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Inverse Electron Demand Diels-Alder Reactions of 3,6-Dichloro-[1,2,4,5]tetrazine

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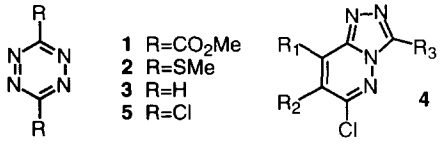
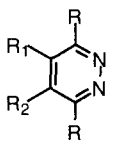
Abstract: 3,6-Dichloro-[1,2,4,5]tetrazine has been found to act as an efficient azadiene equivalent in inverse electron demand [4+2] cyclisations with a range of alkenes and alkynes, allowing rapid access to a range of highly functionalised pyridazines.

1,2,4,5-Tetrazines are well known to act as electron deficient dienes in inverse electron demand Diels-Alder reactions, giving access to highly functionalised pyridazines.[1] [1,2,4,5]Tetrazine-3,6-dicarboxylic acid dimethyl ester **1** has found widespread use in natural product and drug target synthesis, in particular the crucial step in the first total synthesis of the antitumour antibiotic (+)-CC 1065.[2] Other tetrazines such as 3,6-bis-methylsulfanyl-[1,2,4,5]tetrazine **2** have also proven synthetically useful, analogues of which have found applications in solid phase synthesis.[3] Unsubstituted [1,2,4,5]tetrazine **3** has recently been used in inverse electron demand Diels-Alder reactions.[4]

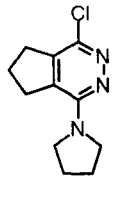


1 R=CO_2Me
2 R=SMe
3 R=H
5 R=Cl

4



6 R=Cl
7 R=SMe



8

Our interest lay in accessing highly functionalised 3,6-dichloropyridazines as precursors to the triazolo[4,3-*b*]pyridazine scaffold **4**, a common feature of a number of $GABA_A$ ligands.[5] This target required using 3,6-dichloro-tetrazine **5** as the azadiene, which to our knowledge has not been reported to undergo inverse electron demand Diels-Alder reactions. The resultant 4,5-substituted-3,6-dichloropyridazines **6** would offer more synthetic flexiblity than the analogous 4,5-substituted-3,6-di(methylthio)pyridazines **7**. The synthesis of 3,6-dichlorotetrazine **5** has been reported, analogues of which have been used as herbicides.[6]

3,6-Dichlorotetrazine **5** was reacted with a variety of alkenes and alkynes, in toluene or dichloromethane to provide pyridazines as identified from ^{1}H NMR and MS data (Table).[7] It can be seen that stannyl and silyl alkynes, enol ethers and enamines reacted to afford substituted pyridazines **6a-f** in good yield (entries **a-f**). A low conversion to **6g** was observed using a dialkyl-substituted alkyne as dienophile (entry **g**).

The greater reactivity of tetrazine **5** (compared to 3,6-bis-methylsulfanyltetrazine **2**) towards the dienophile in entry **d** was also demonstrated. After heating for 72 h at 150°C in mesitylene with an excess of the enol ether, tetrazine **2** gave no pyridazine products, whereas **6d** was smoothly formed from **5** at reflux in toluene in 66% yield (entry **d**). Tetrazine **1** is known to be highly reactive towards even electron poor alkenes.[2]

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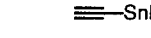
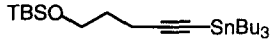
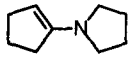
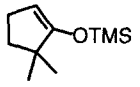
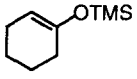
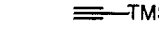
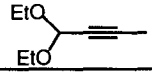
Table. Reaction Conditions for the Synthesis of Pyridazines **6a-g**.

Entry	Dienophile[a]	Product 6	R	R'	Time (h)[7]	Yield (%)[b]
a		**a**	$SnBu_3$	H	1.25	86
b		**b**	$TBSO(CH_2)_3$	$SnBu_3$	1.25	87
c		**c**	$-(CH_2)_3-$		0.08	73[c]
d		**d**	$-(CH_2)_2CMe_2-$		1.5	66
e		**e**	$-(CH_2)_4-$		1	66
f		**f**	TMS	H	5	64[d]
g		**g**	$(EtO)_2CH$	Me	72	10

[a] Commercially available except entries **b**[8] and **d**[9]; [b] After chromatography except entry **g**, estimated from crude ^1H nmr; [c] A byproduct identified as **8** was isolated in 16% yield; [d] Reaction performed in a sealed tube at 120°C.

In summary, we have demonstrated that 3,6-dichlorotetrazine **5** undergoes inverse electron demand Diels-Alder reactions with a range of alkenes and alkynes, allowing access to highly functionalised dichloropyridazines.

References and Notes

1. Sauer, J. *Comprehensive Heterocyclic Chemistry II*, Pergamon: London, **1996**; Vol 6, pp 901-965.
2. Boger, D.L.; Coleman, R.S. *J. Am. Chem. Soc.* **1987**, *109*, 2717; Boger, D.L.; Coleman, R.S. *J. Org. Chem.* **1986**, *51*, 3250.
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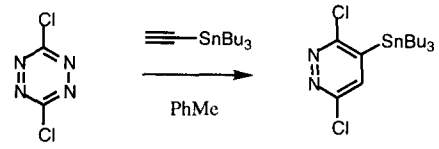
5. Tarzia, G.; Occelli, E.; Toja, E.; Barone, D.; Corsico, N.; Gallico, L.; Luzzani, F. *J. Med. Chem.* **1988**, *31*, 1115.
6. Schirmer, U.; Wuerzer, B.; Meyer, N.; Neugebauer, F.A.; Fischer, H. *Ger. Offen.*, DE 3508214.
7. Typical procedure: inverse electron demand Diels-Alder reaction of tetrazine **5** with tributyl(ethynyl)tin;



5 **6a**

A mixture of 3,6-dichlorotetrazine **5** (0.4 g, 2.65 mmol) and tributyl(ethynyl)tin (0.92 ml, 3.18 mmol) in toluene was heated to reflux for 75 mins (except for **6c** where the enamine was addeed dropwise to a solution of the tetrazine cooled to 0°C in dichloromethane). The crude reaction mixture was concentrated in vacuo and purified on silica eluting with 30% dichloromethane/hexane to afford **6a** as a colourless oil (1.0 g, 86%). ^1H NMR 360 MHz ($CDCl_3$); 7.46 (m, 1H, ^3J ^{119}Sn=14.6Hz, CH), 1.55 (m, 6H, CH_2), 1.35 (m, 6H, CH_2), 1.27 (m, 6H, CH_2), 0.88 (m, 9H, CH_3); MS (ES), 435 [MH^+], 437 [MH^+], 439 [MH^+], 441 [MH^+], 443 [MH^+], 445 [MH^+].

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