SYNTHESIS OF 4-(TRIBUTYLSTANNYL)PYRIDAZINES BY INVERSE ELECTRON-DEMAND DIELS-ALDER REACTION OF 1,2,4,5-TETRAZINES WITH TRIBUTYLSTANNYLACETYLENES

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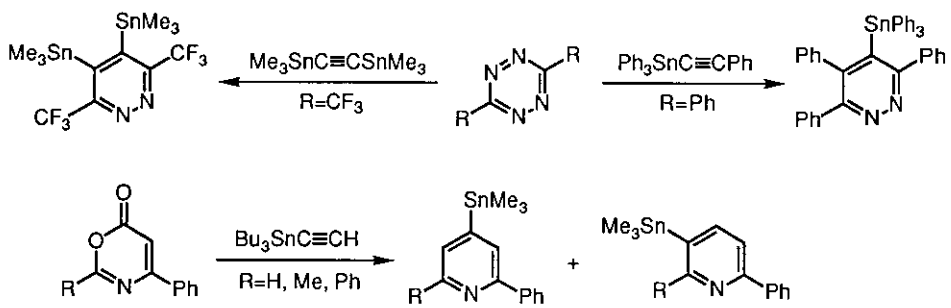
Abstract — Inverse electron-demand Diels-Alder reaction of 3,6-disubstituted 1,2,4,5-tetrazines with tributylstannylacetylenes containing a substituent gave 4-(tributylstannyl)pyridazines. Particularly, dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate gave 4-(tributylstannyl)pyridazines in good yields. Substitution reaction of 3,6-diphenyl-4-(tributylstannyl)pyridazine was also described.

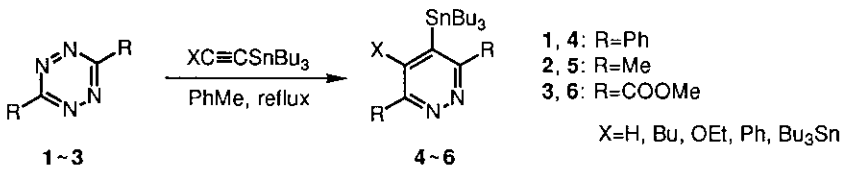
Inverse electron-demand Diels-Alder reaction of electron-deficient nitrogen heteroaromatics with electron-sufficient olefins or acetylenes has been becoming a useful method for the synthesis of various aromatics or heteroaromatics.[1] Meanwhile, it has been recognized that trialkylstannyl group is useful to introduce a functional group into heteroaromatics,[2] but there is a few papers for the synthesis of trialkylstannyl heteroaromatics by inverse electron-demand Diels-Alder reaction. For example, Neumann *et al.* reported that 3,6-diphenyl-1,2,4,5-tetrazine reacts with phenytriphenylstannylacetylene at 130-150°C to give 3,5,6-triphenyl-4-(triphenylstannyl)pyridazine in 22% yield[3] and Barlow *et al.* described that 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine readily reacts with 1,2-bis(trimethylstannyl)acetylene at 0°C to give 3,6-bis(trifluoromethyl)-4,5-bis(trimethylstannyl)pyridazine in 78% yield.[4] Recently, Yamamoto *et al.* reported the synthesis of trialkylstannylpyridines from the reaction of 1,3-oxazin-6-ones with trialkylstannylacetylenes.[5]



Scheme 1

On the basis of these backgrounds, we describe, in this paper, the synthesis of 3,6-disubstituted 4-tributylstannylpyridazines by the Diels-Alder reaction of 3,6-disubstituted 1,2,4,5-tetrazines with various tributylstannylacetylenes and some reactions of 3,6-diphenyl-4-(tributylstannyl)pyridazine.

In order to examine the reactivity of the substituted tributylstannylacetylenes, the Diels-Alder reaction of 3,6-diphenyl-1,2,4,5-tetrazine (**1**) was carried out. When **1** was heated with tributylstannylacetylene in toluene under reflux for 60 h, 3,6-diphenyl-4-(tributylstannyl)pyridazine (**4a**) was obtained in 85% yield, as a viscous liquid. But the reaction of **1** with butyltributylstannylacetylene, phenyltributylstannylacetylene, and bis(tributylstannyl)acetylene gave rise to the corresponding pyridazines (**4b,c,e**) in 25-38% yields, and ethoxytributylstannylacetylene did not afford expected product (**4c**).



Scheme 2

Table I. Diels-Alder Reaction Products of 3,6-Diphenyl-1,2,4,5-tetrazines with Tributylstannylacetylenes

Compd. No.	R	X	Reaction time (h)	Yield (%)	^{1}H-Nmr (δ: $CDCl_3$/TMS)
4a	Ph	H	60	85	0.4-1.6 (27H, m), 7.24 (1H, s), 7.4-7.7 (8H, m), 8.0-8.2 (2H, m)
4b	Ph	Bu	48	38	0.4-1.8 (34H, m), 1.5-2.9 (2H, m), 7.2-7.7 (10H, m)
4c	Ph	EtO	48	0	
4d	Ph	Ph	36	25	0.5-1.7 (27H, m), 7.2-7.7 (15H, m)
4e	Ph	Bu_3Sn	32[a]	30	0.5-1.7 (54H, m), 7.3-7.7 (10H, m)
5a	Me	H	15	81	0.5-1.8 (27H, m), 2.53 (3H, s), 2.60 (3H, s), 7.17 (1H, s)
5b	Me	Bu	72	5	0.7-1.7 (34H, m), 2.3-2.7 (2H, m), 2.63 (3H, s), 2.70 (3H,s)
6a	COOMe	H	54	70	0.7-1.8 (27H, m), 4.13 (6H, s), 8.50 (1H, s)
6b	COOMe	Bu	14	78	0.7-1.8 (27H, m), 2.6-3.2 (2H, m), 4.03 (6H, s)
6c	COOMe	EtO	2	75	0.7-1.7 (30H, m), 4.08 (6H, s), 4.17 (2H, q, *J*=7 Hz)
6d	COOMe	Ph	1	77	0.6-1.5 (27H, m), 3.70 (3H, s), 4.10 (3H, s), 7.1-7.6 (5H, m)
6e	COOMe	Bu_3Sn	6	64	0.6-1.7 (54H, m), 4.09 (6H, m)

a) Reflux in mesitylene.

From the results shown in Table I, it is found that the reactivity of the substituted tributylstannylacetylenes as dienophile decreases in the following order: tributylstannylacetylene > butyltributylstannylacetylene ≈ phenyltributylstanny-

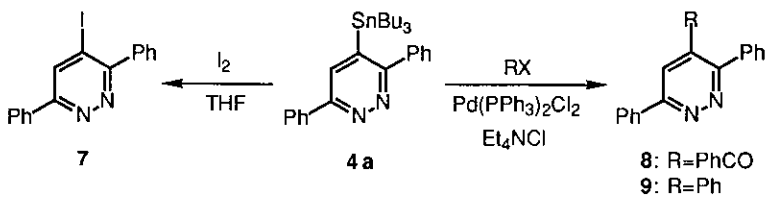
lacetylene > bis(tributylstannyl)-acetylene > ethoxytributylstannylacetylene. A similar tendency was also observed in the reaction of 3,6-dimethyl-1,2,4,5-tetrazine (**2**), although examples are few.

Since it is expected that the presence of electron-withdrawing groups on 1,2,4,5-tetrazine ring accelerates the inverse electron-demand Diels-Alder reaction,[4] we next carried out the reaction using dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**3**) as a diazadiene. As shown in Table I, all the reaction with tributylstannylacetylenes used afforded the tributylstannylpyridazines in good yields.

Although 1,2,4,5-tetrazine is considered to be highly electron-deficient heteroaromatic, it was found that alkyl- or aryl-substituted 1,2,4,5-tetrazines are relatively less reactive toward the Diels-Alder reaction with tributylstannylacetylenes and that the presence of electron-withdrawing groups is necessary to occur the reaction smoothly.

It is well known that electron-deficient nitrogen heteroaromatics such as pyridine, quinoline, and their aza-analogs, in principle, have not enough reactivity towards electrophilic reagents. Thus, in order to make sure synthetic utility of the trialkylstannyl groups on pyridazine ring, some substitution reactions of 3,6-diphenyl-4-tributylstannylpyridazine (**4a**) were investigated.

The iodination of **4a** with iodine in tetrahydrofuran proceeded at room temperature to give 4-iodo-3,6-diphenylpyridazine (**7**) in 77% yield. The benzoylation of **4a** with benzoyl chloride in the presence of dichlorobis(triphenylphosphine)-palladium and tetraethylammonium chloride in boiling benzene gave 3,6-diphenyl-4-pyridazinyl phenyl ketone (**8**), although the yield was unsatisfactory. According to the similar manner, the palladium-catalyzed cross-coupling of **4a** with iodo- and bromobenzene gave 3,4,6-triphenylpyridazine (**9**) in 39 and 26% yields, respectively.



7 **4a** **8**: R=PhCO
9: R=Ph

Scheme 3

EXPERIMENTAL

General Procedure of the Diels-Alder Reaction of 1,2,4,5-Tetrazines with Tributylstannylacetylenes

A solution of a 1,2,4,5-tetrazine (2 mmol) and a tributylstannylacetylene (3 mmol) in toluene or mesitylene (10 ml) was refluxed for the time shown in Table I. After removal of the solvent, the residue was purified by silica gel column chromatography to give a product as a pale yellow viscous liquid which gave satisfactory value by high-resolution mass spectroscopy.

4-Iodo-3,6-diphenylpyridazine (7)

A solution of 3,6-diphenyl-4-(tributylstannyl)pyridazine (**4a**) (0.52 g, 1 mmol) and iodine (0.25 g, 1 mmol) in THF (15 ml) was stirred at room temperature for 24 h. The reaction mixture was diluted with ether, washed with satd. $NaHCO_3$, satd.

Na_2SO_3, and 0.5M KF aqueous solution, and dried over $MgSO_4$. The residue obtained from the ethereal solution was purified by silica gel column chromatography using benzene-$CHCl_3$ (1:4). The crude product was recrystallized from hexane-AcOEt to give colorless scales, mp 167-168°C. Yield 0.28 g (77%). ^{1}H-Nmr ($CDCl_3$/TMS) δ (ppm): 7.3-7.8 (8H, m), 8.0-8.2 (2H, m), 8.39 (1H, s). *Anal.* Calcd for $C_{16}H_{11}N_2I$: C, 53.66; H, 3.10; N, 7.82. Found: C, 53.46; H, 3.13; N, 7.74.

3,6-Diphenyl-4-pyridazinyl Phenyl Ketone (8)

A mixture of **4a** (0.78 g, 1.5 mmol), benzoyl chloride (0.25 g, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (53 mg, 0.075 mmol), and Et_4NCl (0.25 g, 1.5 mmol) in dry benzene (10 ml) was refluxed for 41 h. After removal of the solvent, the residue was dissolved in $CHCl_3$ and washed with satd. $NaHCO_3$ aqueous solution. The residue obtained from the $CHCl_3$ extract was purified by silica gel column chromatography using AcOEt-hexane (1:3). The crude product was recrystallized from EtOH to give colorless needles, mp 183-184°C. Yield 0.19 g (38%). Ir (KBr) cm^{-1}: 1670. ^{1}H-Nmr ($CDCl_3$/TMS) δ (ppm): 7.1-7.7 (13H, m), 7.75 (1H, s), 8.0-8.2 (2H, m). *Anal.* Calcd for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.33. Found: C, 82.30; H, 5.06; N, 8.40.

3,4,6-Triphenylpyridazine (9)

A mixture of **4a** (1.04 g, 2 mmol), iodobenzene (0.49 g, 2.4 mmol), $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol), and Et_4NCl (0.33 g, 2.4 mmol) in dry DMF (10 ml) was heated at 80°C for 30 h. After removal of the solvent, the residue was purified by silica gel column chromatography using AcOEt-hexane (1:3). The crude product was recrystallized from EtOH to give colorless needles, mp 171-173°C (lit.[6] mp 170-172°C). ^{1}H-Nmr (CCl_4/TMS) δ (ppm): 7.1-7.6 (13H, m), 7.75 (1H, s), 8.0-8.3 (2H, m).

According to the above procedure, **9** was obtained in 26% from bromobenzene.

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