5-Bromo-2-iodopyrimidine: a novel, useful intermediate in selective palladium-catalysed cross-coupling reactions for efficient convergent syntheses

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A simple synthesis of the novel 5-bromo-2-iodopyrimidine is described and examples are provided of the use of the compound in selective palladium-catalysed cross-coupling reactions with a wide range of arylboronic acids and alkynylzincs to give the efficient syntheses of many substituted pyrimidine compounds.

Pyrimidine-containing compounds are extremely important in a broad range of applications such as liquid crystals,[1–3] natural products,[4] agrochemicals[5–7] and pharmacological compounds.[8–10] The pyrimidine moiety is widely found in natural products, and cytosine, thymine and uracil are especially important as components of nucleic acids. Pyrimidine compounds are widely used as inhibitors of human immunodeficiency viruses,[10] they can act as effective anti-cancer drugs[9] and are also used as anti-rejection drugs in transplantations.[8]

Pyrimidine materials are of particular importance as liquid crystals for a wide range of applications,[1–3,11–13] for example, in chiral nematic mixtures for thermochromic devices, and in nematic mixtures for both displays and third-order non-linear optical applications. Most significantly of all, however, pyrimidine compounds make excellent achiral host materials and chiral dopants for ferroelectric mixtures used in fast-switching ferroelectric displays.[2,11,13] The work reported has evolved from long standing research in the synthesis of liquid crystalline compounds by palladium-catalysed cross-coupling reactions and the need for more efficient ways of preparing pyrimidine derivatives.

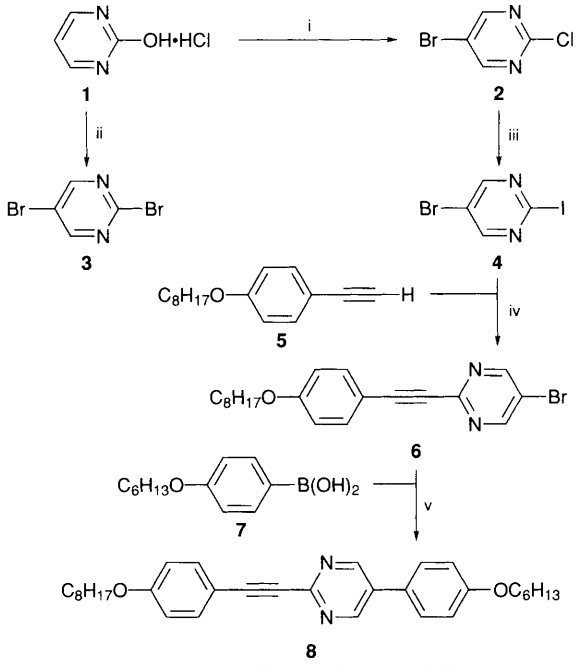
Traditionally, the synthesis of pyrimidines involves the preparation of suitably substituted nitrogen-containing intermediates followed by a condensation–cyclisation process to yield the pyrimidine core.[1,3] There are different variants of the cyclisation method but in all cases the overall synthetic route is tedious, gives poor yields and is not general because a separate synthesis needs to be performed for each analogue. Hence, the traditional routes are inefficient and greatly restrict the types of pyrimidines available for evaluation.

In order to obtain liquid crystalline pyrimidines or other pyrimidines suitable for liquid crystal mixtures, a 2,5-disubstitution pattern is required in order that a long, lath-like structure is generated. The substituents at the 2- and 5-positions are generally aryl, alkyl and alkoxy, but oxycarbonyl and carbonyloxy units are also useful.

The efficiency of palladium-catalysed cross-coupling reactions in the synthesis of liquid crystals is now well-recognised.[14,15] Selective couplings involving 1-bromo-4-iodobenzene are particularly useful in the general and efficient convergent synthesis of liquid crystals. Accordingly, the synthesis of pyrimidines has recently been effected by using 5-bromo-2-chloropyrimidine **2**.[12] Compound **2** was easily prepared from commercially available 2-hydroxypyrimidine hydrochloride by bromination followed by the replacement of the hydroxy group with a chloro substituent on treatment with phosphorus oxychloride.[6]

Compound **2** has been subjected to selective palladium-catalysed cross-coupling reactions where the first leaving group exploited is the bromo substituent.[12] Normally the chloro substituent is not a good leaving group for palladium-catalysed cross-coupling reactions and boronic acids do not normally react with aryl chlorides. However, the nitrogens of the pyrimidine ring enhance the reactivity of the 2-chloro substituent so that it is effective in palladium-catalysed cross-coupling reactions. Nonetheless, the reactivity of the chloro substituent in compound **2** in coupling reactions is still unreliable and at best low yields result, especially when reactions involve arylboronic acids that are prone to hydrodeboronation (*e.g.*, 2-fluorophenylboronic acids, **9**). Compound **3** would appear to be the ideal alternative in that the more reactive bromo substituent should improve yields. However, compound **3** is very difficult to obtain pure and, even when isolated, selectivity in palladium-catalysed cross-coupling reactions is surprisingly poor due to a similar reactivity of the two leaving group sites. The obvious alternative is to use the bromo-iodo material **4**, but the preparation of this compound has not been reported and it was initially assumed that the iodo leaving group may be too labile for a stable compound to be obtained. However, on treating compound **2** with aqueous hydrogen iodide, the chloro substituent was replaced by an iodo substituent to give a near-quantitative yield of compound **4** as a crystalline solid.†

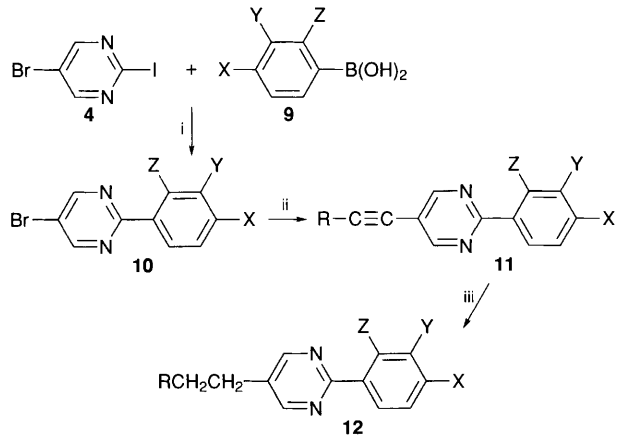
Compound **4** was, in all cases, efficiently employed in selective palladium-catalysed cross-coupling reactions to afford high yields of a wide range of materials (Schemes 1–3 and



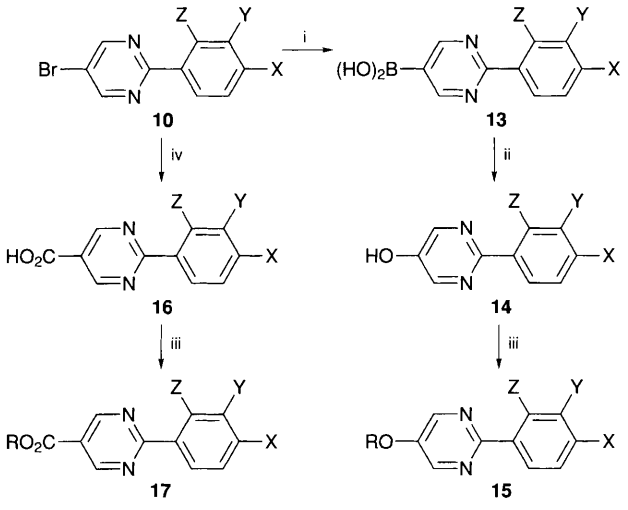
C 105.5 S_C 172.3 N 217.0 I (°C)

Scheme 1 *Reagents and conditions*: i, Br_2, water, then $POCl_3$; ii, Br_2, water, then $POBr_3$; iii, HI, water; iv, $Pd(PPh_3)_4$, CuI, Pr^i_2NH; v, $Pd(PPh_3)_4$, Na_2CO_3, DME, water

Table 1). The first palladium-catalysed cross-coupling reaction occurs in excellent yield, solely at the iodo site. The bromo substituent that remains was exploited in a variety of ways. For example, in Scheme 1, the leaving groups were involved in two

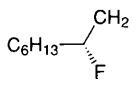
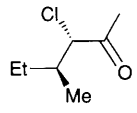
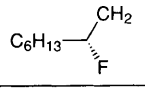
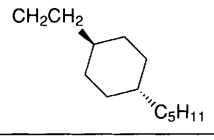


Scheme 2 *Reagents and conditions*: i, $Pd(PPh_3)_4$, Na_2CO_3, DME, water; ii, R–C≡C–H, CuI, Pr^i_2NH; iii, H_2, Pd–C, EtOAc



Scheme 3 *Reagents and conditions*: i, BuLi, THF, then $(MeO)_3B$, THF, then 10% HCl; ii, 30% H_2O_2, diethyl ether; iii, ROH, DEAD, PPh_3, THF; iv, BuLi, THF, then CO_2 (solid), then 10% H_2SO_4

Table 1 Compounds prepared from 5-bromo-2-iodopyrimidine

Compound	R	X	Y	Z
11a	C_7H_{15}	OC_8H_{17}	F	F
11b	Pr	F	H	H
11c	Pr	F	F	H
11d	Pr	CF_3	H	H
12a	C_7H_{15}	OC_8H_{17}	F	F
12b	Pr	F	H	H
12c	Pr	F	F	H
12d	Pr	CF_3	H	H
15a		C_5H_{11}	F	F
15b		OC_8H_{17}	F	F
17a			F	F

different types of palladium-catalysed cross-coupling reaction to produce a mesogenic pyrimidine **8**. The synthesis of the more orthodox liquid crystalline phenylpyrimidines was efficiently effected using the route shown in Scheme 2. Initially a boronic acid **9** coupled efficiently at the iodo site to provide a bromophenylpyrimidine **10**. The introduction of a terminal alkyl chain was effected by the efficient, but indirect, route of alkynyl coupling followed by hydrogenation. Such a synthetic route allows for the inclusion of lateral fluoro substituents (useful in liquid crystals for ferroelectric mixtures) and any other lateral substituents that can be incorporated into the boronic acid (Table 1).

Scheme 3 shows two other ways of exploiting the bromo substituent after the initial coupling reaction. The conversion to the boronic acid **13** not only allows further coupling reactions but oxidation provides an excellent yield of the phenol **14**. Pyrimidinol **14** was involved in alkylations and esterifications using Mitsunobu conditions[16] to yield a range of materials **15**. Such a substitution pattern with the alkoxy unit in the pyrimidine ring is particularly important for liquid crystalline phenylpyrimidines and yet these materials cannot be synthesised by the conventional cyclisation routes described above. The examples (**15**, Table 1) included are all chiral but straight, non-chiral terminal chains can, of course, also be introduced. The bromo substituent was also converted into the carboxylic acid function by low temperature lithiation followed by carboxylation with solid carbon dioxide. The resultant acids **16** were then esterified with chiral alcohols to give esters (**17**, Table 1), however, straight-chain, non-chiral alcohols can also be used.

Compounds **15** and **17** shown in Scheme 3 and Table 1 could not be prepared by using the bromochloropyrimidine **2** because the site between the two heterocyclic nitrogens must be exploited first and this is not possible with compound **2**. Although compounds **11** and **12** could be prepared *via* compound **2**, the efficiency and yields would be poor.

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Footnote

† 5-Bromo-2-iodopyrimidine **4**. Cold 57% hydroiodic acid (281 ml, 2.17 mol) was added dropwise to a cooled (−5 °C), stirred solution of compound **2** (80.6 g, 0.42 mol) in dichloromethane (250 ml). The mixture was stirred at 0 °C for 5 h and neutralised carefully with solid potassium carbonate and decolourised by the addition of aqueous sodium metabisulfite. Water was added until a solution was formed; the organic layer was separated and the aqueous layer was washed with dichloromethane. The combined organic extracts were dried (Na_2CO_3) and the solvent was removed *in vacuo*. The resulting solid was recrystallised from the light petroleum fraction (bp 60–80 °C) to yield colourless crystals. Yield (99 g, 83%), mp 101–102 °C. The product gave satisfactory NMR, IR, MS and CHN analyses and was found to be 99.9% pure by HPLC.

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