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-phenyl[5)] 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-benzothiazole[6)] 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 regio chemistries 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 ^{1}H-NMR spectra including NOE

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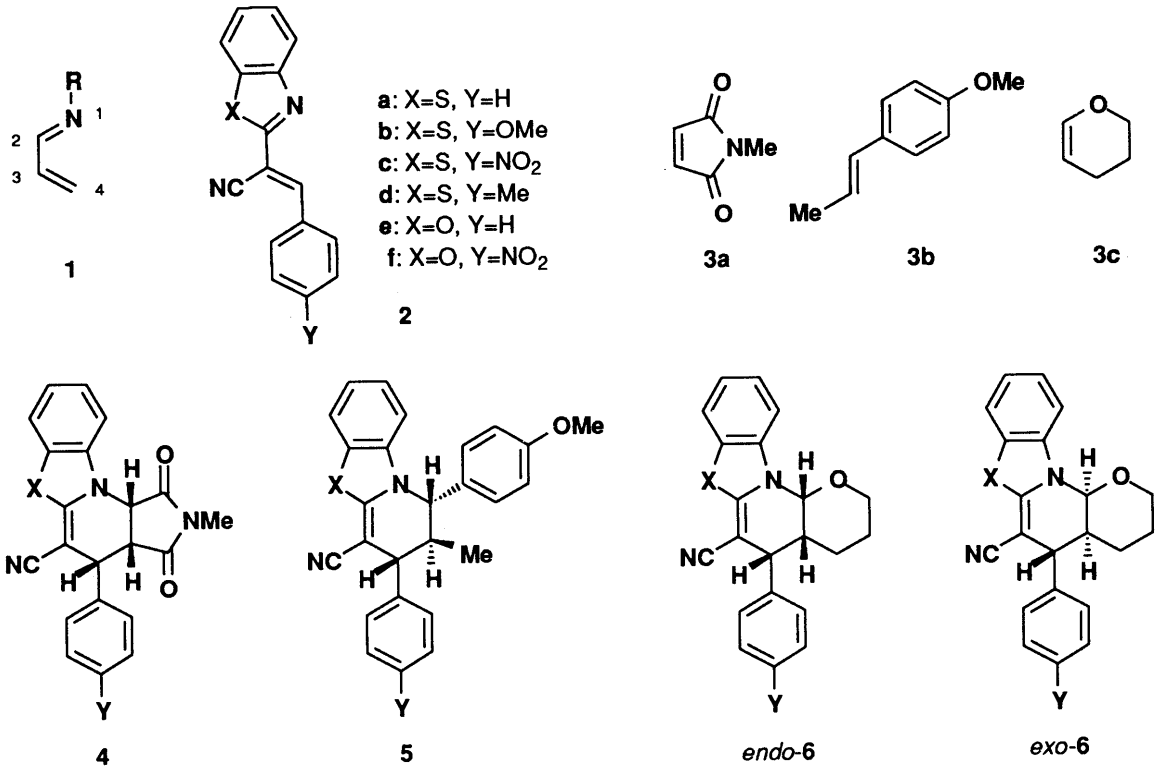

Chart 1

Table I. Diels-Alder Reaction of Benzylidenecyanomethyl-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 ^{1}H-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 transfused forms exclusively, arising from *exo*-transition states,[7] in good to

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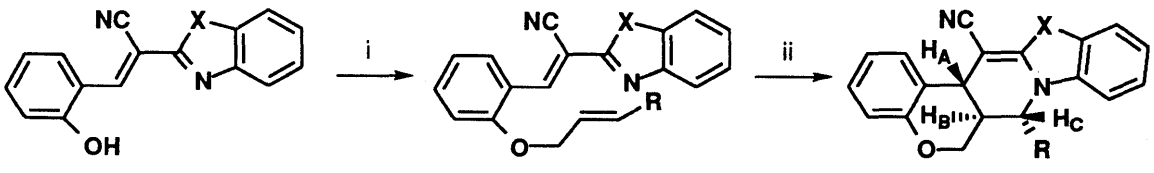

7 8 9

a: X=S
b: X=O

a: X=S, R=Me **c**: X=O, R=Me
b: X=S, R=Ph **d**: X=O, R=Ph

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 ^{1}H-NMR spectra (J_{AB}, J_{BC} both 10-11 Hz)[7] and on NOE difference experiments of **9d**.

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

REFERENCES AND NOTES

1) a) D. L. Boger, *Tetrahedron*, **39**, 2869 (1983); b) D. L. Boger, S. M. Weinreb, "Hetero Diels-Alder Methodology in Organic Synthesis," Academic Press, SanDiego, 1987; c) S. M. Weinreb, in "Comprehensive Organic Synthesis," ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 4, p. 401; d) D. L. Boger, in "Comprehensive Organic Synthesis," ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 4, p. 451.

2) a) Y.-S. Cheng, F. W. Fowler, A. T. Lupo, Jr., *J. Am. Chem. Soc.*, **103**, 2090 (1981); b) Y.-S. Cheng, A. T. Lupo, Jr., F. W. Fowler, *J. Am. Chem. Soc.*, **105**, 7696 (1983); c) Y. C. Hwang, F. W. Fowler, *J. Org. Chem.*, **50**, 2719 (1985); d) M. Teng, F. W. Fowler, *Tetrahedron Lett.*, **30**, 2481 (1989); e) M. Teng, F. W. Fowler, *J. Org. Chem.*, **55**, 5646 (1990); T. Uyehara, I. Suzuki, Y. Yamamoto, *Tetrahedron Lett.*, **31**, 3753 (1990); f) M. E. Jung, Y. M. Choi, *J. Org. Chem.*, **56**, 6729 (1991).

3) a) D. L. Boger, A. M. Kasper, *J. Am. Chem. Soc.*, **111**, 1517 (1989); b) D. L. Boger, W. L. Corbett, J. M. Wiggins, *J. Org. Chem.*, **55**, 2999 (1990); c) D. L. Boger, T. T. Curran, *J. Org. Chem.*, **55**, 5439 (1990); d) D. L. Boger, W. L. Corbett, T. T. Curran, A. M. Kasper, *J. Am. Chem. Soc.*, **113**, 1713 (1991); e) D. L. Boger, S. Nakahara, *J. Org. Chem.*, **56**, 880 (1991); f) D. L. Boger, K. C. Cassidy, S. Nakahara, *J. Am. Chem. Soc.*, **115**, 10733 (1993).

4) B. Serckx-Poncin, A.-M. Hesbain-Frisque, L. Ghosez, *Tetrahedron Lett.*, **23**, 3261 (1982); Y. Tamura, T. Tsugoshi, Y. Nakajima, Y. Kita, *Synthesis*, **1984**, 930; K. T. Potts, E. B. Walsh, and D. Bhattacharjee, *J. Org. Chem.*, **52**, 2285 (1987); K. T. Potts, D. Bhattacharjee, E. B. Walsh, *J. Chem. Soc., Chem. Commun.*, **1984**, 114; T. Ota, S. Masuda, H. Tanaka, *Chem. Lett.*, **1981**, 411; M. Chigr, H. Fillion, A. Rougny, *Tetrahedron Lett.*, **29**, 5913 (1988).

5) N. J. Sisti, F. W. Fowler, D. S. Grierson, *Synlett*, **1991**, 816; M. E. Tran Huu Dau, J.-P. Flament, J.-M. Lefour, C. Riche, D. S. Grierson, *Tetrahedron Lett.*, **33**, 2343 (1992); C. Trione, L. M. Toledo, S. D. Kuduk, F. W. Fowler, D. S. Grierson, *J. Org. Chem.*, **58**, 2075 (1993).

6) K. Saito, S. Kambe, Y. Nakano, *Synthesis*, **1983**, 210.

7) This term *exo* refers to the orientation of the dienophile-to-aryl connecting side chain rather than the R group. See, J. Barluenga, M. Tomas, A. Ballesteros, L. A. Lopez, *J. Org. Chem.*, **56**, 5680 (1991).

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