

# Competitive thermal ene reaction and Diels–Alder reactions of 2-[*N*-(alk-2-enyl)benzylamino]-3-vinylpyrido[1,2-*a*]pyrimidin-4(4*H*)-ones

Michihiko Noguchi,<sup>a,\*</sup> Toshiya Sunagawa,<sup>a</sup> Ryosuke Akao,<sup>a</sup> Hisashi Yamada,<sup>a</sup>  
Hidetoshi Yamamoto<sup>b</sup> and Akikazu Kakehi<sup>c</sup>

<sup>a</sup>Department of Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University, Tokiwadai, Ube 755-8611, Japan

<sup>b</sup>Department of Advanced Materials Science and Engineering, Graduate School of Science and Engineering, Tokiwadai, Ube 755-8611, Japan

<sup>c</sup>Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan

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**Abstract**—Thermal reaction of 2-[*N*-(alk-2-enyl)benzylamino]-3-(2-substituted and 2,2-disubstituted)vinylpyrido[1,2-*a*]pyrimidin-4(4*H*)-ones gave azepine, the desired ene products, and/or pyran derivatives. The formation of the latter was responsible for the [4+2] cycloaddition reaction between the  $\alpha,\beta$ -unsaturated ester carbonyl moiety as a diene part and the alkenylamino moiety as an ene one. The reaction features depended upon the kinds of substituents both on the vinyl and alkenyl counterparts; strongly electron-withdrawing substituents on the vinyl moiety or an electron-donating substituent on the alkenyl one changed the reaction feature from the ene reaction to the hetero Diels–Alder reaction.

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## 1. Introduction

Recently, we have reported on a facile and stereoselective azepine-ring formation at the periphery of heterocyclic systems via thermal imine- and carbonyl-ene reactions<sup>1</sup> classified as a 7-(1,4) intramolecular ene reaction (Scheme 1).<sup>2</sup>

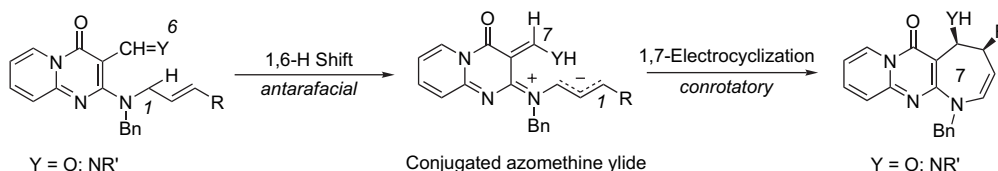
In order to develop the ene reaction, our next concern was focused on the reaction of the similar substrates bearing vinyl moiety as an enophile. The thermal reaction of 2-(*N*-alk-2-enyl)-benzylamino-3-(2-substituted and 2,2-disubstituted)vinylpyrido[1,2-*a*]pyrimidin-4(4*H*)-ones gave the desired ene products and the hetero Diels–Alder adducts. The latter products, therein, were formed by the [4+2] cycloaddition reaction of the  $\alpha,\beta$ -unsaturated ester carbonyl moiety of the substituted vinyl as a diene and the alkenyl moiety as a dienophile. The reaction features depended on the kinds

of the substituents both on the vinyl and alkenylamino parts; when electron-withdrawing substituents such as cyano or ethoxycarbonyl group resided on the vinyl moiety or an electron-donating substituent such as methyl or phenyl one did on the alkenyl moiety, the hetero Diels–Alder reaction was competing with or superior to the ene reaction. The scope and limitations of these thermal reactions will be discussed.

## 2. Results and discussion

### 2.1. Thermal reaction of 2-[*N*-(alk-2-enyl)benzylamino]-3-vinylpyrido[1,2-*a*]pyrimidin-4(4*H*)-ones

The starting 3-vinylpyridopyrimidines **2**, **3**, and **4** were prepared by the reaction of 2-(*N*-allylbenzylamino)-3-formylpyrido[1,2-*a*]pyrimidin-4(4*H*)-ones **1** with a Horner–



**Scheme 1.** Reaction: (i) 7-(1,4) intramolecular ene reaction.

**Keywords:** Competitive reaction; Ene reaction; Diels–Alder reaction.

\* Corresponding author. Tel.: +81 836 85 9261; fax: +81 836 85 9201; e-mail: [noguchi@yamaguchi-u.ac.jp](mailto:noguchi@yamaguchi-u.ac.jp)

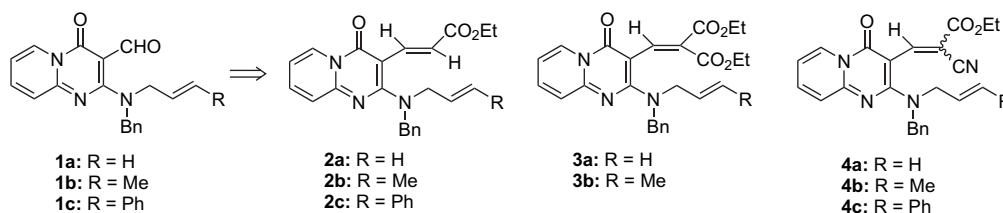
Emmons reagent for **2**, with diethyl malonate in refluxing benzene in the presence of piperidine and acetic acid<sup>3</sup> for **3**, and with ethyl cyanoacetate in ethanol in the presence of potassium carbonate for **4** (Scheme 2). Vinyl substrates **2a** and **4a** were composed of inseparable mixtures of *E*- and *Z*-isomers and the *E/Z* ratios were deduced to be >19:1 for **2** and >6:1 for **4** from their <sup>1</sup>H NMR spectral data.

The reaction of vinyl substrates **2a** in refluxing xylene gave the desired ene product, pyrido[1',2':1,2]pyrimido[4,5-*b*]azepine **5a** in good yields. The structure of **5a** was established by spectroscopic data in comparison with those of the related azepine derivatives.<sup>1</sup> In order to obtain further information on the reaction features, substrates **2b** and **2c** were allowed to react. While the thermal reaction of **2b** in refluxing xylene gave only azepine **5b**, the similar reaction of **2c** yielded a mixture of three isomeric products, azepine **5c**, homo Diels–Alder adduct **6**, and hetero Diels–Alder adduct **7**, in a good total yield (Scheme 3). The structure of **6** was also accomplished on the basis of its spectroscopic data; the <sup>1</sup>H–<sup>1</sup>H COSY spectra of **6** elucidated two sets of alignment of methylene ( $\delta$ =ca. 3.0; 7-*H*<sub>2</sub>)-methine (2.49; 7a-*H*)-methylene protons (2.64 and 3.30; 8-*H*<sub>2</sub>) and methine (2.49; 7a-*H*)-methine (4.01; 13a-*H*)-methine one (3.89; 13-*H*). This suggested that the framework of **6** was deduced to be benzo[*g*]pyrido[1',2':1,2]pyrimido[4,5-*c*]isoquinoline arising from the Diels–Alder reaction between the styrene and vinyl moiety of **2c**. The configurations among the 7a-*H*, 13a-*H*, and 13-*H* were deduced to be *cis* ( $J_{7a-13a}$ =4.6 Hz) and *trans* ( $J_{13a-13}$ =8.6 Hz) compared with the coupling constants of the related ring systems obtained by the intramolecular Diels–Alder reaction of the substrates bearing styrene moiety as diene components such as *N*-(*E*)-cinnamylmethyl fumaramic acid ethyl ester.<sup>4</sup> On the other hand, product **7** was not so stable and converted to **8** during the

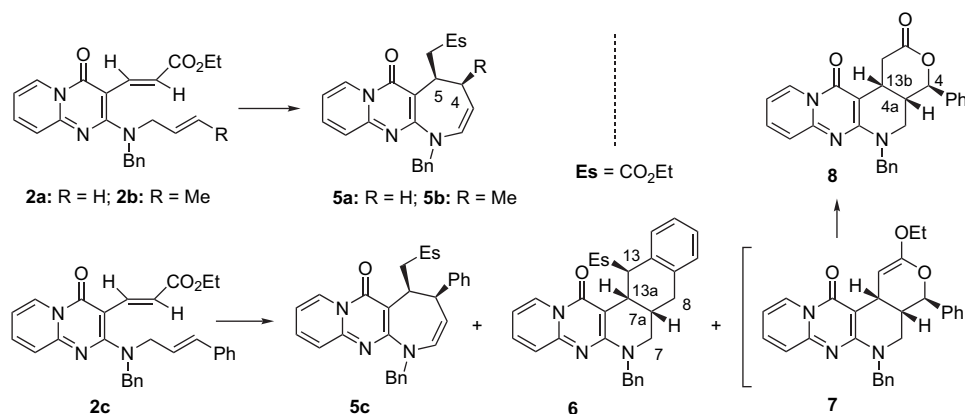
chromatographic purification on silica gel. The structure of **8** was also established by its spectroscopic data; the <sup>1</sup>H–<sup>1</sup>H COSY spectra of **8** elucidated two sets of alignment of methylene ( $\delta$ =2.54 and 3.21; 5-*H*<sub>2</sub>)-methine (2.17; 4a-*H*)-methine proton (4.34; 4-*H*) and methine (2.17; 4a-*H*)-methine (4.15; 13b-*H*)-methylene ones (2.29 and 3.04; 1-*H*<sub>2</sub>). The configurations among the 4-*H*, 4a-*H*, and 13b-*H* were deduced to be *trans* ( $J_{4-4a}$ =9.9 Hz) and *cis* ( $J_{4a-13b}$ : small) also based on the coupling constants. The formation of **8** was explained by hydrolysis of ketene acetal moiety of **7**.

These reaction features were explained by the frontier molecular orbital (FMO) analysis<sup>5</sup> using the model compounds;<sup>6</sup> the occupied  $\pi$ -electron energy level of the ene moiety in **2c** shifted upward and both Diels–Alder reactions could be competitive with the ene reaction.

The thermal reaction of **4a** gave the only product **11a** in 76% yield. In the <sup>1</sup>H NMR spectrum of **11a**, no signals assigned to olefinic protons were shown and no absorption bands assignable to ester carbonyl were observed in its IR spectrum. The <sup>13</sup>C NMR spectra including DEPT measurement of **11a** showed seven sp<sup>3</sup>-carbon signals; one methyl ( $\delta$ =14.9), four methylene (30.2, 50.1, 64.6, and 69.6), and two methine ones (27.5 and 28.6). The <sup>1</sup>H–<sup>13</sup>C and <sup>1</sup>H–<sup>1</sup>H COSY spectra of **11a** elucidated two sets of the alignment of methylene ( $\delta$ =ca. 4.3; 4-*H*<sub>2</sub>)-methine (2.23; 4a-*H*)-methylene protons (3.18 and 3.37; 5-*H*<sub>2</sub>) and methine (2.23; 4a-*H*)-methine proton (ca. 4.3; 13b-*H*). The structure of **11a** was deduced to be 6-benzyl-1-cyano-2-ethoxy-4a,5,6,13b-tetrahydropyrano[4',3':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidin-13(4*H*)-one comparing with the proton signal patterns of the similar intramolecular hetero Diels–Alder adducts extensively studied by Tietze and other workers.<sup>7</sup> Although the configuration between the 4a-*H* and 13b-*H* in **11a** could not be established



Scheme 2. Mono(ethoxycarbonyl)- **2**, bis(ethoxycarbonyl)- **3**, and cyano(ethoxycarbonyl)-substituted vinyl substrates **4**.



Scheme 3. Thermal reaction of **2** leading to ene products **5** and/or Diels–Alder products **6** and **7**.

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