One-pot synthesis of Acanthus ilicifolius Linn alkaloid 2-benzoxazolinone derivatives via a tandem Ugi 4-component coupling/haloform cyclization

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Abstract
A one-pot, base-mediated approach to Acanthus ilicifolius Linn alkaloid 2-benzoxazolinone derivatives is developed. Starting from trichloroacetic acid, o-aminophenol, substituted benzaldehydes and alkyl isocyanides, the desired 2-benzoxazolinone derivatives are obtained in good yields via a tandem Ugi condensation and intramolecular haloform cyclization at room temperature in the presence of Et3N.

Keywords
2-benzoxazolinone derivatives, Acanthus ilicifolius Linn alkaloid, one-pot, synthesis, Ugi 4-component coupling/haloform cyclization

Date received: 25 April 2021; accepted: 25 May 2021

Introduction
Acanthus ilicifolius Linn is a mangrove plant growing in tropical coastal zones, which has antioxidant, hepatoprotective, anti-inflammatory and anti tumor activities.1,2 Researchers3 discovered four new 2-benzoxazolinone-type alkaloids from the mangrove plant Acanthus ilicifolius, named acanthosides A-D (Figure 1). As an active substance of plant secondary metabolites, benzoxazolones play an important role in plant self-defense. The toxicological and pharmacological properties of benzoxazinoids have been reported as chemical resistance factors against insects, fungi, bacteria and viruses in many crop plants of the family Gramineae,4,5 as well as mutagenic activities,6 can also be used as lead compounds for the development of new drugs.

Urea fusion reactions with o-aminophenols or their hydrochloride salts7 in harsh condition is one of the oldest and most widely employed syntheses of 2-benzoxazolinones.8,9 Herein, Ugi reactions of o-aminophenol under mild condition with subsequent haloform cyclization are proposed for the synthesis of 2-benzoxazolinones. The classical Ugi reaction is a four-component coupling reaction (U-4CR) between an amine, a carbonyl compound (aldehyde or ketone), a carboxylic acid, and an isocyanide. This 4-CR has been widely used in modern synthetic chemistry10-15 and has tentatively been used for direct bioconjugation.16-20 The construction of heterocyclic rings is a key stone of natural product and artificial drug synthesis, therefore, the Ugi reaction is now a cornerstone of isocyanide based multicomponent reactions (I-MCR) for the construction of natural products and diverse heterocyclic scaffolds.21-26 We synthesized 2-benzoxazolinones by Ugi reactions and introduced different substituents to synthesize a series of new compounds (Scheme 1).

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Scheme 1. The strategy for the choice of 2-(2-oxobenzol[d] oxazol-3(2H)-yl) acetamides as targets.

Herein, we report a direct synthesis of Acanthus ilicifolius Linn alkaloid 2-benzoxazolinone derivatives 6 from trichloroacetic acid (1), o-aminophenol (2), substituted benzaldehydes (3) and alkyl isocyanides (4) via a tandem Ugi condensation and intramolecular haloform cyclization (Scheme 2). Seven new compounds with a benzoxazolinone core structure are obtained.

Results and discussion

Based on tandem I-MCR/SN cyclization, we previously prepared (E)-2-aroyl-4-arylidene-5-oxopyrrolidine\(^27\) and (E)-2-aroyl-4-arylidene-5-oxotetrahydro rhopaladin analogs furan.\(^28\) In the analogous way, seven Acanthus ilicifolius Linn alkaloid 2-benzoxazolinone derivatives 6 have been obtained in good to excellent yields, and the highest yield is 90%. The yields of compounds 6 were mainly related to the nature of the Ar substituent on the benzaldehyde (2), and not on the R group of the alkyl isocyanides (3). The stronger the electron-withdrawing effect of the Ar substituent, the higher the reaction yield.

The structures of compounds 6a-g were confirmed from their spectroscopic data. The \(^1\)H NMR spectra of compounds 6 showed chemical shifts for the aromatic hydrogens generally between 7.72 ppm and 6.68 ppm, with the NH being between 6.72 ppm and 6.10 ppm. The signal for the NCH of the ethanoyl moiety occurs as a singlet between 2.40 ppm and 1.52 ppm. The \(^13\)C NMR spectral data of compounds 6 show the characteristic chemical shifts of the endocyclic and exocyclic amide carbonyls around 155 ppm and 165 ppm, respectively. The MS spectra of 6 show that molecular ion peaks are very weak, but peaks of M\(^+\)-CONHR are stronger\(^27\). For instance, the MS spectrum of 6a shows molecular ion peak and M\(^+\)-CONH\(_2\) at m/z 384 and 258 with 2% and 57% abundance, respectively.

Conclusion

Based on a one-pot, base-mediated approach proceeding via a tandem Ugi condensation and intramolecular haloform cyclization at room temperature, seven novel 2-benzoxazolinone derivatives have been obtained. And in the intramolecular haloform cyclization step, the triethylamine is deprotonating the phenol to generate the phenoxide which then displaces the chloromethyl anion from the carboxyl carbon by an addition elimination process. The products were obtained in high yields under mild conditions using a simple procedure. During the experimental process, the Ugi reaction intermediates are not separated or purified, and can be directly used in the intramolecular haloform cyclization step.

Experimental section

General

Melting points were measured with an X-4 melting point instrument (uncorrected thermometer) produced by Beijing Ruili Analytical Instrument Co., Ltd. Mass spectrometry was performed with a Finnigan trace MS analyzer (direct injection method). Elemental analysis was performed using a Vario EL III analyzer. \(^1\)H NMR and \(^13\)C NMR spectra were measured at 400 MHz using model spectrometers. The solvent was CDCl\(_3\) with TMS as the internal standard.
General procedure for the preparation of 2-benzoxazolinone derivatives 6a-g

Trichloroacetic acid (1) (1 mmol), o-aminophenol (2) (1 mmol), substituted benzaldehyde (3) (1 mmol) and alkyl isocyanide (4) (1 mmol) were added consecutively to a flask containing methanol (5 mL), and the resulting mixture was stirred for 24 h at room temperature. Triethylamine (1 mL) was added and the mixture was stirred for a further 24 h at room temperature. The solvent was removed under reduced pressure and the residue was recrystallized from ether to obtain the 2-benzoxazolinone derivatives 6a-g.

2-(2-Chlorophenyl)-N-cyclohexyl-2-(2-oxobenz[d]oxazol-3(2H)-yl) acetamide (6a). White solid (0.34 g, 87%), mp 209-210 °C; 1H NMR (400 MHz, CDCl3): \( \delta = 7.72-6.83 \) (m, 8H, Ar-H), 6.60 (s, 1H, NH), 6.29 (s, 1H, CH), 3.89-3.85 (m, 1H, CH), 1.99-1.13 (m, 10H, 5CH2). 13C NMR (100 MHz, CDCl3): \( \delta = 165.3, 154.4, 142.5, 138.4, 134.9, 131.2, 130.5, 129.1, 127.7, 123.8, 122.5, 115.1, 111.0, 58.9, 49.7, 32.5, 24.7, 21.1. \) MS (EI): \( m/z = 384 \) (M+), (2), 258 (57), 134 (33), (113 (100), 126 (24), 83 (18). Anal. Calcd for C21H21ClN2O3: C, 65.54; H, 5.59; N, 7.28. Found: C, 65.48; H, 5.62; N, 7.18.

2-(2-Chlorophenyl)-N-cyclohexyl-2-(2-oxobenz[d]oxazol-3(2H)-yl) acetamide (6b). White solid (0.34 g, 89%), mp 176-178 °C; 1H NMR (400 MHz, CDCl3): \( \delta = 7.40-6.95 \) (m, 8H, Ar-H), 6.29 (s, 1H, NH), 6.04 (s, 1H, CH), 3.89-3.85 (m, 1H, CH), 2.01-1.14 (m, 10H, 5CH2). 13C NMR (100 MHz, CDCl3): \( \delta = 165.3, 149.3, 142.5, 135.4, 135.0, 130.3, 129.2, 128.3, 126.2, 124.0, 122.9, 111.9, 110.1, 60.1, 49.2, 32.6, 25.3, 24.7. \) MS (EI): \( m/z = 364 \) (M+), (4), 258 (57), 134 (37), (113 (100), 126 (33). Anal. Calcd for C19H17ClN2O3: C, 65.54; H, 5.50; N, 7.28. Found: C, 65.43; H, 5.59; N, 7.21.

2-(2-Bromophenyl)-N-butyl-2-(2-oxobenz[d]oxazol-3(2H)-yl) acetamide (6c). White solid (0.30 g, 88%), mp 146-147 °C; 1H NMR (400 MHz, CDCl3): \( \delta = 7.56-6.97 \) (m, 8H, Ar-H), 6.67 (s, 1H, NH), 6.07 (s, 1H, CH), 3.89-3.85 (m, 2H, CH2), 1.56-1.52 (m, 2H, CH2), 1.33–1.28 (m, 2H, CH2). 11C NMR (100 MHz, CDCl3): \( \delta = 166.2, 154.7, 150.9, 142.4, 135.5, 132.1, 131.1, 130.5, 129.4, 126.7, 124.0, 122.9, 111.8, 110.1, 60.1, 39.8, 32.1, 20.0, 13.6. \) MS (EI): \( m/z = 354 \) (M+), (3), 254 (57), 134 (42), (126, 31), 107 (100), 100 (24), 57 (26), 43 (19). Anal. Calcd for C16H15BN2O4: C, 67.66; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.37; N, 7.84.

N-Butyl-2-(4-flurophenyl)-2-(2-oxobenzo[d]oxazol-3(2H)-yl) acetamide (6d). White solid (0.29 g, 86%), mp 165-166 °C; 1H NMR (400 MHz, CDCl3): \( \delta = 7.34-6.86 \) (m, 8H, Ar-H), 6.72 (s, 1H, NH), 6.08 (s, 1H, CH), 3.77 (s, 3H, CH3), 3.34-3.25 (m, 2H, CH2), 1.51-1.47 (m, 2H, CH2), 1.34-1.28 (m, 2H, CH2), 0.89 (s, \( J = 7.66z \), 3H, CH3). 13C NMR (100 MHz, CDCl3): \( \delta = 167.1, 159.8, 154.7, 142.4, 129.6, 125.2, 123.7, 122.3, 114.3, 111.8, 109.7, 108.6, 60.2, 55.2, 39.6, 31.1, 19.9, 13.6. \) MS (EI): \( m/z = 354 \) (M+), (4), 254 (54), 134 (42), 126 (31), 107 (100), 100 (24), 57 (26), 43 (19). Anal. Calcd for C16H16F2N2O4: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.37; N, 7.84.

Author contributions
Zhu J, Tian XQ, Kong LQ and Wang HM contributed to the designing, conceptualization and synthesis. Ke LN, Ran FY and Wu L performed data analysis and statistical analysis. Chen QH and Zeng XH performed data acquisition and manuscript editing.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Natural Science Foundation of China (81872509), Bao’an TCM Development Foundation (2020KICX-KTYJ-200), the Internal Research Project of Shenzhen Baoan Authentic TCM Therapy Hospital (BCZY2021003 and BCZY2021007), Baohan District Medical and Health Basic Research Project (2020JD491), the Chinese Medicine Research Fund of Health Commission of Hubei Province (ZY2021M051), the Hubei Province Health and Family Planning Scientific Research Project (WJ2021M063 and WJ2021M062), the Scientific Research Project of the Educational Commission of Hubei Province of China (B2020106), and the Postgraduate Innovation Project of Hubei University of Medicine (YC2020041).
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Supplemental material
Supplemental material for this article is available online.

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