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Synthesis of Metallated (Metal = Si, Ge, Sn) Pyridazines by Cycloaddition of Metal Substituted Alkynes to 1,2,4,5-Tetrazine

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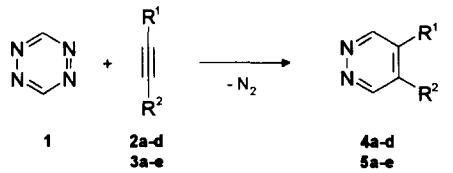
Abstract: MR_3-substituted alkynes **2** and **3** (M = Si, Ge, Sn; R = alkyl) show high reactivity in inverse-type Diels-Alder reactions with the π-electron-deficient 1,2,4,5-tetrazine **1** in strict contrast to the corresponding carbon compounds. Kinetic data prove the huge accelerating effect of the trialkyltin substituent, offering a simple access to new heteroaromatic organotin derivatives, which can be easily transformed by standard methods of organotin chemistry. © 1997 Elsevier Science Ltd.

Simple organotin alkynes, like ethynyltributyltin **2d**, are known to be sluggish dienophiles in Diels-Alder reactions. According to the literature,[1] they undergo [4+2] cycloadditions only if a second electronwithdrawing substituent (e.g. -COOMe), which lowers the energy of the LUMO, is also present in the alkyne. But, from the opposite point of view, this fact implies, that these 2π-systems should be reactive dienophiles in inverse-type Diels-Alder reactions. Nevertheless, only few examples have been reported in the literature (e.g. hexachlorocyclopentadiene,[2a] 3,6-disubstituted tetrazines[2b]). In order to examine this reactivity problem, several mono- and disubstituted alkynes **2** and **3** were prepared according to published procedures. 1,2,4,5-Tetrazine **1**[3] was chosen as an electron-poor diene in order to minimize steric interactions in the transition state.

Pyridazines **4** and **5** (all previously unknown, except **5a**) could easily be prepared by [4+2] cycloaddition in high yields (Scheme 1, Tables 1a and 1b).[4]



1 **2a-d** **3a-e** **4a-d** **5a-e**

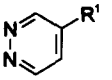
Scheme 1

	R^1	R^2
2a,4a	-CMe_3	-H
2b,4b	-$SiMe_3$	-H
2c,4c	-$GeMe_3$	-H
2d,4d	-$SnBu_3$	-H
3a,5a	-CMe_3	-CMe_3
3b,5b	-$SiMe_3$	-$SiMe_3$
3c,5c	-$GeMe_3$	-$GeMe_3$
3d,5d	-$SnBu_3$	-$SnBu_3$
3e,5e	-$SnMe_3$	-$SnMe_3$

The structure of the pyridazines obtained was characterized by spectroscopic data (^1H, ^{13}C-NMR, EI-MS (70eV), IR) and correct elemental analysis. The purity of the liquid monosubstituted pyridazines was also checked by means of gas chromatography. 4,5-Disubstituted pyridazines are colourless, crystalline compounds (except **5d**: yellow oil).

Table 1a. Reaction conditions for the synthesis of monosubstituted pyridazines (R^2 = -H)

Product	R^1	Solvent	T (°C)	t	Yield (%)	Purity (GC)[a]
4a	$-CMe_3$	-	RT[5]	4 weeks	74	97.9
4b	$-SiMe_3$	Acetonitrile	80[5]	2 h	94	100
4c	$-GeMe_3$	Acetonitrile	80	1.5 h	80	98.8
4d	$-SnBu_3$	Toluene	RT	12 h	76	97.5

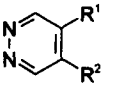


4a-d

[a] area in %

Table 1b. Reaction conditions for the synthesis of 4,5-disubstituted pyridazines

Product	$R^1 = R^2$	Solvent	T (°C)	t (h)	Yield (%)	Mp. (°C)
5a	$-CMe_3$	Chloroform	65[5]	120	12	108
5b	$-SiMe_3$	Acetonitrile	80	12	93	94-95
5c	$-GeMe_3$	Dioxane	RT	120	93	93-94
5d	$-SnBu_3$	Dichloromethane	RT	2	71	yellow oil
5e	$-SnMe_3$	Dichloromethane	RT	2	82	79-80



5a-e

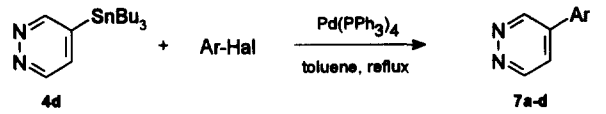
Experimental conditions indicate an increase in reactivity, if the substituent is changed from carbon to tin (**4a** → **4d**, **5a** → **5e**). This fact was also demonstrated by kinetic rate measurements. Second order rate constants were determined in dioxane at 20°C,[6] in order to achieve comparability with existing kinetic data.[7] The rate constants increase rapidly, when the substituent is varied systematically within the fourth main group of the periodic system. In comparison with literature data for unsubstituted acetylene (k_2*10^5 = 2.91 l/mol s)[7] the activating effect of $-MR_3$ substituents (M = Si, Ge or Sn) on the triple bond towards inverse-type Diels-Alder reactions is evident. As expected, organotin alkynes offer the highest reactivity.

Table 2. Rate constants k_2*10^5 [l/mol s], 20°C, dioxane, for the reaction of 1,2,4,5-tetrazine **1** with alkynes **2** and **3**

M	R	$H-\equiv-MR_3$ **2**	$R_3M-\equiv-MR_3$ **3**
C	Me	0.169	-
Si	Me	4.16	7.63
Ge	Me	19.0	106
Sn	Bu	58.2	366
Sn	Me	-	1242

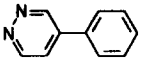
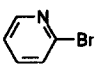
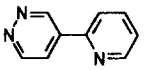
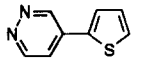
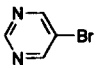
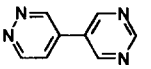
The cycloadditions of organotin alkynes to 1,2,4,5-tetrazine offer an easy way for the rapid synthesis of stannylated pyridazines under mild conditions. Palladium-catalysed cross-coupling reactions are a well known tool for the synthesis of complex biaryls. Thus 4-tributylstannyl-pyridazine **4d** was examined to serve as a synthon for the introduction of the pyridazine moiety into various aromatic ring systems. Successful couplings could be achieved by refluxing **4d** with an 1.5-fold excess of **6a-d** in dry toluene in the presence of 1-2mol%

$Pd(PPh_3)_4$ for the time indicated in Table 3, followed by flash chromatographic work-up for **7a-c**.[8] **7d** crystallized upon cooling of the reaction mixture.

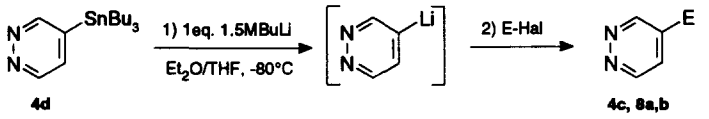


Scheme 2

Table 3. Reaction conditions for the Pd-catalysed coupling reactions of **4d** in refluxing toluene

Ar-Hal		t (h)	Coupling product		Yield (%)	Mp. (°C).
6a		48	**7a**		51	86-87
6b		48	**7b**		60	86-87
6c		24	**7c**		74	77-78
6d		24	**7d**		93	177

The tin-lithium exchange is a common procedure for vinyltin compounds. Analogous treatment of **4d** at low temperature with n-butyl lithium led to an orange suspension, which was quenched by various strong electrophiles (Scheme 3, E-Hal: **4c**: Me_3SiCl, **8a**: Ph_2PCl, **8b**: PhSeBr). The expected substituted pyridazines could be isolated by flash chromatography in modest yields of approximately 35%.[9]



	E	yield (%)
4c	$SiMe_3$	38
8a	PPh_2	34
8b	SePh	39

Scheme 3

Due to the fact, that in all cases starting material could be recovered, reaction conditions have to be optimized. Further investigations on the synthetic applications of the reaction studied are in progress.

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References and Notes:

Dedicated to Prof. Dr. E. Winterfeldt on the occasion of his 65th birthday.

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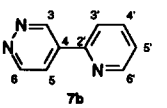
3. Hetzenegger, J. *Ein Beitrag zur (4+2)-Cycloaddition mit heterocyclischen Dienen*, University of Regensburg, 1989. Synthesis of **1**: Hydrazine hydrate (120 g, 2.40 mol) was added to formamidine acetate (120 g, 1.15 mol) in CH_3OH (200 ml) at 0°C. Glacial acetic acid (375 ml) was added over a period of 60 min at 0-10°C. Finally solid $NaNO_2$ (150 g, 2.15 mol) was added in small portions, maintaining the temperature below 10°C. Stirring was continued for 1h at 10°C and for one more hour at ambient temperature. Solid $NaHCO_3$ (250g) and water (300ml) were added and the resulting suspension was stirred for 30 min. Undissolved $NaHCO_3$ was filtered off with suction. The filtrate was extracted with CH_2Cl_2 (10 x 100 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 x 100 ml), water (100 ml) and were dried over $CaCl_2$. The red solution was concentrated at atmospheric pressure using a 30 cm vigreux column to a volume of 50 ml, purified by chromatography (Kieselgel 60, CH_2Cl_2) and concentrated again. The last 50 ml of the solvent were removed under reduced pressure (-40°C, 0.1Torr). Sublimation (bath 10°C, cooling finger -50°C, 0.1 Torr) yielded pure **1** (10.0 - 12.2 g, 21-26%). M.p. 94-95°C.
4. 4,5-Bis-trimethylsilanyl-pyridazine **5b**: The red solution of **1** (175 mg, 2.13 mmol) and **3b** (375 mg, 2.20 mmol) in dry acetonitrile (5 ml) was refluxed overnight. After 12h the bright yellow solution was concentrated in vacuo and the residue was recrystallized from light petroleum 40/60 to give pure **5b**. Colourless needles (445 mg, 93%). M.p. 94-95°C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.40 (s, 9H, Si-C$\underline{H}_3$), 9.18 (s, 2H, C-H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$): δ 0.64, 144.81, 154.34 ppm. IR (KBr): 3080, 2960, 2910, 1460, 1410, 1250, 1190, 1160, 1120, 1090, 840, 760 cm^{-1}. Calcd. for $C_{10}H_{20}N_2Si_2$ (224.5): C, 53.51; H, 8.98; N, 12.48. Found: C, 53.60; H, 9.04; N, 12.36. MS (EI-70eV): 224 (40) [M$^+$], 209 (19) [M$^+$-CH$_3$], 73 (100) [Me$_3$Si$^+$].
5. An 8-10 fold excess of the volatile dienophile was used in order to accelerate the reaction.
6. UV-kinetic measurements were possible by following the decrease of the n→π* transition of **1** (λ = 525 nm, ε = 706 l mol^{-1} cm^{-1}). Deviations for at least four runs were always less than 4%.
7. Sauer, J. 1,2,4,5-Tetrazines. In *Comprehensive Heterocyclic Chemistry II*; Katritzky A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1997; Vol. 6, pp. 901-957.
8. 4-Pyridin-2-yl-pyridazine **7b**: Pd(PPh$_3$)$_4$ (15 mg, 0.01 mmol, 1 mol%) and 2-bromopyridine (284 mg, 1.80 mmol) in dry toluene (12 ml) were stirred for 5 min. Then **4d** (354 mg, 0.96 mmol) was added and the mixture was heated to reflux for 48h. After 24h, more Pd(PPh$_3$)$_4$ (15 mg, 0.01 mmol, 1 mol%) was added. The solvent was evaporated, the semi-solid residue was purified by flash chromatography (20g Kieselgel 60, CH_2Cl_2 / EtOAc 1:1), sublimed (100°C/0.05 Torr) and recrystallized from light petroleum 40/60 to give pure **7b** (90 mg, 60%). M.p. 86-87°C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.43 (ddd, 1H, ^{3}J=4.8Hz, ^{4}J=3.8Hz, H^5), 7.84-7.92 (m, 2H, H^3/H^4), 8.09 (dd, 1H, ^{4}J=2.4Hz, ^{3}J=5.4Hz, H^5), 8.79 (ddd, 1H, ^{3}J≈^{4}J=4.8Hz, ^{5}J=1.3Hz, H^6), 9.31 (dd, 1H, ^{3}J=5.4Hz, ^{5}J=1.3Hz, H^6), 9.82 (dd, 1H, ^{4}J=2.4Hz, ^{5}J=1.3Hz, H^3) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ 121.13 (C$^{3'}$), 122.93 (C^5), 124.67 (C$^{5'}$), 136.49 (C^4), 137.49 (C$^{4'}$), 149.19 (C^3), 150.66 (C$^{6'}$), 151.72 (C^6), 151.87 (C$^{2'}$) ppm, assignment by ^{1}H-^{13}C-correlation. IR (KBr) 3040, 1580, 1460, 1350, 1280, 980, 960, 860, 760, 735, 660 cm^{-1}. Calcd. for $C_9H_7N_3$ (157.2): C, 68.77; H, 4.49; N 26.73. Found: C, 68.76; H, 4.69; N, 26.89. MS (EI-70eV): 157 (25) [M$^+$], 156 (100) [M$^+$-H], 130 (41) [M$^+$-HCN], 79 (74) [pyridyl$^+$].



7b

9. 4-Diphenylphosphanyl-pyridazine **8a**: **4d** (188 mg, 0.51 mmol) was dissolved in a dry 2:1 Et$_2$O/THF-mixture (12 ml) and cooled below -80°C (2-propanol/liq. N_2-bath). 1.5M BuLi in hexanes (0.3 ml) was added dropwise by means of standard syringe/septa techniques within a period of 5 min. The resulting orange suspension was stirred for 75 min at -80°C, and then quenched by the addition of 0.5 mmol freshly distilled chlorodiphenylphosphane (110 mg, 0.50 mmol) in dry THF (1 ml). The brown solution was allowed to reach RT slowly and was hydrolyzed by the addition of H_2O (10 ml). The organic phase was separated, concentrated in vacuo, and the brown oil was purified by flash chromatography (20g Kieselgel 60, PE 40-60 / EtOAc 1:1). 1. Product (R_f=0.78, Bu_4Sn), 2. Product (R_f=0.22, recovered starting material **4d**, 24%), 3. Product (R_f=0.15, **8a**, 34%). Recrystallization from PE 40/60. M.p. 86-88°C. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.17 (1H), 7.33-7.48 (5H), 7.61-7.69 (5H), 8.96 (1H), 9.04 (1H) ppm. ^{13}C-NMR (63MHz, $CDCl_3$): δ 129.19 (4C), 129.39 (1C), 130.13 (2C), 133.24 (2C), 134.27 (4C), 140.80 (1C), 150.51 (1C), 153.94 (1C) ppm. IR (KBr): 3070, 3050, 1545, 1470, 1430, 1240, 845, 740, 690 cm^{-1}. Calcd. for $C_{16}H_{13}N_2P$ (264.3): C, 72.72; H, 4.96; N, 10.60; Found C, 72.47; H, 5.00; N, 10.55. MS (EI-70eV): 264 (100) [M$^+$], 185 (22) [M$^+$-C$_4$H$_3$N$_2$], 183 (43) [Ph$_2$P$^+$-2H], 108 (12) [PhP$^+$], 107 (14) [PhP$^+$-H].

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