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Preparation and Inverse Electron Demand Diels-Alder Reactions of 3-Methoxy-6-methylthio-1,2,4,5-tetrazine

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Abstract: The selective preparation of 3-methoxy-6-methylthio-1,2,4,5-tetrazine (**2**) and 3,6-dimethoxy-1,2,4,5-tetrazine (**3**) from 3,6-bis(methylthio)-1,2,4,5-tetrazine (**1**) is described. A preliminary investigation into the participation of **2** in [4+2] cycloaddition reactions with electron rich and neutral dienophiles along with the resulting regioselective formation of the products (**5**) are discussed.

Applications of the heterocyclic azadiene Diels-Alder reactions to the synthesis of natural products have been well documented.[1] Among the many electron deficient azadiene systems, the symmetrically disubstituted 1,2,4,5-tetrazine system has been the most widely studied and has been effectively utilized for the preparation of heterocyclic systems not easily attainable by other methods.[1,2] Typically, it has been the symmetrically substituted tetrazines that have been examined and employed and little has been disclosed on the synthetically less accessible unsymmetrically substituted tetrazines. One recent report detailed the intermolecular [4+2] cycloaddition reactions of an unsymmetrically disubstituted tetrazine on a polymer support system,[3] and the regiospecific [4+2] cycloaddition reactions of the monosubstituted 3-phenyl-1,2,4,5-tetrazine has also been studied.[4] Here we detail our study on the preparation and the Diels-Alder reactions of the unsymmetrically disubstituted tetrazine 3-methoxy-6-methylthio-1,2,4,5-tetrazine (**2**), which was prepared from the versatile 3,6-bis(methylthio)-1,2,4,5-tetrazine (**1**).[2,5]

The selective preparation of **2** or **3** was accomplished by treating **1** with catalytic sodium methoxide in methanol. The use of a catalytic amount of sodium methoxide and low temperatures with varying length of time allowed for selectivity (Scheme 1, Table 1). Minor amounts of the dihydro tetrazine **4** (<10%) was always detected in the crude mixture which was reoxidized to **2** upon treatment with ferric chroride. The preparation of **3** has been previously reported but involves the use of both phosgene and diazomethane.[6] Thus, its preparation from **1** is technically more convenient.[7]

The results of the Diels-Alder reactions of **2**, which could potentially yield regioisomeric products (Figure 1), with electron rich and neutral dienophiles are highlighted in Table 2. It undergoes Diels-Alder reaction in a predictable manner with electron rich (enamines, silyl enol ethers) as well as neutral dienophiles (conjugated and unconjugated alkynes). It participates in [4+2] cycloaddition with electron rich enamines at 0 - 25°C, similar to the symmetrical tetrazine **1**,[2] to provide the diazine cycloadducts **5a, 5b** and **5c** (entries

Scheme 1

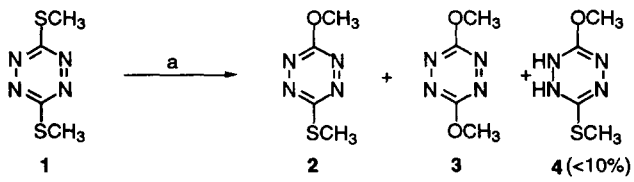


Table 1. Selective Preparation of **2** and **3**

[a]NaOMe Equiv.	Solvent	Temperatures	Time	2	3
1.2	THF	0°C	20 min	<5%	22%
1.1	THF	-78°C, -30°C	2 h, 1 h	60%	22%
0.1	MeOH	-15°C, 0°C	2 h, 1 h	< 5%	56%
0.1	MeOH	-15°C	3 h	65%	<5%
0.1	MeOH	-15°C, 0°C, RT	2 h, 16 h, 2 h	7%	63%
0.1	MeOH	-78°C, -30°C	24 h, 4 h	72%	5%

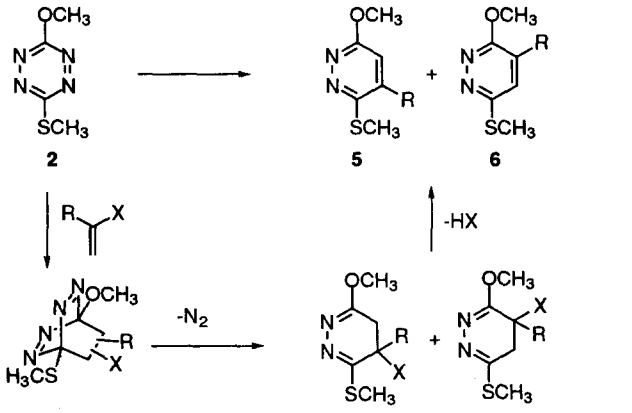
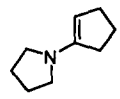
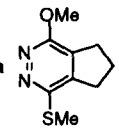
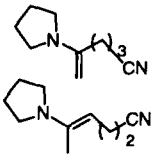
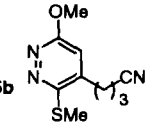
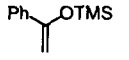
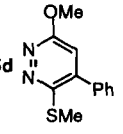
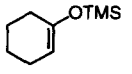
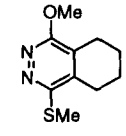
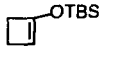
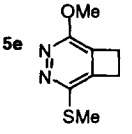
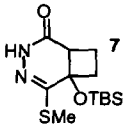
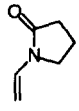


Figure 1. Diels-Alder Reaction Pathway of 2.

1 and 2). The 1,1-disubstituted enamines and enol ether (entries 2 and 3) provided regiospecific cycloadducts **5b, 5c** and **5d**. Only a single cycloadduct could be detected by NMR of the reaction mixtures for both the enamines, which reacted at low temperatures, and for the silyl enol ethers, which required much higher reaction temperatures. The regiochemistry of the cycloadducts was determined by NMR methods. Unlike the trisubstituted enamine 1-pyrrolidino-1-cyclopentene (entry 1) the trisubstituted cyclohexene trimethylsilyl enol ether failed to provide the desired cycloadduct (entry 4) even at 150°C. The ring strained cyclobutene t-butyldimethylsilyl enol ether, however, underwent cycloaddition at 110°C to provide the aromatized product **5e** in low yield. The major product was the initial regioselective cycloadduct which was hydrolized to **7** upon chromatographic purification (entry 5). Neutral and conjugated mono substituted alkynes underwent [4+2]cycloaddition reactions to provide both regioisomeric cycloadducts **5d:6d** and **5b:6b** as a 1:1 mixture

(entries 6 and 7). Vinyl pyrrolidinone also provided the cycloadduct **5f** in moderate yield after prolonged heating at 110°C.[7]

Table 2. Diels-Alder Reactions of 3-methoxy-6-methylthio-1,2,4,5-tetrazine

Entry	Dienophiles	Condition, equiv. (solv., temp, time)	Product	% Yield[a]
1.		1.5 eq (CH_2Cl_2, 0°C - RT, 1 h)	**5a** 	63
2.[b]		1.5 eq (CH_2Cl_2, 0°C - RT, 2h)	**5b**  **5c** 	(**5b**) 71 (**5c**) 27
3.		1.5 eq (Xylene, 140°C, 22 h)	**5d** 	89.9
4.		1.5 eq (Mesitylene, 150°C, 68 h)		trace
5.		1.5 eq (Dioxane, 100°C, 20 h; 110°C, 20 h)	**5e**  **7** 	(**5e**) 23 (**7**) 72
6.		1.5 eq (Mesitylene, 180°C, 18 h)	**5d:6d,** (1:1 ratio)[c]	60
7.		2.5 eq (Xylene, 140°C, 20 h)	**5b:6b,** (1:1 ratio)[c]	76
8.		2.5 eq (Dioxane, 100°C, 20 h; 110°C, 76 h)	**5f** 	41

[a] Isolated yield after purification by chromatography. The regiochemistry was determined by NMR methods. [b] The enamine was prepared from 5-oxo hexanitrile in benzene with the aid of azeotropic removal of water(cf. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovic, J.;Terell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207). The crude enamine mixture was obtained after removal of the solvent and pyrrolidine and was used as is. Attempts at distillation failed to give pure material. [c]The inseparable mixture of isomers was obtained and ratio determined by ^{1}H NMR analysis.

In conclusion, we have demonstrated that the unsymmetrically disubstitutred tetrazine **2** can be used to provide regioselectively substituted diazine cycloadducts based on the electron rich character of the dienophiles, and that the azadiene **3** is less reactive than **1** in its participation in inverse [4+2] cycloaddition reactions.

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‡ Wyeth-Ayerst Research internship participant from Ramapo College of New Jersey.

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6. Neugebauer, F. A.; Fisher, H. *Liebigs Ann. Chem.* **1982**, 387.
7. **General procedure for preparation of 2 and 3**. A solution of **1** (5.0 g, 28.7 mmol) in anhydrous methanol (287 ml, 0.1 M) at -78°C was treated with dropwise addition of NaOMe (0.7 ml of 4.37 M, 0.1 equiv.) over 5 min. The red solution darkened and was stirred until TLC showed complete reaction (24 h at -78°C, 4 h at -30°C). It was then quenched with saturated aqueous NH_4Cl (~20 ml) and water (~100 ml) and extracted with ethyl acetate (3 x 100 ml). The organic layer was washed with brine (50 ml), dried with sodium sulfate, and concentrated in vacuo. The resulting red oil was purified by silica gel chromatography (gradient elution of 0-50%EtOAc:Hexane) to provide **2** as a red oil (3.27 g, 4.54 g thoretical, 72 %) and **3** as a bright pink solid (231 mg, 5 %). For **2**: ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.27 (s, 3H, OMe), 2.72 (s, 3H, SMe); For **3**: ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.26 (s, 6H, OMe).
   Sample Diels-Alder reaction: A solution of **2** (200 mg, 1.26 mmol) in dry methylene chloride (2.26 ml) at 0 °C was treated with 1-pyrrolidino-1-cyclopentene (0.275 ml, 1.89 mmol, 1.5 equiv) and the resulting solution was allowed to warm to room temperature and stirred for 1 h. After removal of the solvent in vacuo, the crude reaction mixture was purified by preparative TLC (2000 microns, 50% EtOAc: hexane) to yield 155.9 mg (248.16 mg theoretical yield, 62.8 %) of the product 3-methoxy 6-methylthio 4,5-cyclopenteno 1,2-diazine (**5a**): Mp 108-110 °C (white grains, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$,) δ 4.10 (s, 3H, OMe), 2.86 (m, 4H), 2.69 (s, 3H, SMe), 2.17 (m, 2H); IR (neat) ν (max) 2997, 2946, 2921, 1588, 1450, 1385, 1319, 1070, 970, 910, 612 cm^{-1}; HRMS: m/z (M^++H) for $C_9H_{12}N_2OS$ 197.0749, found 197.0749. Anal. Calcd. for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27. Found: C, 55.12; H, 6.23; N, 14.27. All other products were similarly characterized.

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