Palladium-Catalyzed Coupling of Organotin Reagents and Alkenes with 4-Iodopyrimidines

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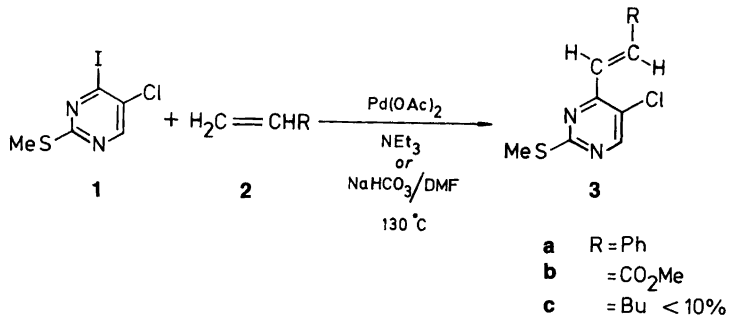
Palladium-catalyzed coupling with vinyltin reagents is a versatile and efficient method for the preparation of 4-vinylpyrimidines from substituted 4-iodopyrimidine. The alternative Heck coupling has been used when the vinyl group is conjugated to an electron-withdrawing substituent. Aryl, heteroaryl, alkyl and substituted alkyl groups are also introduced into the pyrimidine ring as organotin derivatives using palladium catalysis.

The pyrimidine ring forms part of several important physiologically and medicinally active molecules. For medicinal investigations of structural analogues it is of interest to develop methodology which allows easy and selective introduction of carbon substituents into the π-electron-deficient pyrimidine ring. Many organometallic compounds have become important synthons, and we are exploring such reagents for the introduction of unsaturated carbon substituents into pyrimidines.

In the synthesis of alkynylpyrimidines, cross-coupling reactions between 4-iodopyrimidines and 1-alkynes using palladium catalysis were used.[1] In an alternative route, when the pyrimidine did not contain a 4(6)-halogen substituent, the carbon–carbon bond formation was effected by 1:1 adduct formation between the organometallic reagent and the pyrimidine, and the adduct was subsequently dehydrogenated to the heteroaromatic structure.[2] The method involving adduct formation may in some cases yield *regio* isomers. We have therefore carried out our studies on the preparation of alkenyl derivatives using conditions suitable for cross-coupling reactions between 1-alkenes and 4-iodopyrimidines. The catalyst was palladium(II) diacetate, which is more efficient in these reactions than dichlorobis (triphenylphosphine)palladium(II) which was used in the preparation of alkynylpyrimidines.[1] In the case of the styrene derivative the base employed was triethylamine, whereas sodium bicarbonate in DMF gave the better yield in the case of the acrylate.



1 2 3

a R = Ph
b = CO_2Me
c = Bu < 10%

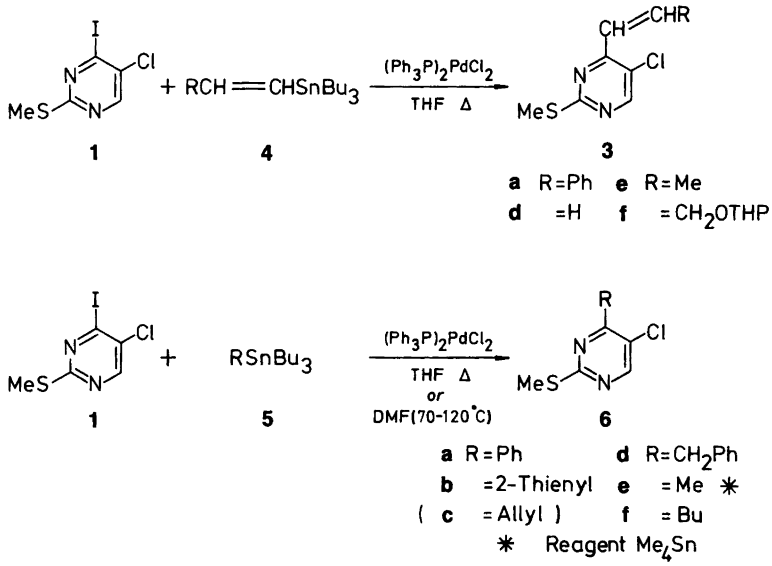
Scheme 1.

The coupling took place exclusively at the activated C-4 position. The coupling products have the *trans*-configuration. In the case of 1-hexene, in contrast to 1-hexyne,[1] the yield was unsatisfactory (ca. 10% by GLC–MS). This method thus appears to be limited to alkenes conjugated to electron-withdrawing groups, in agreement with literature data on related heterocyclic and carbocyclic system.[3,4] Simple vinylation of aryl halides, however, can be achieved under ethylene pressure,[5] or by the use of vinyltrimethylsilane as an ethylene equivalent.[6] Such compounds are also available from the reaction between arylmercurials and vinyl halides by catalytic cross-coupling using rhodium(I) catalysis.[7] We were looking for a safe and simple method for vinylation of heterocycles and have studied palladium-catalyzed reactions between vinyltins and pyrimidines.

Organotin reagents are claimed to be one of the most versatile groups of organometallic reagents, and there is a rapidly growing literature on palladium-catalyzed coupling of organotin reagents.[8] Functionalized styrenes are prepared by palladium-catalyzed coupling between aryl bromides and vinyltin reagents, and the rate of the reaction is promoted by electron-withdrawing substituents and retarded by electron-donating substituents in the aryl reactant.[9] These results correlate well with our own findings from studies of the coupling of vinyltin reagents with 5-chloro-4-iodo-2-methylthiopyridine (**1**). In all cases coupling occurs exclusively at the activated 4-iodo position. The reaction proceeds under mild conditions, simply heating the reactants together under reflux with the catalyst, dichlorobis-(triphenylphosphine)palladium(II), in THF.

The tin reagent is converted to tributyltin iodide in the reaction, and is removed as the sparingly soluble fluoride by the addition of saturated aqueous potassium fluoride.[8a] Water should not be added to the reaction mixture before the fluoride solution, in order to prevent the formation of tin oxides which are difficult to remove (chromatography, recrystallization) from the products.

The reaction is independent of the presence of an electron-withdrawing or electron-donating substituent in the vinyl group. In the literature it is reported that vinyltin reagents will couple stereospecifically with aryl halides.[8b] ^{1}H NMR monitoring in our work showed that the double bond configuration of the vinyltin reagent was retained in the products: *trans*-**4f** gave *trans*-**3f**; β-styryltributyltin (**4a**) (*cis:trans* ~ 1:9) gave **3a** (crude product; *cis:trans* ~ 1:9), and propenyltributyltin (**4e**) (*cis:trans* ~ 9:1) gave **3e** (crude product; *cis:trans* ~ 8:2). Minor changes in the stereoisomer ratios between starting materials and products are to be expected because of possible differences in the reaction rates of the iso-



Scheme 2.

mers, and the use of 1.1 molar equivalents of the tin reagent. In the case of the formation of the product **3e**, however, there is a significant change in the stereoisomer ratios which could have been caused by palladium-induced isomerization, but more likely the isomerization has arisen because the methyl group in **3e** is highly activated by homoconjugation with the π-electron-deficient pyrimidine ring; deprotonation and subsequent protonation will favour formation of the *trans*-isomer.

When an equimolar mixture of the iodopyrimidine, iodobenzene and β-styryltributyltin was allowed to react under the influence of palladium catalysis, exclusive coupling between the pyrimidine and the tin reagent was observed. Hence the iodine in the activated pyrimidine 4-position is more readily substituted by cross-coupling than in iodobenzene. In the absence of the palladium catalyst there was no reaction between the styryltin and the 4-iodopyrimidine under our standard conditions for the reaction.

The ready coupling reactions with alkenes led to studies on the introduction of other types of carbon substituents. With palladium catalysis, compound **1** reacted both with the phenyltin and the thienyltin reagent on heating in THF to yield the products **6a** and **6b**. In a related reaction it has recently been shown that the thienyl substituent can also be introduced into heterocyclic systems by palladium-catalyzed coupling using thiopheneboronic acids.[10]

Alkyltins are less reactive than their unsaturated analogues, but coupling reactions can be carried out using tetraalkyltins. In studies of palladium-catalyzed reactions between tetramethyltin and substituted bromobenzenes it was observed that the reaction was accelerated by the presence of electron-withdrawing substituents in the benzene ring.[11] For the reaction between compound **1** and tetramethyltin or tetrabutyltin to be effected efficiently, the solvent had to be changed from THF to DMF. The latter was also the solvent of choice for effecting the reactions with the benzyltin and allyltin reagents, the reaction time at 100 °C being 15 and 2 h, respectively. The product from the allyltin reaction, however, was not the expected **6c**, but the *trans*-4-propenyl isomer **3e**. The *cis*-isomer of the latter was prepared, as described above, by coupling with the corresponding *cis*-propenyltin reagent.

Presumably the coupling with the allyltin reagent occurs to give **6c** as the initial product, by analogy with the formation of allylbenzenes in the palladium-catalyzed coupling between allyltributyltin and aryl halides.[12] In the case of **6c**, however, the allylic carbon is highly activated by the π-electron-deficient ring. The palladium may be involved in the isomerization.[13] Alternatively, the highly activated allylic carbon may be deprotonated. Reprotonation will be preferentially on the terminal carbon, whereby the double bond becomes conjugated with the heteroaromatic system with preference for the *trans* form. The allyl intermediate **6c** was not detected by GLC during the work-up of the reaction.

Experimental

The ^{1}H NMR spectra were recorded at 60 MHz or at 300 MHz (specified). The mass spectra under electron impact conditions were recorded at 70 eV ionizing voltage.

Starting materials prepared by literature methods: β-Styryltributyltin,[14] propenyltributyltin,[15] [2-(tetrahydropyranyl-2-oxymethyl)ethenyl]tributyltin,[16] phenyltributyltin,[17] benzyltributyltin,[18] thienyltributyltin,[19] allyltributyltin[20] and 5-chloro-4-iodo-2-methylthiopyrimidine (**1**).[1]

*5-Chloro-2-methylthio-4-*trans*-β-styrylpyrimidine* (**3a**) *from styrene.* Palladium(II) diacetate (8 mg, 3.5×10^{-2} mmol) was added to a mixture of 5-chloro-4-iodo-2-methylthiopyrimidine (1.00 g, 3.49 mmol), styrene (0.61 ml, 5.24 mmol) and triethylamine (0.73 ml, 5.25 mmol). The mixture was heated at 130 °C for 15 h under N_2 in a sealed glass tube and the cold reaction mixture was dissolved in chloroform (100 ml). The solution was washed with water (3×50 ml), the dried ($MgSO_4$) chloroform solution evaporated and the product purified by flash chromatography on silica gel using dichloromethane; yield 0.72 g (78 %), m.p. 81 °C (EtOH). Anal. $C_{13}H_{11}ClN_2S$: C,H. ^{1}H NMR ($CDCl_3$): δ 2.60 (SMe), 7.2–7.9 (6H, Ph and CH=, m), 8.11 (1H, CH=, d, *J* 15 Hz), 8.42 (1H, H-6). MS: 264/262 (36/100, *M*), 263 (24), 261 (27), 229 (17), 227 (30), 215 (25), 191 (10), 189 (33).

*5-Chloro-2-methylthio-4-*trans*-(methoxycarbonylethenyl)pyrimidine* (**3b**) *from methyl acrylate.* Palladium(II) diacetate (8 mg, 3.5×10^{-2} mmol)

was added to a mixture of 5-chloro-4-iodo-2-methylthiopyrimidine (1.00 g, 3.49 mmol), methyl acrylate (0.63 ml, 6.98 mmol) and sodium bicarbonate (0.32 g, 3.84 mmol) in dry DMF (6 ml). The mixture was heated at 130 °C for 15 h under N_2 in a sealed glass tube and the cold reaction mixture was dissolved in dichloromethane (150 ml). The solution was washed with water (3×100 ml), the dried ($MgSO_4$) dichloromethane solution evaporated and the product purified by flash chromatography on silica gel using dichloromethane; yield 0.39 g (46 %), m.p. 110 °C (EtOH). Anal. $C_9H_9ClN_2O_2S$: C,H. ^1H NMR ($CDCl_3$): δ 2.58 (SMe), 3.87 (OMe), 7.23 (1H, d, *J* 16 Hz), 7.93 (1H, d, *J* 16 Hz), 8.52 (1H, H-6). MS: 246/244 (25/73, *M*), 215/213 (11/33), 214/212 (38/100), 198 (13), 187 (13), 186 (22), 185 (37), 184 (52), 177 (73).

General procedure for palladium-catalyzed coupling with organotin reagents. Dichlorobis(triphenylphosphine)palladium(II) (70 mg, 0.10 mmol) was added to a solution of 5-chloro-4-iodo-2-methylthiopyrimidine (1.43 g, 5.00 mmol) and the organotin reagent (5.50 mmol) in anhydrous THF or DMF (10 ml), and the mixture heated in a dry N_2-atmosphere. The temperature and the duration of the reaction are given below. The progress of the reactions was monitored by TLC or GLC. A concentrated aqueous solution of potassium fluoride (20 ml) was added to the cold reaction mixture and ether (30 ml) was added. The mixture was stirred vigorously for 30 min, water (100 ml) was added and the mixture was extracted with ether (3×100 ml). The ether extracts were combined, washed with water (3×100 ml), dried ($MgSO_4$), evaporated and the product purified by flash chromatography on silica gel and/or by "Kugelrohr" distillation.

5-Chloro-2-methylthio-4-β-styrylpyrimidine (**3a**). Compound **3a** was obtained from β-styryltributyltin (*cis:trans* ~ 1:9) after heating under reflux in THF for 6 h. Toluene was used in the flash chromatography; yield 90 % (*cis:trans* ~ 1:9). Recrystallization from ethanol gave pure *trans*-**3a**. Physical data are given above.

5-Chloro-2-methylthio-4-vinylpyrimidine (**3d**). Compound **3d** was obtained from vinyltributyltin in 71 % yield after heating under reflux in THF for 4 h. Toluene/hexane (2:1) was the eluent during flash chromatography. The liquid product was distilled by the "Kugelrohr" technique at 65 °C/0.03 mmHg. Found: C 45.62; H 3.74. Calc. for $C_7H_7ClN_2S$: C 45.04; H 3.78. The product polymerizes on heating. ^1H NMR (300 HMz, $CDCl_3$): δ 2.56 (SMe), 5.76 (1H, dd, *J* 10.9, 2.0 Hz), 6.75 (1H, dd, *J* 17.2, 2.0 Hz), 7.07 (1H, dd, *J* 17.2, 10.0 Hz), 8.42 (1H, H-6). MS: 188/186 (38/100, *M*), 189 (4), 187 (24), 185 (43), 142 (16), 141 (11), 140 (49), 113 (16).

5-Chloro-2-methylthio-4-propenylpyrimidine (**3e**). Compound **3e** was obtained from propenyltributyltin (*cis:trans* ~ 9:1) in 90 % yield after heating under reflux in THF for 17 h. Toluene/hexane (2:1) was the eluent during flash chromatography. The liquid product (*cis:trans* ~ 8:2) was distilled by the "Kugelrohr" technique at 100 °C/0.01 mmHg. Anal. $C_8H_9ClN_2$: C,H. ^1H NMR (300 MHz, $CDCl_3$): δ(*cis*) 2.25 (3H, dd, *J* 7.3, 2.3 Hz), 2.56 (SMe), 6.34 (1H, dd, *J* 11.7, 7.3 Hz), 6.63 (1H, dd, *J* 12.6, 2.1 Hz), 8.39 (1H, H-6); δ(*trans*) 2.01 (3H, dd, *J* 6.9, 1.7 Hz), 2.56 (SMe), 6.78 (1H, dd, *J* 15.1, 1.7 Hz), 7.35 (1H, dd, *J* 15.1, 7.0 Hz), 8.37 (1H, H-6). MS: 202/200 (36/100, *M*), 187/185 (26/71), 169 (13), 167 (45), 165 (13).

*5-Chloro-2-methylthio-4-*trans-*[2-(2-tetrahydropyranyloxymethyl)ethenyl]pyrimidine* (**3f**). Compound **3f** was obtained from *trans*-[2-(2-tetrahydropyranyloxymethyl)ethenyl]tributyltin in 66 % yield after heating under reflux in THF for 3 h. The reaction mixture, after the treatment with aqueous KF, was shaken with aqueous $NaHCO_3$ and the ether solution dried over K_2CO_3. The latter was used instead of magnesium sulfate because of stability problems.[21] Toluene/ethyl acetate (98:2) was the eluent in flash chromatography; m.p. 65 °C (Hexane). Anal. $C_{13}H_{17}ClN_2O_2S$: C,H. ^1H NMR (300 MHz, $CDCl_3$): δ 1.53–1.95 (6H, m), 2.57 (SMe), 3.51–3.59 and 3.85–3.94 (2H, m, O−CH_2−, THP), 4.22–4.32 and 4.48–4.58 (2H, m, =CH−CH_2−), 4.72 (1H, t), 7.04 (1H, m, J_{trans} 15.3 Hz), 7.37 (1H, m, J_{trans} 15.4 Hz), 8.40 (1H, H-6). MS: 300 (0.1, *M*), 219/217 (1/4), 218/216 (13/36), 215 (3), 202 (2), 201 (10), 200 (6), 199 (22), 85 (100).

5-Chloro-2-methylthio-4-phenylpyrimidine (**6a**). Compound **6a** was obtained from phenyltributyltin in 62 % yield after heating under reflux in

THF for 25 h. Toluene was the eluent in flash chromatography; m.p. 70 °C (EtOH). Anal. $C_{11}H_9ClN_2S$: C,H. ^1H NMR ($CDCl_3$): δ 2.63 (SMe), 7.5–7.9 (Ph), 8.55 (1H, H-6). MS: 238/236 (37/100, *M*), 237 (27), 235 (33), 191 (12), 190 (26), 189 (14), 155 (30).

5-Chloro-2-methylthio-4-(2-thienyl)pyrimidine (**6b**). Compound **6b** was obtained from 2-thienyltributyltin in 90 % yield after heating in THF under reflux for 7 h. The crude product was purified by recrystallization from ethanol; m.p. 75 °C. Anal. $C_9H_7ClN_2S_2$: C,H. ^1H NMR ($CDCl_3$): δ 2.65 (SMe), 6.92 (1H, dd, *J* 5, 4 Hz), 7.68 (1H, d, *J* 5 Hz), 8.38 (1H, d, *J* 4 Hz), 8.54 (1H, H-6). MS: 244/242 (40/100, *M*), 243 (22), 241 (26), 198 (12), 197 (18), 196 (30), 195 (31).

Attempts to prepare 4-allyl-5-chloro-2-methylthiopyrimidine (**6c**). Attempts to prepare compound **6c** by standard procedure from allyltributyltin by heating in DMF at 100 °C for 2 h resulted in the isolation of *trans*-4-propenyl-5-chloro-2-methylthiopyrimidine (**3e**) in 69 % yield. Toluene was the eluent in flash chromatography; m.p. 77 °C (EtOH). Physical data as above.

4-Benzyl-5-chloro-2-methylthiopyrimidine (**6d**). Compound **6d** was obtained from benzyltributyltin in 60 % yield after heating in DMF at 100 °C for 15 h. Toluene was the eluent in flash chromatography. The product was further purified by "Kugelrohr" distillation at 200 °C/0.01 mmHg. Anal. $C_{12}H_{11}ClN_2S$: C,H. ^1H NMR ($CDCl_3$): 2.53 (SMe), 4.20 ($-CH_2-$), 7.36 (Ph), 8.42 (1H, H-6). MS: 252/250 (36/100, *M*), 253 (5), 251 (22), 249 (22), 206 (4), 204 (12).

5-Chloro-4-methyl-2-methylthiopyrimidine (**6e**). Compound **6e** was obtained from tetramethyltin in 78 % yield after heating in DMF at 70 °C for 2 d. The crude product was purified by "Kugelrohr" distillation at 150 °C/8 mmHg. Anal. $C_6H_7ClN_2S$: C,H. ^1H NMR (300 MHz, $CDCl_3$): 2.534 and 2.545 (SMe, 4-Me, 2×s), 8.36 (1H, H-6). MS: 176/174 (38/100, *M*), 175 (21), 173 (33), 130 (18), 129 (14), 128 (56).

4-Butyl-5-chloro-2-methylthiopyrimidine (**6f**). Compound **6f** was obtained from tetrabutyltin in 62 % yield after heating in DMF at 120 °C for 14 h. Toluene/light petroleum (2:1) was the eluent in flash chromatography. The product could also be distilled by the "Kugelrohr" technique at 90 °C/0.01 mmHg. Anal. $C_9H_{13}ClN_2S$: C,H. ^1H NMR ($CDCl_3$): δ 0.7–2.1 (7H, m), 2.55 (SMe), 2.83 (2H, t, *J* 7 Hz), 8.35 (1H, H-6). MS: 218/216 (1.5/4, *M*), 203/201 (2/6), 189/187 (5/13), 176/174 (37/100).

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