synthesis of compounds **3** and **6**

Product	Time[a] (h)	Yield[b,c] (%)
3a	4	85
3b	4	81
3c	6	80
3d	4	83
3e	5	83
3f	5	91
3g	5	80
3h	6	80
3i	4	88
3j	5	93
3k	5	82
3l	6	88
6a	6	83
6b	7	80
6c	8	85
6d	6	79
6e	9	84
6f	7	82

[a] Time for oil-bath heating at 60 °C.
[b] Yield of isolated and purified products.
[c] All compounds gave C, H and N analyses within ±0.36% and satisfactory spectral (IR, ^1H NMR, ^{13}C NMR and EIMS) data.



Scheme 4. Postulated intermediates leading to the formation of strained tricyclic β-lactams **3**.

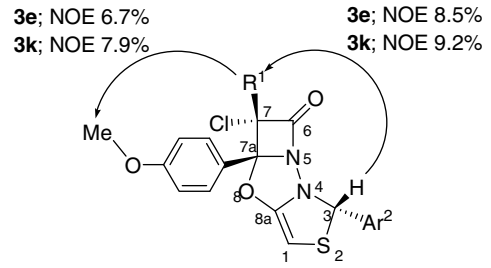


Figure 2. Observed NOE's in compounds **3e** and **3k**.

are located on the same face of the molecule, that is, *cis* to one another, and thus the 4-$MeOC_6H_4$ and Ar^2 groups are *trans* to each other.

In the preliminary in vitro antibacterial assay of compounds **3** and **6** against *Escherichia coli* and *Staphylococcus aureus*, it was found that trinems **3** bearing a β-lactam ring were much more active against both the tested bacteria than their precursors **6**. Of these, **3i** and **3l** exhibited antibacterial activity comparable with amoxicillin at 1000 ppm concentration. A detailed study on the antibacterial potential of trinems **3**, including their co-administration as a suicide inhibitor with an antibiotic, is in progress and will be published elsewhere.

In summary, we have developed a general, Lewis acid-promoted and straightforward synthetic protocol for structurally novel and strained tricyclic β-lactams using readily available substrates. The protocol is conceptually new as it offers an easy access to the trinem class of antibiotics incorporating a 2-azetidinone motif fused with heterocyclic rings of biological potential instead of carbocyclic rings.

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19. *General procedure for the synthesis of 2,5-diaryl-5H-thiazolo-[4,3-b][1,3,4]-oxadiazoles* **6**: A solution of $CeCl_3{\cdot}7H_2O$ (1.25 mmol) and NaI (1.25 mmol) in ethanol (15 mL) and a few drops of water was stirred at 60 °C for 15 min. Then, *N*-aroyl-*N*′-arylidenehydrazine **1** (5 mmol) and mercaptoacetic acid **2** (6 mmol) were added with stirring at 60 °C. The reaction mixture was further stirred at 60 °C for 6–9 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and treated with a saturated solution of sodium bicarbonate to neutralize the unreacted acid. Water (10 mL) was added, the mixture was extracted with dichloromethane (3 × 20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The crude product **6** thus obtained was crystallized from ethanol to afford an analytically pure sample of **6**. Physical data of representative compound **6a**: Yellowish solid, yield 83%, mp 130–131 °C. IR (KBr) ν_{max} 3011, 1763, 1635, 1608, 1587, 1449 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 4.32 (s, 1H, =CH), 5.54 (s, 1H, PhCHS), 7.13–7.85 (m, $10H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 58.5, 73.2, 122.8, 124.2, 125.9, 127.5, 128.8, 129.9, 130.8, 131.5, 152.1, 161.3. EIMS (*m*/*z*): 280 (M^+). Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.21; H, 4.45; N, 9.87.
20. *General procedure for the synthesis of 3H-azetidino[2,1-b]-thiazolo[3,4-d][1,3,4]-oxadiazol-6-ones* **3**: To a well-stirred solution of thiazolo-oxadiazole **6** (5 mmol) and triethylamine (10 mmol) in dioxane (15 mL) was added dropwise a solution of acetyl chloride (5 mmol) in dioxane (15 mL) with stirring at room temperature. After the addition was complete, the solution was further stirred at rt for 4–6 h. The precipitated material ($Et_3N{\cdot}HCl$) was filtered off, the solvent evaporated under reduced pressure and the residue was purified by column chromatography using AcOEt and *n*-hexane as eluent to afford an analytically pure sample of **3**. Physical data of representative compounds: Compound **3a**: Yellowish solid, yield 85%, mp 150–152 °C. IR (KBr) ν_{max} 3011, 1761, 1605, 1583, 1455 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 3.35 (d, 1H, *J* = 15.7 Hz, HaC=O), 3.67 (d, 1H, *J* = 15.7 Hz, HbC=O), 4.31 (s, 1H, =CH), 5.57 (s, 1H, PhCHS), 7.09–7.81 (m, $10H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 48.2, 57.9, 72.5, 102.6, 124.5, 125.8, 126.9, 127.5, 128.3, 129.2, 130.5, 131.4, 152.1, 172.3. EIMS (*m*/*z*): 322 (M^+). Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.27; H, 4.59; N, 8.55. Compound **3f**: Yellowish solid, yield 91%, mp 174–176 °C. IR (KBr) ν_{max} 3008, 1765, 1601, 1585, 1451 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 4.38 (s, 1H, =CH), 4.63 (s, 1H, HC=O), 5.61 (s, 1H, PhCHS), 7.07–7.68 (m, $7H_{arom}$), 7.73–7.89 (m, $2H_{arom}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 58.1, 73.0, 73.5, 103.7, 125.3, 126.1, 126.9, 128.5, 129.8, 130.7, 131.5, 132.9, 152.5, 172.6. EIMS (*m*/*z*): 390, 392 (M, M+2). Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_2S$: C, 55.25; H, 3.09; N, 7.16. Found: C, 55.03; H, 2.97; N, 7.33.
21. *Isolation of the intermediate compound* **5a** *and its conversion into the corresponding product* **6a**: The procedure followed was the same as described above for the synthesis of **6** except that the time of stirring in this case was 3 h instead of 6–9 h. Compound **5a** was recrystallized from ethanol to give an analytically pure sample. To a well-stirred solution of $CeCl_3{\cdot}7H_2O$ and NaI (each 25 mol% with respect to **5a)** in ethanol containing a few drops of water was added **5a** and the stirring continued for 5 h at 60 °C. Then, the reaction mixture was cooled to rt, water (10 mL) was added, the mixture extracted with dichloromethane (3 × 20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The crude product **6a** thus obtained was crystallized from ethanol to afford an analytically pure sample in quantitative yield. Physical data of isolated intermediate compound **5a**: Yellowish solid, yield 42%, mp 188–190 °C. IR (KBr) ν_{max} 3368, 3015, 1743, 1710, 1608, 1588, 1453 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS) δ: 3.05 (d, 1H, *J* = 14.5 Hz, 5-Ha), 3.19 (d, 1H, *J* = 14.5 Hz, 5-Hb), 6.21 (s, 1H, 2-H), 7.19–7.92 (m, $10H_{arom}$), 8.43 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (100 MHz; $CDCl_3$/TMS) δ: 42.8, 55.7, 125.5, 126.8, 127.9, 128.8, 129.7, 130.5, 131.8, 133.0, 172.2, 173.8. EIMS (*m*/*z*): 298 (M^+). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.19; H, 4.68; N, 9.51.