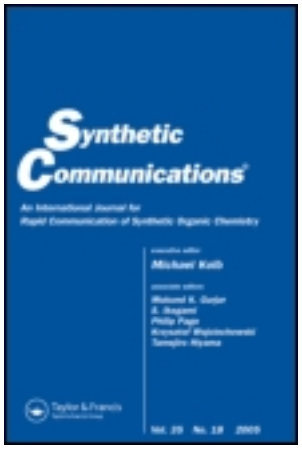

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Easy Access to 2-Alkyl and 2-Arylthiazolines Using a Modified Heteropolyacid Catalysis: Application to the Synthesis of Bacillamide A

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EASY ACCESS TO 2-ALKYL AND 2-ARYLTHIAZOLINES USING A MODIFIED HETEROPOLYACID CATALYSIS: APPLICATION TO THE SYNTHESIS OF BACILLAMIDE A

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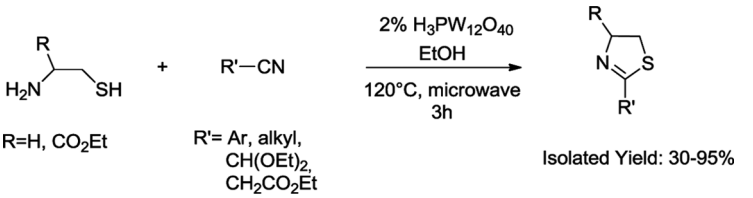
Université de Lyon, Institut de Chimie de Lyon, Villeurbanne, France

GRAPHICAL ABSTRACT



Abstract *A straightforward access to 2-alkyl and 2-arylthiazolines by condensation of β-aminothiols on nitriles, catalyzed by phosphotungstic acid (2%) under microwave irradiation, is described. This method has been directly applied to a short and efficient synthesis of bacillamide A (**16**).*

Keywords Bacillamide A; heteropolyacid; microwave irradiation; thiazoline synthesis

INTRODUCTION

The 2-thiazoline ring is present in numerous biologically active compounds such as telomestatin,[1] cyclothiazomycin,[2] and largazole.[3] 2-Thiazolines have also found applications in flavor chemistry[4] and as radioprotective agents.[5] Several methodologies is available for the formation of such derivatives, which have been extensively reviewed by Gaumont et al.[6] A further aromatization of theses heterocycles can lead to thiazoles, rings present in a large number of natural compounds.[7] This aromatization may proceed smoothly[8] compared to the drastic conditions applied for the aromatization of thiazolidines.[9] In the course of our studies on the applications of heterogeneous catalysis to fine chemistry,[10] we were attracted by the results published by Mohammed poor-Battork et al., who synthesized 2-arylthiazolines from 2-aminoethanethiol and various aromatic nitriles catalyzed by phosphotungstic acid under solvent-free conditions.[11] However, only aromatic

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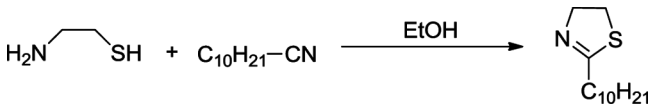
nitriles were used as substrates, thereby limiting the scope of the method. In particular, nothing was reported on the possible application of these conditions to cysteine. Microwave irradiation has already been used to synthesize thiazolines from acylbenzotriazoles by Katritzky et al.,[12] from aryl keto nitriles by Sukanta and Biehl,[13] and from aldehydes by Kodomari et al.,[14] but only with 2-aminoethanethiol or aminothiophenol as sulfur-containing nucleophiles, without mention of the use of natural cysteine. As we planned to obtain functionalized thiazolines for natural product synthesis, there was a need for a more general method.

Here we report the direct access to 2-alkyl or 2-arylthiazolines from β-aminothiols and nitriles under microwave irradiation using a catalytic amount of phosphotungstic acid. To select the best reaction parameters, we first studied the reaction between 2-aminoethanethiol and undecanitrile in both conventional heating conditions or microwave irradiation and in the presence or absence of heteropolyacid (HPA) (Table 1).

Using conventional oil-bath heating conditions, only moderate conversions were observed (Table 1, entries 1 and 2). Under microwave irradiation, the conversion was better, and the greatest isolated yield was obtained only when both microwave irradiation and HPA were used (Table 1, entries 4 and 5). It is difficult to conclude whether it is a real microwave effect. The article very recently published by Obermayer and Kappe[15] showed that most of the literature reports claiming this effect are in fact a result of artifacts of the experimental protocols. Nevertheless, if we compare entries 3 and 5, performed in the same conditions except for the heating mode, it is clear that microwave activation and conventional heating led to different results. Profiles of power, temperature, and pressure registered in the seal tube during a typical experiment are depicted in Fig. 1. An initial power of 100 W was necessary to reach very rapidly (about 1 min) the desired temperature (120 °C), and a power of 35 W was sufficient to maintain this value. The inside pressure was kept around 2 bar, a relatively low pressure for the reaction vessel, which could bear up to 20 bar.

Table 1. Influence of reaction parameters



Entry	Heating conditions: Microwave	Heating conditions: Conventional heating	HPA	Conversion[a] (%)	Isolated yield (%)
1	–	80 °C, 5 h	—	40	25
2	–	80 °C, 5 h	$H_3PW_{12}O_{40}$	35	26
3[b]	–	120 °C, 3 h	$H_3PW_{12}O_{40}$	50	32
4	+	120 °C, 3 h	—	60	40
5	+	120 °C, 3 h	$H_3PW_{12}O_{40}$	100	60

[a]Measured by ^{1}H NMR.
[b]Performed in a sealed tube.

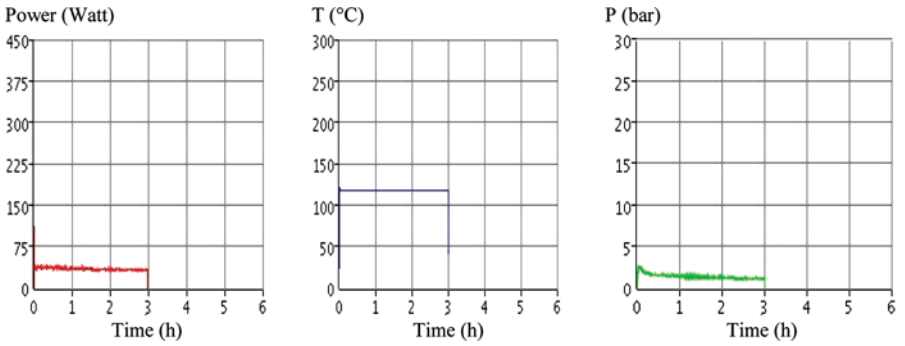


Figure 1. Profiles of power, temperature, and pressure registered inside the sealed tube during a typical experiment. (Figure is provided in color online.)

We thus applied microwave conditions to a large variety of β-aminothioles and nitriles (Table 2). Isolated yields up to 95% were obtained, and even di-thiazolines can be synthesized starting from dicyano derivatives (Table 2, entries 3 and 5), giving access to potential ligands for catalysis.[16] It is noteworthy that aliphatic nitriles have been used with success as numerous published methods are only applied to aryl derivatives; the poor isolated yield of compound **1** is due to its volatility.[5]

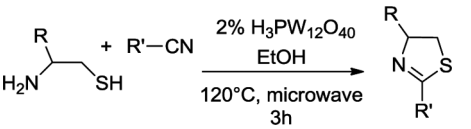
Among the various nitriles used in this study, two of them turned out to be of particular interest, ethyl cyanoacetate (Table 2, entries 7 and 10) and diethoxy acetonitrile (Table 2, entries 6, 8, and 9), as they allowed the introduction of an additional interesting functional group on which further chemical transformations could be performed. More specifically, compound **9** can be easily aromatized into compound **11**, which is the key intermediate of numerous syntheses as shown in Fig. 2.[17] Compound **11** has been previously prepared in two steps by a classical Hantszch synthesis from diethoxyacetamide and ethyl 3-bromopyruvate using P_2S_5, a particularly hazardous reagent.[18]

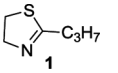
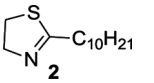
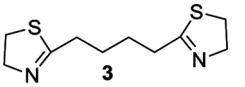
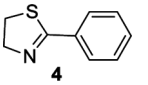
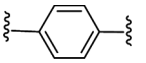
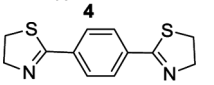
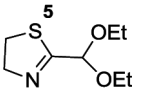
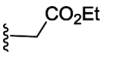
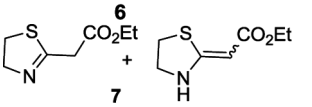
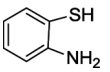
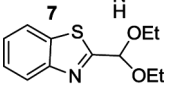
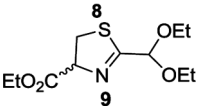
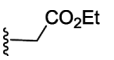
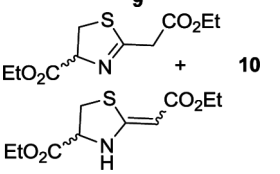
As an illustration, we applied the method described therein to the synthesis of bacillamide A, an algicide against dinoflagellates (Scheme 1).

Bacillamide A was isolated and its structure elucidated for the first time in 2003 by Jeong et al. in Japan,[19] and since this discovery many other thiazole alkaloids with similar skeletons have been identified.[20] Nevertheless, to our knowledge, only one synthesis of this molecule has been reported so far.[21]

The first step of the synthesis was the illustration of our method applied to cysteine and 2,2-diethoxyacetonitrile, which gave compound **9** with 68% isolated yield. Compound **9** was easily aromatized into compound **11** following the method described by Williams et al.[8b] Acidic hydrolysis of the acetal **11** gave the aldehyde **12**, and a Grignard reaction using methylmagnesium bromide led to alcohol **13**, easily oxidized by Dess–Martin periodinan. Every attempt to increase our yield for the Grignard reaction became a failure: working at low temperature (−78 °C) or with $CeCl_3$ to limit side reactions were unsuccessful. Alkylation according to Barbier procedure with Zn and methyl bromide also was not possible. Saponification of the ester **14** followed by peptidic coupling with tryptamine using the classical

Table 2. Microwave-assisted synthesis of thiazolines from nitriles using HPA



Compound	R	R′	Product[a]	Yield (%)[b]
1	H	C_3H_7	 1	30
2	H	$C_{10}H_{21}$	 2	60
3	H	__-$(CH_2)_4$-_	 3	60
4	H	Ph	 4	80
5	H		 5	90
6	H		 6	82
7	H		 7	54
8			 8	95[c]
9	COOEt		 9	68
10	COOEt		 10	50

[a]For details reaction conditions, see Experimental section.
[b]Isolated yields.
[c]80 °C, 2 h.

reagents N,N′-dicyclohexylcarbodiimide (DCC) and HOBt led to bacillamide in seven steps with an overall yield of 5.6%.

In summary, we have developed a general microwave-assisted straightforward method for the synthesis of alkyl and aryl functionalized 2-thiazolines. It gives access

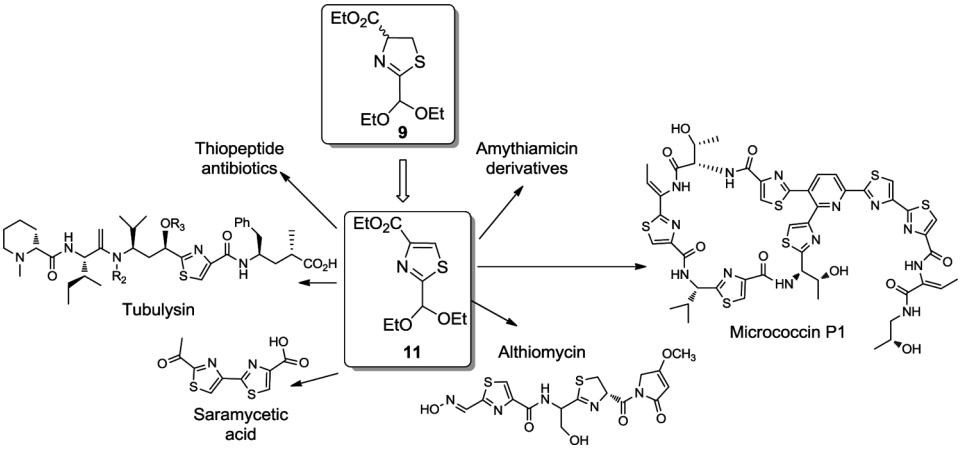
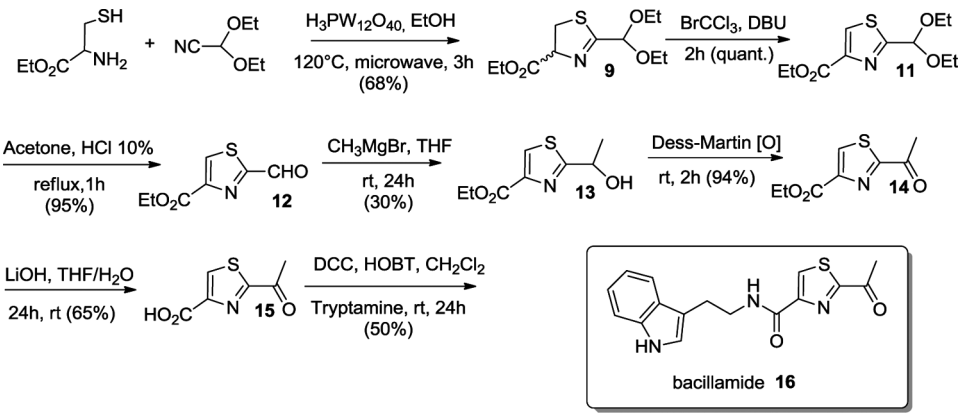


Figure 2. Natural products synthesized starting from compound **11**.[17]

to intermediates of interest in total synthesis and avoids the use of P_2S_5 as the source of sulfur. Finally, we report its application to the synthesis of the natural product bacillamide A. We believe that this procedure provides a valuable addition to current methodologies.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer as thin films or directly with solids. ^1H and ^{13}C NMR spectra were recorded respectively at 300 and 75 MHz in solution in $CDCl_3$ using the residual solvent peak as a reference standard (7.26 ppm and 77.36 ppm respectively). Chemical shifts are reported in parts per million (ppm) on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of



Scheme 1. Synthesis of bacillamide A starting from cysteine via the 2-thiazoline intermediate **9**.

doublets of doublets, etc.), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in hertz. Microwave-assisted synthesis was carried out in an Initiator single-mode microwave cavity producing controlled irradiation at 2.45 GHz (Biotage AB, Uppsala). The reactions were run in sealed vessels (0.5 to 20 mL), and magnetic stirring was used. Variable power was employed to reach the temperature desired and then to maintain it in the vessel during the period of time programmed. Flash column chromatography purifications were performed with Geduran Si from Merck (particle size 60–200 μm). Analytical thin-layer chromatgraphy (TLC) was performed on 0.25 mm thick plates precoated with Merck Kieselgel 60 F_{254} silica gel. TLC was visualized under UV (254 nm) and by oxidative staining with aqueous phosphomolybdic acid. When necessary, reactions were performed under an argon atmosphere and in dried flasks. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone under nitrogen, and CH_2Cl_2 was distilled from CaH_2. Phosphotungstic acid was purchased from Acros and used as received.

Typical Procedure for the 2-Thiazoline Synthesis

β-Aminothiol (1 mmol) 1.1 mmol of nitrile, and 0.02 mmol (58 mg) of $H_3PW_{12}O_{40}$ were stirred in 1 mL of EtOH in a sealed tube under microwave irradiation at 120 °C for 3 h. After evaporation of the solvent, the reaction mixture was purified by flash chromatography.

2-(Propyl)-2-thiazoline (1)[5]

Isolated yield 30% (39 mg); colorless liquid; R_f 0.3 (AcOEt/hexanes 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (t, $J = 7.5$ Hz, 2H, CH_2N), 3.30 (t, $J = 8.3$ Hz, 2H, CH_2C=N), 2.53 (t, $J = 7.5$ Hz, 2H, CH_2S), 1.65–1.72 (m, 2H, CH_2CH_3), 0.97 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (*C*=N), 38.5 (CH_2N), 37.9 (CH_2C=N), 29.7 (CH_2S), 19.1 (CH_2CH_3), 13.8 (CH_3); IR (neat) (cm^{-1}) 2961, 2926, 1642, 1549 HRMS calcd. for $C_6H_{11}NS$ (M^+) 129.0612; found 129.0616.

2-(Decyl)-2-thiazoline (2)

Isolated yield 60% (136 mg); colorless liquid; R_f 0.3 (AcOEt/hexanes 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) 4.16 (t, $J = 7.5$ Hz, 2H, CH_2N), 3.22 (t, $J = 8.3$ Hz, 2H, CH_2C=N), 2.45 (t, $J = 7.5$ Hz, 2H, CH_2S), 1.55–1.62 (m, 2H, CH_2CH_2C=N), 1.22–1.26 (m, 14H, CH_2), 0.83 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 172.0 (*C*=N), 64.7 (CH_2N), 34.6 (CH_2C=N), 34.1 (CH_2S), 32.1, 29.8, 29.7, 29.5, 29.4, 27.7, 22.9 ($CH_2CH_2CH_2$), 14.3 (CH_3); IR (neat) (cm^{-1}) 2960, 2930, 1640; HRMS calcd for $C_{13}H_{25}NS$ (M^+) 227.1708, found 227.1707.

2,2′-Tetramethylenebis(2-thiazoline) (3)[22]

Isolated yield 60% (137 mg); colorless liquid; R_f 0.3 (AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$) 4.18 (t, $J = 8.3$ Hz, 4H, CH_2N), 3.24 (t, $J = 8.5$ Hz, 4H, CH_2C=N), 2.48–2.52 (m, 4H, CH_2S), 1.68–1.70 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 171.5 (*C*=N), 64.7 (CH_2N), 34.2 (CH_2C=N), 34.1 (CH_2S), 27.1

(CH_2CH_2); IR (neat) (cm^{-1}) 2939, 2855, 1625, 1542, 1436, 922; HRMS calcd for $C_{10}H_{17}N_2S_2$ $(M+H)^+$ 229.0833, found 229.0832.

2-Phenyl(2-thiazoline) (4)

Data were in accord with the literature.[12] Isolated yield: 80% (130 mg).

2,2′-(1,4-phenylene)bis[2-thiazoline] (5)

Data were in accord with the literature.[12] Isolated yield: 90% (223 mg).

2-(Diethoxymethyl)-2-thiazoline (6)[23]

Isolated yield: 82% (155 mg); colorless liquid; R_f 0.3 (AcOEt/hexanes 2:8); ^1H NMR (300 MHz, $CDCl_3$) 5.16 (s, 1H, C*H*O), 4.28 (t, $J=8.3$ Hz, 2H, CH_2N), 3.53–3.74 (m, 4H, CH_2CH_3), 3.24 (t, $J=8.3$ Hz, 4H, CH_2S), 1.22 (t, $J=7.1$ Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 171.5 (*C*=N), 99.4 (CHO), 64.7 (CH_2N), 62.7 (CH_2O), 32.7 (CH_2S), 15.3 (CH_3); IR (neat) (cm^{-1}) 2977, 2931, 2886, 1686, 1627, 1523, 1444, 1370, 1332, 1061, 993. HRMS calcd. for $C_8H_{16}NO_2S$ $(M+H)^+$ 190.0902, found 190.0902.

2-Thiazoline-2-acetic Acid, Ethyl Ester (7)[24]

Isolated yield: 54% (94 mg); colorless liquid; R_f 0.3 (AcOEt/hexanes 3:7); ^1H NMR (300 MHz, $CDCl_3$) **7a**: 4.02 (m, 2H, CH_2O), 3.72 (m, 2H, CH_2N), 3.27 (m, 2H, CH_2S), 3.13 (m, 2H, CH_2C=N), 1.19 (m, 3H, CH_3); **7b**: 8.16 (s, 1H, NH), 4.66 (s, 1H, *H*C=C), 4.13 (m, 2H, CH_2O), 3.72 (m, 2H, CH_2N), 3.53 (m, 2H, CH_2S), 1.19 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) **7a** 169.8 (C=O), 165.5 (C=N), 62.0 (CH_2N), 42.8 (OCH_2), 41.4 (CH_2CO), 24.7 (CH_2S), 14.4 (CH_3); **7b** 169.8 (C=O), 166.9 (*C*=CH), 87.5 (C=*C*H), 77.4 (OCH_2), 62.0 (CH_2N), 24.4 (CH_2S), 14.5 (CH_3); IR (neat) (cm^{-1}) 2981, 2936, 1736, 1655, 1549, 1444, 1370, 1335; HRMS calcd for $C_7H_{11}NO_2S$ $(M)^+$ 173.0511, found 173.0511.

2-(Diethoxymethyl)-benzothiazole (8)

Isolated yield: 95% (225 mg); colorless liquid; R_f 0.3 (AcOEt/hexanes 1:9); ^1H NMR (300 MHz, $CDCl_3$) 8.10 (d, $J=9$ Hz, $1H_{aro}$), 7.89 (d, $J=9$ Hz, $1H_{aro}$), 5.81 (s, 1H, C*H*O), 3.70–3.82 (m, 4H, OCH_2), 1.30 (t, $J=7.1$ Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 170.3 (C=N), 155.2, 135.4, 126.3, 125.7, 123.8, 122.1 ($6C_{aro}$), 99.4 (OCH), 62.7 (OCH_2), 15.4 (CH_3); IR (neat) cm^{-1} 3062, 2977, 2930, 2884, 1521, 1435, 1317, 1060, 761, 731. HRMS calcd for $C_{12}H_{16}NO_2S$ $(M+H)^+$ 238.0902; found 238.0904.

Ethyl 2-(Diethoxymethyl)-2-thiazoline-4-carboxylate (9)

Isolated yield: 68% (178 mg); colorless liquid; R_f 0.35 (AcOEt/hexanes 3:7); $[\alpha]_D$ −2.1 (c 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 5.23 (s, 1H, C*H*O), 5.14 (t,

$J = 9.2$ Hz, 1H, C*H*CO_2Et), 4.24 (q, $J = 7.2$ Hz, 2H, *CH_2*OCO), 3.48–3.77 (M, 8H), 3.58–3.69 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H, *CH_3*CH_2OCO), 1.26 (t, $J = 7.2$ Hz, 6H, *CH_3*CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) 174.2 (C=O), 170.5 (*C*=N), 99.0 (O-C-O), 78.0 (*C*N=), 62.9, 62.5, 61.8 ($3CH_2O$), 34.3 (CH_2S), 15.1 (CH_3O), 14.2 (*CH_3*CH_2); IR (neat) (cm^{-1}) 2978, 2932, 1739, 1623, 1184, 1062; HRMS calcd for $C_{11}H_{20}NO_4S$ $(M + H)^+$ 262.1112; found 262.1111.

Ethyl 2-Ethoxycarbonylmethylenethiazolidine-4-carboxylate (10)[25]

Isolated yield: 65% (159 mg); colorless liquid; R_f 0.25 (AcOEt/hexanes 3:7); $[\alpha]_D$ −9.2 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) **10b**: 8.49 (s, 1H, NH), 5.04 (t, $J = 8.9$ Hz, 1H, C*H*CO_2Et), 4.76 (s, 1H, C*H*=C); **10a**: 4.59 (t, $J = 5.7$ Hz, 1H, C*H*CO_2Et); Mixture: 4.06–4.24 (M, 4H, O*CH_2*CH_3), 3.71–3.77 (m, 2H, C*H_2*CO_2Et), 3.58–3.69 (m, 2H, CH_2S), 3.44–3.56 (m, 2H, CH_2S), 1.21–1.29 (M, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ, 170.7 (C=O), 170.0 (C=O), 169.4 (C=O), 167.8 (C=N), 167.1 (*C*=CH), 80.1 (C=*C*H), 78.0, 62.4, 62.2, 62.1, 60.6, 59.2, 40.3 (OCH_2), (C*H*CO_2Et), 36.4, 31.6, (CH_2S), 24.7, 14.8, 14.4, 14.3 (3 CH_3); IR (neat) (cm^{-1}) 3320, 2982, 2937, 1741, 1657, 1571, 1192, 1042; HRMS calcd for $C_{10}H_{15}NO_4S$ (M^+) 245.0722; found 245.0722.

Ethyl 2-(Diethoxymethyl)-4-thiazolecarboxylate (11)

A solution of ethyl 2-(diethoxymethyl)-2-thiazoline-4-carboxylate (**9**) (235 mg, 0.9 mmol) in dry CH_2Cl_2 (8 mL) was cooled to 0 °C and DBU (269 μL, 1.8 mmol) was added. After 10 min of stirring, bromotrichloromethane (88 μL, 0.9 mmol) was introduced dropwise via syringe over a period of 10 min. The reaction was complete after 1 h. Upon washing with saturated aqueous NH_4Cl (10 mL), the aqueous phase was extracted twice with EtOAc (2×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The desired product **(11)** was obtained quantitatively as an oil and used without further purification (233 mg, 0.9 mmol). Isolated yield >99%. Data were in accord with the literature.[2]

Ethyl 2-Formyl-4-thiazolecarboxylate (12)

A solution of ethyl 2-(diethoxymethyl)-4-thiazolecarboxylate (**11**) (233 mg, 0.9 mmol) was heated at reflux in acetone (25 mL) with aqueous 2 N hydrochloric acid (2.5 mL) for 1 h. After cooling and concentration, the reaction mixture was extracted with chloroform (3×10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. An amount of 158 mg (0.85 mmol) of the title compound was obtained in an acceptable pure form and used in the next step without further purification. Isolated yield 95%. Data were in accord with the literature.[2]

Ethyl 2-(1-Hydroxyethyl)-4-thiazolecarboxylate (13)[26]

A solution of methyl magnesium bromide (1.4 M in THF/toluene, 570 μL, 0.8 mmol) was added dropwise to a solution of ethyl 2-formyl-4-thiazolecarboxylate

(**12**) (158 mg, 0.8 mmol) in 5 mL THF at 0 °C, and the mixture was stirred for 12 h. Saturated aqueous ammonium chloride solution (10 mL) was added, and the mixture was concentrated in vacuo. The aqueous layer was further extracted with chloroform (3×10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (silica) eluting with light petroleum–ethyl acetate (5:5) to give the title compound (**13**) as oil.

Isolated yield: 30% (60 mg); colorless liquid; R_f 0.3 (AcOEt/hexanes 5:5); ^{1}H NMR (300 MHz, $CDCl_3$) 8.11 (s, $1H_{thiazole}$), 5.20 (q, $J = 6.5$ Hz, 1H, C*H*OH), 4.40 (q, $J = 7.2$ Hz, 2H, CH_3CH_2), 1.64 (d, $J = 6.5$ Hz, 3H, (CH_3CH), 1.37 (t, $J = 7.2$ Hz, 3H, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 177.5 (*C*=N), 161.7 (C=O), 147.2 (*C*=CO_2Et), 127.7 (C=*C*H), 68.6 (*C*HOH), 61.8 (CH_2O), 24.5 (CH_3CH_2), 14.7 (CH_3); IR (neat) cm^{-1} 3409, 3122, 2982, 2932, 1722, 1218, 1100, 1018. HRMS calcd. for $C_8H_{11}NO_3S$ $(M)^+$ 201.0460; found 201.0459.

Ethyl 2-Acetylthiazole-4-carboxylate (14)

To a solution of **13** (48 mg, 0.24 mmol) in 1.5 mL of CH_2Cl_2 was added 0.88 mL (1.1 eq, 0.264 mmol) of a commercial Dess–Martin reagent solution (0.3 M in CH_2Cl_2). The reaction mixture was stirred at room temperature under argon for 2 h. After addition of water (5 mL) and extraction with 3×5 mL of CH_2Cl_2, the organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica) eluting with light petroleum–ethyl acetate (7:3) to give the title compound (**14**). Isolated yield: 94% (45 mg). Data were in accord with the literature.[7b]

2-Acetylthiazole-4-carboxylic Acid (15)

Compound **14** (55 mg, 0.28 mmol) was added to a solution of LiOH (10 mg, 0.42 mmol) in 2.4 mL THF and 0.6 mL H_2O. The reaction mixture was stirred at room temperature for 24 h and extracted with AcOEt (10 mL). The aqueous phase was then acidified with HCl 1 N to pH 1–2 and extracted with AcOEt (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed in vacuo to give 31 mg of pure **15**. Isolated yield: 65%; data were in accord with the literature.[21]

Bacillamide A (16)[21]

DCC (30 mg, 0.145 mmol), HOBt (18 mg, 0.133 mmol), and tryptamine (25 mg, 0.156 mmol) were mixed with acid **15** (27 mg, 0.158 mmol) in 1 mL of dichloromethane at 0 °C and stirred overnight at room temperature. After extraction with dichloromethane and water, the organic phase was dried on $MgSO_4$ and evaporated. The crude sample was separated by preparative TLC (CH_2Cl_2/MeOH 96:5) to give the final compound **16** (24 mg, 0.078 mmol).

Isolated yield: 50%; solid, mp. 168–169 °C (lit. 169–170 °C[21]) R_f 0.5 (CH_2Cl_2/MeOH 96:5); ^{1}H NMR (400 MHz, $CDCl_3$) 8.40 (s, $1H_{thiazole}$), 8.09 (bs, 1H, NH), 7.67 (d, $J = 8$ Hz, $1H_{aro}$), 7.40 (m, $2H_{aro}$), 7.11–7.24 (m, 3H), 3.82 (q, $J = 8$ Hz, 2H, CH_2CH_2NH), 3.13 (t, $J = 8$ Hz, 2H, CH_2CH_2NH), 2.61 (s, 3H, CH_3); ^{13}C NMR

(100 MHz, $CDCl_3$) 191.5 (C=O), 166.8 (C=N), 160.7 (NH-*C*=O), 152.1 (*C*-CONH), 136.7 (*C* indole), 129.9 (H*C*-S), 127.7 (*C* indole), 122.6 (*C* indole–NH), 122.4 (*C* indole), 119.9 (*C* indole), 118.1 (*C* indole), 113.4 (*C* indole-CH2), 111.6 (*C* indole), 40.3 (*C*H2-NH), 26.3 (*C*H3-C=O), 25.8 (*C*H2); IR (neat) cm^{-1} 3408, 3122, 2982, 2932, 1686, 1655, 1547, 1481, 1263. HRMS calcd. for $C_{16}H_{16}N_3O_2S$ $(M+H)^+$ 314.0963; found 314.0963.

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