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Ethynyltributyltin - a Synthetic Equivalent for Acetylene, Aryl, Acyl and Halogeno Alkynes in [4+2] Cycloadditions

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Dedicated to Professor Dr. E. Vogel on the occasion of his 70th birthday.

Abstract: Ethynyltributyltin **2** cycloadds to 5-phenyl-1,2,4-triazine-3-carboxyclic acid methyl ester **1** to furnish mainly 4-tributylstannyl-6-phenyl-pyridine-2-carboxyclic acid methyl ester **3a** besides a small amount of the 3-tributylstannyl isomer **3b**. The tributyltin substituent of pyridine **3a** can be replaced by Pd-catalyzed acylation and arylation, by halogenation and protonation to yield functionalized pyridines **4** - **7**, which are not available by direct cycloaddition of the corresponding alkynes. © 1998 Elsevier Science Ltd. All rights reserved.

A number of reports concerned with the use of organotin compounds in organic synthesis have been described. The trialkylstannyl group undergoes numerous transformations under mild conditions.[1] From this laboratory, the application of ethynyltributyltin as an electron rich dienophile in inverse electron demand Diels-Alder reactions with the highly electron deficient 1,2,4,5-tetrazine has been reported quite recently.[2] The resulting stannylated pyridazines have been used in Pd-catalyzed Stille cross-coupling reactions to yield various heteroaromatic biaryls. Thus, the cycloaddition pathway has to be considered as a very specific, but also very effective method for the synthesis of heteroaromatic organotin compounds.

In this communication we wish to extend the scope of the cycloaddition route towards the synthesis of stannylated pyridines. 1,2,4-Triazines are known to participate as electron poor dienes in inverse electron demand Diels-Alder reactions with electron rich dienophiles to yield pyridine derivatives after extrusion of molecular nitrogen.[3] According to kinetic measurements, the reactivity of the 2,3-diazadiene system towards cyclooctyne as dienophile drops by a factor of about 10^4-10^5 when the diene is changed from 3-phenyl-1,2,4,5-tetrazine to 3-phenyl-1,2,4-triazine.[4] It seemed clear to us, that this lack of reactivity had to be overcome by drastic reaction conditions like prolonged heating. Therefore, triazine **1**[5] and ethynyltributyltin (**2**) were heated at 180°C in 1,2-dichlorobenzene as solvent for 16h. In principle, two regioisomeric pyridines **3a** and **3b** had to be expected as final cycloadducts after loss of molecular nitrogen due to the asymmetry of 1,2,4-triazines. To our great delight, **3a** was formed predominantly along with **3b** as minor isomer.[6] Both isomers could be separated by flash column chromatography using petroleum ether/ethyl acetate as eluent. As has been already observed for unsymmetrically 3-aryl-1,2,4,5-tetrazines,[7] regioselectivity again was controlled by steric repulsive forces between the ester functionality of the triazine and the bulky tributyltin substituent of the alkyne. Hence, the transition state where the tributyltin substituent is located above the hydrogen H-6 of the triazine nucleus is favored and consequently a preference for the formation of **3a** results. The

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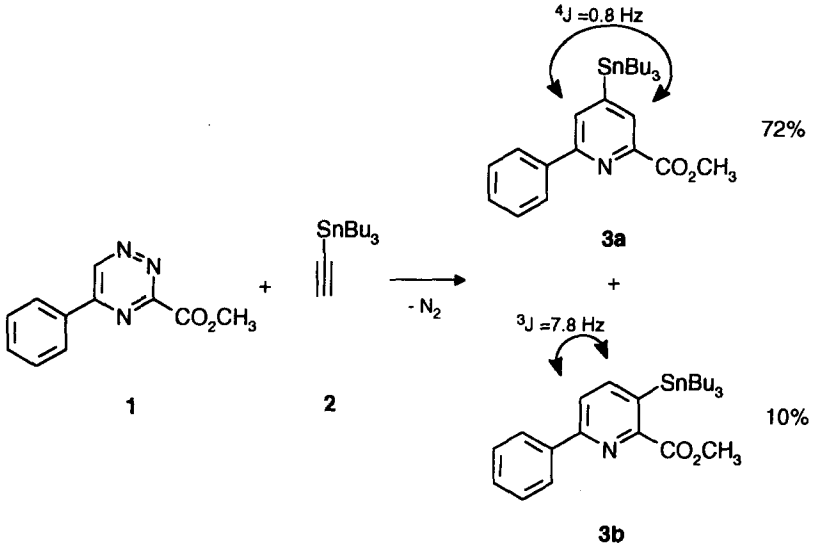
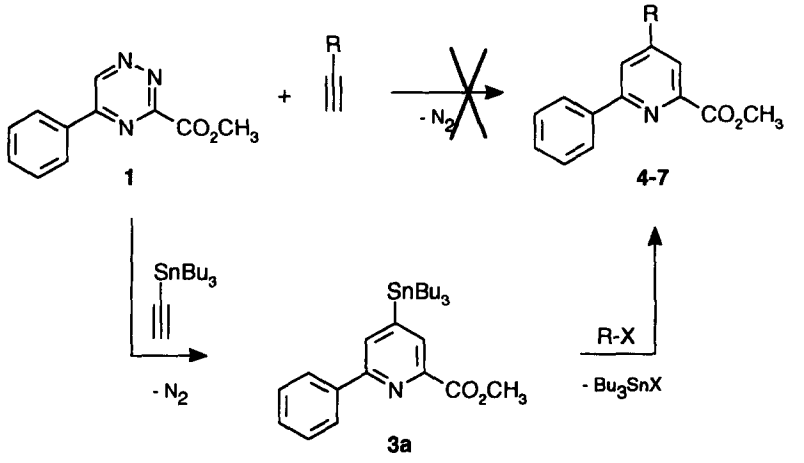
regiochemistry was assigned to **3a** and **3b** by comparing the coupling constants of the doublets of the pyridine protons in the ^{1}H NMR spectra as shown in Scheme 1.



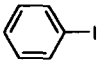
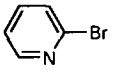
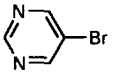
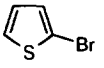
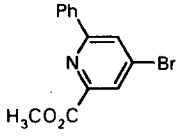
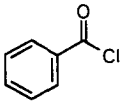
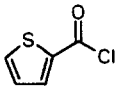
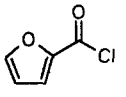
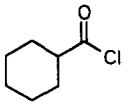
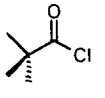
Scheme 1. [4+2] Cycloaddition of ethynyltributyltin (**2**) with 1,2,4-triazine **1**.

Frontier molecular orbital (FMO) theory offers a qualitative and semi-quantitative description of pericyclic reactions.[8] This simple, but still correct model allows to distinguish three mechanistic types of Diels-Alder reactions. For the case of inverse-type [4+2] cycloadditions it implies the combination of electron poor dienes with electron rich dienophiles. However, from an opposite point of view, it also stands for the most important restriction on the Diels-Alder reaction: A combination of electron deficient dienes and electron deficient dienophiles is not possible. Hence, the subsequent replacement of the trialkyltin group by electron withdrawing groups like halogens or acyl groups outplays this restriction by a two-step procedure (Scheme 2) and should be of general synthetic importance. Our results are summarized in Table 1.



Scheme 2. A roundabout route makes cycloadducts available, which originate from the combination of electron deficient dienes and electron deficient dienophiles (R = electron withdrawing group).

Table 1. Conditions and yields for the reactions summarized in Scheme 2.

product[9]	R-X	reaction conditions and reaction times	isolated yield [%]	m.p. [°C]
4	HCl	HCl in Et_2O, RT, 15 min	62	46-47.5
5a	Cl_2	CCl_4/CH_2Cl_2, RT	67	90-90.5
5b	Br_2	$CHCl_3$, -60°C	70	99-101
5c	I_2	THF, RT, 20h	76	123-123.5
6a		Toluene, 110°C, 2h, 1.5 mol% $Pd(PPh_3)_4$	63	112
6b		Toluene, 110°C, 48h, 2 x 1.5 mol% $Pd(PPh_3)_4$ (per 24h)	39	134-136
6c		Toluene, 110°C, 24h, 1.5 mol% $Pd(PPh_3)_4$	74	186
6d		Toluene, 110°C, 7h, 1.5 mol% $Pd(PPh_3)_4$	69	101-102
6e		Toluene, 110°C, 2h, 1.5 mol% $Pd(PPh_3)_4$	50	226-228
7a		$CHCl_3$, 65°C, 18h, 1.5 mol% $BnPdCl(PPh_3)_2$	86	132
7b		$CHCl_3$, 65°C, 18h, 1.7 mol% $BnPdCl(PPh_3)_2$	70	139-140
7c		$CHCl_3$, 65°C, 20h, 1.7 mol% $BnPdCl(PPh_3)_2$	73	145.5-146.5
7d		$CHCl_3$, 65°C, 15h, 1.7 mol% $BnPdCl(PPh_3)_2$	52	122
7e		$CHCl_3$, 65°C, 14h, 1.7 mol% $BnPdCl(PPh_3)_2$	72	91-92

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References and Notes

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4. a) Balcar, J.; Chrisam, G.; Huber, F.X.; Sauer, J. *Tetrahedron Lett.* **1983**, *24*, 1481-1484. b) Sauer, J.; 1,2,4,5-Tetrazines. In *Comprehensive Heterocyclic Chemistry II*; Pergamon Press: Oxford, 1996; Vol. 6, pp. 901-955.
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6. Analytical data for **3a**: IR (film): $\tilde{\nu}$ = 3060, 3040, 2970, 2930, 2880, 2860, 1740, 1715 1560, 1530, 1450, 1430, 1410, 1375, 1310, 1260, 1190, 1145, 1075, 875, 770, 720, 690 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.2 Hz, 9 H, $-CH_3$), 1.14-1.21 (m, 6 H, $-CH_2-$), 1.28-1.42 (m, 6 H, $-CH_2-$), 1.51-1.61 (m, 6 H, $-CH_2-$), 4.02 (s, 3 H, $-OCH_3$), 7.38-7.52 (m, 3 H, aromatic H), 7.96 (d, J = 0.8 Hz, $=C-H$, pyridine), 8.00-8.04 (m, 2 H, aromatic H), 8.15 (d, J = 0.8 Hz, $=C-H$, pyridine) ppm. – ^{13}C NMR (63 MHz, $CDCl_3$, DEPT): δ = 9.85 (3C, –, J_{Sn-C} = 345.6 Hz, $Sn-CH_2-$), 13.57 (3C, +, $-CH_3$), 27.24 (3C, –, $^3J_{Sn-C}$ = 56.3 Hz, $-CH_2-$), 28.97 (3C, –, $^2J_{Sn-C}$ = 21.0 Hz, $-CH_2-$), 52.65 (1C, +, $-OCH_3$), 127.37 (2C, +), 128.77 (2C, +), 129.10 (1C, +), 131.05 (1C, +, J_{Sn-C} = 27.9 Hz), 131.86 (1C, +, J_{Sn-C} = 25.9 Hz), 139.25 (1C, 0), 146.28 (1C, 0), 155.51 (1C, 0), 155.93 (1C, 0), 166.77 (1C, 0, C=O) ppm. – EI-MS (70eV); *m/z* (%): 503 (4) [M^+], 446 (100) [M^+-C_4H_9], 390 (18) [446-C_4H_8], 334 (39) [390-C_4H_8], 272 (5), 154 (11). – $C_{25}H_{37}NO_2Sn$ (502.3): calcd. C 59.78, H 7.43, N 2.79; found C 59.96, H 7.09, N 3.49. – **3b** was also characterized by all analytical methods.
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8. a) Fukui, K. *Fortsch. Chem. Forsch.* **1970**, *15*, 1-85. b) Sauer, J.; Sustmann, R.; *Angew. Chem.* **1980**, *92*, 773-802; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 779-807.
9. Typical procedures for the preparation of substituted pyridines **4-7**: (fcc = flash column chromatography)

   Protonation (**4**): **3a** (150 mg, 0.32 mmol) was dissolved in dry Et_2O (3 ml) under an inert atmosphere and 1.0M HCl in Et_2O (0.8 ml, Aldrich) was added dropwise. The reaction mixture was stirred for further 15 min, then concentrated by a stream of nitrogen (Caution: gaseous HCl is very corrosive). Purification by fcc (petroleum ether 40/60 : ethyl acetate 65:35) yielded **4** as a colorless oil, which slowly solidified within a few days upon standing in a refrigerator.

   Halogenation (**5**): **3a** (210 mg, 0.42 mmol) was cooled to -60°C in dry $CHCl_3$ (4 ml). Bromine (68 mg, 0.43 mmol) in dry $CHCl_3$ (4 ml) was added dropwise. After completion of the addition the cooling bath was removed and the reaction mixture allowed to reach room temperature. The solvent was evaporated and the residue purified by fcc (petroleum ether 40/60 : ethyl acetate 90:10) and recrystallized from petroleum ether 40/60 to furnish **5b** as colorless crystals.

   Cross-coupling with aryl halides (**6**)[10]: $Pd(PPh_3)_4$ (app. 8 mg, 1.5 mol%) was dissolved in toluene (3 ml). The arylhalide (0.75 mmol) was added and the reaction mixture stirred for 3-5 min. After this period **3a** (0.5 mmol) in toluene (3 ml) was added and the reaction mixture heated to reflux for the time indicated in table 1. For most cases the precipitation of colloidal palladium indicated the end of the reaction. The palladium was filtered off, the solvent evaporated under reduced pressure and the residue purified by fcc (petroleum ether 40/60 : ethyl acetate) and recrystallization. **6c** and **6e** crystallized upon cooling of the reaction mixture and were filtered off with suction. No fcc was necessary for these compounds.

   Acylation with acyl chlorides (**7**)[10]: The acid chloride (0.45 mmol) was added to a stirred solution of benzylchloro-bis-(triphenylphosphino)-palladium ($BnPdCl(PPh_3)_2$, 5 mg, 1.7 mol%) in dry $CHCl_3$ (0.5 ml) in a 10ml flask. After stirring for 3 min **3a** in dry $CHCl_3$ (1.5 ml) was added and the flask closed loosely with a stopper. The reaction mixture was heated at 65°C (bath temperature) for the time indicated in table 1. Precipitated palladium (not always the case) was filtered off, the reaction mixture concentrated under reduced pressure, purified by fcc (petroleum ether 40/60 : ethyl acetate) and recrystallized (**7a-c**: cyclohexane : ethyl acetate; **7d-e**: petroleum ether 40/60).

   Analytical and spectroscopic data for compounds **4-7** are in full accordance with those of the proposed structures. For details see the forthcoming *Ph. D. thesis* of Dieter Heldmann, University of Regensburg, 1998.
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