BENZYLIDENECYANOMETHYL-1,3-BENZAZOLES AS 1-AZA-1,3-BUTADIENES

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Diels-Alder reactions of benzylidenecyanomethyl-1,3-benzothiazoles and -1,3-benzoxazoles **2a-f** as 1-aza-1,3-butadienes are described. The dienes **2**, featuring the stabilized imine moieties by constituting heteroaromatic rings, react with both electron-deficient and electron-rich dienophiles **3a-c** to give corresponding cycloadducts **4-6**, regioselectively. The cycloadditions of the intramolecular systems **8a-d** smoothly undergo *via* *exo*-transition state, stereoselectively affording polycyclic compounds **9a-d** in good to excellent yields.

KEYWORDS benzylidenecyanomethyl-1,3-benzazole; stabilized imine moiety; regioselective Diels-Alder reaction; polycyclic compound

Nitrogen-containing six-membered ring system (piperidine ring) is a common partial structure of biologically active compounds. One of the most direct approaches of the structure is obviously the nitrogen-containing hetero Diels-Alder reaction.¹⁾ However, Diels-Alder reaction of 1-aza-1,3-butadienes (α,β -unsaturated imines) **1** themselves have been difficult due to their low reactivities as dienes, side reactions and instabilities arising from the imine moieties.^{1a)} To solve these problems, various 1-aza-1,3-butadienes carrying modified substituents at 1-position were developed in the last decade. 1-Acyl,²⁾ 1-sulfonyl,³⁾ 1-dimethylamino,⁴⁾ and 1-phenyl⁵⁾ derivatives are especially noteworthy. While 1-acyl and 1-sulfonyl derivatives tend to react with electron-rich dienophiles (inverse type Diels-Alder reaction), 1-dimethylamino derivatives react with electron-deficient dienophiles (normal type Diels-Alder reaction), and 1-phenyl derivatives give rise to Diels-Alder reaction with both of them. We now report here a new type of 1-aza-1,3-butadiene, benzylidenecyanomethyl-1,3-benzazoles **2**, in which the imine moieties are stabilized by constituting hetero aromatic rings. The dienes **2** have enough reactivity, and cause Diels-Alder reaction with both electron-rich and electron-deficient dienophiles to give the corresponding cycloadducts **4-6**. Furthermore, the cycloaddition is efficiently applicable to intramolecular system.

The starting dienes **2a-f**, stable crystalline materials, were readily prepared from 2-cyanomethyl-1,3-benzothiazole⁶⁾ or 2-cyanomethyl-1,3-benzoxazole. The reactions of **2** with dienophiles **3a-c** possessing different electronic requirements were performed as shown in Chart 1 and Table I. Surprisingly, **2** reacted with highly electron-deficient dienophile **3a** (runs 1-4) as well as with electron-rich dienophiles **3b,c** (runs 5-11). The regiochemistries of **5** were opposite to that of the product from the related 1-acetyl-2-cyano-4-phenyl-1-aza-1,3-butadiene and β -methylstyrene,^{2e)} and similar to that of the product from the related 4-ethoxycarbonyl-1-phenylsulfonyl-1-aza-1,3-butadiene and **3b**.^{3d)} The reactions of the dienes **2** with conjugated dienophiles **3a** and **3b** gave *endo*-products **4-5** as the only isolable products, probably due to the secondary orbital interactions (runs 1-8). In the cases of the reactions with **3c**, the reaction also proceeded regioselectively, but giving a mixture of *endo*- and *exo*-products **6** (runs 9-11). Regio- and stereochemical assignments of **4-6** were made on the basis of their ¹H-NMR spectra including NOE

Chart 1

Table I. Diels-Alder Reaction of Benzyldenecyanomethyl-1,3-benzazoles 2a-f with Dienophiles 3a-c

Run	2	3	Time (hr) ^a	Product	Yield (%) ^b	Run	2	3	Time (hr) ^a	Product	Yield (%) ^b
1	2a	3a	66	4a	52	7	2c	3b	12	5c	82
2	2b	3a	72	4b	33	8	2e	3b	18	5e	69
3	2c	3a	60	4c	85	9	2a	3c	12	6a ^c	39
4	2f	3a	12	4f	71	10	2d	3c	36	6d ^d	49
5	2a	3b	24	5a	77	11	2e	3c	42	6e ^e	56
6	2b	3b	36	5b	42						

a) Conditions: 120 °C, with 3a or 3b; sealed tube, 190 °C, with 3c. b) Not optimized. c) *endo/exo* = 1.3/1. d) *endo/exo* = 1/1.5. e) *endo/exo* = 1.3/1.

difference experiments (4a) and x-ray diffractions (5c and endo-6d). The structures of the other products were assigned by comparing their ¹H-NMR spectra with those of 4a, 5c, and endo-6d.

With these results on the intermolecular Diels-Alder reactions of 2 with 3 in hand, we turned our attention to application of this reaction to the intramolecular version. As shown in Chart 2, 7a and 7b prepared from salicylaldehyde and 2-cyanomethyl-1,3-benzazoles were treated with crotyl bromide or cinnamyl bromide in the presence of potassium carbonate to give four types of the substrates 8a-d. During preparation of 8d, the intramolecular cycloadduct 9d was produced in 21% yield as well as 8d due to the high reactivity of 8d. The successful intramolecular cycloadditions of 8a-d were achieved by heating in refluxing *o*-dichlorobenzene to afford 9a-d in transused forms exclusively, arising from *exo*-transition states,⁷⁾ in good to

Reagents and conditions: i, crotyl bromide or cinnamyl bromide, K_2CO_3 , acetone, reflux, **8a**, 59%; **8b**, 46%; **8c**, 46%; **8d**, 35%. ii, o-dichlorobenzene, reflux, 20-40 min, **9a**, 62%; **9b**, 90%; **9c**, 72%; **9d**, 94%.

Chart 2

excellent yields. The stereostructures of **9a-d** were assigned based on axial-axial coupling constants in their 1H -NMR spectra (J_{AB} , J_{BC} both 10-11 Hz⁷⁾) and on NOE difference experiments of **9d**.

Further applications of this hetero Diels-Alder reaction are currently being undertaken.

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