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Isothiazoles. Part VII.[1] An Efficient Palladium-Catalyzed Functionalization of 3-Amino-4-aryl-isothiazole 1,1-Dioxides with Organostannanes.

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Abstract: The palladium-catalyzed reaction of 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**3**) with a variety of vinyl-, aryl- , heteroaryl- and alkynylstannanes **4** provides a general and efficient method for the synthesis of 5-substituted isothiazole 1,1-dioxides **5**. Different reaction conditions (catalyst, solvent, temperature) were tested for the coupling. The best results were obtained using toluene at reflux and benzylchloro*bis*(triphenylphosphine)palladium as catalyst. When organostannanes appeared to be less reactive, prolonged heating resulted in the formation of variable amounts of the reduction product 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**1**).

INTRODUCTION

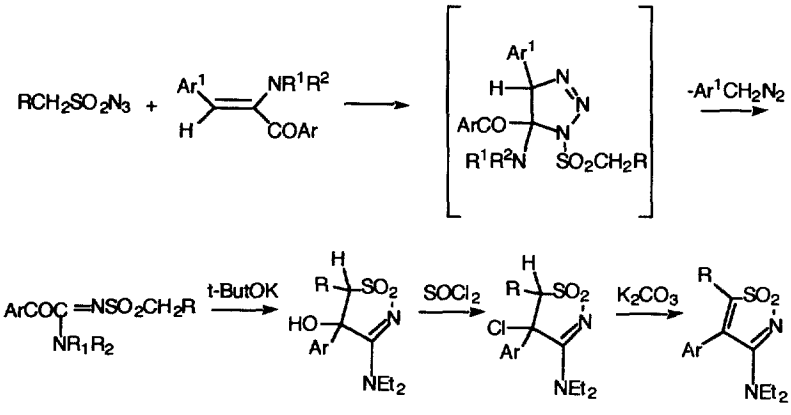
In recent years many papers from our laboratory have dealt with the reactivity of 3-aminoisothiazole 1,1-dioxides.[1-5] Through cycloaddition reactions with several dipoles, cycloadducts with high degree of regioselectivity were formed. The primary bicyclic cycloaddition products could undergo easy transformations affording functionalized single-ring heterocycles by cleavage of one ring. Through these reactions substituted pyrroles[4], pyrazoles[1,3], 1,2,6-thiadiazine 1,1-dioxides, 1,2-thiazete 1,1-dioxides and pyrimidines[1] could be obtained. As 3-aminoisothiazole dioxides have been demonstrated to be promising synthons in heterocyclic synthesis it appeared useful to develop a simple method to functionalize them. Several representatives of 3-aminoisothiazole dioxides which have an aryl substituent on C-4 are available by a method developed in our laboratory.[6] The cycloaddition reaction of sulfonylazides and β-ketoenamines afforded β-ketoamidines which were cyclized and finally transformed into the isothiazoles (Scheme 1). This procedure, however, suffers a severe limitation: the residue on C-5 derives from the sulfonylazides we used as a reagent and the scarce availability of this starting material severely limitates the scope of the reaction.

In recent years the palladium-catalyzed cross-coupling between aryl or vinyl halides with organostannanes (the Stille reaction) has been widely used for the construction of carbon-carbon bonds.[7] We reasoned that a rapid

entry to 5-functionalized 3-amino-4-aryl-isothiazole 1,1-dioxide derivatives would be *via* Stille type coupling.

In this paper we report a mild and highly efficient route to a variety of 3-amino-5-substituted isothiazole 1,1-dioxides utilizing palladium-catalyzed coupling procedures.

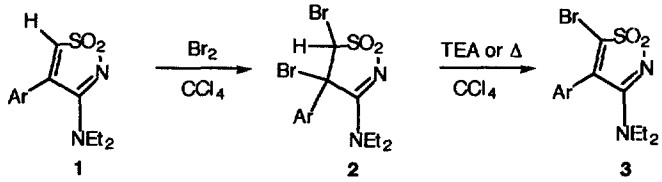
Scheme 1



RESULTS AND DISCUSSION

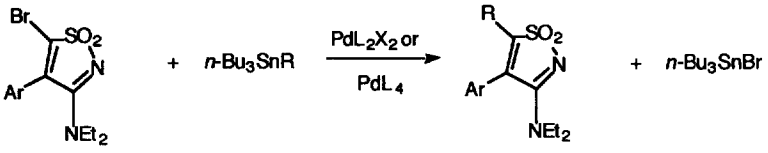
The key intermediate for this reaction was identified in the corresponding bromoisothiazole. 3-Diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**1**) readily reacted with an equimolecular amount of bromine affording 4,5-dibromo-3-diethylamino-4,5-dihydro-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**2**) which gave, on heating or by treatment with triethylamine 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**3**) (Scheme 2).

Scheme 2



Ar=4-OMe-Ph

Scheme 3



Ar=4-OMe-Ph

4a; 5a R=vinyl-
4b; 5b R= 2-phenylethynyl-
4c; 5c R=phenyl-
4d; 5d R= 2-pyridyl-
4e; 5e R=3-(1-ethoxycarbonyl)indolyl-
4f; 5f R=1-ethoxyvinyl-
4g; 5g R=1-methoxycarbonylvinyl-

Table 1.

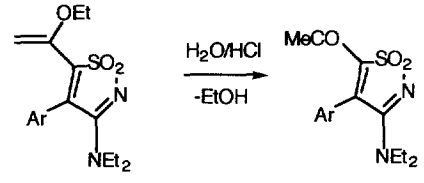
Entry	Stannane	Catalyst	Solvent	Temp. (°C)	Reac. time (h)	Product	Yield (%)	Yield of red. product **1** (%)
1	**4a**	$(PPh_3)_2PhCH_2ClPd$	Toluene	110	0.25	**5a**	70	traces
2	**4a**	$(PPh_3)_2Cl_2Pd$	Toluene	110	16	**5a**	20	20
3	**4a**	$(PPh_3)_2Cl_2Pd$	THF	25	16	**5a**	56	-
4	**4a**	$(PPh_3)_4Pd$	THF	25	16	**5a**	<10	-
5	**4b**	$(PPh_3)_2PhCH_2ClPd$	$CHCl_3$	61	1	**5b**	86	-
6	**4c**	$(PPh_3)_2PhCH_2ClPd$	Toluene	110	1	**5c**	70	<5%
7	**4d**	$(PPh_3)_2PhCH_2ClPd$	Toluene	110	1	**5d**	60	5%
8	**4e**	$(PPh_3)_2PhCH_2ClPd$	Toluene	110	1	**5e**	65	5%
9	**4f**	$(PPh_3)_2PhCH_2ClPd$	Toluene	110	3	**5f**	52	25%
10	**4f**	$(CH_3CN)_2Cl_2Pd$	DMF	25	16	**5f**	<10	-
11	**4f**	$(PPh_3)_2PhCH_2ClPd$	$CHCl_3$	61	8	**5f**	<5	-
12	**4f**	$(CH_3CN)_2Cl_2Pd$	THF	25	16	**5f**	<10	-
13	**4g**	$(PPh_3)_2PhCH_2ClPd$	Toluene	110	4	**5g**	35	30%
14	**4g**	$(PPh_3)_2PhCH_2ClPd$	Benzene	80	8	**5g**	45	-

The bromide was found to be an excellent substrate for Stille-based functionalization and underwent efficient palladium-catalyzed coupling with a range of stannanes. In an effort to arrive at the optimum reaction conditions

for the coupling, different reaction conditions (catalyst, solvent and temperature) were varied for the coupling reactions of **3** and organostannanes (**4a-g**) (Scheme 3, Table 1).

The reaction of tri(*n*-butyl)vinylstannane (**4a**) and **3** took place in toluene at 110°C using benzylchloro*bis*(triphenylphosphine)palladium as catalyst. The reaction was complete in 20-25 min. and compound **5a** could be obtained in 70% isolated yield (entry 1). Utilizing the same solvent at reflux, dichloro*bis*(triphenylphosphine)palladium catalyst was less effective (entry 2) and the reaction in THF as the solvent required longer times to obtain a comparable yield of **5a** with the same catalyst (entry 3). Tetrakis(triphenylphosphine)palladium gave unsatisfactory results (entry 4). As observed, the best reaction conditions appeared to be as in entry 1, i.e. benzylchloro*bis*(triphenylphosphine)palladium as catalyst and toluene as the solvent. Other coupling reactions were carried out with aryl-, heteroaryl- and substituted alkynylstannanes (entries 5, 6, 7, 8) under these conditions affording good results as shown in Table 1. Couplings of **3** with allyltributylstannane and ethynyltributylstannane gave unsatisfactory results because of the formation of a complex mixture of unidentifiable products. In the coupling reaction 1-ethoxyvinyltributylstannane (**4f**) and 1-methoxycarbonyl- vinyltributylstannane (**4g**) were less reactive than the other tin reagents cited before. The reaction of 1-ethoxyvinyltributylstannane (**4f**) and **3** using the usual reaction conditions (entry 9) gave only a 52% yield of coupling product. We varied the reaction conditions in order to obtain better yields (entries 10,11,12) with poor results. 5-(1-Ethoxyvinyl)-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**5f**) could be quantitatively hydrolyzed by treatment with EtOH/HCl to the ketone **6** (Scheme 4).

Scheme 4

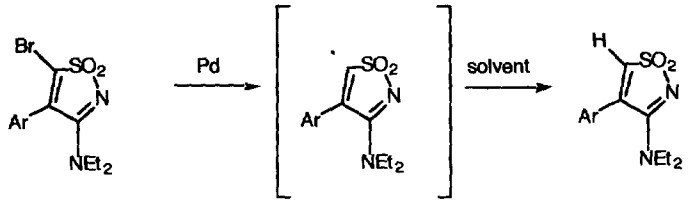


5f **6**

Ar=4-MeO-Ph

It has to be noted that in performing the reaction between **3** and **4a-g**, a variable amount of the reduction product **1** was found in the mixture. When we coupled **3** with 2-phenylethynylstannane **4b**, phenylstannane **4c**, 2-pyridylstannane **4d**, 3-(1-ethoxycarbonyl)indolylstannane **4e**, using the reaction conditions chosen as the best ones (entries 5, 6, 7, 8), the reactions were complete in a few minutes (max. 1 hour) and the amount of **1** was very low. Also in the case of vinylstannane **4a** performing the reaction under the usual conditions (entry 1) the reaction proceeded very fast and we found **1** only in traces. In the other cases (entries 2, 3, 4) where the conditions adopted were less effective and the reactions proceeded much slower giving a poor yield of coupled product, we found a significative amount of **1**, especially when the temperature was high. Ethoxyvinyltributylstannane (**4f**) and 1-methoxycarbonylvinyltributylstannane (**4g**) coupled with **3** relatively slowly in the best conditions (3-4 hours) and we found a 20-30% yield of **1**. A reasonable pathway for the generation of **1** is represented in Scheme 5.

Scheme 5



3 **A** **7**

Ar=4-MeO-Ph

It appears that the competition between the coupling reaction and the reduction favours the former when reaction times are short and temperature can be kept low.

In conclusion, we can say that our aim to functionalize 3-aminoisothiazole 1,1-dioxides was gained. The coupling between aryl-, heteroaryl-, vinyl-, alkynylstannanes and 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide **3** provides by an appropriate choice of the catalytic system an excellent and general method for the introduction of such groups into the isothiazole 5-position.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were obtained with Bruker AC 200, Bruker AC 300 and Varian Gemini 200 instruments. Melting points were deteremined using a Büchi 510 (capillary) or an Electrothermal 9100 apparatus. Mass spectra were obtained by an electron impact ionization technique at 70 eV from a Finningan INCOS 50 instrument using the direct exposure probe (DEP).

Materials. Compound **1**[6] has already been described. The catalysts and tin reagents **4a-c,f** were purchased from Aldrich, while **4d,g**[8,9] were prepared according to known procedures.

1-(Ethoxycarbonyl)indolyl-3-tri(n-butyl)stannane (**4e**): A solution of ClCOOEt (2.9 mL) in CH_2Cl_2 (5 mL) was dropped into a solution of 3-iodoindole (4.9 g, 20 mmol) in CH_2Cl_2 (50 mL) containing TEA (5.6 mL) under stirring at 0°C. After 30' the reaction was complete. The reaction mixture was washed with water (3x20 mL) and the organic layer separated, dried over Na_2SO_4 and evaporated under reduced pressure. 1-(Ethoxycarbonyl)-3-iodoindole crystallized from diethyl ether/petroleum ether. M.p. 69°C. ^{1}H-NMR 1.49 (t, 3H, CH_3, J=7.1); 4.50 (q, 2H, CH_2, J=7.1); 7.29-7.45 (m, 3H, Aryl-H); 7.78 (s, 1H, H-2); 8.17-8.20 (m, 1H, Aryl-H).

A mixture of 1-ethoxycarbonyl-3-iodoindole (2.9 g, 9.2 mmol), $Bu_3SnSnBu_3$ (5.8 mL, 11.6 mmol), $Pd(OAc)_2$ (64 mg, 0.29 mmol) and PPh_3 (150 mg, 0.57 mmol) in DMF (10 mL) was stirred at 75°C for 2 h under N_2. The

reaction mixture was then diluted with brine and extracted with ether. The organic layer was washed twice with water, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel washed with pentane/TEA (2%) using pentane/CH_2Cl_2 10/0.5 afforded **4e** (23 yield%) as an oil. ^{1}H-NMR: 0.9 (t, 9H, CH_3); 1.1-1.7 (m, 21H, CH_2 and CH_3); 4.5 (q, 2H, CH_2, J=7.12 Hz); 7.2-7.6 (m, 4H, aryl-H); 8.15-8.18 (m, 1H, aryl-H). IR (nujol): 1720 cm^{-1} C=O.

5-Bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**3**): Isothiazole 1,1-dioxide (**1**) (1g, 3.4 mmol) was dissolved in CCl_4 (10 mL) and CH_2Cl_2 (5 mL) and a solution of Br_2 (3.4 mmol, 0.19 mL) in CCl_4 (2 mL) was dropped in at 25°C. Stirring was continued until disappearance of the reactant (^{1}H-NMR analysis of a sample, about 2h). Usually compound **2** was not isolated and triethylamine (3.4 mmol, 0.5 mL) in CH_2Cl_2 (5 mL) was added to the mixture and stirring was continued until the reaction was complete (^{1}H-NMR analysis of a sample, about 8h). The reaction mixture was washed with a water solution af $Na_2S_2O_5$ (30 mL), the organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. Compound **3** crystallized from diethyl ether. See Table 2 for data.

5-Substituted-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**5**).*Typical procedure*:
Compound **3** (0.373 g, 1 mmol) and benzylchloro*bis*(triphenylphosphine)palladium (0.075 g, 0.1 mmol) was suspended in toluene (15 mL) and refluxed under nitrogen. Tin reagent (1.1 mmol) was added in portions (10 mL each) during 30'. The reaction mixture was refluxed until disappearance of the reactants (T.L.C. analysis, see Table 1 for reaction time) and purified by chromatography on silica gel (ethyl acetate/cyclohexane 0--->100) affording pure **5**. See Table 2 for data.

Table 2. Analytical and Spectroscopic data

Compound	Ms m/z	m.p. °C	^{1}H-NMR ($CDCl_3$) δ, J (Hz)	^{13}C-NMR ($CDCl_3$) δ
2	454	109-110	0.90 (t, 3H, J=7, CH_3); 1.30 (t, 3H, J=7, CH_3); 3.10-3.15 (m, 2H, CH_2); 3.55-3.70 (m, 2H, CH_2); 3.85 (s, 3H, OCH_3); 4.90 (s, 1H, CH); 6.95-7.60 (m, 4H, aryl-H).	11.7 (CH_3); 12.5 (CH_3); 44.7 (CH_2); 45.2 (CH_2); 56.0 (OCH_3); 66.8 (C-4); 69.5 (C-5); 115.5 (aryl-CH); 128.4; 161.1; 165.1.
3	a	163-164	0.90 (t, 3H, J=7, CH_3); 1.30 (t, 3H, J=7, CH_3); 3.10 (q, 2H, J=7, CH_2); 3.70 (q, 2H, J=7, CH_2); 3.90 (s, 3H, OCH_3); 7.00 (d, AB system, 2H, J=9, aryl-H); 7.20 (d, AB system, 2H, J=9, aryl-H).	12.4 (CH_3); 14.6 (CH_3); 44.4 (CH_2); 47.0 (CH_2); 56.0 (OCH_3); 115.5 (aryl-CH); 123.7; 129.6 (aryl-CH); 137.0; 139.1; 161.2; 161.8.
5a	320	147	0.80-0.90 (m, 3H, CH_3); 1.30-1.35 (m, 3H, CH_3); 3.00-3.20 (m, 2H, CH_2); 3.50-3.60 (m, 2H, CH_2); 3.90 (s, 3H, OCH_3); 5.70 (dd, 1H, J*cis* =11, J*gem*=1); 6.05 (dd, 1H, J*cis* =11, J*trans*=18); 6.35 (dd, 1H, J*gem*=1, J*trans*=18); 7.00 (d, AB system, 2H, J=7, aryl-H); 7.20 (d, AB system, 2H, J=7, aryl-H).	12.1 (CH_3); 14.3 (CH_3); 43.4 (CH_2); 46.7 (CH_2); 55.5 (OCH_3); 114.8 (aryl-CH); 123.0 (vinyl-C); 125.1 (aryl-C); 127.8 (vinyl-C); 129.7 (aryl-CH); 131.1; 152.1; 160.4; 161.5.

Table 2. (continued)

5b	394	134-135	0.90-1.15 (m, 3H, CH_3); 1.15-1.40 (m, 3H, CH_3); 3.10-3.30 (m, 2H, CH_2); 3.60-3.80 (m, 2H, CH_2); 3.90 (s, 3H, OCH_3); 7.00(d, AB system, 2H, J=9, aryl-H); 7.30-7.40 (m, 7H, aryl-H).	12, 15 (CH_3); 44, 46 (CH_2); 56.0 (OCH_3); 78.0; 109.0; 115.0; 121.5; 124.0; 129.0; 129.5; 130.0; 130.5; 133.0; 137.7; 141.0; 161.1; 162.0.
5c[b]	a	157-159		
5d	371	188-190	0.90-1.00 (m, 3H, CH_3); 1.25-1.40 (m, 3H, CH_3); 3.10-3.20 (m, 2H, CH_2); 3.60-3.70 (m, 2H, CH_2); 3.90 (s, 3H, OCH_3); 7.00 (d, AB system, 2H, J=8, aryl-H); 7.1-7.3 (m, 2H, pyridyl-H); 7.25 (d, AB system, 2H, J=8, aryl-H); 7.55 (dt, 1H, J_{ortho}=8, J_{meta}=1, pyridyl-H); 8.65 (dd, 1H, J_{ortho}=4, J_{meta}=1, pyridyl-H).	12-15 (CH_3); 44-46 (CH_2); 56.0 (OCH_3); 115.4; 124.2; 124.6; 125.1; 130.0; 134.0; 136.6; 148.0; 150.5; 153.0; 160.9.
5e	481	186	0.90-1.15 (m, 3H, CH_3); 1.20-1.45 (m, 3H, CH_3); 1.45 (t, 3H, J=7, CH_3); 3.10-3.20 (m, 2H, CH_2); 3.60-3.80 (m, 2H, CH_2); 3.80 (s, 3H, OCH_3); 4.45 (q, 2H, J=7, CH_2); 6.95 (d, AB system, 2H, J=9, aryl-H); 7.05-7.10 (m, 4H, aryl-H); 7.20-7.35 (m, 4H, aryl-H); 7.50 (s, 1H); 8.15 (d, AB system, 2H, J=9, aryl-H).	12-15 (CH_3); 42-46 (CH_2); 55.5 (OCH_3); 63.1 (OCH_2); 109.0; 115.0; 122.0; 123.5; 124.5; 125.0; 127.5; 129.0; 130.0; 131.0; 135.0; 150.1; 160.5; 162.0.
5f	a	195	0.80 (t, 3H, J=7, CH_3); 0.80-0.90 (m, 3H, CH_3); 1.20-1.25 (m, 3H, CH_3); 3.00-3.10 (m, 2H, CH_2); 3.50 (q, 2H, J=7, CH_2); 3.60-3.70 (m, 2H, CH_2); 3.85 (s, 3H, OCH_3); 4.60 (d, AB system, 1H, J=4, CH_2); 5.20 (d, AB system, 1H, J=4, CH_2); 6.90 (d, AB system, 2H, J=9, aryl-H); 7.20 (d, AB system, 2H, J=9, aryl-H).	12-14 (CH_3); 43.5 (CH_2); 47.2 (CH_2); 55.5 (OCH_3); 63.1 (OCH_2); 95.3 (CH_2-vinyl); 113.0 (aryl-CH); 125.0; 129.4 (aryl-CH); 131.7; 149.1; 149.9; 160.0; 161.1.
5g	378	139	0.90-0.95 (m, 3H, CH_3); 1.25-1.35 (m, 3H, CH_3); 3.10-3.15 (m, 2H, CH_2); 3.50 (s, 3H, $COOCH_3$); 3.60-3.70 (m, 2H, CH_2); 3.80 (s, 3H, OCH_3); 6.40 (s, 1H, CH_2); 6.55 (s, 1H, CH_2); 6.90 (d, AB system, 2H, J=9, aryl-H); 7.15 (d, AB system, 2H, J=9, aryl-H).	11-14 (CH_3); 43.9, 46.9 (CH_2); 55.4, 55.5 (OCH_3); 68.1 (CH_2-vinyl); 114.5 (aryl-CH); 123.2; 128.8 (aryl-CH); 133.9; 134.7; 160.4; 161.2; 164.1.
6	a	167-169	0.90 (t, 3H, J=7, CH_3); 1.30 (t, 3H, J=7, CH_3); 2.30 (s, 3H, CH_3); 3.05 (q, 2H, J=7, CH_2); 3.65 (q, 2H, J=7, CH_2); 3.85 (s, 3H, OCH_3); 7.00 (d, AB system, 2H, J=9, aryl-H); 7.20 (d, AB system, 2H, J=9, aryl-H).	

[a] Elemental Analysis. **3**: Calcd. for $C_{14}H_{17}BrN_2O_3S$ (373): C 45.04% H 4.56% N 7.51% Found: C 45.40% H 5.00% N 7.35%; **5f**: Calcd. for $C_{18}H_{24}N_2O_4S$ (364): C 59.34% H 6.59% N 7.69% Found: C 59.40% H 6.70% N 7.40%; **6**: Calcd. for $C_{16}H_{20}N_2O_4S$ (336): C 57.14% H 5.95% N 8.33% Found: C 57.50% H 6.20% N 8.40%.

[b] Compound **5c** has already been described.[6]

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