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SHORT COMMUNICATION



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Rapid continuous photoflow synthesis of naturally occurring arylnaphthalene lignans and their analogs

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ABSTRACT

Naturally occurring arylnaphthalene lignans (ANLs) are subclass of lignans in many dietary or medicinal plants. The progressing interest of ANLs is due to their diversified biological activities. Herein, we developed a convenient method for the preparation of naturally occurring ANLs and their analogs through the continuous photoflow intramolecular Diels–Alder reaction in several minutes under mild conditions with good yields and regioselectivities.



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Arylnaphthalene lignans; continuous photoflow synthesis; intramolecular Diels–Alder reaction

1. Introduction

Arylnaphthalene lignans (ANLs) are widely distributed in dietary or medicinal plants, which serve as sources of diversified structures due to good biological activities, such as tumour or cancer cell line inhibition activities, antioxidant, anti-inflammatory, antimicrobial, antiviral, etc. (Li et al. 2020). Structurally, these naturally occurring ANLs can be divided into type I and type II ANLs based on the position of lactones and phenyl groups (Figure S1). The desire to access ANLs for further investigation has led to the development of many successful synthetic methods for them. They can be roughly classified into two approaches: transition metal-mediated annulations and pericyclic reactions (Zhao et al. 2018; Park et al.

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	A 175W Hg lamp DCM, 0°C, 10 min		+ B O O O
	1a~1e	2a~2e type I	3a~3e type II
Reactant ^a	Ring A	Ring B	Products ^b
1a	or the second se		2a (63.1%) 3a (15.3%)
1b			2b (47.1%) 3b (13.1%)
1c	$ \bigcirc \underbrace{3}_{4} \underbrace{1}_{6} \underbrace{1}_{6$		2c (52.2%) 3c (17.3%)
1d			2d (41.8%) 3d (14.5%)
1e		0 3 1 ² / ₂ Bn0 4 6	2e (38.2%) 3e (23.6%)

Table 1. Continuous photoflow synthesis of naturally occurring ANLs and their analogs.

0

^aConcentration: 0.005 M.

^blsolated yields.

2020). Among them, the utilisation of 3-phenylprop-2-yn-1-yl 3-phenylpropiolates to form the ANLs *via* intramolecular Diels-Alder (D-A) reaction is an atom-economic method. However, the poor regioselectivity and the high temperature conditions limit its application (Stevenson and Weber 1991). Photochemistry reactions use light as the energy source to initiate chemical transformations, which contribute in a significant way to the existing repertoire of carbon-carbon bond-forming reactions, especially in the key cyclisation steps in the total synthesis of some complex natural products (Bach and Hehn 2011). In recent years, the continuous photoflow synthesis approaches have received widespread attentions in the field of photocatalysis. The large surface area to volume ratio of a microreactor maximises the illumination, and at the same time allows for efficient cooling, which may shorten reaction times and provides higher selectivity (Oelgemöller and Shvydkiv 2011; Cambié et al. 2016).

The progressing interest of ANLs is due to their significant biological activities. In order to meet the needs of structural diversity for further studies on their biological activities and structure–activity relationships, we carried out the continuous photoflow intramolecular D–A reaction method for the synthesis of naturally occurring ANLs and their analogs in several minutes under mild conditions with good yields and regioselectivities.

2. Results and discussion

Inspired by the intramolecular D–A approach developed by Stevenson and the method of photochemical reaction in the preparation of naphthalenes reported by Wessig et al. (2005). The photochemistry reaction of 3-(4-methoxyphenyl)prop-2-yn-1-yl 3-(4-methoxyphenyl) propiolate (**1a**) was exploited. As expected, under a high-pressure mercury lamp (175 W) irradiation for 12 h, most of the ester was converted to the corresponding ANLs in 70% yield and the ratio of **2a** (type I) to **3a** (type II) is 2.3:1 (Scheme S1).

On the basis of this experiment, we attempted a continuous photoflow method for the reaction. The reactor consists of a simple design in which fluorinated ethylene propylene (FEP) capillary tubing (ID 1.0 mm) was coiled around the UV lamp. A solution of ester 1a in 1,2-DCE (0.005 M) was injected into the photoreactor used for the photochemical reaction by a syringe pump. Encouragingly, after exposure for 6 min (the average time that the reactants spend in the reactor), the reaction reached a modest conversion rate of 50.3%. Moreover, the regioselectivity was also improved (\sim 4.8:1) (Entry 6, Table S1). In general, the selection of a proper solvent is a crucial step in continuous photoflow as the solvent needs to be able to solubilise the chemicals and products to prevent reactor clogging and undesired light scattering. In the following experiments, different solvents were selected for the reaction. Protonic solvents, such as methanol, HFIP and acetic acid exhibited lower conversion rate of 19.5%, 22.8% and 13.3%, respectively (Entries 10–12, Table S1). In contrast, most of the aprotic solvents showed moderate conversions and excellent regioselectivity. The optimal choice are haloalkanes, represented by DCM or 1,2-DCE (Entries 1, 6 and 13-17, Table S1). The UV exposure time is also an important factor in the photoflow reactions. In Entries 1-8 (Table S1), experiments showed that the conversion of ester 1a to products 2a and **3a** was fast at the beginning several minutes, but the situation turned in after 10 min, which suggested that the prolonged irradiation may cause degradation of the reactants or products. The initial concentration of **1a** was also discussed. The conversion rates were similar at the concentrations of 0.0025 and 0.005 M, however, with the increase of concentrations (0.01 and 0.02 M), the conversion rates were decreased (Entries 2, 6, 9 and 18–20, Table S1). In summary, the most efficient conditions of this reaction seem to be: 1a in haloalkanes (0.005 M) was pumped through the FEP tubing for a total exposure time (175 W Hg lamp) of 10 min.

The conditions of continuous photoflow method provide the possibilities for the rapid preparation of ANLs and their analogs. For the preparation of those ANLs, the corresponding 3-phenylprop-2-yn-1-yl 3-phenylpropiolates were prepared at first. Herein, as shown in Scheme S3, we take the preparation of **1a** as an example: Anisaldehyde was first converted to dibromoalkene **4a**, which was subjected to the Corey–Fuchs alkyne synthesis condition (2.5 equiv of *n*-BuLi in THF, -78 °C) to generate alkyne anion, followed by addition of dry ice to give the desired 3-phenylpropiolic acid **5a**; while **6a** was prepared by addition of paraformaldehyde to the alkyne anion solution at -78 °C. Coupling reaction of **5a** and **6a** was performed using DCC and DMAP in DCM to afford the ester **1a**.

With a series of 3-phenylprop-2-yn-1-yl 3-phenylpropiolates (**1a**–**1e**) in hands, rapid pipelining preparation of naturally occurring ANLs were undertaken (Conditions:

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0.005 M in DCM solution, the 175 W mercury lamp as light source, exposure for 10 min). Herein, we listed the preparation of some well-known naturally occurring ANLs as examples, they are justicidin E (**2b**), taiwanin C (**3b**), retrochinensin (**2c**), justicidin B (**3c**), retrojusticidin B (**2d**) and chinensin (**3d**). The corniculin (**2e1**) can be easily obtained by hydrogenolysis of compound **2e** (Table 1, Scheme S4).

Taken overall, all these reactants (**1a–1e**) convert to the corresponding ANLs in good yields (56.3%–79.6%) and regioselectivities (1.6:1–4.1:1) (Table 1). It is noteworthy that except for the regioselectivities in the position of lactones, the cyclisation sites for those of 3,4-di-substituted benzyls were mainly at C-6 (reactants **1b–1e**). In general, the good performance of continuous photoflow reactions may attributed to the homogeneous irradiation the enhanced mass-, heat- and photon-transport phenomena observed in microchannels.

In summary, we provided a rapid, convenient and catalysts free synthetic method for the preparation of naturally occurring ANLs and their analogs by 3-phenylprop-2yn-1-yl 3-phenylpropiolates in good yields and regioselectivities. Utilisation of the continuous photoflow reactions may break through the limitation of natural product separation and provide the possibilities for the preparation of numerous structurally diversities of naturally occurring ANLs and their analogues in a short time. The further structure activity relationships investigations of those ANLs with diversified biological activities are ongoing.

Disclosure statement

No potential conflict of interest was reported by the authors.

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