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Efficient Coupling of 2-Halopyrimidines to 2,2′-Bipyrimidines

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EFFICIENT COUPLING OF 2-HALOPYRIMIDINES TO 2,2'-BIPYRIMIDINES

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Summary. 2-chloropyrimidine, 2-chloro- and 2-bromo-4,6-dimethylpyrimidines, 2-chloro- and 2-bromo-4,6-diphenylpyrimidines have been dimerized to the corresponding 2,2'-bipyrimidines in good yields by Tiecco's method using $NiCl_2$, triphenylphosphine and zinc in DMF.

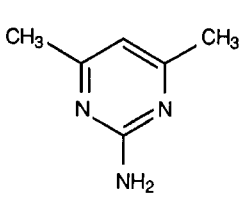
In our continuing search [1] for ligands able to complex transition metal ions, we became interested in 2,2'-bipyrimidines which give binuclear complexes [2]. The Ullmann dimerization of aryl bromides is usually the method of choice to synthesize biaryls; when applied to 2-bromopyrimidines, this copper-induced coupling is, however, difficult to control and seems to be rather irreproducible [3].

More recently, Tiecco *et al.* [4] were able to perform efficient couplings of halo*pyridines* to bipyridines by using the triphenylphosphine complex of Ni(0). We report here on the excellent results obtained when this method is applied to the dimerization of 2-halo*pyrimidines*.

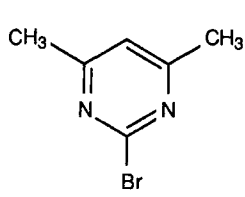
Results.

2-Halopyrimidines can be made *via* the corresponding 2-aminopyrimidines by diazotization followed by the substitution of the diazonio group by a halide ion; this is the route followed by several authors, but the results are sometimes highly irreproducible and by-products are often found. When we followed the literature procedure [5] to obtain 2-bromo-4,6-dimethylpyrimidine **2** from 1-amino-4,6-dimethylpyrimidine **1**, we achieved a 28 % crude yield, quite comparable to the authors' data. A TLC analysis of this material showed, however, that it was a 2:1 mixture of

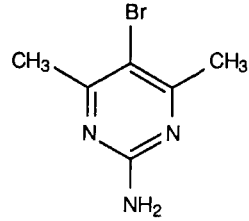
the expected compound **2** and 2-amino-5-bromo-4,6-dimethylpyrimidine **3** respectively. **3** was synthesized unambiguously by the action of elemental bromine on **1** in chloroform. Large variations of the amount of sodium nitrite, of the temperature or of duration of the addition of HBr resulted in no improvement of the yield of **2**.



1



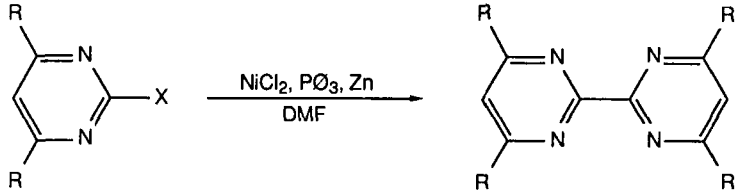
2



3

We nevertheless tried to dimerize bromopyrimidine **2** according to Bly's procedure [6] with copper in DMF but, in perfect agreement with Mc Omie's results, no bipyrimidine could be isolated, even after treating the medium with potassium cyanide to free any formed ligand from its copper complex. Musgrave and Westcott's [7] method, using no solvent, gave 15 % of the expected bipyrimidine.

In view of these disappointing findings, we decided to resort to the procedure introduced by Tiecco *et al.* (Ref 4) who dimerized hal*opyridines* by $Ni(PPh_3)_4$ generated *in situ* by the reduction of nickel chloride with zinc in the presence of triphenylphosphine in DMF. In these conditions, 2-bromo-4,6-dimethylpyrimidine **2** gave 4,4',6,6'-tetramethyl-2,2'-bipyrimidine **4** in 60 % yield.



2 :	X = Br; R = CH_3	**4** : R = CH_3	60 %
5 :	X = Cl; R = CH_3	**4** : R = CH_3	61 %
6 :	X = Br; R = Ph	**7** : R = Ph	80 %
8 :	X = Cl; R = Ph	**7** : R = Ph	85 %
9 :	X = Cl; R = H	**10** : R = H	60 %

Since chloropyrimidines are usually easier to synthesize than their bromo analogs, we wondered whether 2-chloro-4,6-dimethylpyrimidine **5** would behave in the same way. **5** was synthesized from 2-hydroxy-4,6-dimethylpyrimidine by reaction with phosphoryl chloride [8] and dimerized with Tiecco's system; the reac-

tion was even faster than with **2**, being complete after 2 h rather than 6 h, and gave practically the same yield. This method is thus definitely a progress compared with the classical Ullman procedure using copper, and which is known to work better with aryl bromides than chlorides.

We then turned to the synthesis of 4,4',6,6'-tetraphenyl-2,2'-bipyrimidine **7**. 2-Hydroxy-4,6-diphenylpyrimidine was obtained by reacting urea with dibenzoylmethane [9] and was subsequently treated with phosphoryl bromide to give **6** [10] or phosphoryl chloride to give **8** [11]. Both were dimerized with the nickel phosphine complex and gave excellent yields of **7** : 80 % from the bromide and 85 % from the chloride.

We finally applied the method to 2-chloropyrimidine which was obtained according to literature data [11]; when this was submitted to the Tiecco coupling, the yield of 2,2'-bipyrimidine was 60 %.

The coupling of 2-halopyrimidines by the nickel phosphine complex is thus presently by far the best way to 2,2'bipyrimidines.

Experimental part.

2-amino-5-bromo-4,6-dimethylpyrimidine **3**.

To 500 mg (4.06 mmol) of 2-amino-4,6-dimethylpyrimidine dissolved in 10 mL of anhydrous chloroform, kept in the dark, is added dropwise a solution of 0.21 mL (4.06 mmol) of bromine in 8 mL of chloroform.After 20 h at room temperature, one adds 25 mL of 1 M aqueous sodium hydroxide, extracts three times with 25 mL of chloroform, the organic layers are dried over $MgSO_4$ and evaporated to dryness.Flash chromatography through silicagel (hexane-ethyl acetate 1:1) followed by a sublimation under 0.13 Pa (10^{-3} Torr) at 100 °C gives 562 mg (2.78 mmol, 69 %) of 2-amino-5-bromo-4,6-dimethylpyrimidine **3**. MP. : 186-188° C; Rf (SiO_2, hexane-ethyl acetate 1:1) = 0.11.. Analysis : calculated for $C_6H_8N_3Br$ (FW = 202.053) : C 35.7, H 4.0, N 20.8; found : C 35.8, H 4.0, N 20.8. MS : 201 and 203 (100 % and 99 %, M^+); 176 and 174 (25 and 27); 162 and 160 (13 and 13). IR ($CHCl_3$, cm^{-1}) : 3520, 3420, 3000, 2960, 1600, 1550, 1440, 1380, 1345, 1200, 1030. ^1H NMR ($CDCl_3$, TMS) : 2.45 (s, 6 H, 4,6-Me_2); 5.19 (broad s, 2 H, NH_2).

4,4',6,6'-tetramethyl-2,2'-bipyrimidine **4**.

a) From 2-bromo-4,6-dimethylpyrimidine **2**. Nickel chloride hexahydrate (252 mg, 1.07 mmol) and triphenylphosphine (1.113 g, 4.28 mmol) are dissolved in 5.35 mL dimethylformamide kept at 50° C Purified nitrogen is bubbled through

the solution and 30 min later, 68.5 mg (1.07 mmol) of zinc dust are added; the medium turns from deep blue to reddish brown. One the adds 200 mg (1.07 mmol) of 2-bromo-4,6-dimethylpyrimidine , the progress of the reaction being followed by TLC (silicagel, hexane-ethyl acetate 1:1). After 6 h, the medium is poured in 20 mL 0.5 M aqueous ammonia, extracted with chloroform and the organic phase washed with water and dried over MgSO4. The solvents are removed under reduced pressure, leaving 977 mg of a yellow solid containing triphenylphosphine (Rf = 0.67), triphenylphosphine oxide (Rf = 0.21) and the product **4** (Rf = 0.11). Dry hydrogen chloride is then bubbled through a benzene solution of this mixture; the white precipitate which forms is collected, dried with anhydrous ether and dissolved in 20 mL of a 0.8 M aqueous solution of $NaHCO_3$. The aqueous phase is extracted with chloroform, the organic layer dried over $MgSO_4$ and evaporated, yielding 68.8 mg of 4,4',6,6'-tetramethyl-2,2'-bipyrimidine **4** which is purified by sublimation at 100 °C under 0.133 Pa (10^{-3} Torr); yield : 60 %. MP : 130-131 °C; litt : [6] 131-132 °C.

b) From 2-chloro-4,6-dimethylpyrimidine **5**. The same procedure is followed using 100 mg (0.701 mmol) of **5**, giving 45.8 mg (0.43 mmol) of **4**.

2-Chloro-4,6-diphenylpyrimidine **8**.

Urea (268 mg, 4.46 mmol), dibenzoylmethane (1.0 g, 4.46 mmol) and 0.6 mL of concentrated hydrogen chloride are dissolved in 3 mL ethanol; after 40 h reflux, 268 mg urea and 0.6 mL concentrated hydrogen chloride are added and reflux is extended for 8 more hours. The medium is cooled, the precipitate is filtered, the solid is collected, dried over phosphorous pentoxide and washed with chloroform, yielding 555 mg of 2-hydroxy-4,6-diphenylpyrimidine. Evaporation of the chloroform filtrate gives a residue which is chromatographed through silicagel (ethyl acetate), giving 229 mg of dibenzoylmethane and 10.5 more mg of 2-hydroxy-4,6-diphenylpyrimidine. The final yield is 66 %. This method, not yet optimized, appears to be more efficient than the co-condensation of benzaldehyde, acetophenone and urea [R.10] which, in our hands, gave only 34 %.

2-Hydroxy-4,6-diphenylpyrimidine (500 mg, 2.02 mmol) are dissolved in 3 mL of phosphoryl chloride containing 51 µL (0.403 mmol) N,N-dimethylaniline; after 7 h reflux, excess $POCl_3$ is removed under reduced pressure, the resulting thick oil is diluted with 10 mL ether and poured onto a 1:1 mixture of ice and ether. The aqueous layer is neutralized with 10 % sodium hydroxide, and extracted several times with ether; the organic layers are collected, dried over $MgSO_4$, and evaporated to dryness. The resulting pale yellow solid is chromatographed through alumina with CH_2Cl_2, and removal of the solvent gives a colorless solid which, after recristallisation from petroleum ether (40-60°) and sublimation at 100° C under 0.13 Pa (10^{-3} Torr) yields 410 mg (1.54 mmol, 76 %; litt.[11] : 35 %) of 2-chloro-4,6-

dimethylpyrimidine **8**; MP : 113-114° C; litt. [11] : 115-116° C. MS : 266 (100 %) and 268 (34 %) : M^+; 231 (88 %, $M^+ - Cl$); 204 (24 %).

4,4',6,6'-tetraphenyl-2,2'bipyrimidine **7**

a) From 2-chloro-4,6-diphenylpyrimidine **8**. A mixture of nickel chloride hexahydrate (178.2 mg, 0.75 mmol), triphenylphosphine (786.7 mg, 3.0 mmol) and zinc dust (70 mg, 1.07 mmol) is kept under argon; to this, 4 mL of degassed DMF are transfered through a thin tubing and the whole system is kept under argon for 1 h at 50 °C. To it is then transfered 2-chloro-4,6-diphenylpyrimidine **8** (200 mg, 0.75 mmol) dissolved in 2 mL of argon-purged DMF and the whole is kept at 50 °C for 6 h. The medium is then poured in 50 mL 2M aqueous ammonia; after extraction with chloroform, the organic phases are dried over anhydrous potassium carbonate; the solvents are removed under reduced pressure, giving 860 mg of a creamy solid containing triphenylphosphine, triphenylphosphine oxide and **8**. Chromatography (silicagel, hexane-ethyl acetate 8:2) followed by a recristalization from benzene or ethanol gives 148 mg (0.64 mmol, 85 %) of pure 4,4',6,6'-tetraphenyl-2,2'bipyrimidine **7**; MP : 257-259 °C, litt [12] : 249-251 °C.

b) From 2-bromo-4,6-diphenylpyrimidine **6**. The same procedure, starting with 200 mg (0.643 mmol) of 2-bromo-4,6-diphenylpyrimidine gave, after 3 h, 119 mg (0.51 mmol, 80 %) of pure **7**.

2,2'-bipyrimidine **9**.

The procedure used for the synthesis of 4,4',6,6'-tetraphenyl-2,2'bipyrimidine is applied to 200 mg (1.75 mmol) of 2-chloropyrimidine (made according to Kuznetsov et al. [13]); work-up gave 83 mg (0.52 mmol, 60 %) of 2,2'-bipyrimidine, MP : 115-117 %C, litt [7] : 113-115 °C.

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