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Synthesis of Aromatic 1,2-Diazines by Inverse Electron Demand Diels-Alder Reaction of Polymer-Supported 1,2,4,5-Tetrazines

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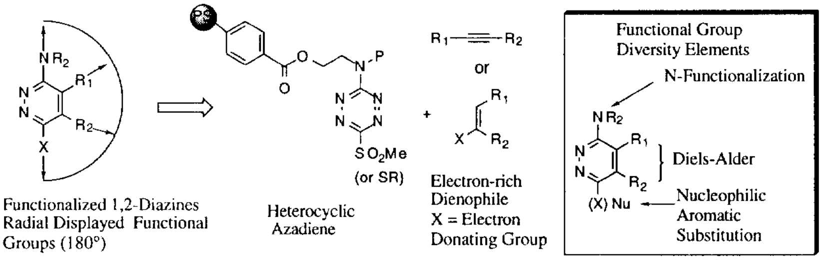
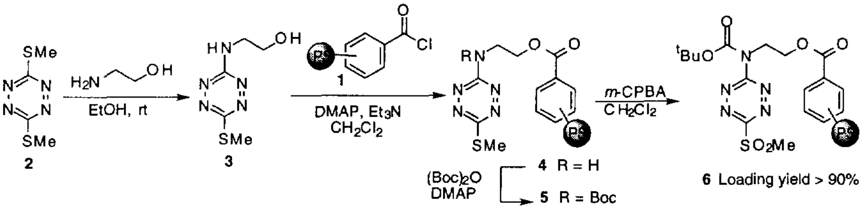
Abstract: Inverse electron demand Diels-Alder reactions of unsymmetrically substituted 1,2,4,5-tetrazines immobilized on a solid support participate in thermally promoted cycloadditions with a wide range of electron-rich dienophiles. The reactions afford functionalized 1,2-diazines bearing a sulfur-based leaving group (-SR or -SO_2R) at the C-6 position. Copyright © 1996 Elsevier Science Ltd

Recent developments of polymer-supported chemistry have been driven by interest in the assembly of libraries of molecular diverse compounds for their use in various screening protocols.[1] The development of reliable procedures that address issues concerning the synthesis of N-bearing aromatic heterocycles would be an important contribution to the field. The well established solution phase Diels-Alder reactions of heterocyclic azadienes[2] prompted us to investigate the validity and efficiency of these reactions on a solid phase format. The purpose of this letter is to report the development of inverse electron demand Diels-Alder reactions of 3,6-substituted-1,2,4,5-tetrazines on a solid phase format. The reaction constructs functionalized 1,2-diazines which have the capacity to display a high degree of functional group diversity. The process should be readily adaptable to the preparation of small molecule libraries of N-bearing heterocycles that project functional group diversity displayed in a 180° array (Figure 1).

Figure 1

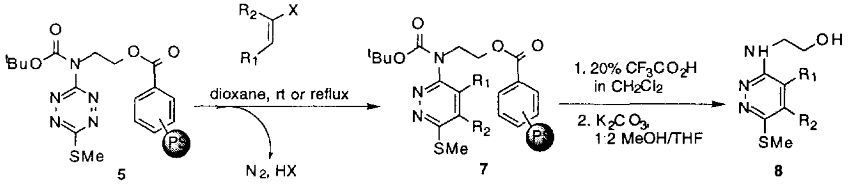


The preparation of the immobilized complexes is summarized in equation 1, and utilized the readily available 3,6-bis(thiomethyl)-1,2,4,5-tetrazine **2**.[3] The choice of tetrazine **2** is based on its easily replaceable thiomethyl groups which provide easy access to suitable linkers as well as other functional groups at the C-3 and C-6 positions.[3,4] Nucleophilic aromatic substitution of one of the thiomethyl groups with amino-ethanol (1.2 equiv, EtOH, rt, 12 h) afforded the unsymmetrical tetrazine **3** in 97% yield bearing the four-atom tether. The tetrazine nucleus was next covalently linked to carboxylated polystyrene **1**[5] through its acid chloride (cat. DMAP, Et_3N, CH_2Cl_2, rt, 48 h) to afford the immobilized amino tetrazine **4**. This material was made more electron deficient by the acylation of the secondary amine with $(Boc)_2O$ (4 equiv, cat. DMAP, THF, rt, 16 h) producing the N-Boc derivative **5** which was followed by oxidation of the methyl sulfide to the sulfone with *m*-CPBA (2.5 equiv, CH_2Cl_2, rt, 6 h) to provide the fully elaborated, immobilized 3,6-disubstituted tetrazine complex **6** as a crimson-red solid with a loading efficiency greater than 90% for four steps.[6]



(1)

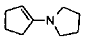
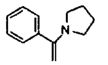
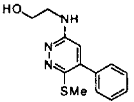
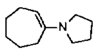
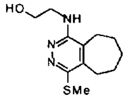
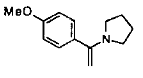
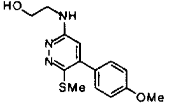
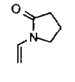
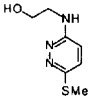
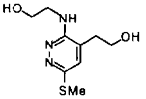
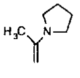
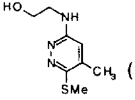
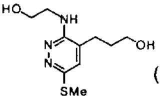
The utility of azadiene complexes **5** and **6** as electron deficient dienes in the inverse electron demand Diels-Alder reaction was examined. The results of these studies are summarized in Tables 1 and 2. Azadiene complex **5** was reacted with various electron-rich olefins in dioxane at room or elevated temperature to give the resin-bound cycloaddition product **7**. To avoid the premature nucleophilic substitution at the C-6 position with OMe, the Boc group of **7** was removed with 20% TFA in CH_2Cl_2 before the product **8** was cleaved from the solid support by base hydrolysis (K_2CO_3, 1:2 MeOH-THF) (equation 2).[7] A series of 3-amino-6-thiomethyl-1,2-pyridazines were synthesized in good to moderate overall yield and is based on the initial loading level of the carboxylic acid on polystyrene-CO_2H, and represents 6 steps (Table 1).



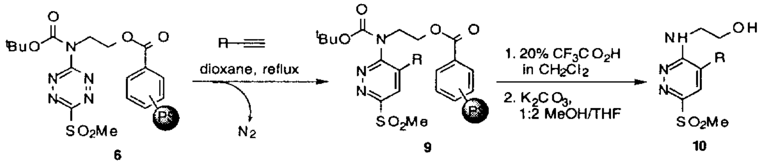
(2)

Azadiene complex **6** bearing the sulfone group is more reactive than **5** in the Diels-Alder reactions as more efficient conversion is generally achieved with less reactive dienophiles[8]. This qualitative assessment is not surprising, given the greater electron withdrawing capacity of the sulfone group. The enhanced reactivity of **6** has been illustrated by its reactions with terminal alkynes and enol ethers. The Diels-Alder reaction gave the resin-bound cycloaddition product **9** which was deprotected by 20% TFA in CH_2Cl_2 before the product **10** was cleaved from the solid support by base hydrolysis (equation 3). Table 2 illustrates the variety of 3-amino-6-sulfonylmethyl-1,2-pyridazines that were synthesized in this reaction. Regioselectivity was achieved in the reactions of both **5** and **6**, which was resulted from the difference of the electron withdrawing ability between the tetrazine's two substituted groups. The more electron-rich end of the dienophile tends to attach to the more electron-difficient carbon of the tetrazine. As the electon withdrawing ability is -SO_2Me > -NBoc > -SMe, the conversion of SMe to SO_2Me inverts the electron dificiency at carbons in **5** and **6** (from C-3 in **5** to C-6 in **6**), reverses the regiochemical course of the reactions of **5** and **6**. Comparing the results in Table 1 and Table 2, we noted that both regioisomers of a 1,2-diazine could be synthesized by utilizing different tetrazines **5** or **6** (see Tables 1 and 2, **8e** *vs* **10e**).

Table 1. Diels-Alder Reactions of Polymer Supported Azadiene **5**

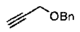
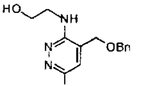
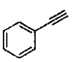
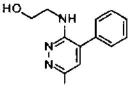
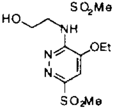
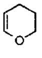
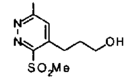
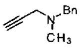
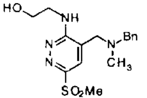
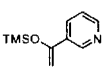
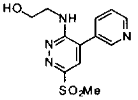
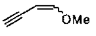
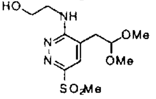
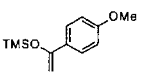
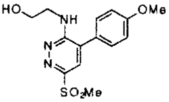
Dienophile[a]	Product	Yield of **8**[b]	Dienophile[a]	Product	Yield of **8**[b]
		**8a** 82%			**8e** 35%
		**8b** 79%			**8f** 30%
		**8c** 61%			**8g** 47% (ratio = 1 : 2)[c]
		**8d** 67% (ratio = 4 : 1)[c]			**8h** 28% (ratio = 2 : 1)[c]

[a] Preparation of enamines: (1) Cyclic ketone: the pyrrolidino enamines were prepared in benzene with the aid of azotropic removal of water (*cf.* Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovic, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207-222). (2) Aycllic ketone: the enamines were prepared in ethyl ether with the aid of 4-A molecular sieves. (*cf.* Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570-1572) [b] The yields are based on the loading level of carboxylic acid on the polystyrene-CO_2H (6 steps overall). [c] The ratio was determined by ^1H NMR (400 MHz) of the crude products. The regioisomers were assigned by ^1H NMR analysis.



(3)

Table 2. Diels-Alder Reactions of Polymer Supported Azadiene **6**

Dienophile	Product	Yield of **10**[b,c]	Dienophile[a]	Product	Yield of **10**[b,c]
		**10a** 50%			**10e** 72%
		**10b** 72%			**10f** 30%
		**10c** 31%			**10g** 49%
		**10d** 66%			**10h** 22%

[a] The enol ethers were prepared from the correspondent ketones $[(TMS)_2NLi$, Et_3N, TMSCl, -78°C to rt, 12 h]. [b] The yields are based on the initial loading level of carboxylic acid on the polystyrene-CO_2H (7 steps overall). [c] A single regioisomer was obtained in all reactions.

In conclusion, we have described the synthesis of functionalized 1,2-diazines using the Diels-Alder reaction of 3,6-substituted 1,2,4,5-tetrazines on solid support. A wide range of electron-rich dienophiles were used, which permits the introduction of two of potentially four diversity elements on an aromatic scaffold. Subsequent nucleophilic aromatic substitution of the C-6 methyl sulfide/sulfone and acylation/alkylation of the C-3 amine will introduce the third and the fourth diversity elements. We are currently preparing a library of functionalized aromatic 1,2-diazines which display (project) functional group diversity on a single plane and in a radial array of 180° and eventually in a 360° format.

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References and Notes

1. *Reviews:* (a) Moos, W. H.; Green, G. D.; Pavia, M. R. *Annu. Rep. Med. Chem.* **1993**, *28*, 315-324. (b) Thompsom, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600. (c) Hermkens, P. H. H.; Ottenheijm, H. C.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554. (d) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233-1251. (e) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385-1401.

2. *Reviews:* (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869-2939. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781-793. (c) Boger, D. L., Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, San Diego, **1987**, *Chapter 10*, pp 300.

3. Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415-1423.

4. Barlin, G. B.; Brown, W. V. *J. Chem. Soc. (C)* **1967**, 2473-2476.

5. Resin **1** was prepared from Polystyrene-CO_2H (commerically available from Advanced ChemTech) with excess of $(COCl)_2$ (4.0 equiv) refluxing in dry benzene for 12 h. The resulting resin was washed with dry benzene under argon and dried *in vacuo* to afford the acid chloride **1** as a light brown colored solid.

6. The loading yield is based on the loading level of carboxylic acid on the polystyrene-CO_2H which is 2.5 mmol/g.

7. Base promoted hydrolysis of **7** without removal of Boc group resulted in the partial loss of Boc group and substitution of the SMe with OMe in the product, thus decreasing the purity of the product.

8. The reaction of tetrazine complex **5** with alkynes produced only trace amounts of cycloaddition products.

9. **General procedure for the Diels-Alder reactions.** The reactions of **5** were performed with 50 mg of resin (0.077 mmol) using 10 equiv of dienophile in 4.0 mL dioxane for 24 h (rt or reflux). The resin was washed with dioxane (3 x 5.0 mL) and CH_2Cl_2 (3 x 5.0 mL) to afford **7** which was then stirred slowly in excess CF_3CO_2H-CH_2Cl_2 1:4 (2.5 mL) for 1 h at room temperature. The resulting resin was washed with CH_2Cl_2 (3 x 5.0 mL) and 1:2 MeOH-THF (2 x 5.0 mL), and then stirred mildly in 3.0 mL 1:2 MeOH-THF with solid K_2CO_3 for 12 h. This reaction mixture was filtered and the filtrate was extracted with EtOAc. The organic phase was concentrated to dryness to afford **8**. The Diels-Alder reaction of **6** was also performed on 50 mg of resin (0.074 mmol). The resin **6** was refluxed with 10~20 equiv of dienophile in 4 mL dioxane for 16 h, followed by treatment with 20% TFA in CH_2Cl_2 for 1h to afford **9.** This material was then washed with CH_2Cl_2 and MeOH-THF, and stirred with solid K_2CO_3 in 1:2 MeOH-THF for 12 h. The reaction mixture was filtered and the filtrate was extracted with EtOAc and the organic solution was dried to afford **10**.

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