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Synthesis of 6-ethynylpurine derivatives

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Dedicated to Professor Heinrich Wamhoff on the occasion of his 70th birthday

Abstract

A series of 6-(arylethynyl)purine derivatives are synthesized from the corresponding 6-halopurines via sequential and 'one-pot' Sonogashira-coupling reactions. The nature of the acetylene source was found to have a profound influence on the efficiency of the process. In sequential couplings, 2-methyl-but-3-yn-2-ol was found to be an efficient acetylene surrogate, while in the 'one-pot' reaction, 1-ethynyl-cyclohexanol gave superior results.
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The structural modification of purine bases, nucleosides and nucleotides has been a prime target in medicinal chemistry since the introduction of a substituent onto the heterocyclic ring may dramatically influence their base-pairing ability and the selectivity of their binding to targets. Purines, bearing a C-substituent at position 6 display a broad spectrum of activity ranging from cytotoxicity[1] to antiviral effects, [2] so it is not surprising that the preparation of these purine derivatives has received considerable attention lately. Cross-coupling reactions in particular, have facilitated the introduction of C-based substituents starting from 6-halopurines. The Suzuki,[3] Stille[4] and Negishi[5] couplings have all been exploited successfully in this respect. The 6-vinyl- and 6-ethynylpurine derivatives were also utilized as a platform for further elaboration.[6,7] The Sonogashira-coupling was extended to some unprotected purines too.[8]

Although the Sonogashira-coupling of 6-halopurines and acetylene derivatives has been reported,[9,10] there are a number of limitations to this process: (i) the number of commercially available monosubstituted acetylenes is limited, and (ii) the economy of such processes is poor due to the price of the aforementioned acetylenes. An alternate approach would involve the coupling of 6-ethynylpurines with different aryl halides, but to date the reagent of choice for this transformation is trimethylsilylacetylene,[11] which is not economic for large scale applications.

Our studies were aimed towards establishing a general synthetic route to 6-ethynylpurine derivatives by devising a scalable synthesis of 6-ethynylpurine and coupling of this compound with a series of aryl halides. We also wanted to study the feasibility of two recently published one-pot procedures,[12,13] which utilize halopurines, aryl halides and a simple acetylene surrogate as coupling partners.

Our choice of purine derivatives was based on the 2-amino-6-halopurine skeleton. Thus, 2-amino-9-benzyl-6-iodo-purine (**1**) was reacted with 2-methyl-3-butyn-2-ol (**2a**) or 1-ethynyl-cyclohexanol (**2b**) in the presence of 2 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI and triethylamine at room temperature[14] to furnish the appropriate ethynylpurine derivatives **3b** or **3c** in good yield (Scheme 1). These reactions took place smoothly on a multigram scale and the products could be obtained in a pure form by filtration and subsequent washing. Using the chloride-analog of **1** led to similar results, although more forcing conditions and prolonged reaction times were required to achieve complete conversion, however, the overall yield decreased. The advantage of the acetylene derivatives **2a** and **2b**, besides their low cost, is the fact that their substituents(R) can

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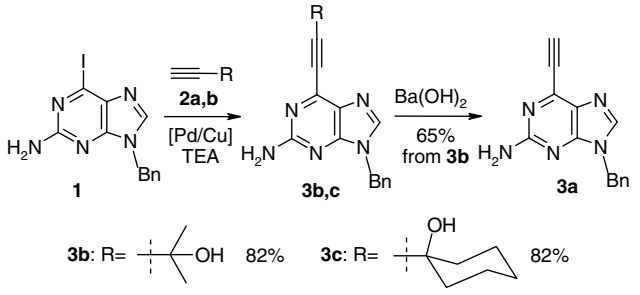


Scheme 1. The synthesis of 6-ethynylpurines **3a–c**.

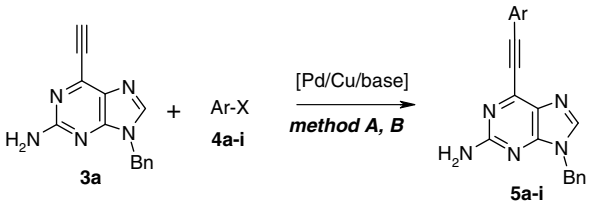
be removed under alkaline conditions. To obtain the 6-ethynylpurine derivative **3a**, a solution of **3b** in toluene or DMA was treated with an inorganic base (KOH or $Ba(OH)_2$, respectively) at elevated temperatures to give **3a** in 65% yield on a 10 g scale. The analogous transformation of **3c** to **3a** was also realized, but with inferior efficiency.[15]

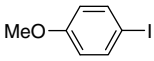
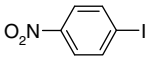
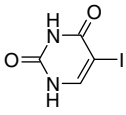
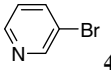
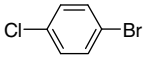
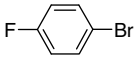
In the first set of coupling reactions, **3a** was reacted with various aryl halides using either the conventional Sonogashira-coupling conditions (Table 1, method A) or the modified conditions of Mori[16] (method B). When aryl iodides were used as coupling partners, the former conditions usually gave superior yields. Electron rich and electron deficient aromatic compounds could both be introduced into the desired products. In the case of the less reactive aryl bromides, however, method A usually gave very poor yields. In these reactions the conditions described in method B gave better results, although these were still mediocre in most cases.

It was also possible to carry out Sonogashira-coupling on **3b** or **3c**, but in these cases the reaction had to be carried out in the presence of a base, which facilitates the removal of the end-groups prior to the coupling.[17] A convenient solution to this problem could be the use of biphasic conditions with a strongly alkaline aqueous phase and phase transfer catalysis,[18] as reported for analogous 4-aryl-2-methyl-3-butyn-2-ols. We conducted a series of experiments with **3b** and different aryl halides (Table 2, method A) but isolated the desired products in very poor yields. The reason behind this poor efficiency is that to achieve complete conversion the reactions had to be run for a prolonged period of time. During this period, we observed the formation of ethynylpurine **3a** and decomposition products of **3a** and **3b**.

The alternative approach to this problem is the use of the cyclohexanone protected 6-ethynylpurine **3c**. In this case, the previously applied biphasic conditions led to no discernible product formation. On screening possible solvent-base combinations, we found that on running the deprotection–coupling sequence in the presence of barium hydroxide in DMF (Table 2, method B), we obtained acceptable yields in most cases.[19] In light of the fact that removal of the cyclohexanone from **3c** was accomplished in mediocre yield, and in this procedure we carried out the two steps sequentially, the yields are even more valuable.

Table 1
The Sonogashira-coupling of **3a** and aryl halides **4a–k**



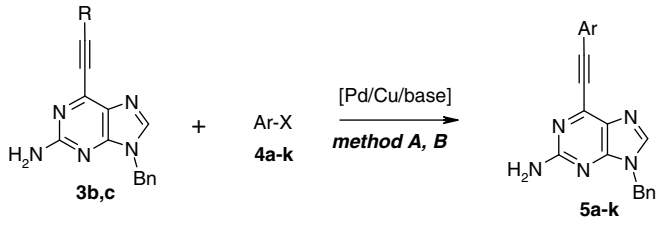
Ar–X	Method	Yield (%)
 **4a**	A	72
	B	55
 **4b**	A	92
 **4c**	A	61
 **4d**	A	68
 **4e**	A	80
 **4f**	A	22
	B	45
 **4g**	A	65
 **4h**	B	44
 **4i**	B	33

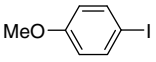
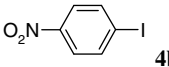
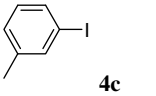
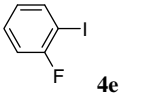
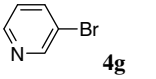
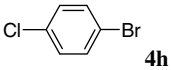
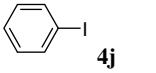
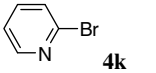
Method A: 5% $PdCl_2(PPh_3)_2$, 5% CuI, 2 equiv TEA, DMF, 80 °C.
Method B: 3% $PdCl_2(PPh_3)_2$, 3% CuI, 2 equiv TBAF, THF, rt.

There is also a third possible, even more elegant way to accomplish the synthesis of arylethynyl-purines, where starting from the halopurine, aryl halide and the masked acetylene, the three steps are performed in the same flask, without isolation of the intermediates. We investigated a series of different conditions to obtain the desired products in this domino process, but even if successful, we obtained only traces of the arylethynyl-purines after tedious chromatographic separation.

In summary, a series of 6-(arylethynyl)purine derivatives were prepared starting from the appropriate 6-iodopurine, aryl halides and an acetylene surrogate (2-methyl-3-butyn-2-ol or 1-ethynyl-cyclohexanol). Attempts were made at carrying out the coupling and deprotection steps both

Table 2
The tandem deprotection–Sonogashira-coupling of protected 6-ethynylpurines **3b**,**c** with different aryl halides



Ar–X	Purine	Method	Yield (%)
 **4a**	**3b**	A	9
	3c	B	80
 **4b**	**3b**	A	18
	3c	B	91
 **4c**	**3b**	A	5
	3c	B	44
 **4e**	**3b**	A	17
	3c	B	75
 **4g**	**3b**	A	28
	3c	B	71
 **4h**	**3b**	A	35
	3c	B	75
 **4j**	**3b**	A	16
	3c	B	53
 **4k**	**3c**	B	47

Method A: 5% $PdCl_2(PPh_3)_2$, 10% CuI, 5M NaOH, TBAB, toluene.
Method B: 3% $PdCl_2(PPh_3)_2$, 3% CuI, 2 equiv TEA, 0.7 equiv $Ba(OH)_2$, DMF.

separately and in a one-pot fashion. Of the possible combinations tested the direct coupling of 6-ethynylpurines with aryl halides and sequential deprotection–coupling of the appropriate ethynyl-cyclohexanol derivative and aryl halides were the most effective. Some of the studied reactions were also carried out on multigram scale.

Acknowledgements

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14. General procedure: A mixture of 5.00 g (14.2 mmol) of **1**, 200 mg (0.285 mmol, 2 mol %) of $PdCl_2(PPh_3)_2$ and 54 mg (0.285 mmol, 2 mol %) of CuI was stirred in 20 ml of THF at ambient temperature, under an argon atmosphere. After 1 min, 16 mmol of 2-methyl-3-butyn-2-ol or 1-ethynyl-cyclohexanol and 5.0 ml (35.5 mmol) of triethylamine were added to the mixture. Stirring was continued until the starting material was consumed (ca. 16 h) and then the resulting thick suspension was filtered. The precipitate was washed with water and cold ethyl acetate and dried in vacuum to yield the appropriate compound (**3b** or **3c**) as a white solid.
15. The coupling reactions of 2-amino-6-iodopurine with **2a** and **2b** were also successful but we were unable to remove the organic end-groups (acetone or cyclohexanone) from the resulting compounds without significant decomposition.
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19. Typical procedure: 100 mg (0.29 mmol) of **3c**, 7 mol % (14 mg, 0.02 mmol) of $PdCl_2(PPh_3)_2$, 7 mol % (4 mg, 0.02 mmol) of CuI, 70 mol % (38 mg, 0.20 mmol) of $Ba(OH)_2$ and 1.1 equiv (75 mg, 0.32 mmol) of 4-iodoanisole (**4a**) were mixed in 3 ml of DMA. Triethylamine (1.2 equiv, 124 μl) was added and the mixture was heated to 85 °C. The reaction reached full conversion in most cases in approximately 24 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (hexane–ethyl acetate gradient from 90:10 to 20:80) to give 82 mg (80%) of **5a** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 7.72 (s, 1H), 7.59 (d, 2H, $J = 8.7$ Hz), 7.29–7.15 (m, 5H), 6.81 (d, 2H, $J = 8.8$ Hz), 5.41 (br s, 2H), 5.18 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 159.90, 158.83, 152.57, 141.58, 141.34, 134.28, 133.45, 131.03, 128.05, 127.41, 126.64, 113.10, 97.41, 82.08, 54.33, 45.78. MS (EI-70 eV): 355 ($M^{+\cdot}$, 10%), 281 (34%), 277 (19%), 147 (43%), 57 (100%). Anal. Calcd for $C_{21}H_{17}N_5O$: C, 70.97; H, 4.82; N, 19.71%. Found: C, 70.56; H, 4.93; N, 19.50%.