Palladium-catalysed cross coupling of perfluoroalkenyl zinc reagents with 5-halo-6-azauracils

Hanna Wójtowicz-Rajchel, Irena Bednarczyk, Andrzej Katrusiak and Henryk Koroniak*

Department of Chemistry, Adam Mickiewicz University, 60-780 Poznan, Poland.
Fax: +48 61 829 1507; e-mail: koroniak@amu.edu.pl

10.1070/MC2004v014n02ABEH001888

The title reactions of 1,3-dimethyl-5-halo-6-azauracils with perfluoroalkenylzinc reagents [CF_2=CFZnI and $CF_3C(ZnBr)$=CF_2] give not only corresponding alkenes but also, unexpectedly, a hexafluoroalkane derivative.

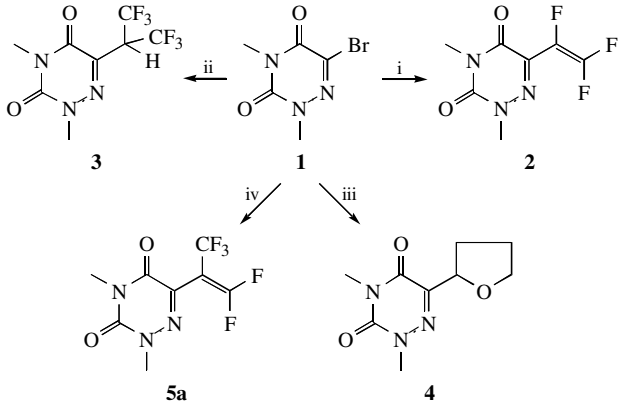
Organofluorine compounds are widely used in biochemistry and medicinal chemistry owing to their unique properties.[1] Fluorinated organometallic reagents are useful synthetic intermediates for introducing a fluorinated unit into organic molecules.[2] Particularly, the palladium-catalysed cross coupling of thermally stable perfluoroalkenyl zinc reagents with aryl iodides is a very convenient and useful tool in the synthesis of arylperfluoroalkenes.[3–5] We reported a synthesis of some perfluoroalkenyl derivatives of uracil as potential synthons of appropriate nucleosides.[6] Our continuing interest in fluorinated analogues of nucleic acid bases prompted us to explore the possibility of using an 6-aza analogue of uracil. Numerous examples of reactions show that uracil and 6-azauracil derivatives behave in a similar way, but sometimes the seemingly simple reactions of 6-azauracil derivatives can make their chemistry fascinating.[7,8]

Here, we describe the palladium(0)-catalysed functionalization of 5-halo-6-azauracil derivatives† with the vinylzinc reagents: CF_2=CF–ZnI and internal $CF_3C(ZnBr)$=CF_2. To the best of our knowledge, in contrary to the synthesis of 5-vinyluracils, it is the first attempt to obtain 5-vinyl-6-azauracil derivatives *via* coupling reactions. The previous synthetic strategy for the preparation of 5-(2-substituted vinyl)-6-azauracils and their biologically active nucleosides involved the synthesis of 5-(chloromethyl)-6-azauracil, the hydrolysis to the corresponding hydroxymethyl derivative, the oxidation to carboxaldehyde and the Wittig reactions.[9]

The coupling reactions of 1,3-dimethyl-5-bromo-6-azauracil **1** with CF_2=CF–ZnI mediated by the $Pd(PPh_3)_4$ or (Pd/C)/PPh_3 catalytic system proceed smoothly in DMF or THF to give compound **2** (54–71% isolated yield). However, the bulky less nucleophilic vinylzinc reagent $CF_3C(ZnBr)$=CF_2 in DMF and THF reacted to the completion of **1** but did not give the expected product (Scheme 1).‡

The coupling reaction of **1** with $CF_3C(ZnBr)$=CF_2 in THF failed, ^{19}F NMR analysis made in the course of the reaction did not show any fluorinated product except a slow hydrolysis of $CF_3C(ZnBr)$=CF_2 with the simultaneous formation of compound **4** (79% isolated yield). This process did not proceed in the reaction carried out without the vinylzinc compound.

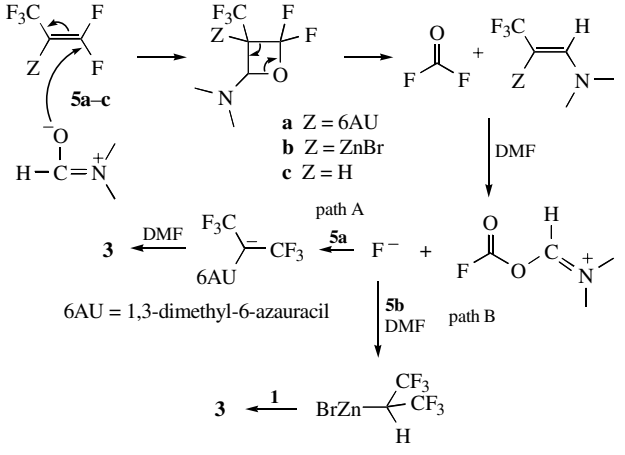
However, the coupling reaction proceeded in an unexpected manner in DMF. The reaction of **1** with $CF_3C(ZnBr)$=CF_2 afforded exclusively 1,3-dimethyl-5-(1,1,1,3,3,3-hexafluoropropyl)-6-azauracil **3** (38% isolated yield) as a coupling product. ^{19}F NMR analysis of the reaction mixture carried out during and after the reaction showed no traces of expected 'normal' coupling product **5a**. Most likely, compound **3** is formed by the reaction of a perfluoroalkenyl moiety (**5a**,**b**) with the fluoride anion to form a carbanion, which can capture a proton from the solvent. The questions are (i) what is the source of the fluoride anion? and (ii) when the attack of F^- occurs?



Scheme 1 *Reagents and conditions*: i, CF_2=CFZnI, DMF or THF, $Pd(PPh_3)_4$ or (Pd/C)/PPh_3, 90–100 °C, 2 h; ii, $CF_3C(ZnBr)$=CF_2, DMF, $Pd(PPh_3)_4$, 100 °C, 8 h; iii, $CF_3C(ZnBr)$=CF_2, THF, $Pd(PPh_3)_4$, 100 °C, 6 h; iv, $CF_3C(ZnBr)$=CF_2, diglyme, $Pd(PPh_3)_4$, 100 °C.

DMF reacts with fluorinated alkenes and alkene derivatives to give a fluoride anion.[10,11] Morken and Burton[5] reported HF addition to activated β,β-difluoro-α-(trifluoromethyl)-*m*-nitrostyrene as a side product of the coupling reaction and proposed a mechanism for the unusual transformation.

We considered two possible mechanisms for this uncommon coupling reaction. In one of them, there are two alternative paths to product **3** (Scheme 2).



Scheme 2

† As a model compound for nucleotide synthesis, we used 1,3-dimethyl-5-bromo-6-azauracil, which can be readily prepared from 6-azauracil. Methylation at the N(1) and N(3) positions was necessary for protecting relatively acidic N–H protons. Comparable results were obtained with an 5-iodo analogue.

‡ *1,3-Dimethyl-5-(1,2,2-trifluorovinyl)-6-azauracil* **2**: colourless oil, 71% yield. ^{1}H NMR ($CDCl_3$) δ: 3.40 [s, 3H, N(1)–Me], 3.72 [s, 3H, N(3)–Me]. ^{19}F NMR ($CDCl_3$) φ: –95.5 (dd, 1F, C=C*F*F, $J^{1,3}_{F,F}$ 32.4 Hz, $J^{1,2}_{F,F}$ 54.5 Hz), –111.3 (dd, 1F, C=CF*F*, $J^{1,3}_{F,F}$ 116.7 Hz, $J^{1,2}_{F,F}$ 54.5 Hz), –178.9 (dd, 1F, C*F*=CFF, $J^{1,3}_{F,F}$ 32.4 Hz, $J^{1,3}_{F,F}$ 116.7 Hz). MS (EI), *m/z*: 221 [M^+] (100), 164 (4), 136 (11), 108 (16).

1,3-Dimethyl-5-(1,1,1,3,3,3-hexafluoropropyl)-6-azauracil **3**: a white crystal (for X-ray analysis, the compound was crystallised from ethanol), 38% yield, mp 140–141 °C. ^{1}H NMR ($CDCl_3$) δ: 3.41 [s, 3H, N(1)–Me], 3.74 [s, 3H, N(3)–Me], 4.96 (septuplet, 1H, $J_{H,F}$ 7.8 Hz). ^{19}F NMR ($CDCl_3$) φ: –65.2 (d, 6F, $J^{3}_{H,F}$ 6.1 Hz). MS (EI), *m/z*: 291 [M^+] (56), 252 (19), 206 (100), 178 (43), 69 (63).

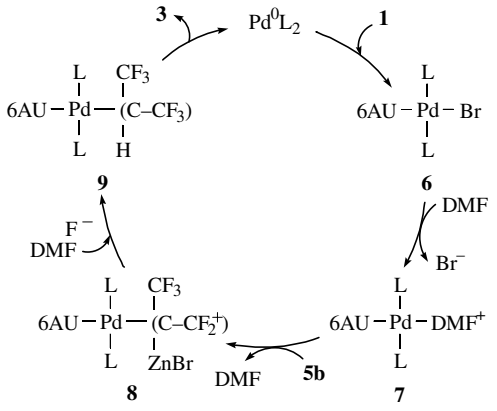
Path A, which is similar to that suggested by Burton, involves a nucleophilic attack of DMF on the terminal difluoromethylene carbon of **5a** to give an intermediate product, which decomposes by loss of carbonyl fluoride. The reaction of carbonyl fluoride with DMF gives the fluoride anion, which can react with **5a** to give compound **3** after proton abstraction from the solvent. Path B involves the reaction of F^- with compound **5b** to give a new concomitant reactive alkylzinc compound able to undergo the coupling reaction. In this path, compounds **5b–c** can serve as precursors of the fluoride anion.

Although the formation of the fluoride anion in DMF seems unquestionable, the absence of at least a noticeable amount of compound **5a** makes path A doubtful. We believe that path B is more probable in view of the above mechanistic consideration.

The second mechanistic interpretation of the reaction of **1** with $CF_3C(ZnBr)=CF_2$ assumes the addition of the fluoride anion at the stage of the reactive complex. Recently, Amatore and co-authors showed that the mechanism of the catalytic cross coupling of aryl halides and alkenyl stannanes mediated by Pd(0) in DMF (Stille reaction) is much more complex than that classically reported. Partial ionization of the complex $PhPdI(PPh_3)_2$ to *trans*-$PhPd(PPh_3)_2DMF^+$ and I^- was observed; consequently, a reaction of $CH_2=CHSnBu_3$ with the cationic complex cannot be excluded, leading to the intermediate *trans*-$PhPd(PPh_3)_2(\eta^2\text{-}CH_2=CHSnBu_3)^+$ complex.[12,13] Based on the above mechanism, the reactive cationic complex $6AUPd(PPh_3)_2$-$(ZnBrCCF_3–CF_2^+)$ was proposed as an intermediate (where 6AU is a 6-azauracil moiety), which affords compound **3** by the reaction with the fluoride anion, transmetallation and the reductive-elimination step (Scheme 3).

The catalytic reaction is initiated by the oxidative addition of **1** to the reactive $Pd(0)(PPh_3)_2$ complex to give 6AU-palladium(II) intermediate **6**. The ionization of **6** in DMF gives cationic species **7**, which can likely react with the nucleophile $CF_3C(ZnBr)=CF_2$. The subsequent reaction of reactive complex **8** with the fluoride anion and proton abstraction from the solvent gives transmetallation product **9**. The reductive elimination of **9** affords final product **3**. Product **3** is a crystalline compound, and X ray crystallography[§] was applied to confirm its structure (Figure 1).

However, we detected coupling product **5a** as the major



Scheme 3

[§] *Crystal data for* **3**: $C_8H_7F_6N_3O_2$, monoclinic, $P2_1/n$, a = 11.460(2), b = 7.0880(12), c = 14.385(3) Å, β = 92.74(2)°, V = 1167.1(4) Å^3, Z = 4, T = 293(2) K, d_{calc} = 1.657 g cm^{-3}; the crystal data measured on a KUMA CCD diffractometer; λ(MoKα) = 0.71073 Å, 3261 reflections measured, final R = 0.0642 for 1967 independent reflections, GOF = = 1.21; all H atoms located from DeltaF maps.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 222721. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

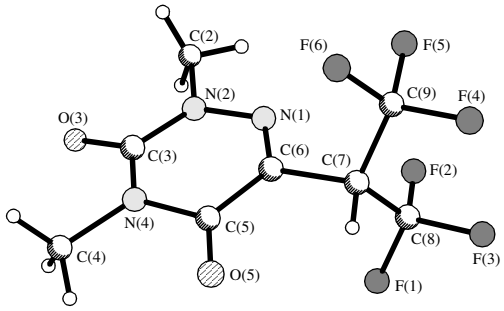


Figure 1 Molecular structure of **3**.

fluorinated product in the reaction carried out in diglyme on the basis of the ^{19}F NMR multiplicity of the test reaction mixture.[¶] Unfortunately, any effort to isolate the compound from the mixture was unsuccessful; moreover, prolonged heating resulted in the complete disappearance of the fluorine signals of **5a**. Compound **3**, as expected, was not detected in the reaction mixture.

In conclusion, the coupling reactions of **1** in DMF carried out with the vinylzinc reagents $CF_2=CF–ZnI$ and $CF_3C(ZnBr)=CF_2$ lead exclusively to fluoroalkenyl and fluoroalkyl derivatives. The electron-withdrawing ability of CF_3 in the internal vinylzinc reagent not only affects its reactivity but also dramatically changes the mechanism of the coupling. On the other hand, having in mind the successful coupling reactions of $CF_3C(ZnBr)=CF_2$ with aryl iodides, we suggest that the structure and reactivity of the reactive complex of **1** should be highly dependent on the electronic nature of the 6-azauracil moiety.

References

1 R. Filler, Y. Kobayashi and L. M. Yagupolskii, *Organofluorine Compounds in Medicinal and Biomedical Applications*, Elsevier, Amsterdam, 1993.
2 D. J. Burton, Zhen-Yu Yang and P. A. Morken, *Tetrahedron*, 1994, **50**, 2993.
3 I. P. Beletskaya, R. S. Sorokina, L. F. Rybakova and I. O. Kalinovskij, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1985, 1647 (*Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1985, **34**, 1506).
4 P. L. Heinze and D. J. Burton, *J. Org. Chem.*, 1988, **53**, 2714.
5 P. A. Morken and D. J. Burton, *J. Org. Chem.*, 1993, **58**, 1167.
6 H. Koroniak, P. Karwatka, D. Pluskota, P. Fiedorow and A. Jankowski, *J. Fluorine Chem*., 1995, **71**, 135.
7 H. Wójtowicz-Rajchel, J. Szczepkowska-Sztolcman, A. Katrusiak and K. Golankiewicz, *Tetrahedron*, 2000, **56**, 5909.
8 J. Szczepkowska-Sztolcman, A. Katrusiak, H. Wójtowicz-Rajchel and K. Golankiewicz, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2549.
9 W. L. Mitchell, P. Ravenscroft, M. L. Hill, L. J. S. Knutsen, B. D. Judkins, R. F. Newton and D. I. C. Scopes, *J. Med. Chem.*, 1986, **29**, 809.
10 T. D. Spawn and D. J. Burton, *Bull. Soc. Chim. Fr.*, 1986, 876.
11 Y. A. Cheburkov and I. L. Knunyantis, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1967, 346 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967, **16**, 328).
12 C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, A. N. Ntepe and L. Ricard, *J. Am. Chem. Soc*., 2003, **125**, 4212.
13 C. Amatore, E. Carre and A. Jutand, *Acta Chem. Scand*., 1998, **52**, 100.

Received: 12th January 2004; Com. 04/2214

[¶] ^{19}F NMR (diglyme/$CDCl_3$) δ: –59.1 (dd, J 18 and 11 Hz), –69.6 (qd, J 18 and 3 Hz), –70.8 (qd, J 11 and 3 Hz).