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Trialkylalanes in Palladium-Catalyzed Chemo- and Regioselective Alkylations.

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Abstract: **Carbosubstitution in halogenoazines with alkyl groups is readily effected under the influence of Pd-catalysis with alanes as the donor of the alkyl group.**

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] Stannanes are especially useful organometallic reagents because of the ease of preparation and handling of organostannanes and their high reactivity in the presence of palladium catalysts.[2] The coupling reactions proceed well when the carbon bound to the metal in stannanes is sp^2- or sp-hybridized, and require more vigorous conditions, or may not proceed at all, for the transfer of an alkyl group unless the sp^3-hybridized metal-attached carbon also carries an electronegative substituent. Because of the difference in reactivity between an alkyl group and alkenyl, alkynyl and (hetero)aryl groups, the reagent of choice is a trialkylstannane which carries an additional more easily transferable group.

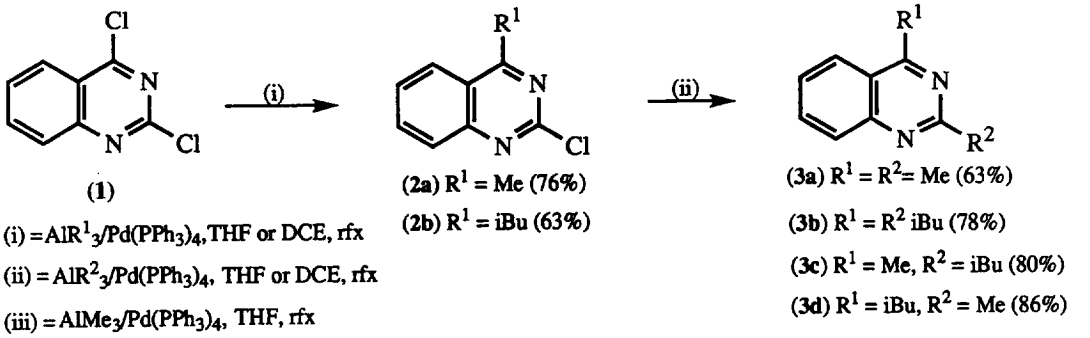
It is highly desirable to find a general procedure to effect alkylation by coupling reactions which proceeds under mild conditions comparable to those used for transfer of alkenyl, alkynyl and (hetero)aryl groups. In the literature transfer of alkyl groups from trialkylboranes to 6-chloropyrazines has been reported to yield alkylpyrazines in moderate yields under relatively hard reaction conditions using Pd-catalysis.[3] Organozinc reagents, however, can effect alkylation reactions as well as the transfer of vinyl or (hetero)aryl substituents using Pd-catalysis.[1,4] Carbosubstitution has also been effected using organomagnesium reagents and nickel-catalysis.[1]

Organoalanes have so far received relatively little attention as reagents for the transfer of alkyl groups into azines in metal-catalyzed carbosubstitutions.[1] The alkylalanes, however, would be expected to offer a wide scope of useful applications since this class of reagents very readily transfer an alkyl group from the aluminum to the palladium(II) complex which is formed after insertion of Pd(0) in a carbon-halogen or carbon-oxygen (*e.g.*) triflate) bond; the subsequent, rapid reductive elimination leads to alkylated product. We now report that this reaction is an excellent and preferable method to achieve alkylations in π-deficient heteroarenes.

Quinazoline, *i.e.* benzo-fused pyrimidine, has been chosen as a substrate for demonstrating the principle in the alkylation reactions. As in pyrimidine, the 2- and 4-positions in quinazoline have electrophilic properties; the 4-position is the more electrophilic. In the electrophilic positions in π-deficient azines we have previously established that the readily available chlorides are well suited for carbosubstitution reactions under the influence of Pd-catalysis. In the benzenoid positions, in the pyrimidine 5-position or the benzene ring in quinazoline, the halogen should be a bromine or iodine; triflates will react in any position.[1,5] Regio- or chemoselectivity can be achieved as demonstrated by the stepwise introduction of three different

carbosubstituents into 5-bromo-2,4-dichloropyrimidine using organostannane and Pd-catalysis; the reactivity order for styrylation, phenylation and thienylation was firstly the 4-, then the 5- and finally the 2-position.[6] A similar series of selective carbosubstitutions has been achieved in azines using organozinc reagents and Pd-catalysis.[7]

We have found that alkylalanes are excellent reagents for C-alkylations in azines under mild reaction conditions, and therefore of potential interest in modifications of biologically important azines, *e.g.* based on pyridine, pyrimidine, pteridine or purine ring systems. Simple alkylalanes are either commercially available or readily available by synthesis.[8] Previously it has been reported that 2-chloropyrazine and 2,5- and 2,6-dichloropyrazine can be dimethylated by trimethylalane,[9] that triflyloxypyridines and -quinolines react with alkylalanes,[10] and that 6-methylpurine nucleosides can be prepared from the corresponding 6-chloro precursor.[11]



(1)

(i) = $AlR^1_3/Pd(PPh_3)_4$, THF or DCE, rfx

(ii) = $AlR^2_3/Pd(PPh_3)_4$, THF or DCE, rfx

(iii) = $AlMe_3/Pd(PPh_3)_4$, THF, rfx

(2a) R^1 = Me (76%)

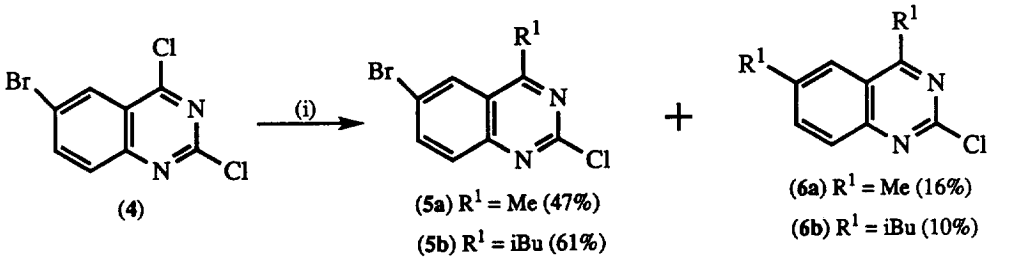
(2b) R^1 = iBu (63%)

(3a) $R^1 = R^2$ = Me (63%)

(3b) $R^1 = R^2$ iBu (78%)

(3c) R^1 = Me, R^2 = iBu (80%)

(3d) R^1 = iBu, R^2 = Me (86%)



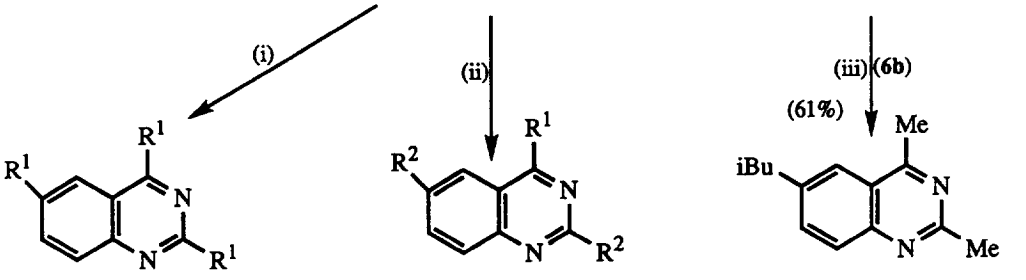
(4)

(5a) R^1 = Me (47%)

(5b) R^1 = iBu (61%)

(6a) R^1 = Me (16%)

(6b) R^1 = iBu (10%)



(7a) R^1 = Me (60%)

(7b) R^1 = iBu (81%)

(8a) R^1 = iBu, R^2 = Me (66%)

(8b) R^1 = Me, R^2 = iBu (72%)

(9)

The emphasis in this work has been to explore and establish selectivity for carbosubstitution in the electrophilic 2- and 4-positions, which are occupied by a chlorine atom, and a further comparison with a benzenoid position carrying a bromine substituent. We find that selectivity for the 4-position (**2**) in 2,4-dichloroquinazoline can be effected with trimethyl- and triisobutylalane under the influence of tetrakis(triphenylphosphine)palladium as catalyst; the reactions proceed under reflux conditions in THF or in 1,2-dichloroethane (DCE). In the presence of another molequivalent or more of an alane, products which carry the same or a different alkyl group in the 2-position (**3**) are formed. Under the reaction conditions used in this study, selectivity for monosubstitution in 5-bromo-2,4-dichloroquinazoline was not fully achieved. The main product was formed by substitution of the chlorine in the 4-position (**5**), the minor product from substitution of the 6-bromine substituent (**6**). The products were readily separated by flash chromatography and were reacted separately with additional amounts of alanes under similar conditions. In this manner trimethyl- (**7**) and triisobutylquinazoline (**7b**) were obtained. Under similar conditions, 5-bromo-2-chloro-4-methyl- or -isobutylquinazoline (**5**) gave the products (**8**) carrying the same alkyl group in the 2,6-positions. In the final example, 2,4-dichloro-6-isobutylquinazoline was 2,4-dimethylated (**9**) by trimethylalane.

General procedure for monoalkylation of 2,4-Dichloroquinazoline (**1**). Trimethyl- or triisobutylalane (1.2 mmol) and 7 mol% tetrakis(triphenylphosphine)palladium were added to a solution of 2,4-dichloroquinazoline (1.0 mmol; 199 mg) in dry THF (3 ml) for methylation, or in DCE (3 ml) for isobutylation, under nitrogen and the mixture heated under reflux for 24 h. The reaction was quenched by addition of water (10 ml), and the mixture extracted with diethyl ether. The etheral solution was washed, dried ($MgSO_4$), and evaporated. The crude product of 4-monoalkylated quinazoline contained about 5% of the 2,4-dialkylated material. The 4-monoalkylated product was isolated by flash chromatography on silica using hexane:EtOAc in the ratio 7:3. The same solvent ratio for flash chromatography was used throughout this work.

^1H NMR and ^{13}C NMR were recorded at 200 MHz and 75 MHz in $CDCl_3$. MS data are by electron impact. Spectroscopy data for only one member in an analogue series are given, but all data were satisfactory.

2-Chloro-4-methylquinazoline (**2a**). M.p. 94 - 95 °C (hexane). ^{1}HNMR: δ 2.94 (Me). ^{13}C NMR: δ 22.35 (Me), 122.29, 124.71, 127.03, 127.57, 133.64, 150.45, 155.75, 170.99. MS: 180 (30, M^+) and 178 (100, M^+), 163 (12), 143 (45), 115 (11), 102 (26), 84 (18), 76 (18).

2,4-Dimethylquinazoline (**3a**) and 2,4-Diisobutylquinazoline (**3b**) were prepared as above using twice the amount of the respective alane. 2,4-Diisobutylquinazoline (**3b**). ^1H NMR: δ 0.95, 2.3 and 2.9 (m, 2 x iBu). ^{13}C NMR: δ 22.50/22.72, 28.75/29.18 and 43.24/48.82 (2 x iBu), 28.73 and 48.78 (iBu), 122.22 (C6), 124.73 (C7), 126.22 (C5), 128.54 (C8), 133.07 (C4a), 150.23 (C4), 166.12 (C8a), 170.56 (C2). MS: 242 (5, M^+), 200 (15), 186 (46), 171 (32), 158 (14), 144 (100), 135 (5), 89 (4), 77 (4).

2-Isobutyl-4-methylquinazoline (**3c**) and 4-Isobutyl-2-methylquinazoline (**3d**) were formed by the general alkylation procedure from the monalkylated substrates (**2a**) and (**2b**). 2-Isobutyl-4-methylquinazoline (**3c**); ^1H NMR: δ 0.73, 2.39 and 2.92 (iBu), 2.91 (Me). ^{13}C NMR: δ 23.08, 29.14 and 49.12 (iBu), 22.53 (Me), 123.55, 124.40, 126.12, 127.98, 132.83, 148.62, 161.35, 168.43. MS: 200 (13, M^+), 185 (16), 158 (100), 144 (8), 130 (4), 103 (5), 91 (8), 77 (6).

6-Bromo-2-chloro-4-methylquinazoline (**5a**) and 2-chloro-4,6-dimethylquinazoline (**6a**). Trimethylalane (1.2 mmol) and 7 mol% tetrakis(triphenylphosphine)palladium were added to a solutoion of 6-bromo-2,4-

dichloroquinazoline (1.0 mmol; 278 mg) in dry THF (3 ml) under nitrogen and the mixture heated under reflux for 24 h. The product mixture was worked up as above. 6-Bromo-2-chloro-4-methylquinazoline (5a); ^{1}H NMR: δ 2.88 (s, Me). ^{13}C NMR: δ 22.35 (Me), 120.98, 123.21, 126.95, 129.16, 137.51, 149.00, 155.98, 169.95. MS: 260 (27, M^+) and 258 (100, M^+), 243 (9), 221 (17), 192 (43), 156 (11), 116 (15), 89 (13).

2-Chloro-4,6-dimethylquinazoline (6a); ^{1}H NMR: δ 2.54 (6-Me), 2.88 (4-Me). ^{13}C NMR: δ 22.30 and 22.47 (2 x Me), 122.17, 123.44, 127.13, 136.28, 137.36, 148.96, 148.96, 154.89, 170.01.

6-Bromo-2-chloro-4-isobutylquinazoline (5b) and 2,4-Dichloro-6-isobutylquinazoline (6b) were formed from (4) using triisobutylalane for alkylation as above. 6-Bromo-2-chloro-4-isobutylquinazoline (5b); ^{1}H NMR: δ 0.99, 2.32 and 3.06 (iBu). ^{13}C NMR: δ 23.33, 29.70 and 43.44 (iBu), 120.91, 122.64, 127.56, 128.96, 138.97, 150.11, 154.48, 172.97. MS: 302 (4, M^+) and 300 (11, M^+), 278 (100), 258 (89), 243 (71), 180 (20), 100 (31), 81 (10).

2,4,6-Trimethylquinazoline (7a) and 2,4,6-Triisobutylquinazoline (7b). Twice the required amounts of alanes were used for their preparation from 6-bromo-2,4-dichloroquinazoline (4). 2,4,6-Trimethylquinazoline (7a). ^{1}H NMR: δ 2.49, 2.77 and 2.83 (s, 2,4,6-Me$_3$). ^{13}C NMR: δ 22.26, 22.36 and 26.87 (2,4,6-Me$_3$), 121.49, 123.10, 127.24, 134.95, 135.74, 147.50, 161.59, 166.13. MS: 172 (100, M^+), 157 (49), 149 (16), 131 (36), 116 (7), 103 (4), 89 (19).

2,6-Dimethyl-4-isobutylquinazoline (8a) and 2,6-Diisobutyl-4-methylquinazoline (8b) were prepared by the dialkylation procedure from (5a) and (5b), respectively. 2,6-Dimethyl-4-isobutylquinazoline (8a); ^{1}H NMR: δ 0.98, 2.36 and 3.05 (iBu), 2.53 (6-Me), 2.82 (2-Me). ^{13}C NMR: δ 22.25 (6-Me), 23.16, 29.60 and 43.45 (iBu), 26.81 (2-Me), 121.73, 123.28, 127.64, 135.10, 135.80, 148.36, 162.04, 169.46.

2,4-Dimethyl-6-isobutylquinazoline (9) was available from (6b) by the monoalkylation procedure; ^{1}H NMR: δ 0.93, 1.94 and 2.65 (iBu), 2.81 (4-Me), 2.89 (2-Me).

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