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A concise and efficient route to the total synthesis of bacillamide A and its analogues

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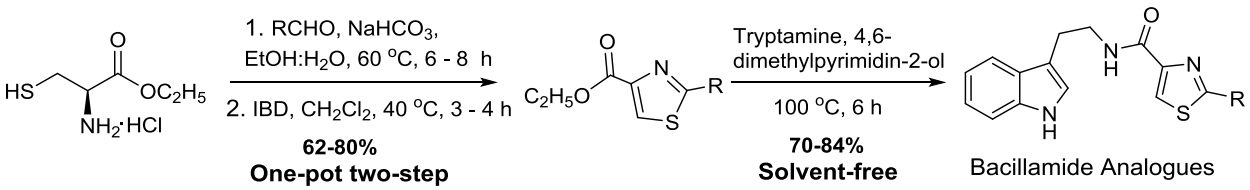
Abstract

The synthesis of bacillamide A, a tryptamide alkaloid of marine origin, and its analogues from L-cysteine ethyl ester hydrochloride through an efficient and convergent synthetic approach is described in this work. The present two-step protocol involves the use of iodobenzene diacetate, a versatile oxidising agent, to synthesize the key intermediate ethyl 2-differently substituted-1,3-thiazole-4-carboxylates in one step. In this work, 4,6-dimethylpyrimidin-2-ol was used as a catalyst for solvent-free aminolysis of esters to achieve the title compounds by taking advantage of its property of simultaneously donating and accepting a hydrogen bond.



Keywords: Bacillamide A; thiazole; 4,6-dimethylpyrimidin-2-ol; tryptamine; hypervalent iodine reagent; amide bond formation.

Introduction

Numerous marine natural products exhibit wide range of biological activities and thus provide good lead in drug discovery but quite often availability of such bioactive compounds is very low from natural resources.[1-3] Hence there is need to synthesize them to obtain requisite quantities and build diversity around their scaffold to further explore their therapeutic potential. The study of natural products, their isolation, characterization and synthesis, have been motivated by a quest for some benefit to mankind. Recently, from marine natural products bioprospecting afforded a significant number of drug candidates. Some of the commercialized products from marine organisms include the antibiotic cephalosporin-C from marine fungi, keramidine from marine sponge having antagonistic activity against serotonergic and cholinergic receptors, the anthelmintic insecticide 3-indolacrylamide from red alga, which have proved to be excellent bioactive compounds (Figure 1).[4-8]

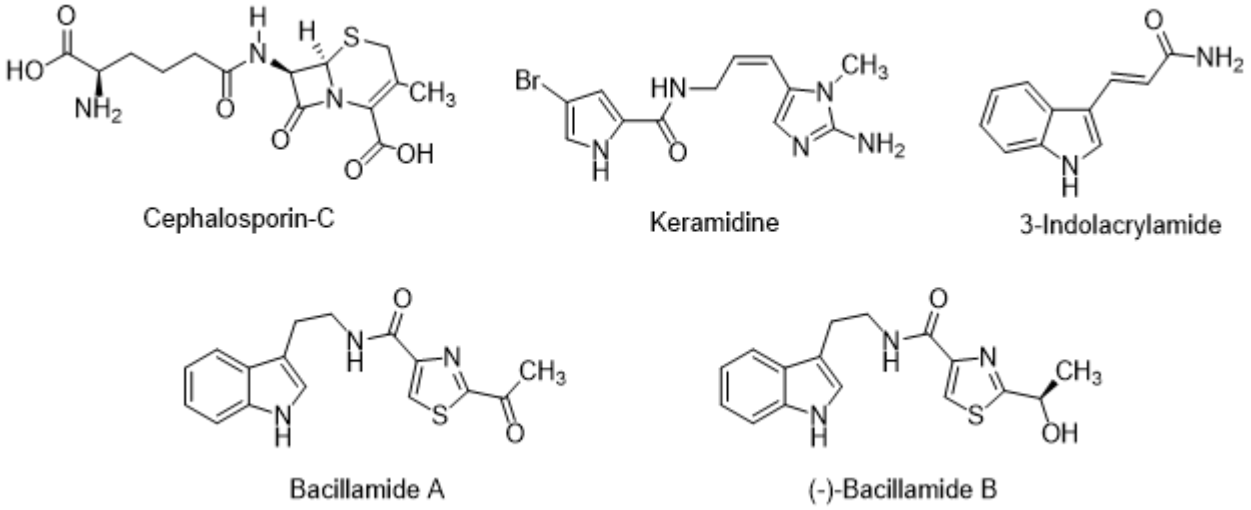


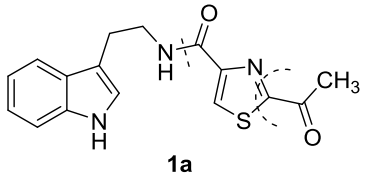
Figure 1. Bioactive compounds from marine organisms.

Bacillamide A (**1a**) is a natural tryptamide alkaloid isolated in 2003 from marine bacterium, *Bacillus species SY-I* during termination of blooms of *Cochlodinium polykrikoides*.[9] Most interestingly, it was found to be the first compound to show excellent algicidal activity against the harmful dinoflagellate *Cochlodinium polykrikoides* but it does not kill or inhibit the growth of bacteria, fungi, yeast and useful microalgae of other phyla such as diatoms, green algae and cyanobacteria. This dinoflagellate is responsible for seafood poisoning and mass mortality of cultured fishes. Rowley and co-workers isolated bacillamide B (enol form of bacillamide A) from a Bahamian hypersaline microbial mat in 2007 as an antimicrobial agent.[10] Bray revised the proposed stereochemistry of the natural bacillamide B from R- to S- configuration.[11] Sun et al described its total synthesis via a cascade disulfide cleavage/thiocarbonylation/Staudinger reduction/aza-Wittig reaction using β-azido disulfide and carboxylic acid as substrates in 30% overall yield.[12]

Outbreaks of seafood poisoning are usually sporadic and unpredictable because fish or shellfish do not produce toxins themselves, but acquire them from marine microorganisms such as dinoflagellate and marine bacteria that they eat. High selectivity exhibited by bacillamide A **1a**, makes it a promising algicidal agent for regulating blooms of harmful dinoflagellate species. However, because of low yields of bacillamide A obtained from natural sources there is a necessity to gain access to large quantities of this substance for further biological screening through improved total synthesis.

The first synthesis of bacillamide A (**1a**) developed by Figueira *et al.* involved a five-step linear approach; starting from 4-methyl-1,3-thiazole, the desired product was obtained in only 14% overall yield.[13] This multistep approach requires tedious workup and purification steps. Formation of by-products, particularly during benzylic bromination of 4-methyl-2-acetyl-1,3-thiazole to synthesize key intermediate 2-acetyl-1,3-thiazole-4-carboxylic acid and coupling of amide bond through mixed anhydride approach, affected the yields adversely. Most importantly, the potential of this method is limited as specified structural variation cannot be introduced in structure of bacillamide to achieve better biological active analogues.

In view of these observations and due to our interest in the synthesis of biological active thiazole compounds,[14-16] we developed a concise route for the total synthesis of bacillamide A. After retrosynthetic analysis of **1a**, we aimed to synthesize it in only two steps from the commercially available L-cysteine ethyl ester hydrochloride, pyruvaldehyde and tryptamine, in a sequence of thiazole ring formation via [4+1] approach in the first step, and amide bond formation by aminolysis of esters in the second (Figure 2). Based on this diversity-driven approach, we also envisaged the synthesis of six analogues of bacillamide having variation at position-2 of the thiazole ring.



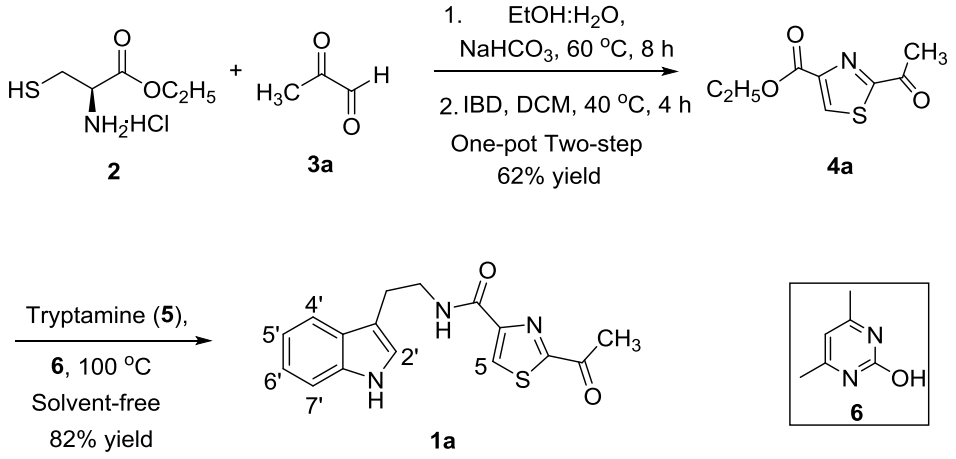
1a

Figure 2. Retrosynthetic analysis of bacillamide A.

Results and Discussion

The key intermediate ethyl 2-acetyl-1,3-thiazole-4-carboxylate (**4a**) was synthesized earlier through [4+1] approach by Hughes *et al.*[17] It was reported that stirring L-cysteine ethyl ester hydrochloride and pyruvic aldehyde in the presence of mild base ($KHCO_3$) under nitrogen atmosphere for 18 h led to the formation of 1:1 diastereomeric mixture of ethyl 2-acetyl-1,3-thiazolidine-4-carboxylate which was subsequently oxidised in the next step with manganese dioxide in 18 h in 55% overall yield. A perusal of the literature revealed that although MnO_2 is the reagent of choice for the oxidation of thiazolidine to thiazole,[18-19] alternative oxidising agents e.g. NBS-benzoyl peroxide[20] and $BrCCl_3$-DBU[21] have also been employed. However, these methods require two steps, carefully controlled reaction conditions, longer reaction periods and low overall yields. Recently there is an increasing interest in hypervalent iodine reagents mainly due to their remarkable oxidising properties combined with their environmental benign nature and commercial viability. Our research group and others have successfully accomplished the synthesis of a wide variety of heterocyclic compounds utilising iodine(III) reagents through *in situ* oxidative cyclisation or dehydrogenation.[22] This encouraged us to develop a one pot protocol for the synthesis of **4** utilising iodobenzene diacetate (IBD) as an oxidising agent.

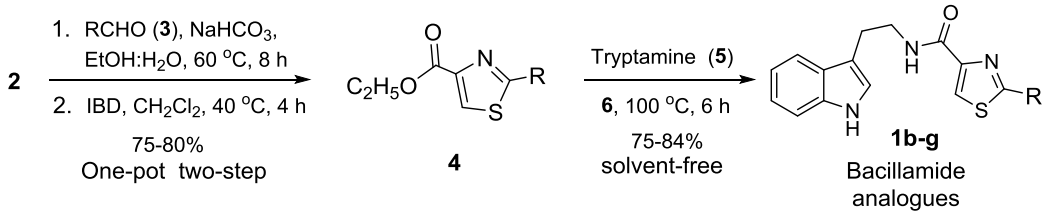
In the present protocol, pyruvaldehyde was stirred with L-cysteine ethyl ester hydrochloride dissolved in EtOH-water (50:50) in the presence of sodium bicarbonate at 60 ^{o}C. The reaction was monitored by TLC at regular intervals. When it indicated the consumption of starting materials, the solvent was distilled off *in vacuo* and the solution was stirred for additional 4 h at 40 ^{o}C after the addition of a solution of IBD in dichloromethane. The workup of the reaction afforded **4a** in 62% yield (Scheme 1).



Scheme 1. Total synthesis of bacillamide A (**1a**).

The final step in the synthesis required aminolysis of ethyl 2-acetyl-1,3-thiazole-4-carboxylate with tryptamine. Though being a potentially attractive approach, limited examples of the direct transformation of esters to amides have been reported in literature, involving catalytic ester-amide exchange utilising zirconium(IV) *tert*-butoxide with activator 1-hydroxy-7-azabenzotriazole,[23] 2-pyridone,[24] DBU (1,8-diazabicyclo[5.4.0]undec-7-ene),[25] diethylaluminium dimethylamide,[26] etc. However, in most of the cases yields were not satisfactory and stoichiometric additives or tailored substrates were necessary. We thought of exploring the potential of pyrimidin-2-one, which may exist and aggregate with tautomeric form pyrimidin-2-ol, as catalyst for the amide synthesis due to its catalytic efficiency based on the property of simultaneously donating and accepting a hydrogen bond. Pyrimidin-2-ol has also been used as ligand to generate structure of high complexity with *trans*-a_2Pt^{II} (a = NH_3, CH_3NH_2) by taking advantage of its H-bonding and metal bonding properties.[27] This reagent leads to an efficient solid phase synthesis of bacillamide A with better yield (51% overall yield) and without giving any side product in this reaction. It has been noted that during the reaction no trans-esterification was observed. The identity of the final compound was confirmed by melting point and ^{1}H NMR and the results are consistent with the reported natural product.[13]

Table 1. Substrate scope for the synthesis of bacillamide analogues



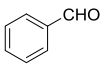
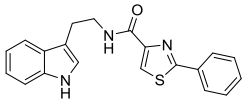
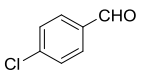
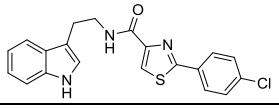
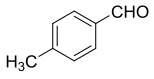
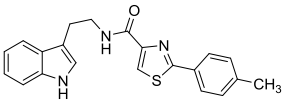
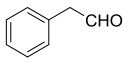
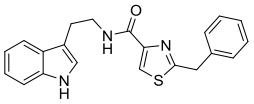
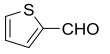
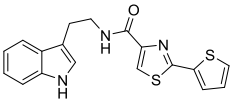
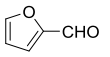
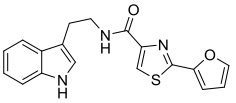
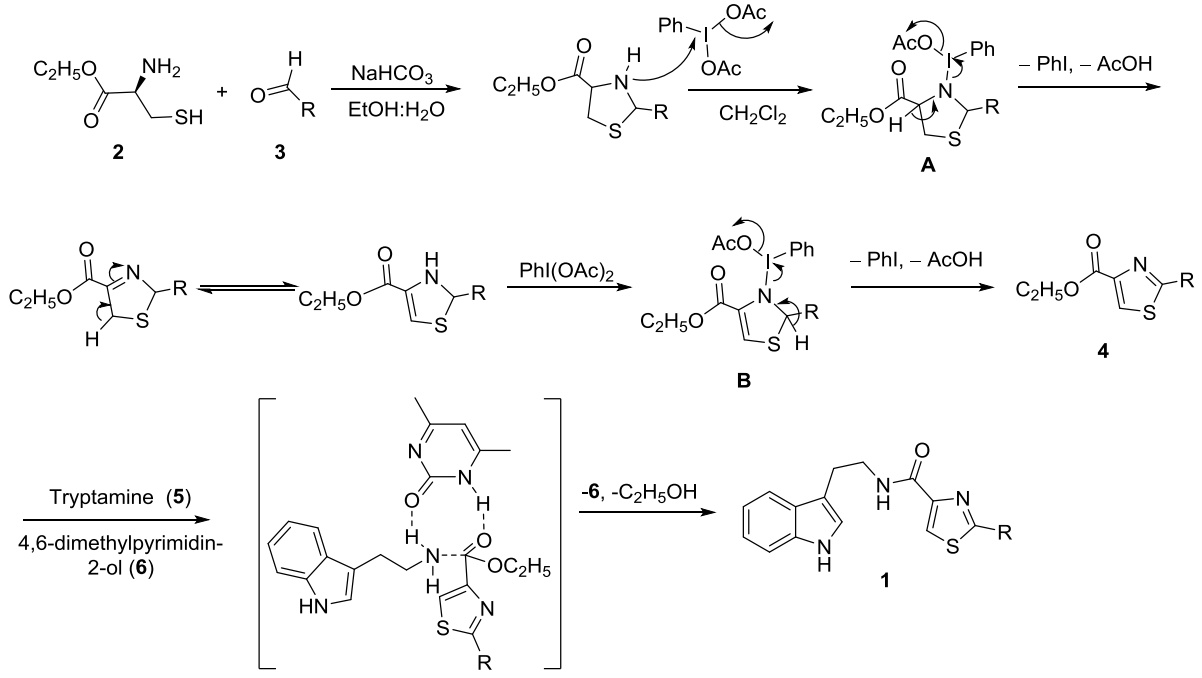
Entry	**3**	% Yield (**4**)[a]	**1**	Obs. M.pt. (Lit.) °C	%Yield (**1**)[b]
b		78		144-145 (145)[14]	82
c		80		162-164 (164)[14]	80

Table 1. Continued

Entry	**3**	% Yield (**4**)[a]	**1**	Obs. M.pt. (Lit.) °C	%Yield (**1**)[b]
d		75		182-183 (183)[14]	84
e		80		140-141 (141)[14]	81
f		78		168-170 (170)[14]	75
g		78		192-193 (193)[14]	78

[a] Percentage yields of thiazole (**4**) from L-cysteine ethyl ester hydrochloride (**2**)
[b] Percentage yields from thiazole (**4**) to bacillamide analogues (**1b-g**)

A similar synthetic approach was used to prepare various bacillamide analogues having variation at position-2 of the thiazole ring by the reaction of differently substituted aldehydes with L-cysteine ethyl ester hydrochloride (**2**). Further, synthesized thiazoles reacted with tryptamine in the presence of 4,6-dimethylpyrimidin-2-ol (**6**) through a solvent-free reaction. After the usual work up the corresponding analogs (**1b-g**) were obtained in good yield. All structures were confirmed by comparing their melting points and ^{1}H NMR data with the literature.[14] Structures, melting points and yields of bacillamide analogues are given in Table 1. These derivatives **1b-g** had been synthesized earlier by us employing an alternative [3+2] approach, Hantzsch thiazole synthesis.[14] However, the present protocol is more promising as it not only provided improved yields and cleaner reactions but also avoided the synthesis of precursors, use of the lachrymatory ethyl bromopyruvate and thioamides.



Scheme 2. Plausible mechanism for the synthesis of bacillamide A and its analogues.

A plausible mechanism for the oxidation of thiazolidine to thiazole and amide coupling is outlined in Scheme 2. The dehydrogenation of thiazolidine to thiazole involves the electrophilic attack of IBD to generate intermediates A and B which undergo reductive loss of iodobenzene along with elimination of acetic acid. The possible reaction mechanism for amide bond formation is analogous to that described for 4,6-dimethylpyrimidin-2-ol involving an eight-membered transition state between ester and amine through simultaneously donating and accepting a hydrogen bond.

Conclusions

In conclusion, our short sequence leads to bacillamide A in only two steps and 51% overall yield from commercially available L-cysteine ethyl ester hydrochloride. The efficiency of our environmental-benign method enabled the synthesis of bacillamide A and its additional derivatives on a milligram scale for the purpose of evaluation in multiple biological assays.

Experimental Section

General. Melting points were determined in open capillaries in electrical apparatus and are uncorrected. IR spectra were recorded on a Buck Scientific IR M500 instrument. The ^{1}H NMR spectra were recorded on a Bruker instrument at 300 MHz. Mass spectra were measured in EI mode on a Kratos MS-50 spectrometer at MS Facilities at CIL-SAIF, Panjab University, Chandigarh, India. The starting materials L-cysteine ethyl ester hydrochloride and tryptamine were purchased from HiMedia.

One-pot two-step procedure for the preparation of ethyl 2-acetyl-1,3-thiazole-4-carboxylate (**4a**). Sodium bicarbonate (0.68 g, 8.1 mmol) was added to L-cysteine ethyl ester hydrochloride (1 g, 5.4 mmol) in water (25 mL). A solution of pyruvaldehyde (0.43 g, 5.9 mmol) in ethanol (25 mL) was added to the reaction mixture. The reaction mixture was stirred at 60 ^{o}C for 8 h and concentrated to evaporate the solvent under vacuum after the consumption of starting materials (checked by TLC). The reaction mixture was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to reduce the solvent to half (30 mL). Iodobenzene diacetate (3.65 g, 11.3 mmol) was added and stirred the reaction mixture at 40 ^{0}C for 4 h. After completion of the reaction (monitored by TLC) the solvent was evaporated. The product was purified by column chromatography (5% Ethyl acetate/hexane).
Ethyl 2-acetylthiazole-4-carboxylate (**4a**): mp 65-67 ^{o}C (lit mp 68 ^{o}C)[14]; yield 62%; IR (cm^{-1}): 1728 (CO, ester), 1695 (CO, acetyl); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.45 (t, 3H, *J* 7.2 Hz), 2.79 (s, 3H), 4.49 (q, 2H, *J* 7.2 Hz), 8.44 (s, 1H, thiazole 5-H).
General procedure for the synthesis of bacillamide A, 2-acetyl-*N*-[2-(1H-indol-3-yl)ethyl]-1,3-thiazole-4-carboxamide (1a) and analogues. A mixture of ethyl-2-acetyl-1,3-thiazole-4-carboxylate (4a, 0.40 g, 2 mmol), tryptamine (5, 0.40 g, 2.5 mmol) and 4,6-dimethylpyrimidin-2-ol (6, 0.12 g, 2 mmol) was ground vigorously using a pestle and mortar. The contents were transferred to a round bottom flask and heated to 100-105 ^{o}C for 6 h. After completion of the reaction (monitored by TLC), water (25 ml) was added. Compound was extracted with ethyl acetate. The organic layer was washed thoroughly with 10% HCl solution (2 × 25 ml) and the combined organic extracts were dried over anh. sodium sulfate. The reaction mixture was concentrated and the crude product crystallized from ethanol.

The contents were transferred to a round bottom flask and heated to 100-105 ^{o}C for 6 h. After completion of the reaction (monitored by TLC), water (25 ml) was added. Compound was extracted with ethyl acetate. The organic layer was washed thoroughly with 10% HCl solution (2 × 25 ml) and the combined organic extracts were dried over anh. sodium sulfate. The reaction mixture was concentrated and the crude product crystallized from ethanol.

Similarly other compounds (**1b-g**) are prepared using the same procedure.

Bacillamide A (**1a**). Brown solid; mp 165-168 ^{o}C (lit[10] mp 169 ^{o}C); yield 82%; IR (cm^{-1}): 3271 (NH), 1697 (CO), 1659 (CONH); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.72 (s, 3H, CH_3), 2.95 (t, 2H, *J* 7.2 Hz, CH_2-indole), 3.61 (dd, 2H, *J* 6.6 Hz, 7.8 Hz, CH_2-NH), 7.05 (t, 1H, *J* 7.2 Hz, 5′ -H), 7.16 (t, 1H, *J* 7.5 Hz, 6′ -H), 7.20 (s, 1H, 2′ -H), 7.37 (d, 1H, *J* 7.5 Hz, 7′ -H), 7.63 (d, 1H, *J* 7.5 Hz, 4′ -H), 8.66 (bs, 1H, thiazole-5H), 10.84 (s, indole-NH, exchangeable with D_2O); ^{13}C NMR (75 MHz, DMSO-d_6, δ): 18.93, 25.47, 40.82, 111.34, 112.07, 118.45, 118.72, 121.42, 122.29, 122.45, 127.22, 136.49, 149.73, 160.99, 165.75, 190.96.

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Supplementary Material

Supplementary data [^{1}H NMR data of the compounds (**1a** and **4a**)] associated with this article can be found in the online version.

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