INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF 3, 6-DIARYL-1, 2, 4, 5-TETRAZINES WITH CYCLOOCTYNE

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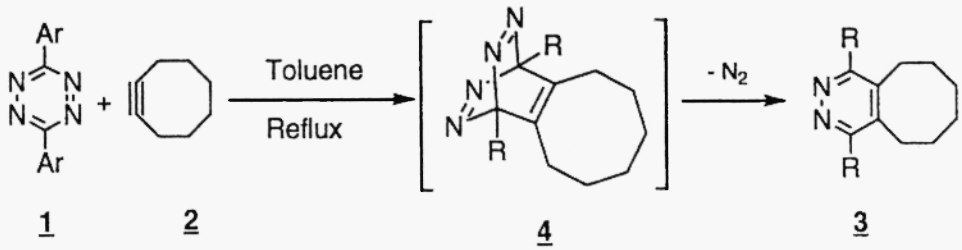
Abstract : Cyclooctyne **2** underwent inverse electron demand Diels-Alder reaction with a variety of 3,6-diaryl-1, 2, 4, 5-tetrazines **1** , giving the corresponding pyridazines **3** in excellent yields. LUMO **1** -HOMO **2** energy gaps between **1** and **2** are obtained by semi-empirical molecular orbital calculations.

Cyclooctyne is the smallest cyclic alkyne that is stable at room temperature and has been prepared by a number of methods which either start from cyclooctene or from cyclooctanone.[1] In spite of high strain and high reactivity of cyclooctyne as well as synthetic potential of its cycloadditions, relatively few examples of cycloaddition reactions have been reported.[2] 1, 2, 4, 5-Tetrazines are well known to act as electron deficient dienes in inverse electron demand Diels-Alder reactions, providing access to highly functionalized pyridazines.[3, 4] The *ab initio* quantum-mechanical and experimental mechanistic studies of this reaction also have been reported.[5] Since only one isolated example of Diels-Alder reaction of the bis-1, 2, 4, 5-tetrazine with cyclooctyne is reported ,[6] it would be desirable to describe more detailed and systematic studies of the reactions.

For example, the reaction of 3,6-bis(4-methoxyphenyl)-1,2,4,5-tetrazine **1a** with 2.7 molar amount of cyclooctyne **2** in refluxing toluene for 1 h gave 1,4-bis(4-methoxyphenyl) cyclooctano[4,10-*d*]pyridazine **3a** in 77 % isolated yield. The reaction is believed to proceed *via* the 1:1 adduct **4**, followed by elimination of nitrogen, giving the corresponding pyridazines. The mechanism has been recently theoretically proven by *ab initio* calculations.[5] The generality of the reaction with cyclooctyne has been confirmed as summarized in Table 1. The ^{13}C NMR spectra of **3** have established their symmetrical structure (see, experimental), while 1,4-aromatic rings often showed either slightly different ^{1}H NMR signals like **3a** or complex signals like **3k**, presumably because of their slow rotation.



1 **2** **4** **3**

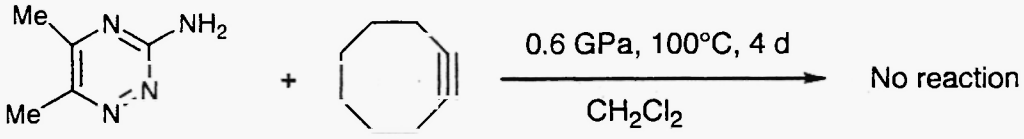
Table 1. Diels-Alder Reactions of 3, 6-Diaryl-1, 2, 4, 5-tetrazines **1** with Cyclooctyne **2**

	Ar	Molar Ratio (**1** : **2**)	Reaction Time (h)		Yield (%)
1a	4-$MeOC_6H_4$	1 : 2.7	1	**3a**	77
1b	2-Pyridinyl	1 : 1.3	1	**3b**	89
1c	3-Pyridinyl	1 : 1.3	1	**3c**	93
1d	4-Pyridinyl	1 : 1.3	1	**3d**	86
1e	Ph	1 : 2	2	**3e**	93
1f	3-MeC_6H_4	1 : 1.3	2	**3f**	92
1g	4-MeC_6H_4	1 : 2	1	**3g**	96
1h	3-FC_6H_4	1 : 1.3	2	**3h**	93
1i	4-FC_6H_4	1 : 1.3	0.5	**3i**	90
1j	3-ClC_6H_4	1 : 1.3	2	**3j**	99
1k	4-ClC_6H_4	1 : 1.3	2	**3k**	91
1l	3-BrC_6H_4	1 : 1.3	1	**3l**	89
1m	4-BrC_6H_4	1 : 1.3	1	**3m**	81

Table 2. HOMO-LUMO Energy Gaps Between **1** and **2** Calculated by PM3.

Ar	HOMO(eV)	LUMO(eV)	HOMO **1**-LUMO **2**	LUMO **1**-HOMO **2**
1a	-8.844	-1.621	10.413	8.541
1b	-9.669	-1.883	11.238	8.279
1c	-9.715	-2.071	11.284	8.091
1d	-10.053	-2.198	11.622	7.964
1e	-9.335	-1.745	10.904	8.417
1f	-9.334	-1.746	11.903	8.416
1g	-9.106	-1.687	10.675	8.475
1h	-9.657	-2.046	11.226	8.116
1i	-9.479	-2.007	11.048	8.155
1j	-9.438	-1.920	11.007	8.242
1k	-9.212	-1.941	10.781	8.221
1l	-9.538	-1.985	11.107	8.177
1m	-9.518	-2.013	11.087	8.149

The HOMO and LUMO energy levels of the 3, 6-diaryl-1, 2, 4, 5-tetrazines were calculated by semi-empirical method (PM3) as shown in Table 2.[7] As a matter of course, the reaction is controlled by LUMO-tetrazine **1** and HOMO- cyclooctyne **2**. Specifically, the tetrazines like **1h** and **1i** which have smaller HOMO-LUMO energy gaps underwent Diels-Alder reaction even upon mixing the reactants. The similar reactions of some triazine and diazines were attempted in order to investigate the scope and limitations of this type of reaction. The reaction of 3-amino-5,6-dimethyltriazine **5** with **2** did not take place even under high pressure conditions (0.6 GPa, 100 °C, 4 d) probably because of the high energy gap of LUMO **5**-HOMO **2** (9.537 eV by PM3). Analogously, pyridazine **6a**, 3, 6-dichloropyridazine **6b**, and 3-chloro-6-phenylpyridazine **6c** (LUMO **6**-HOMO **2** energy gaps by PM3 are 9.650, 9.157, and 9.056 eV, respectively) did not undergo Diels-Alder reaction under the same conditions. According to the qualitative experience in our laboratory, the reactions whose HOMO-LUMO energy gaps are greater than ca. 9 eV, did not take place at normal pressure.



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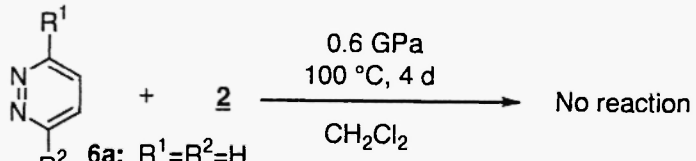

6a: $R^1=R^2=H$
6b: $R^1=R^2=Cl$
6c: $R^1=Ph$, $R^2=Cl$

Further work on reactions with cyclooctyne employing other kinds of heterocycles such as five membered heterocycles are in progress.

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EXPERIMENTAL

Melting points were taken on a Yanagimoto micro melting point apparatus and were uncorrected. The ^{1}H nmr spectra were measured either on a JEOL JNM-EX270 (270MHz), or JNM-ALPHA500 (500MHz) instrument. ^{13}C nmr spectra were recorded either on a JNM-EX270 or JNM-ALPHA500 pulsed Fourier-transform spectrometer operating at 67.80 Hz and 125.65 Hz, respectively. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Either partial proton decoupling or DEPT method was used to distinguish between individual carbon atoms. Preparative medium-pressure liquid

chromatography was carried out using a column ex 310 nm) prepacked with silica gel(Lobar, LiChroprep Si60, Merck).

General Procedure for the Reaction of 1 with 2: A Typical Example for Preparation of 1,4-bis(4-methoxyphenyl) cyclooctano[4,10-*a*]pyridazine 3a

A mixture of **1a** (0.79 mmol, 0.1121g) and **2** (1.03 mmol, 0.1141 g) was refluxed in toluene (10 ml) under nitrogen for 1 h. After cooling to room temperature, the colorless precipitates were filtered, giving **3a** (0.0748 g). Concentration of the filtrate afforded an additional amount (0.0356 g) of **3a**. mp. 202- 203 °C ^{1}H NMR (270MHz, $CDCl_3$) δ 1.34- 1.48 (m, 4H), 1.51- 1.66(m, 4H), 2.74- 2.86 (m, 4H), 3.87(s, OCH_3, 6H), 7.01(ABq, J=8.64 Hz, 4H) 7.45(ABq, J=8.91 Hz, 4H); ^{13}C NMR (67.94MHz, $CDCl_3$) δ 25.97(t, sp^3), 27.22(t, sp^3), 30.39(t, sp^3), 55.34(q, OCH_3), 113.71(d, sp^2), 130.46(d, sp^2), 130.74(s, sp^2), 139.19(s, sp^2), 159.75(s, sp^2), 160.64(s, sp^2); *Anal.* Calcd. for $C_{24}H_{26}N_2O_2$: C,76.97; H, 6.99: N, 7.48. Found: C, 76.79; H, 7.01; N, 7.46.

1,4-Bis(2-pyridinyl)cyclooctano[4,10-*a*]pyridazine 3b: mp 169- 170 °C ; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.38- 1.50(m, 4H), 1.68- 1.85(m, 4H), 3.05(bt, J= 6.2 Hz, 4H), 7.33- 7.42(m, 2H), 7.83- 7.91(m, 4H), 8.62-8.74(m, 2H) ; ^{13}C NMR(67.94MHz, $CDCl_3$) δ 26.09(t, sp^3), 26.59(t, sp^3), 30.44(t, sp^3), 123.25(d, sp^2), 125.03(d, sp^2), 136.75(s, sp^2), 141.08(s, sp^2), 148.55(d, sp^2), 157.12(s, sp^2), 158.88(s, sp^2); *Anal.* Calcd. for C20H20N4: C, 75.92; H, 6.37; N,17.70. Found: C, 75.62; H, 6.30; N, 17.87.

1,4-Bis(3-pyridinyl)cyclooctano[4,10-*a*]pyridazine 3c: mp 193- 194 °C ; ^{1}H NMR(270MHz, $CDCl_3$) δ 1.40- 1.50(m, 4H), 1.57- 1.68 (m, 4H), 2.81- 2.89(m, 4H), 7.47(dd, J=7.8, 4.8 Hz, 2H), 7.91(d, J=7.8 Hz, 2H), 8.75(d, J=4.8 Hz, 2H), 8.82(bs, 2H); ^{13}C NMR (67.94MHz, $CDCl_3$) δ 25.80(t, sp^3), 27.19(t, sp^3), 30.33(t, sp^3), 123.29(d, sp^2), 133.82(s, sp^2), 136.69(d, sp^2), 139.87(s, sp^2), 149.65(d, sp^2), 149.86(d, sp^2),158.69(s, sp^2); *Anal.* Calcd. for C20H20N4: C, 75.92; H, 6.37; N,17.70. Found: C, 75.83; H, 6.29; N,17.94.

1,4-Bis(4-pyridniyl)cyclooctano[4,10-*a*]pyridazine 3d: mp 210- 211 °C ; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.37- 1.70(m, 8H), 2.76- 2.88(m, 4H), 7.48, 8.79(ABq, J=5.9Hz, 4H) 8.79(ABq, J=5.9Hz, 4H); ^{13}C NMR (67.94MHz, $CDCl_3$) δ 25.80(t, sp^3), 27.03(t, sp^3),30.44(t, sp^3), 123.88(d, sp^2), 139.47(s, sp^2), 145.59(s, sp^2),150.01(s, sp^2),159.44(s, sp^2); *Anal.* Calcd. for C20H20N4: C, 75.92; H, 6.37; N, 17.70. Found: C, 75.88; H, 6.45; N, 17.75.

1,4-Diphenylcyclooctano[4,10-*a*]pyridazine 3e: mp 161- 162 °C ; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.21-1.72 (m, 8H), 2.26- 2.92(m, 4H), 7.35- 7.61(m, 10H) ; ^{13}C NMR(67.94MHz, $CDCl_3$) δ 25.8(t, sp^3), 27.0(t, sp^3), 30.2(t, sp^3), 128.1, 128.3,129.0, 138.1, 139.0,161.0; *Anal.* Calcd. for $C_{22}H_{22}N_2$. C, 84.17; H, 7.65; N, 8.18. Found: C, 84.11; H,7.57; N, 7.95.

1,4-Bis(3-methylphenyl)cyclooctano[4,10-*a*]pyridazine 3f : mp 152- 153 °C ; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.26- 1.49(m, 4H), 1.51- 1.72(m, 4H), 2.43(s, 6H), 2.73- 2.84(m, 4H), 7.23- 7.41(m, 8H); ^{13}C NMR(67.94MHz, $CDCl_3$) δ 21.51(q, CH_3), 25.95(t, sp^3), 27.19(t, sp^3), 30.39(t, sp^3), 126.11(d, sp^2), 128.08(d,sp^2), 129.13(d, sp^2), 129.86(d, sp^2) 137.97(s, sp^2), 138.18(s, sp^2), 139.08(s, sp^2), 161.31(s, sp^2); *Anal.* Calcd. for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.11; H, 7.57; N, 7.95.

1,4-Bis(4-methylphenyl)cyclooctano[4,10-*a*]pyridazine 3g: mp 255- 256 °C ; ^{1}H NMR(270MHz, $CDCl_3$) δ 1.34- 1.49 (m, 4H),1.51- 1.68 (m, 4H), 2.43(s ,6H), 2.73-2.88(m, 4H), 7.29(ABq, J=7.8Hz, 4H)

7.41(ABq, J=8.4 Hz, 4H); ^{13}C NMR (67.94MHz, $CDCl_3$) δ 21.35(q, $\underline{C}H_3$), 25.97(t, sp^3), 27.21(t, sp^3), 30.40(t, sp^3), 128.93(d, sp^2), 129.04(d, sp^2), 135.40(s, sp^2), 138.17(s, sp^2), 139.10(s, sp^2), 161.08(s, sp^2); *Anal.* Calcd. for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.20; H, 7.45; N, 8.01.

1,4-Bis(3-fluorophenyl)cyclooctano[4,10-*a*]pyridazine 3h : mp166- 167 °C; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.21- 1.67 (m, 8H), 2.76- 2.85(m, 4H), 7.13- 7.34(m, 6H) 7.51(m, 2H); ^{13}C NMR(67.94MHz, $CDCl_3$) δ 25.84(t, sp^3), 27.12(t, sp^3), 30.36(t, sp^3), 115.40(J_{CF} = 21 Hz), 116.38(J_{CF} = 23 Hz), 124.30(J_{CF} = 3.7 Hz), 129.08(J_{CF} = 8.6 Hz), 139.39(s, sp^2), 140.03(J_{CF} = 7.3 Hz), 160.24(s),162.53(J_{CF} = 247 Hz); *Anal.* Calcd. for $C_{22}H_{20}F_2N_2$: C, 75.41; H, 5.75; N, 7.99. Found: C,75.49; H,5.84; N,8.00.

1,4-Bis(4-fluorophenyl)cyclooctano[4,10-*a*]pyridazine 3i ; mp 222- 223 °C; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.35- 1.67(m, 8H), 2.75- 2.85(m, 4H), 7.19(t, J= 8.6 Hz, 4H), 7.51(q, J= 5.1, 8.6 Hz, 4H); ^{13}C NMR(67.94MHz, $CDCl_3$) δ 25.88(t, sp^3), 27.21(t, sp^3), 30.30(t, sp^3), 115.40(J_{CF} = 87 Hz), 130.97(J_{CF} = 34 Hz), 134.04(J_{CF} = 3.7 Hz), 139.51(s), 160.43(s),162.99(J_{CF} = 248 Hz); *Anal.* Calcd. for $C_{22}H_{20}F_2N_2$: C, 75.41; H, 5.75; N, 7.99. Found: C, 75.20; H, 5.64; N, 7.96.

1,4-Bis(3-chlorophenyl)cyclooctano[4,10-*a*]pyridazine 3j : mp 174- 175 °C; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.37- 1.51(m, 4H), 1.53- 1.68(m, 4H), 2.74- 2.85(m, 4H), 7.38-7.55(m, 8H); ^{13}C NMR(67.94MHz, $CDCl_3$) δ 25.86(t, sp^3), 27.15(t, sp^3), 30.31(t, sp^3), 127.31(d, sp^2), 128.80(d, sp^2), 129.32(d, sp^2), 129.67(d, sp^2), 134.34(s), 139.42(s), 139.69(s), 160.23(s); *Anal.* Calcd. for $C_{22}H_{20}Cl_2N_2$: C, 68.93; H, 5.26; N, 7.31. Found: C, 68.68; H, 5.40; N, 7.06.

1,4-Bis(4-chlorophenyl)cyclooctano[4,10-*a*]pyridazine 3k : mp 252- 253 °C; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.36- 1.47(m, 4H), 1.51- 1.65 (m, 4H), 2.74- 2.85(m, 4H), 7.47(bs, 8H); ^{13}C NMR(67.94MHz, $CDCl_3$) δ 25.86(t,sp^3),27.15(t,sp^3),30.33(t,sp^3),128.61(d,sp^2),130.53(d,sp^2),134.79(s),136.49(s),139.33(s),160.32(s); *Anal.* Calcd.for $C_{22}H_{20}Cl_2N_2$: C, 68.93; H, 5.26; N,7.31. Found: C, 68.71; H, 5.40; N, 7.39.

1,4-Bis(3-bromophenyl)cyclooctano[4,10-a]pyridazine 3l : mp 171.5- 172.5 °C; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.37- 1.48(m, 4H), 1.52- 1.67(m, 4H), 2.73- 2.85(m, 4H), 7.37(t, J = 7.6 Hz, 2H), 7.45(d, J=7.8 Hz, 2H), 7.62(d, J=7.8 Hz, 2H), 7.68(s, 2H); ^{13}C NMR (67.94MHz, $CDCl_3$) δ 25.86(t, sp^3), 27.17(t, sp^3), 30.31(t, sp^3),122.46(s),127.76(d),129.90(d), 131.71(d), 132.16(d), 139.42(s), 139.94(s),160.14(s); *Anal.* Calcd. for $C_{22}H_{20}Br_2N_2$: C, 55.96; H, 4.27; N, 5.93. Found: C, 56.06; H, 4.36; N, 5.76.

1,4-Bis(4-bromophenyl)cyclooctano[4,10-*a*]pyridazine 3m : mp 284- 285 °C; ^{1}H NMR (270MHz, $CDCl_3$) δ 1.33- 1.67(m, 8H), 2.73- 2.86(m, 4H), 7.40(ABq, J=8.6 Hz, 4H), 7.64(ABq, J=8.6 Hz, 4H); ^{13}C NMR (67.94MHz, $CDCl_3$) δ 25.84(t, sp^3), 27.13(t, sp^3), 30.33(t, sp^3), 123.00(s), 130.78(d), 131.53(d), 136.93(s), 139.32(s),160.34(s); *Anal.* Calcd. for $C_{22}H_{20}Br_2N_2$: C, 55.96; H, 4.27; N, 5.93. Found: C, 55.69.; H, 4.35; N, 6.19.

REFERENCES AND NOTES

(1) a) A. T. Blomquist and L. H. Liu, *J. Am. Chem. Soc.*, **75**, 2153(1953); b) G. Wittig and H. L. Dorsch, *Liebigs Ann.*, **74**, 46 (1968); c) H. Meier and I. Menzel, *J. Chem. Soc. D*, 1059 (1971); d) P. Caubere and G. Coudert, *Bull. Soc. Chim. Fr.*, 3067 (1973); e) L. Brandsma and H. D. Verkruijesse, *Synthesis*, 290 (1978)

(2) P. Konig, J. Zountsa, K. Bleckmann, and H. Meier, *Chem. Ber.*, **116**, 3580 (1983); C. Germinghous, A. Kummel, and G. Seitz, *Chem. Ber.*, **126**, 733 (1993); W. Tochtermann and P. Kraft, *Synlett*, 1029 (1996)

(3) J. Sauer, 'Comprehensive Heterocyclic Chemistry II', Pergamon Press, London, 1996, Vol6, pp. 901-965

(4) Most recent examples: J. Sauer and D. K. Heldmann, *Tetrahedron*, **54**, 4297 (1998); S. C. Benson, L. Lee, and J. K. Snyder, *Tetrahedron Lett.*, **37**, 5061 (1996); J. S. Panek and B. Zhu, *Tetrahedron Lett.*, **37**, 8151 (1996); C. Glidewell, P. Lightfoot, B. J. L. Royles, and D. M. Smith, *J. Chem. Soc., Perkin trans., 2*, 1167 (1997); T. Klindert, P. von Hagel, L. Bauman, and G. Seitz, *J. prakt. Chem.*, **339**, 623 (1997); A. Kotschy, G. Hajos, G. Timari, and A. Messmer, *J. Org. Chem.*, **64**, 4423 (1996); S. M. Sakya, T. W. Strohmeyer, S. A. Lang, and Y.-I. Lin, *Tetrahedron Lett.*, **38**, 5913 (1997; A. Kotschy, D. M. Smith, and A. Cs. Benyei, *Tetrahedron Lett.*, **39**, 1945 (1998); T. J. Sparey and T. Harrison, *Tetrahedron Lett.*, **39**, 5873 (1998)

(5) J. Cioslowski, J. Sauer, J. Hetzenegger, T. Karcher, and T. Hierstetter, *J. Am. Chem. Soc.*, **115**, 1353 (1993)

(6) N. Biedermann and J. Sauer, *Tetrahedron Lett.*, **35**, 7935 (1994)

(7) The HOMO and LUMO energy levels of **1** and **2** were obtained using CAChe systems (Version 3.7, CAChe Scientific, Oxford Molecular Group; PM3: J. J. P. Stewart, *J. Comp. Chem.*, **10**, 209 (1989)

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