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Synthesis of dinucleoside pyridylphosphonates involving palladium(0)-catalysed phosphorus–carbon bond formation as a key step

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Dinucleoside 3-pyridylphosphonates, as well as their 2- and 4-pyridyl positional isomers, have been synthesised using a palladium(0)-catalysed cross coupling strategy.

A pyridine ring is found in many natural products, *e.g.* in pyridine alkaloids, vitamins (niacin, pyridoxal), nicotinamide adenine dinucleotide phosphate (NADP), and constitutes a functionality often present in drugs (*e.g.* isoniazid—antitubercular activity; sulfapyridine—antibacterial and antiviral properties; pyrilamine—antihistaminic drug).[1]

These prompted us to develop a synthetic method for incorporation of a pyridine moiety in the form of pyridylphosphonate functionality (Chart 1) into natural product derivatives. Since the position of the phosphonyl group on the pyridine ring may be important for biological activity, all three isomeric compounds of type **1**, **2**, and **3** should be accessible for chemical and biological studies.

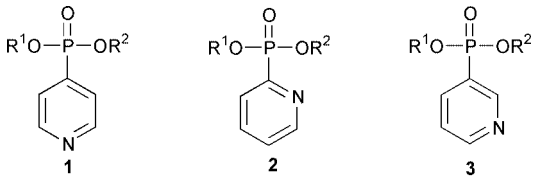


Chart 1

Recently, we have developed efficient and general protocols for the preparation of dinucleoside 2-pyridyl-[2] and 4-pyridylphosphonates[3] but, unfortunately, 3-pyridylphosphonates of type **3** cannot be prepared by these methods.

Introduction of a phosphonyl group into the 3-position of a pyridine ring is rather difficult and the few methods available for this purpose are usually low yielding.[4] Encouraged by the promising results of Hirao *et al.*[5] in the synthesis of diethyl 3-pyridylphosphonate **3**, we have embarked on a more detailed investigation of chemistry and stereochemistry of this palladium(0)-catalysed reaction, as a viable way for preparing dinucleoside pyridylphosphonates **6**–**8**.

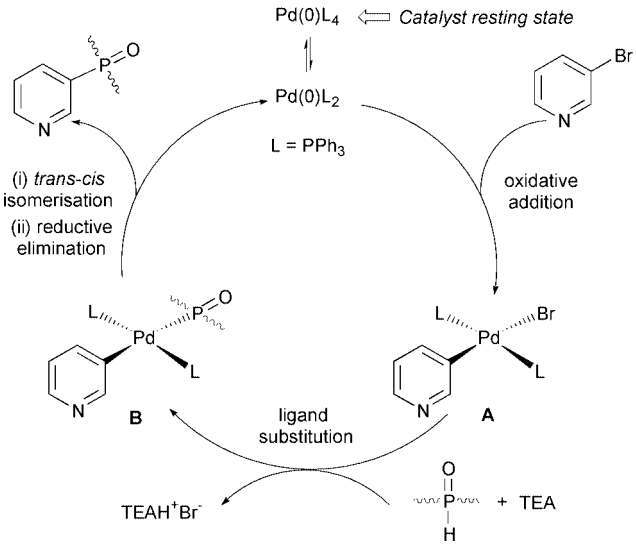
We set out to prepare dinucleoside 3-pyridylphosphonates **6**, for which there was no synthetic method available. This required considerable experimentation to develop the best conditions of solvents and reagents, as well as the nature and quantity of the catalyst. Eventually, the use of equimolar amounts of dinucleoside H-phosphonate **4** and 3-bromopyridine **5a** in the presence of 0.2 equiv. of $Pd(PPh_3)_4$, and 1.2 equiv. of triethylamine (TEA) under reflux in THF, was found to serve most needs.† Using these conditions, a cross coupling of dinucleoside H-phosphonate **4** with 3-bromopyridine **5a** (Scheme 2) in the presence of a base (TEA) catalysed by the added $Pd(PPh_3)_4$ proceeded quantitatively (^{31}P NMR) and afforded the desired 3-pyridylphosphonate derivatives **6** in *ca.* 85% yield.

A palladium(0) catalytic cycle[6] expected for this type of reaction and supported by ^{31}P NMR experiments, is depicted in Scheme 1. It seemed that the most energy demanding step in this cycle was the ligand substitution, *i.e.* the formation of a *trans*-adduct **B** *via* nucleophilic attack of a phosphorus nucleophile on the initial intermediate, *trans*-adduct **A**. Since the only intermediate observed by ^{31}P NMR spectroscopy during the course of the reaction was that of *trans*-adduct **A** [δ_P = 24.2 ppm], the two consecutive steps in which **B** collapsed to the pyridylphosphonate products (see Scheme 1), both had to be fast.‡

To investigate the stereochemical outcome of this palladium(0)-catalysed cross coupling, separate diastereomers of dinucleoside H-phosphonate **4** were subjected to the reaction with 3-bromopyridine **5a** (Scheme 2). We found that the P–C bond formation was completely stereospecific as the R_P diastereomer **4a**, (δ_P = 6.9 ppm) afforded exclusively the diastereomer **6a**, (δ_P = 16.3 ppm), while the S_P diastereomer **4b** (δ_P = 8.6 ppm) produced the other diastereomer of 3-pyridylphosphonate **6b** (δ_P = 17.2 ppm).

To find out if the formation of the P–C bond in this reaction occurred with retention or with inversion of configuration at the phosphorus center in **4**, we decided to synthesise separate diastereomers of dinucleoside 2-pyridylphosphonates **7** and 4-pyridylphosphonates **8** using palladium(0) chemistry and compare them with the same compounds obtained in another way.[2,3]

Dinucleoside 4-pyridylphosphonates **8** were prepared using the protocol developed for 3-pyridylphosphonate **6**, by reacting separate diastereomers of dinucleoside H-phosphonate **4** with



Scheme 1

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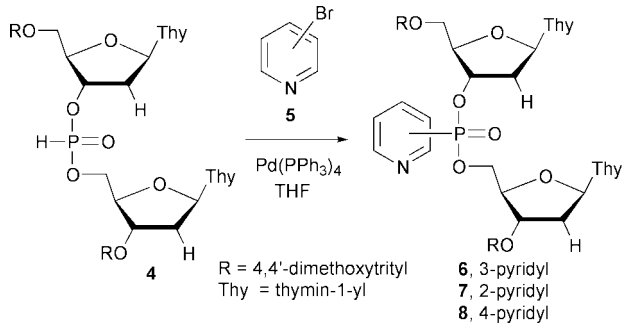

4a, (R_P) ("fast") (δ_P = 6.9 ppm)
4b, (S_P) ("slow") (δ_P = 8.6 ppm)
5a, 3-bromopyridine
5b, 2-bromopyridine
5c, 4-bromopyridine

6a, (R_P) ("fast") (δ_P = 16.3 ppm)
6b, (S_P) ("slow") (δ_P = 17.2 ppm)
7a, (R_P) ("fast") (δ_P = 10.6 ppm)
7b, (S_P) ("slow") (δ_P = 11.0 ppm)
8a, (R_P) ("fast") (δ_P = 15.0 ppm)
8b, (S_P) ("slow") (δ_P = 16.0 ppm)

Scheme 2

4-bromopyridine **5c** in the presence of $Pd(PPh_3)_4$. The reactions were stereospecific and afforded products **8**§ with the same stereochemistry as those formed in the reaction of H-phosphonates **4** with the pyridine–trityl chloride–DBU reagent system.[3] Since the latter provided products **8** most likely with retention of configuration at the phosphorus center,[3] we could tentatively conclude that the palladium(0)-catalysed cross coupling of H-phosphonate **4** with 4-bromopyridine **5c**, and probably also that with 3-bromopyridine **5a**, occurred with the same stereochemistry, *i.e.* with retention of configuration of the phosphorus center of **4**.

Attempted preparation of dinucleoside 2-pyridylphosphonate **7** by a palladium(0)-catalysed coupling of H-phosphonate **4** with 2-bromopyridine **5b**, turned out to be a more difficult task as the protocol developed for the 3-pyridyl isomer **6** afforded the desired product in less than 30% (^{31}P NMR analysis).

Inspired by the recent findings of Hartwig *et al.*[7] that chelating, sterically hindered phosphines are superior (in terms of yields and kinetics) ligands in palladium(0)-catalysed *N*-arylation of amines, we replaced in our catalytic system triphenylphosphine by 1,1′-bis(diphenylphosphino)ferrocene (DPPF). With this modification, the efficiency of 2-pyridylphosphonates **7** formation increased to *ca* 80% (^{31}P NMR analysis) and **7a** and **7b** were isolated in >50% yield.¶‖ By comparing the stereochemistry of 2-pyridylphosphonates **7** formed in this and in a DBU-catalysed reaction,[2] we conclude that both of them provided products with the same stereochemistry at the phosphorus centre. Thus, palladium(0)-catalysed formation of the P–C bond in this instance also most likely occurred with retention of configuration as was found for 3- and 4-pyridylphosphonates **6** and **8**.

It is worth noting that using DPPF in the synthesis of 3-pyridylphosphonates **6** shortened the reaction time from 4 to 2 h.†† Unfortunately, due to separation problems, yields of the isolated products **6** were lower (*ca.* 55%) than those where triphenylphosphine acted as a ligand.

In conclusion, we have developed a new method for the preparation of dinucleoside pyridylphosphonates **6**–**8** based on a palladium(0)-catalysed cross coupling of the corresponding H-phosphonate diesters **4** and halopyridines **5**. The reaction is stereospecific, occurring most likely with retention of configuration and can be considered as a general entry to isomeric pyridylphosphonate derivatives.

We are indebted to Professor P. J. Garegg for his interest in this work. Financial support from the Swedish Natural Science Research Council and the Swedish Foundation for Strategic Research is gratefully acknowledged

Notes and references

† *Typical protocol for the preparation of dinucleoside 3-pyridylphosphonates* **6**. Dry, degassed (argon) THF was used throughout and the reactions were carried out under an atmosphere of argon. A separate diastereomer **4a** or **4b**, (0.529 mmol), $Pd(PPh_3)_4$ (0.20 equiv.), triethylamine (1.2 equiv.) and 3-bromopyridine (1.0–1.2 equiv.) in freshly distilled and degassed THF (10 mL) was refluxed for 4–5 h. After concentration and partition of the reaction mixture between sat. aq. $NaHCO_3$ and CH_2Cl_2, the product was purified by silica gel column chromatography using a stepwise gradient of methanol (0.5–5%) in CH_2Cl_2 containing 0.1% TEA. White solids, purity >98% (^{1}H NMR). **6a** (85% from **4a**, probably R_P diastereomer). HRMS [M + H]$^+$, found 1212.4376. $C_{67}H_{67}N_5O_{15}P$ requires 1212.4371. **6b** (80% from **4b**, probably S_P diastereomer). HRMS [M + H]$^+$, found 1212.4373. $C_{67}H_{67}N_5O_{15}P$ requires 1212.4371. Some diagnostic spectral data (in $CDCl_3$) [compound, δP; δH(H-2 py); δH1′; δC(C-3 py) (J_{CP})]: **6a**, 16.3 ppm; 8.42–8.75 ppm (with pyr-H6, 2H); 6.38 (1H) & 6.26 (1H) ppm; 123.68 ppm (190 Hz). **6b**, 17.2 ppm; 8.86 ppm (1H); 6.39 (1H) & 6.20 (1H) ppm; 123.61 ppm (189 Hz).

‡ The same course of the reaction was observed when H-phosphonate **4** was allowed to react with a separately prepared intermediate **A**[8] in THF under reflux in the presence of TEA.

§ Compounds **8a** (from **4a**, 66% yield) and **8b** (from **4b**, 69% yield) were identical to those obtained in another way.[3] White solids, purity >98% (^{1}H NMR).

¶ The reaction was carried out as described above for 3-pyridylphosphonates **6**, with the exception that $Pd(PPh_3)_4$ was replaced by 0.2 equiv. of $Pd(OAc)_2$ and 0.4 equiv. of DPPF. Compounds **7a** (from **4a**, 54% yield) and **7b** (from **4b**, 51% yield) were identical to those obtained in another way.[2]

‖ The stereochemical course of the reaction was the same as that with $Pd(PPh_3)_4$. In contradistinction to DPPF, conformationally more flexible 1,3-bis(diphenylphosphino)propane (DPPP) was found to be unreactive, which may indicate the importance of rigidity of the ligand in this reaction.

†† With chelating ligands such as DPPF, oxidative addition (Scheme 1) results in the formation of *cis*- rather than *trans*-adducts (of type **A**). This may change geometry and electron distribution in the adduct and facilitate substitution of bromide by a phosphorus nucleophile, which was assumed to be the rate-determining step for the catalytic cycle.

1 *The Merck Index*, Merck & Co, Inc., Rahway, NJ, 1989.
2 T. Johansson, A. Kers and J. Stawinski, *Tetrahedron Lett.*, 2001, **42**, 2217.
3 A. Kers and J. Stawinski, *Tetrahedron Lett.*, 1999, **40**, 4263.
4 R. D. Bennett, A. Burger and W. A. Volk, *J. Org. Chem.*, 1958, **23**, 940.
5 T. Hirao, T. Masunaga, Y. Ohshiro and T. Agawa, *Synthesis*, 1981, 56.
6 C. Amatore and A. Jutand, *Acc. Chem. Res.*, 2000, **33**, 314.
7 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7217.
8 P. Fitton and E. A. Rick, *J. Organomet. Chem.*, 1971, **28**, 287.