

Ethenylation and Alkynylation in Palladium-Catalyzed Carbosubstitution in Heteroazines

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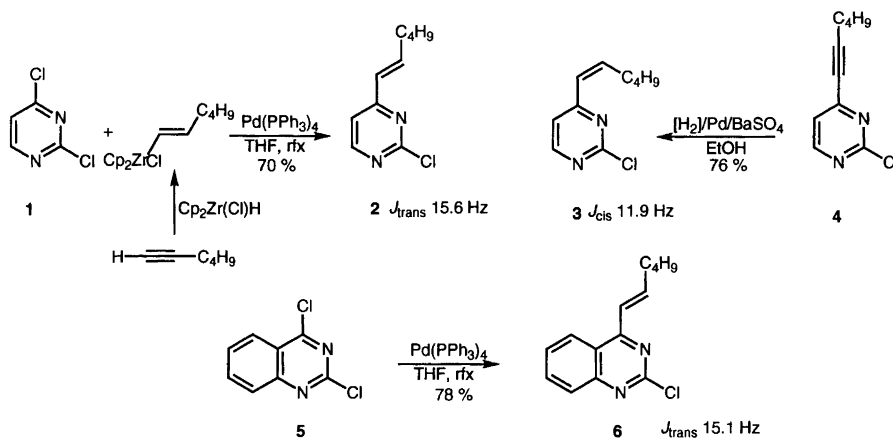
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Hydrozirconated alkynes can be used for regioselective *E*-alkenylation of 2,4-dichloro-pyrimidine or -quinazoline with Pd-catalysis. Partial saturation of an alkynylpyrimidine by catalytic hydrogenation gave the corresponding *Z*-alkenyl derivative. Alkynyl derivatives have been prepared by carbosubstitution in regio- and chemo-selective reactions.

Organometallics have become important reagents for transition metal catalyzed cross-coupling reactions leading to carbosubstitution in heteroarenes in general, and in π -deficient azines in particular.¹ Palladium-catalyzed coupling reactions with organostannanes proceed well when the carbon bound to the metal in the stannanes is sp^2 - or sp -hybridized.² Vigorous reaction conditions are required, however, for the transfer of an alkyl group from a stannane to palladium unless the sp^3 -hybridized metal-attached carbon also carries an electronegative substituent.² Organoboranes seem, in general, less applicable than stannanes, but alkyl groups can be transferred as demonstrated in the Pd-catalyzed alkylation of 6-chloropyrazines to yield alkylpyrazines under relatively vigorous conditions.³ Organozinc reagents are generally applicable and of importance for alkylation reactions.^{1,4} Alanes have recently been found very useful for the transfer of alkyl groups and carbosubstitution under the influence of Pd-catalysis.⁵ In this report we describe

Pd-catalyzed ethenylation reactions in π -deficient azines using alkenylzirconocenes. Previously the alkenylzirconocenes have been used most widely for vinylation of arenes and alkenes.⁶ An example involving a π -deficient system is a reaction on deoxyuridine; iodine was exchanged for ethene in the benzenoid 5-position.⁷ Alkenylzirconocenes are readily available by hydrozirconation of terminal alkynes.⁶ The emphasis in this work has been on the elucidation of selectivity for alkenylation in the electrophilic 2- and 4-positions in quinazoline, i.e., benzo-fused pyrimidine, as well as in pyrimidine. We have previously established that the readily available pyrimidines with chloro substituents in the electrophilic 2- and 4-positions are well suited for carbosubstitution reactions under the influence of Pd-catalysis, whereas in the benzenoid pyrimidine 5-position, or the benzene ring in quinazoline, the halogen should be a bromine or iodine; triflates will react in any position.^{5,8,9}



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Selectivity for the more electrophilic 4-position in 2,4-dichloropyrimidine leading to the 4-hexenyl derivative (**2**) could be effected with hexenylzirconocene chloride under the influence of tetrakis(triphenylphosphine)palladium as catalyst; the reaction proceeds under reflux conditions in THF. The vicinal coupling constant (J 15.6 Hz) of the olefinic protons of the hexenyl group shows that the product **2** has the expected *E*-configuration. *cis*-Hydrozirconation of the acetylene will yield an (*E*)-hexenylzirconium complex which is to become the substrate for the Pd-catalyzed coupling. The assignment of the configuration was confirmed by partial saturation of the corresponding 4-hexynylpyrimidine (**4**) to form the 4-[(*Z*)-hexenyl]pyrimidine (**3**) by hydrogenation over palladium on barium sulfate; coupling constant 11.9 Hz. Under these conditions hydrogenolysis of the chlorine substituent in the 2-position was insignificant. In the coupling of 2,4-dichloroquinazoline the same selectivity for the more electrophilic 4-position was observed; the (*E*)-product **6** was formed (15.1 Hz). These findings correlate well with previous results from Pd-mediated coupling reactions which have demonstrated a stepwise carbo-substitution in 5-bromo-2,4-dichloropyrimidine using either stannanes or organozinc reagents.^{8,9}

In the second part the emphasis was on alkynylations to furnish series of versatile substrates for subsequent reactions, e.g., partial reduction yields alkenyl derivatives such as in the formation of the (*Z*)-product **3**. Alkynyl derivatives can also be regarded as intermediates for the introduction of alkyl groups which may be more difficult to achieve by direct alkylation reactions since these require more vigorous conditions, or may not proceed at all (*vide supra*).

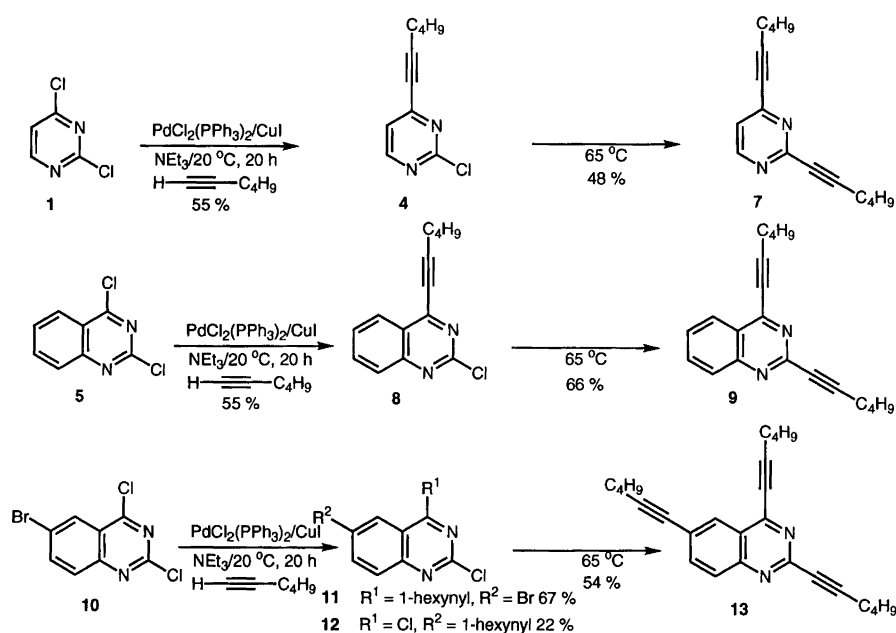
Copper(I) iodide is a particularly effective cocatalyst in Pd-mediated coupling reactions of alkynes,¹⁰ and was used in the present work. At ambient temperature select-

ive alkynylation was effected in the more reactive 4-position in 2,4-dichloropyrimidine to form **4**. The second hexynyl group is substituted into the 2-position (**7**) on slight warming of the reaction mixture. With 2,4-dichloroquinazoline the same selectivity for initial hexynylation in the 4-position was achieved, with subsequent hexynylation in the less reactive 2-position (**9**). In 6-bromo-2,4-dichloroquinazoline competitive reactions between the 4-chloro position and the 6-bromo position led to a mixture of the corresponding hexynyl derivatives; chloride substitution gave the major product (**11**), the ratio between **11** and **12** being 3:1. Either product is a substrate for the introduction of two additional alkynyl groups to furnish the trialkynylated quinazoline **13**.

Experimental

¹H NMR and ¹³C NMR were recorded at 200 MHz and 75 MHz for samples in CDCl₃. MS data are by electron impact.

2-Chloro-4-[(E)-1-hexenyl]pyrimidine (2). Freshly distilled 1-hexyne (8 mmol) was added to a slurry of zirconocene chloride hydride [Cp₂Zr(Cl)H; 4 mmol] in dry benzene (8 ml) at room temperature and the mixture stirred under nitrogen in the absence of light for 2 h. Removal of the solvent by distillation left the hydrozirconation adduct which was reacted further by the addition of a mixture of tetrakis(triphenylphosphine)palladium (5%), zinc dichloride (5%) and 2,4-dichloropyrimidine (1 mmol, 149 mg) in THF (4 ml). The resulting mixture was heated under reflux for 20 h before the reaction was quenched by the addition of water (0.1 ml). Light petroleum (8 ml) was added to the mixture, which was stirred for 10 min, then dried



(MgSO₄), the solution evaporated and the product isolated from the residue by flash chromatography on silica using hexane–EtOAc 4:1; yield 70%. ¹H NMR: δ 0.88/1.3/1.3/2.25 (Bu), 6.32 (2 t, H1', J 15.6, 1.4 Hz) 7.0–7.2 (H5, H2'), 8.42 (H6, J 5.2 Hz). ¹³C NMR: δ 14.55/22.87/30.95/33.11 (Bu), 115.52 (C2'), 126.23 (C1'), 143.41, 158.32, 160.31, 164.83. MS: 198 (7) and 196 (21, M⁺), 167 (100), 161 (31), 153 (37), 141 (23), 128 (41), 92 (14).

2-Chloro-4-[(Z)-1-hexenyl]pyrimidine (3). A solution of 2-chloro-4-(1-hexynyl)pyrimidine (1 mmol) in ethanol (10 ml) was hydrogenated over 5% Pd–Ba₂SO₄ (2 × weight%) at 60 psi for 20 h. The catalyst was thereafter removed by filtration, the filtrate evaporated and the product isolated after flash chromatography on silica using hexane–EtOAc 4:1; yield 76%. ¹H NMR: δ 0.90/1.3/1.3/2.65 (Bu), 6.16 (2 t, H1', J 11.9, 1.3 Hz), 6.27 (dd, J 11.9, 6.7 Hz, H2'), 7.06 (H5), 8.45 (H6, J 5.1 Hz). ¹³C NMR: δ 14.62/23.01/29.69/31.87 (Bu), 118.25 (C2'), 124.87 (C1'), 144.87, 158.18, 160.05, 165.40. MS: 198 (5) and 196 (12, M⁺), 181 (7), 167 (100), 152 (10), 128 (21), 106 (8), 92 (8).

2-Chloro-4-[(E)-1-hexenyl]quinazoline (6) was prepared in the same way as its pyrimidine analogue (2); yield 78%. ¹H NMR: δ 0.93/1.4/1.4/2.40 (Bu), 7.16 (H1', J 15.1, 1.5 Hz), 7.54 (H2'). ¹³C NMR: δ 14.51/22.91/31.02/33.69 (Bu), 121.35, 122.47, 124.91, 128.22, 128.51, 135.08, 137.84, 153.31, 166.12, 176.31. MS: 248 (4) and 246 (10, M⁺), 217 (31), 203 (23), 191 (27), 178 (100), 142 (21), 97 (20).

General procedure for monoalkynylation. A mixture of bis(triphenylphosphine)palladium dichloride (0.02 mmol), cuprous iodide (0.005 mmol), triethylamine (10 ml) and 2,4-dichloropyrimidine (1 mmol, 149 mg), or 2,4-dichloroquinazoline (1 mmol, 199 mg) or 6-bromo-2,4-dichloroquinazoline¹¹ (1 mmol, 278 mg) was stirred at ambient temperature under nitrogen for 20 h. The mixture was evaporated to dryness under reduced pressure, water (10 ml) was added and the mixture extracted with chloroform. The washed and dried (MgSO₄) solution was evaporated and the product isolated by flash chromatography on silica gel using hexane–EtOAc 5:1 (4, 8) or hexane–CH₂Cl₂ 5:1 (11, 12).

2-Chloro-4-(1-hexynyl)pyrimidine (4). Yield 58%. ¹H NMR: δ 0.88/1.4/1.4/2.44 (Bu), 7.20 (H5), 8.50 (H6, J 5.1 Hz). ¹³C NMR: δ 14.25/19.86/22.65/30.39 (Bu), 78.01 (C2'), 99.14 (C1'), 121.07, 152.82 158.17, 160.33. MS: 196 (31) and 194 (49, M⁺), 195 (43), 193 (54), 179 (74), 165 (81), 152 (100), 116 (38), 78 (35).

2-Chloro-4-(1-hexynyl)quinazoline (8). Yield 90%. ¹H NMR: δ 0.93/1.52/1.72/2.58 (Bu), 7.5 (m), 7.87 (1 H, J 8.5, 5.9, 1.1 Hz), 7.94 (1 H, J 8.5, 1.1 Hz), 8.19 (1 H, J 8.3, 1.1). ¹³C NMR: δ 13.49/19.50/22.09/29.94 (Bu),

77.76 (C2'), 104.05 (C1'), 125.89, 126.75, 127.81, 128.24, 135.15, 151.66, 155.47, 156.80. MS: 246 (14, M⁺) and 244 (45, M⁺), 229 (8), 215 (100), 202 (94), 179 (21), 166 (46), 139 (22), 102 (10), 76 (18).

6-Bromo-2-chloro-4-(1-hexynyl)quinazoline (11) and 2,4-dichloro-6-(1-hexynyl)quinazoline (12). The products were not separated satisfactorily by flash chromatography but were separated by fractional crystallization from hexane; compound 11 was obtained in 67%, m.p. 77°C. The isomer 12 was isolated from the remaining solution in 22% yield. When the reaction was run at –15°C for 7 days, product 11 was the exclusive product (40%) besides the starting material.

11 ¹H NMR: δ 0.97/1.70/1.72/2.63 (Bu), 7.81 (H8, J 9.2 Hz), 7.95 (H7, J 9.2, 2.0 Hz), 8.36 (H5, J 2.0 Hz). ¹³C NMR: δ 13.49/19.66/22.10/29.85 (Bu), 77.75 (C2'), 105.14 (C1'), 120.16, 122.14, 124.74, 128.96, 129.33, 131.83, 138.65, 150.39. MS: 326 (16, M⁺) and 324 (63, M⁺), 295 (95), 282 (100), 244 (19), 179 (14), 165 (51), 152 (10), 139 (21), 113 (7), 100 (11).

12 ¹H NMR: δ 0.96/1.6/1.6/2.46 (Bu), 7.78–7.83 (H7, H8), 8.21 (H5). ¹³C NMR: δ 13.71/19.63/22.23/30.62 (Bu), 78.63 (C2'), 105.34 (C1'), 122.04, 124.56, 127.59 129.25, 130.01, 138.24, 148.52, 157.85.

General procedure for bis- and tris-alkynylation. A mixture of bis(triphenylphosphine)palladium dichloride (0.04 mmol), cuprous iodide (0.01 mmol), triethylamine (14 ml) and 2,4-dichloropyrimidine (1 mmol, 149 mg) or 2,4-dichloroquinazoline (1 mmol, 199 mg) or 6-bromo-2,4-dichloroquinazoline (1 mmol, 278 mg) was stirred at 65°C under nitrogen for 20 h. Equimolar amounts of reagents were used for trialkynylation, i.e., in the preparation of compound 13. The mixture was evaporated to dryness under reduced pressure, water (10 ml) added and the mixture extracted with chloroform. The washed and dried (MgSO₄) solution was evaporated and the product isolated by flash chromatography on silica using hexane–EtOAc 5:1 (7, 9) or in the ratio 10:1 for 13.

2,4-Di(1-hexynyl)pyrimidine (7). Yield 60%. ¹H NMR: δ 0.88, 0.89/1.4–2.2 (8 H)/2.38–2.45 (4 H) (2 × Bu), 7.13 (H5), 8.54 (H6, J 5.2 Hz). ¹³C NMR: δ 13.52/18.91/19.11/21.99/29.98 (2 × Bu), 78.54/79.75 (C2'/C2''), 90.84/97.27(C1'/C1''), 121.07 151.57 153.17, 157.01. MS: 240 (68, M⁺), 225 (17), 211 (76), 198 (100), 169 (13), 155 (13), 91 (6), 77 (6).

2,4-Di(1-hexynyl)quinazoline (9). Yield 80%. ¹H NMR: δ 0.85, 0.92/1.7–2.4 (8 H)/2.45, 2.56 (2 × Bu), 7.57 (1 H, J 8.3, 8.4, 0.8 Hz), 7.81 (1 H, J 8.3, 7.7, 0.8 Hz), 7.90 (1 H, J 8.4, 0.8), 8.20 (1 H, J 7.7, 0.8 Hz) ¹³C NMR: δ 14.19/14.71/19.73/20.09/21.75/22.22/30.71/30.79 (Bu), 78.20/80.94 (C2', C2''), 90.96/102.55 (C1', C1''), 124.28, 127.05, 128.62, 128.75, 134.87, 149.51, 150.82, 153.86. MS: 290 (34, M⁺) 275 (2), 261 (48), 248 (37), 149 (73), 97 (45), 83 (85), 71 (52), 57 (100).

2,4,6-Tri(1-hexynyl)quinazoline (13). Yield 62%. ^1H NMR: δ 0.86, 0.92, 0.96/1.2–1.4 (12 H)/2.26/2.47/2.60 (3 \times Bu), 7.79 (C7, J 8.8 Hz), 7.85 (H8, J 8.8 Hz), 8.19 (H5). ^{13}C NMR: δ 13.62 (2 \times Me)/14.12, 20.09/21.75/19.16/19.25/19.57/22.06/22.19/22.65, 30.09/30.63/31.58, (Bu), 77.76/79.86/80.37 (3 \times C2'), 90.88/93.80/102.57 (3 \times C1'), 123.62, 124.22, 128.13, 129.12, 137.40, 149.03, 149.46, 152.71. MS: 370 (71, M^+) 355 (15), 341(100), 328 (89), 313 (8), 299 (17), 286 (13), 269 (13), 255 (16), 244 (11), 190 (5), 115 (4).

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