Tetrahedron Letters 54 (2013) 6758–6763

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient iodine catalyzed chemoselective synthesis of aminals—an access to *N,N*-acetals by the addition of lactams to *N*-acyl imines

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ARTICLE INFO

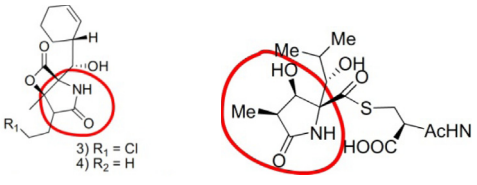
Article history:
Received 16 July 2013
Revised 1 October 2013
Accepted 3 October 2013
Available online 10 October 2013

Keywords:
Iodine
Aminals
N,N-Acetals
N-Acyliminium ion

ABSTRACT

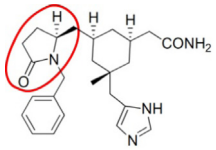
A highly efficient protocol has been developed for the synthesis of aminals from γ-butyrolactam and benzaldehyde using iodine as Lewis acid catalyst. The attack of γ-butyrolactam nucleophile to intermediate *N*-acyliminium ion was more favorable, when aryl aldehyde bears the electron donating group (EDG). Iodine plays a key role in these reaction transformations. This current mild protocol is environmentally benign and cost-effective method for the synthesis of industrially and pharmaceutically useful scaffolds.

Aminals, termed as *N,N*-acetals[1a] are useful intermediates for the construction of heterocyclic compounds and are also most useful building blocks in numerous organic syntheses.[1] The reactivity and stability of ketene aminals mostly rely on the substitution on the nitrogen atom with an electron withdrawing group.[2] The stability of the aminals increases if aryl groups are substituted on chiral carbon of aminals. From the literature, it is clearly evident that there exists a lack of synthetic method for the synthesis of such



Salinosporamide A (3), B (4)

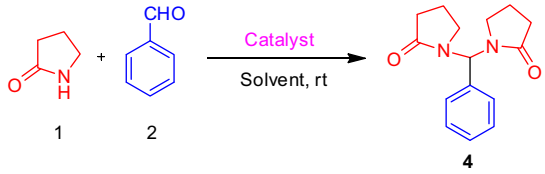
Lactacystin



Glp-His-Pro-NH2 (TRH)

Figure 1. Biologically active compound containing γ-butyrolactam unit.

Table 1
Screening of catalyst and solvent for the condensation reaction of γ-butyrolactam and benzaldehyde[a]



Entry	Catalyst (mol %)	Solvent (ml)	Yield[b] (%)
1	None	DCM	—
2	$FeCl_3$ (20)	DCM	69
3	$HgCl_2$ (20)	DCM	22
4	$AlCl_3$ (20)	DCM	11
5	$ZnCl_2$ (20)	DCM	56
6	$SnCl_2$ (20)	DCM	43
7	CAN (20)	DCM	52
8	Iodine (20)	DCM	91
9	Iodine (15)	DCM	91
10	Iodine (10)	DCM	90
11	Iodine (5)	DCM	81
12	Iodine (3)	DCM	74
13	Iodine (10)	None	—
14	Iodine (10)	THF	67
15	Iodine (10)	CH_3CN	61
16	Iodine (10)	DMC	68
17	Iodine (10)	*n*-Butanol	45
18	Iodine (10)	Ethanol	39
19	Iodine (10)	Methanol	28
20	Iodine (10)	IPA	22

[a] Reaction conditions: γ-butyrolactam (10 mmol) and benzaldehyde (5 mmol) at room temperature (30 °C), time: 4 h.
[b] Isolated yield, DCM-dichloromethane, DMC-dimethyl carbonate, THF-tetrahydrofuran, CH_3CN-acetonitrile, and IPA-isopropyl alcohol.

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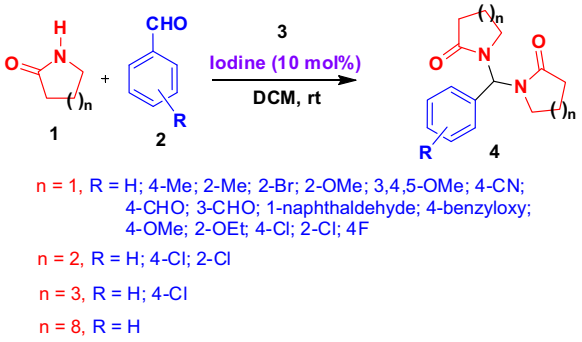
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.10.009



Scheme 1. Synthesis of aminals from lactams and aryl aldehyde.

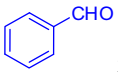
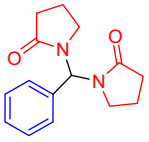
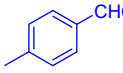
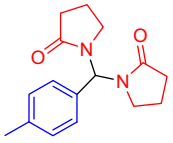
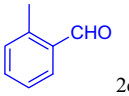
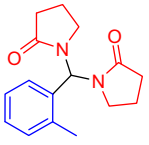
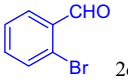
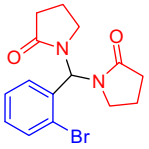
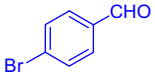
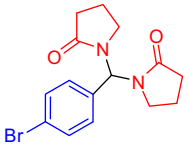
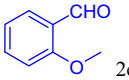
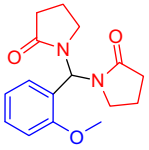
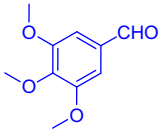
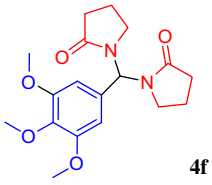
stable aminals.[3] Synthesis of such stable aminals provides a great potential in synthetic organic chemistry.[3]

The most efficient bioactive compounds could be synthesized using a simple starting material in a single step serving a great potential in synthetic organic chemistry.[4] Five membered ring aminals of lactams and their derivatives are found in numerous parts of biologically active compounds and also in numerous natural products.[5] To develop a more appropriate synthetic route for the synthesis of N-substituted γ-butyrolactam is a great deal of concern for the synthetic community.[6] In numerous biological compounds, γ-butyrolactam ring is implanted as a subunit structure.[7] In numerous natural products, γ-butyrolactam (2-pyrrolidinone) derivatives such as salinosporamides A–B, lactacystin, dysibetaine, cinnabaramides etc. are found as shown in Figure 1.[8]

In recent decades, the use of molecular iodine, Lewis acid, has attracted considerable attention.[9] It requires only a short reaction time, simple work-up, use of simple precursors to synthesize complex molecules and it is a moisture-stable mild Lewis acid in synthetic organic chemistry.[9] Molecular iodine enhances the utility of its catalytic property in organic synthesis emerging as an effective Lewis acid catalyst to accomplish several organic transformations.[10] The utility and the importance of this process have been drawing attention in recent organic syntheses.

The aminals exist in equilibrium,[11] and in order to shift the equilibrium toward product side, a classical method is used by using various drying agent, like boric anhydride,[11a] potassium

Table 2
Condensation reaction of lactams and aromatic aldehyde using iodine as catalyst leading to the formation of product aminals (**4**)

Entry	Benzaldehyde	Product	Yield[a] (%)
1	 2a	 **4a**	90
2	 2b	 **4b**	83
3	 2c	 **4c**	84
4	 2d	 **4d**	94
5			–
6	 2e	 **4e**	78
7	 2f	 **4f**	88

(*continued on next page*)

Table 2 (*continued*)

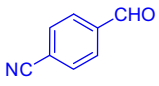
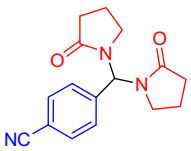
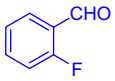
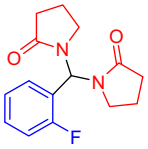
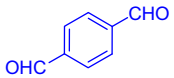
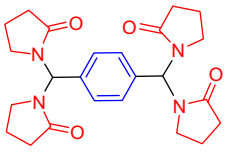
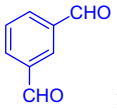
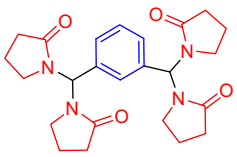
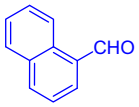
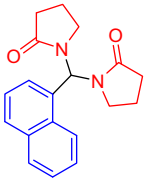
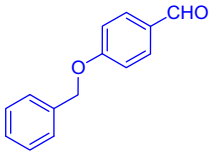
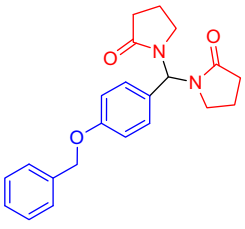
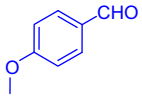
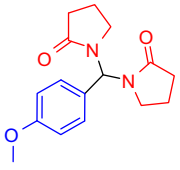
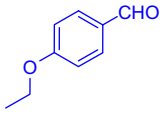
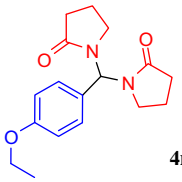
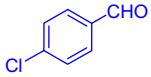
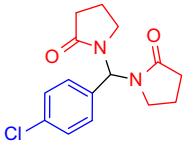
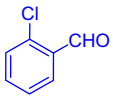
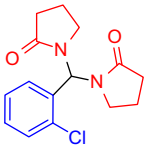
Entry	Benzaldehyde	Product	Yield[a] (%)
8	 2g	 **4g**	78
9			–
10	 2h	 **4h**	89
11	 2i	 **4i**	84
12	 2j	 **4j**	89
13	 2k	 **4k**	91
14	 2l	 **4l**	86
15	 2m	 **4m**	81
16	 2n	 **4n**	78
17	 2o	 **4o**	72

Table 2 (*continued*)

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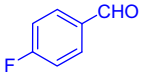
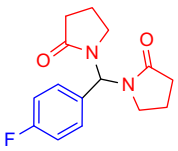
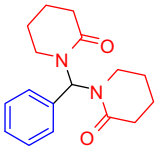
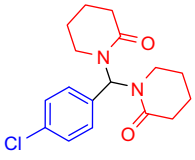
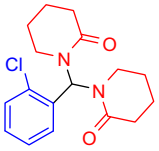
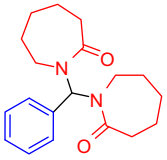
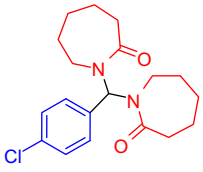
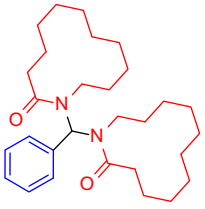
18	 2p	 **4p**	76
17	2a	 **4q**	88
18	2n	 **4r**	87
19	2o	 **4s**	81
20	2a	 **4t**	72
21	2n	 **4u**	71
22	2a	 **4v**	65

Reaction conditions: lactams (10 mmol), aryl aldehydes (5 mmol) and iodine (10 mol %) at room temperature (30 °C), time: 4 h.
[a] Isolated yield.

carbonate[11b] or method like azeotropic distillation with benzene[11c] to make free from water.

Herein, for the first time, we have developed a simple and efficient synthetic method for the synthesis of stable aminals—such as 1,1′-(phenylmethylene)bis(pyrrolidin-2-one) using iodine as catalyst. Addition of lactams to *N*-acyliminium ion leads to the formation of *N,N′*-acetals. The results obtained in the prior studies[12] using iodine as catalyst for a domino reaction have encouraged us to study the reaction further involving iodine as catalyst. Encouraging results were obtained in these studies, and due to the lack of a synthetic method for the synthesis of aminals, we have investigated the optimized reaction condition between γ-butyrolactam and benzaldehyde to assess the efficiency of the catalyst under various conditions. Initially, we used numerous Lewis acid metal chloride catalysts such as $FeCl_3$, $HgCl_2$, $AlCl_3$, $ZnCl_2$ and $SnCl_2$ in this reaction, and we got unsatisfactory yields. While the same reaction was carried out using 20 mol % of ceric ammonium nitrate as catalyst, we got 52% yield. In order to attain better yield, we used highly active Lewis acid catalyst iodine in this reaction and we got an excellent yield. Molecular iodine remarkably played a significant role in this reaction (Table 1).

Thus, to evaluate the catalyst, molar percentage was used in this reaction to produce excellent yield. We carried out the same reaction with 3 mol % catalyst and increased it upto 20 mol %. Good yield was obtained when10 mol % of iodine was used in this reaction, whereas the use of increased quantities of catalyst did not further improve the yield.

So, we carried out all the reactions with 10 mol % of iodine as the catalyst. To explore the generality of the reaction in other systems, we carried out the same reaction condition with a diverse

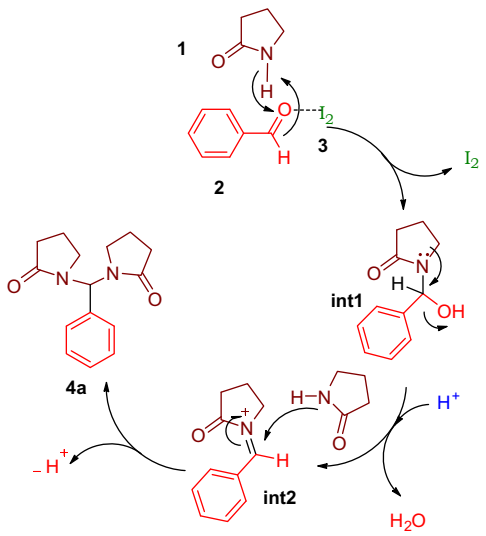


Figure 2. Most feasible mechanism for the formation of product via *N*-acyliminium ion.

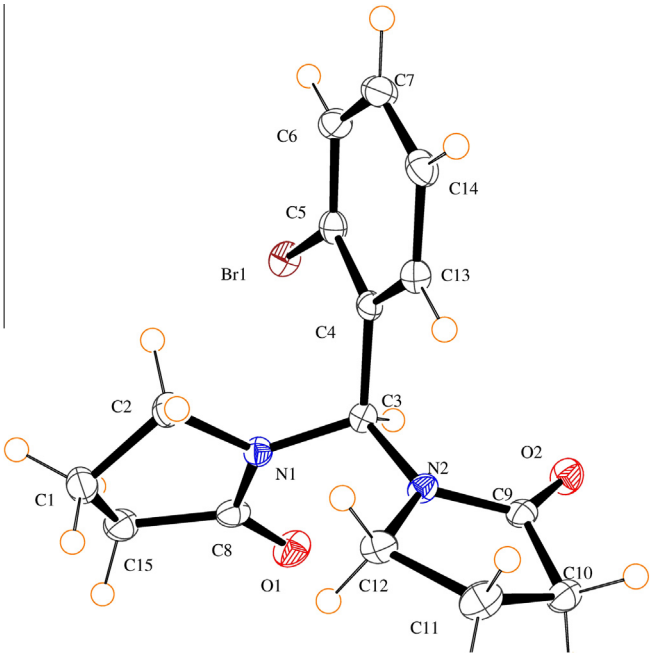


Figure 3. ORTEP diagram of compound **4d**.

range of aryl aldehyde and lactams. A schematic representation for the formation of aminals is shown in Scheme 1. The obtained results are summarized in Table 2. The arrangement of atoms of a compound 4d was further confirmed by the single crystal X-ray diffraction analysis as shown in Figure 3.[12b] The scope and the limitation of this reaction were also examined. We also tried with various lactams to check whether the reaction yields aminals and found that the reaction with other lactams also proceeds smoothly. When the same reaction was carried out with aliphatic aldehyde, reaction did not proceed to form product. We tried to prepare unsymmetrical aminal derivatives by reacting 1 equiv of γ-lactam, 1 equiv of δ-lactam and benzaldehyde, to create a chiral asymmetric carbon in the molecules but we got a mixture of **4a** and **4q** as shown in Scheme 2.

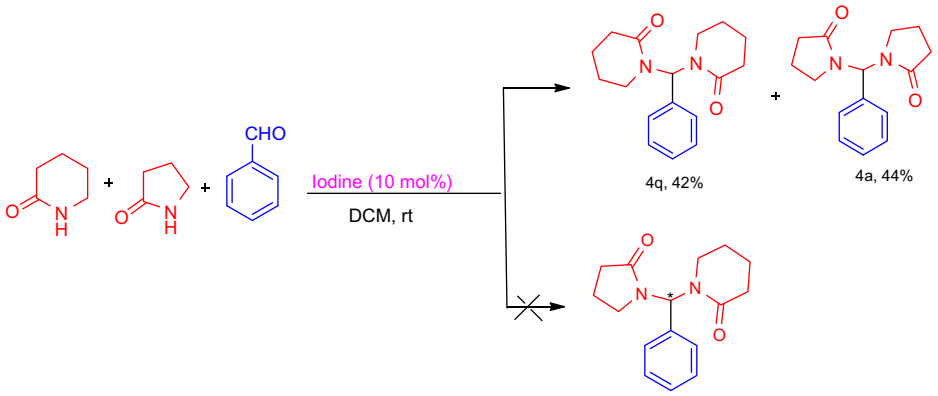
The substitution in phenyl ring and the orientation of the phenyl ring of benzaldehyde influenced the outcome of the reaction (Table 2). We carried out the reaction with aryl aldehyde bearing electron withdrawing (EWG) and electron donating groups (EDG), but excellent yield was obtained only when EDG on aryl aldehyde was used.

The initial step of the mechanism was the attack of iodine catalyst on the carbonyl oxygen of aryl aldehyde, and this gave rise to the formation of intermediate, **int1** (1-(hydroxy (phenyl) methyl) pyrrolidin-2-one). The transformation of intermediate, **int1** to **int2** was obtained by the removal of water molecule. Thereby, *N*-acyliminium cation (**int2**) was formed. Nucleophile attack of one more lactam on the *N*-acyliminium cation **int2** led to the formation of the desired product (**4**). The most feasible mechanism for the formation of product **4** is proposed in Figure 2.

In summary, we successfully developed an efficient method for the synthesis of aminals from lactams and aryl aldehyde using iodine as an efficient catalyst. Iodine played a remarkable role in this reaction transformation that provided better yield. Nucleophile attack of lactams on *N*-acyliminium ion intermediate was more feasible pathway for the formation of aminals. Further increase in the ring of lactam motifs was also used to raise diversity for preparing a library of 20 novel derivatives in good yields and high purities without column chromatography. Thus the present modest procedure affords numerous advantages like simple synthetic method, excellent yield, convenient work-up and no column chromatography.

Acknowledgment

The DST-FIST NMR facility at VIT University is greatly acknowledged.



Scheme 2. Synthesis of unsymmetrical aminals bearing chiral asymmetric carbon.

Supplementary data

Supplementary data (Spectroscopic characterization of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.009.

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