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Regioselective Sonogashira cross-coupling reactions of 6-chloro-2,8-diiodo-9-THP-9*H*-purine with alkyne derivatives

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ABSTRACT

Lithiation of 6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine with LiTMP, gave access to 6-chloro-2,8-dihalogenated purine derivatives. In particular, the 6-chloro-2,8-diiodopurine derivative is an interesting new intermediate which gave regioselectively various 2-alkynylated compounds or 2,8-dialkynylated purines by using an excess of alkyne.

1. Introduction

Metallation reactions remain as very useful methods for the regioselective functionalization of heterocycles. Thus, lithiation of purine nucleosides with *n*-BuLi or lithium diisopropylamide (LDA), followed by reaction with various electrophiles has led to the synthesis of 8-substituted purine derivatives (methyl, ethyl, formyl, etc).[1,2] The 8-methoxycarbonyl derivative of adenosine or inosine[2] and 8-halogeno purine derivatives was also obtained by this methodology.[3–6] From these pioneering works, it can be stated that lithiation of a 6-*N*,*N*-dimethylaminopurine derivative with *n*-BuLi[1] or of 6-chloropurine derivatives with LDA[2,5] occurs exclusively at the C-8 position, the reason being that the C-8 hydrogen is more acidic than the C-2 hydrogen. Tanaka's group was the first to obtain 2-tributylstannyl-purine derivatives, using lithium tetramethyl piperidylamide (LiTMP) as a lithiation agent. The mechanism involved an initial lithiation of the 6-chloropurine nucleoside with LiTMP at the 8-position. However, reaction of the 8-lithiated species with tin and silicon electrophiles furnished 2-functionalized products, which resulted from an anionic transfer of the stannyl or silyl group from the 8- to the 2-position.[5] In a later study, the authors suggested that direct C-2 lithiation becomes a feasible event once C-8 is substituted with a stable triisopropylsilyl group, permitting thereby to skip the C-2 stannylation step.[7] In these examples, direct lithiation was achieved with the purpose of obtaining C-2 or C-8-substituted purines. However, to the best of our knowledge 2,6,8-trihalogenated purine derivatives have not been synthesized from 6-chloropurine before, although Nolsoe obtained a 6-chloro-2,8-dibromopurine derivative in very low yield (<5%),[8] whereas Hocek and Pohl,[9] reported the preparation of a 2,6,8-trichloropurine by 8-lithiation (LDA) followed by chlorination (C_2Cl_6) of 2,6-dichloro-9-THP-purine. Following these works, our interest was to synthesize in one step 2,8-disubstituted purines as 6-chloro-2,8-dibromo- and 6-chloro-2,8-diiodo-purines. These intermediates are attractive to synthesize variously functionalized purine derivatives of potential biological interest.[10] Furthermore, our hypothesis was that cross-coupling reactions with 6-chloro-2,8-diiodopurine intermediate would show selectivity for alkynylation at C2, although the selectivity of previously described Suzuki-Miyaura cross-coupling reaction with 2,6,8-trichloro-9-THP-purine was quite low.[9] In this context, we report in this communication the synthesis of new 2,8-dibromo- and 2-8-diiodopurine derivatives from 6-chloropurine and show that they can be used in regioselective cross-coupling reactions.

2. Results and discussion

For the purpose of functionalizing the 2- and 8-positions in one pot, 6-chloropurine derivative **1**[11] was treated with 5 equiv of LiTMP, followed by addition of various electrophiles. This led to various 2,8-disubstituted purines **2** as outlined in Scheme 1. It should be noticed that the yield decreased when using less than 5 equiv of LiTMP. On the other hand, treatment of the 8-phenyl derivative **5** with 5 equiv of LiTMP, followed by an excess of I_2, led to the 2-iodopurine derivative **6** in 51% yield, confirming that lithiation occurred at position 2 (Scheme 2). Again, the yield of this reaction decreased with less than 5 equiv of LiTMP as already observed.[7] When DMF was

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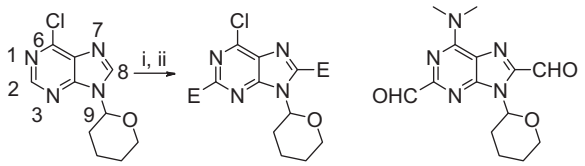
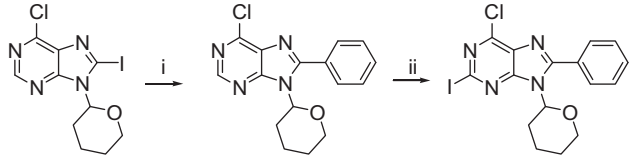


Scheme 1. Reagents and conditions: (i) LiTMP, 5 equiv, −78 °C, THF, 2 h; (ii) electrophile: (a) I_2, (b) 1,3-dibromo-5,5-dimethyl-hydantoin, (c) CCl_3CCl_3, (d) PhCHO, (e) $(i\text{-PrSi})_3OTf$, −78 °C→rt.



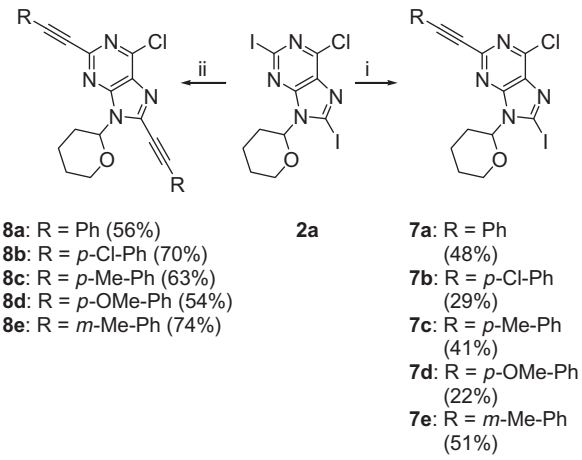
Scheme 2. Reagents and conditions: (i) $PhB(OH)_2$, K_2CO_3, anhydrous toluene, $Pd(PPh_3)_4$, 100 °C, 24 h, under Argon; (ii) (a) LiTMP, −78 °C, THF, 30 min, (b) I_2, −78 °C→rt.

used as an electrophile, 2,8-diformylated compound **3** was obtained but the chlorine atom was substituted by a dimethylamino group resulting from the reaction of organolithium species with DMF. The synthesis of 8-iodopurine derivative **4** was performed from **1** with LDA/I_2 at −78 °C, in 80% yield as described.[7,8]

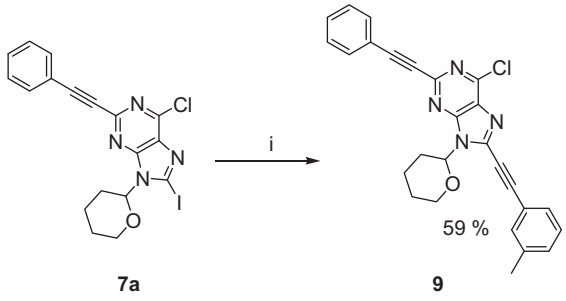
Particularly interesting is the formation of diiodo purine **2a** in high yield (80%) which was never described before, to our best knowledge. 2,8-Dibromo- and 2,8-dichloropurines **2b** and **2c** were obtained in moderate yield with mild reagents such as 1,3-dibromo-3,5-dimethylhydantoin and hexachloroethane, respectively. Use of Br_2 as a brominating agent did not lead to **2b** but to the decomposition of **1**.

We next examined the regioselective Sonogashira alkynylation of di-iodopurine **2a**.

Using 1 equiv of alkyne under Sonogashira conditions gave the monoalkynylated derivative **7a**–**e** in 22–51% yield, whereas more than 1 equiv of alkyne (2–3 equiv) led to the dialkynylated derivative **8** in 54–74% yield (Scheme 3). C2 and C8 resonances in **1** (^{13}C NMR signals at 151.9 ppm and 143 ppm respectively) are shifted upfield in the bis-iodo derivative **2a** to 116.8 ppm (C2-I) and 106.3 ppm (C8-I). In the monoalkynylated compounds **7**, the C8-I signal around 106 ppm remains present, whereas the C2-I signal at 116.8 ppm[11] is not observed. Further evidence of C2 monoalkynylation was given by the presence of a correlation between THP H1′ and C8-I. The moderate yield of the monoalkynylated compounds **7b**,**d** is due, in part, to some homocoupling of the alkyne reactant. In addition to trace amounts of bis-alkynylated compounds (**8b**,**d**) (<5%), unreacted starting compounds (<5%) as well as some other minor unidentified compounds were observed in these experiments. However, the regioselectivity of the alkynylation under controlled conditions is interesting since it allows a further nucleophilic aromatic substitution or cross-coupling reaction on the 8-position, resulting in different substituents on the 2 and 8 positions of **2a**. Thus **7a** was used in a supplementary Sonogashira coupling at position 8, using *meta*-tolyl acetylene (Scheme 4). The second cross-coupling leading to the bis-alkynylated purine **9** was faster (2 h, Scheme 4) than the first couplings at C2 (24 h, Scheme 3, **2a** → **7**).



Scheme 3. Reagents and conditions: (i) alkyne, 1.05 equiv, CuI, 12 mol %, $Pd[(PPh)_3]_4$, 25 mol %, Cs_2CO_3, 1 equiv, DMF, 24 h; (ii) alkyne, 3 equiv, CuI, 12 mol %; $Pd[(PPh)_3]_4$, 6 mol %, Cs_2CO_3, 3 equiv; DMF, 2–3 h.



Scheme 4. Reagents and conditions: (i) alkyne, 1.05 equiv, CuI, 12 mol %, $Pd[(PPh)_3]_4$, 6 mol %, Cs_2CO_3, 1 equiv, DMF, 2 h.

3. Conclusions

In conclusion, we report in this communication a new method for the synthesis of 2,6,8-trihalogenated purine derivatives. Preliminary results indicate that regioselective cross-coupling at position 2 can be obtained with 6-chloro-2,8-diiodopurine. It should also be noted that in all these experiments, the chlorine at position 6 remained unsubstituted and available for further functionalization. Additional functionalization at position 9 is also possible after acidic hydrolysis of the THP group.[12,13]

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Supplementary data

Supplementary data associated with (detailed experimental procedures, and compound characterization data for all new compounds) this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.033.

References and notes

1. Barton, H. R.; Hedgecock, C. J. R.; Lederer, E.; Motherwell, W. B. *Tetrahedron Lett.* **1979**, *20*, 279–280.
2. Hayakawa, H.; Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1987**, *35*, 72–79.
3. Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. *Tetrahedron Lett.* **1990**, *31*, 5877–5880.

4. Liu, F.; Dalhus, B.; Gundersen, L.-L.; Rise, F. *Acta Chem. Scand.* **1999**, *53*, 269–279.
5. Kato, K.; Hayakawa, H.; Tanaka, H.; Kumamoto, H.; Shindoh, S.; Shuto, S.; Miyasaka, T. *J. Org. Chem.* **1997**, *62*, 6833–6841.
6. Ghosh, A. K.; Lagisetty, P.; Zajc, B. *J. Org. Chem.* **2007**, *72*, 8222–8226.
7. Kumamoto, H.; Tanaka, H.; Tsukioka, R.; Ishida, Y.; Nakamura, A.; Kimura, S.; Hayakawa, H.; Kato, K.; Miyasaka, T. *J. Org. Chem.* **1999**, *64*, 7773–7780.
8. Nolsoe, J. M. J.; Gundersen, L.-L.; Rise, F. *Synth. Commun.* **1998**, *28*, 4303–4315.
9. Hocek, M.; Pohl, R. *Synthesis* **2004**, 2869–2876.
10. Legraverend, M.; Grierson, D. S. *Bioorg. Med. Chem.* **2006**, *14*, 3987–4006.
11. Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron* **2002**, *58*, 7911–7923.
12. Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8165–8167.
13. Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8169–8171.