Intramolecular nitrone- and azomethine ylide-cycloaddition reactions at the periphery of pyrido[1,2-*a*]pyrimidin-4(4*H*)-one system

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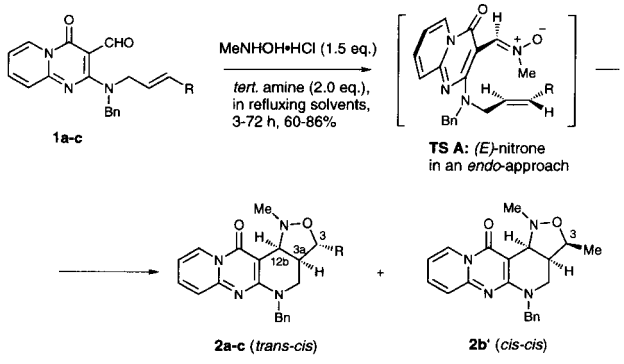
Isoxazolo[4′,3′:4,5]pyrido- and pyrrolo[2′,3′:4,5]pyrido-[2,3-*d*]pyrido[1,2-*a*]-pyrimidines were obtained in the intramolecular cycloaddition reactions of the nitrone and azomethine ylide at the periphery of pyrido[1,2-*a*]pyrimidin-4(4*H*)-one system, respectively.

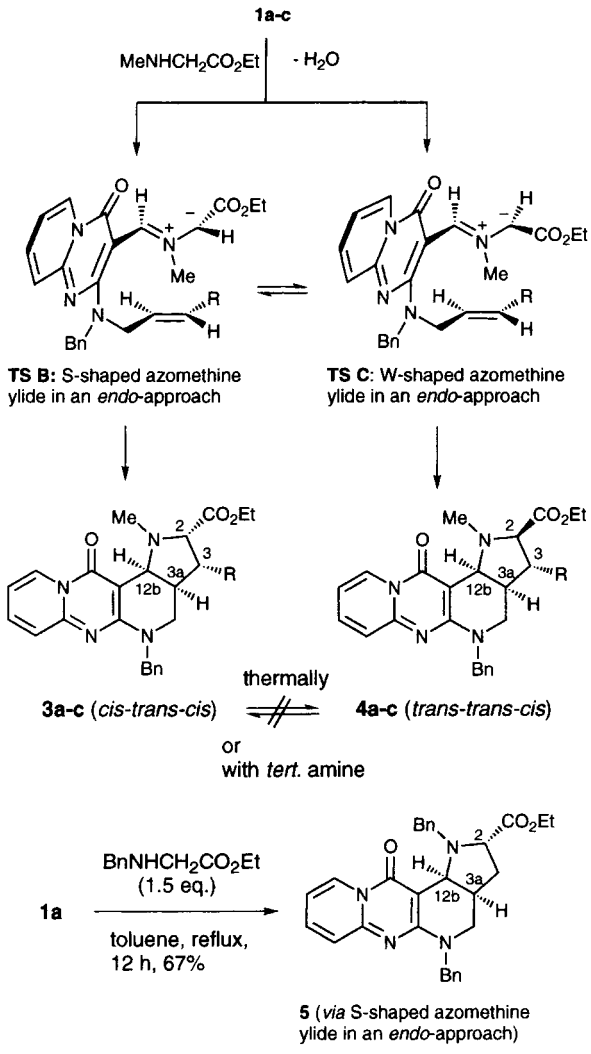
In previous papers, we reported the stereoselective intramolecular cycloaddition reactions of NH-nitrone[5] and NH-azomethine imine[6] at the periphery of pyrido[1,2-*a*]pyrimidin-4(4*H*)-one system to afford isoxazolo[4',3':4,5]pyrido- and pyrrazolo-[2',3':4,5]pyrido-[2,3-*d*]pyrido[1,2-*a*]pyrimidines, respectively. In this paper the intramolecular cycloaddition reactions of *N*-methyl nitrones and *N*-methyl azomethine ylides in the pyrido[1,2-*a*]pyrimidin-4(4*H*)-one system are reported. The features of the intramolecular cycloaddition step are also discussed.

The reaction of 2-(*N*-allylbenzylamino)-3-formylpyrido-[1,2-*a*]pyrimidin-4(4*H*)-one (**1a**) with *N*-methylhydroxylamine in EtOH at reflux gave the desired nitrone–cycloadduct **2a** in 86% yield as a single isomer. Similar reaction using *N*-(*E*)-but-2-enyl substrate **1b** and *N*-(*E*)-cinnamyl one **1c** also gave isoxazolidines **2b** and **2c** in moderate to good yields (Scheme 1). In the reaction of **1b**, a trace amount of another product **2b'** was also formed. The structures of isoxazolidines **2a–c** were easily assigned on the basis of their elemental analyses and spectroscopic data in comparison with those of the corresponding nitrone–cycloadducts.[4, 5, 7] On the basis of the structures of cycloadducts **2**, the formation of cycloadducts **2a–c** was ascribed to the transition state **A**, in an *endo*-approach of the more reactive (*E*)-nitrone. On the other hand, the structure of another isomer **2b'** was assigned to be the epimer of cycloadduct **2b** at the 3-position A similar stereo-mutation of the dipolarophile moiety in the intramolecular nitrone–cycloaddition has been found in the literature.[9,10]

In order to extend this method to an azomethine ylide–cycloaddition, we next examined the reaction of **1** with sarcosine ethyl ester. The reaction of aldehyde **1a** with sarcosine ethyl ester hydrochloride in EtOH at reflux in the presence of triethylamine for 10 h gave two isomeric azomethine ylide–cycloadducts **3a** and **4a** in 62 and 18% yields, respectively. From the coupling constants between the 3a- and 12b-H of **3a** and **4a**, the ring-fusion of **3a** and **4a** is suggested to be *cis* and, therefore, the two isomers are corresponding to the epimers at the 2-position. The stereochemistry of the pyrrolidine-ring of **3a** was deduced to be *trans* (2- and 3a-H) and *cis* (3a- and 12b-H), because its signal patterns of the 2-H and 12b-H were consistent with those of the 2-H and 9b-H of the azomethine ylide–cycloadduct in the reaction of 6-(*N*-allyl-



Scheme 1



Scheme 2

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Table 1 Reaction of aldehydes **1** with *N*-methylhydroxylamine hydrochloride in the presence of *tert.* Amines

Run	Aldehyde	R	Solvent	*tert* amine	Time/h	Product (Yield/%)[a]
1	**1a**	H	EtOH	Et_3N	3	**2a** (86)
2[b]	**1b**	Me	EtOH	Et_3N	5	**2b** (75)
3[b]	**1b**	Me	benzene	Et_3N	72	**2b** (66)
4	**1c**	Ph	EtOH	Et_3N	7	**2c** (72)
5	**1c**	Ph	toluene	$(i\text{-Pr})_2EtN$	12	**2c** (60)

[a]Based on isolated product.

[b]Another product **2b'** was also obtained in a trace amount (2%).

Table 2 Reaction of Aldehydes **1** with Sarcosine Ethyl Ester Hydrochloride in the Presence of *tert.* Aimines

Run	Aldehyde	R	Solvent	*tert.* Amine	Time/h	Products (Yield/%)[a]	
1	**1a**	H	benzene	Et_3N	10	**3a** (34)	**4a** (4)
2	**1a**	H	MeCN	Et_3N	10	**3a** (65)	**4a** (11)
3	**1a**	H	MeCN	None[b]	22	**3a** (64)	**4a** (26)
4	**1a**	H	EtOH	Et_3N	10	**3a** (62)	**4a** (22)
5	**1a**	H	toluene	$(i\text{-Pr})_2EtN$	10	**3a** (62)	**4a** (35)
6	**1b**	Me	toluene	$(i\text{-Pr})_2EtN$	20	**3b** (52)	**4b** (40)
7	**1c**	Ph	toluene	$(i\text{-Pr})_2EtN$	10	**3c** (57)	**4c** (16)

[a]Based on isolated product.

[b]Molecular sieves (3Å) was added for a dehydrant.

benzylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione with *N*-benzylglycine ethyl ester, which were characterized unumbigously by X-ray single-crystal structure analysis.[3] The stereochemistry of another isomer **4a** was also deduced to be *cis* (2- and 3a-H) and *cis* (3a- and 12b-H), from its signal patterns and coupling constant in its ^{1}H NMR spectrum. Similar reaction of aldehydes **1b** and **1c** with sarcosine ethyl ester in toluene at reflux gave **3b** and **4b**, and **3c** and **4c**, respectively (Scheme 2 and Table 2). The *cis*-relationship between the 2- and 3-H in **3b** and **3c** was confirmed by the coupling constants. On the other hand, the stereochemistry between the 2- and 3-H in **4b** and **4c** was deduced to be *trans* also from their coupling constants. Fortunately, the structure of **4b** was confirmed (the stereochemistry among the 2-, 3-, 3a-, and 12b-H: *trans–trans–cis*) by its X-ray single–crystal structure analysis.

In the similar intramolecular azomethine ylide–cycloaddition of pyrimidine-2,4(1*H*,3*H*)-dione system,[3] we proposed that the formation of two epimeric pyrrolidine derivatives was ascribed to the epimerisation of the kinetically favorable 2,3-*cis* isomer to the more stable 2,3-*trans* isomer when base was utilised. In the present case, however, the interconversion between cycloadducts **3** and **4** under the reaction conditions was ruled out; heating **3a** and **4a** in toluene at reflux for 3d with or without *tert.* amines did not provide any changes of the **3a** and **4a**. On the other hand, the similar reaction of aldehyde **1a** with sarcosine ethyl ester hydrochloride without base in MeCN gave also **3a** and **4a** (Table 2, run 3).

These results suggested that the formation of cycloadducts **3** and **4** was ascribed to the transition state **B** and **C** of the resulting azomethine ylides, respectively. The *endo*-approach of an S-shaped azomethine ylide (transition state **B**), therein, affords the cycloadducts **3** (2-, 3-, 3a-, and 12b-H: *cis–trans–cis*) and the *endo*-one of a W-shaped azomethine ylide (transition state **C**) does the cycloadduct **4** (2-, 3-, 3a-. and 12b-H: *trans–trans–cis*) (Scheme 2). It is reasonable that the W-shaped azomethine ylide is a less stable isomer than the S-shaped one due to steric repulsion between the ester moiety and the methyl group on the nitrogen. Therefore, a little attention has been paid to the participation of W-shaped azomethine ylides in intermolecular cycloaddition reactions of azomethine ylides. The steric hindrance around the dipole and dipolarophile in the transition states **B** and **C** would make the energy differences between the two transition states smaller than those of intermolecular processes.

To check this working model, we next examined the reaction of an azomethine ylide bearing a more bulky substituent on the azomethine ylide nitrogen. Interestingly, the similar reaction of aldehyde **1a** with *N*-benzylglycine ethyl ester in toluene at reflux gave only cycloadduct **5** through the *endo*-approach of the S-shaped azomethine ylide in 67% yield (Scheme 2).

Techniques used: ^{1}H NMR, ^{13}C NMR, IR, Mass spectra, X-ray single crysral structure analysis

References: 14

Schemes: 3

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