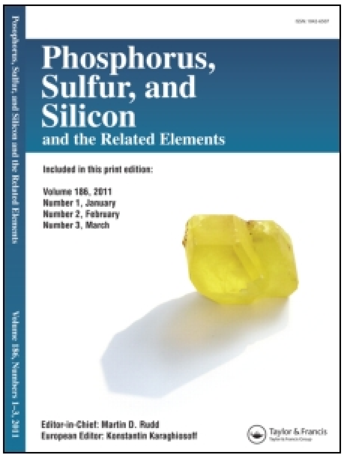


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

NOVEL OBSERVATION ON BASE-CATALYZED BENZOYLATION OF DIALKYL PHOSPHORANILIDATES

Janina Baraniak[a]; Wojciech J. Stec[a]
[a] Department of Bioorganic Chemistry, Lodz, Poland

To cite this Article Baraniak, Janina and Stec, Wojciech J.(1987) 'NOVEL OBSERVATION ON BASE-CATALYZED BENZOYLATION OF DIALKYL PHOSPHORANILIDATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 29: 1, 115 — 119

To link to this Article: DOI: 10.1080/03086648708072845

URL: http://dx.doi.org/10.1080/03086648708072845

Phosphorus and Sulfur, 1986, Vol. 29, pp. 115–119
0308-664X/86/2901-0115/$10.00/0

COMMUNICATION

Novel Observation on Base-Catalyzed Benzoylation of Dialkyl Phosphoranilidates

JANINA BARANIAK and WOJCIECH J. STEC*

Polish Academy of Sciences, Centre of Molecular and Macromolecular Studies, Department of Bioorganic Chemistry, 90-362 Lodz, Boczna 5, Poland

(*Received January 15, 1986*)

N-Benzoylated dialkyl phosphoranilidates undergo stereoretentive rearrangement to (*N*-phenylimino) benzylidynoxy derivatives. These derivatives hydrolyse in pyridine exclusively via attack by water at *N*-phenylimino carbon.

We previously reported that the reaction of adenosine 3′,5′-cyclic phosphoranilidate (diastereomeric ratio Rp : Sp = 5:7) with benzoyl chloride, performed in pyridine, followed by aqueous work-up of the reaction mixture, yields the expected $N^6,N^6,O^{2\prime}$-tribenzoyladenosine cyclic 3′,5′-phosphoranilidate, but the yield of this desired product was moderate only and the overall process was accompanied by the dramatic change of diastereomeric composition (ratio Rp : Sp = 10:1).[1] $N^6,N^6,O^{2\prime}$-Tribenzoyladenosine 3′,5′-cyclic phosphate was isolated as a preponderant but unexpected product. The latter observation indicated, that aroylation of the phosphoranilidate functional group predominates over N^6- and $O^{2\prime}$-benzoylation.

To elucidate the mechanism responsible for the poor yield of key-intermediates for the preparation of diastereomers of cAMPS[2] and $|^{18}O|$cAMP,[3] we undertook model studies on the reaction of diastereomeric 2-*N*-phenylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes (**1**)[4] with benzoyl chloride in pyridine solvent. The reaction progress was followed by ^{31}P NMR. Thus, the spectra of the reaction mixture of *trans*-**1**[5] (1 mmole) with benzoyl chloride (5 mmole) in pyridine (1.5 ml) have shown the slow disappearance of the signal at −1.1 ppm corresponding to substrate *trans*-**1** and the appearance of two new signals: at −7.8 ppm and −17.2 ppm. A similar picture was obtained if *cis*-**1** ($\delta\ {}_{^{31}P(C_5H_5N)}$ = −5.4 ppm) was used as the substrate. Figure 1 shows the reaction dynamics for both diastereomers.

An inspection of figure 1 clearly indicates that reactivity was lower for *cis*-**1** and that compounds absorbing at −7.8 ppm and −11.1 ppm, respectively, presented transient intermediates undergoing transformation to final products absorbing at −17.2 ppm.[6,7]

Our working hypothesis included *N*- and *O*-benzoylation in both *cis*- and *trans*-**1**, leading to the corresponding *cis*- and *trans*-**2** and **3**, respectively.

To check this hypothesis we prepared *cis*-$|^{15}N|$-**1** (isotopic enrichment 50%, ${}^1J_{^{31}P-^{15}N}$ 34 Hz) and treated it with benzoyl chloride in pyridine medium. ^{31}P NMR spectrum of resulting reaction mixture, recorded after 2 hr revealed an overlapped

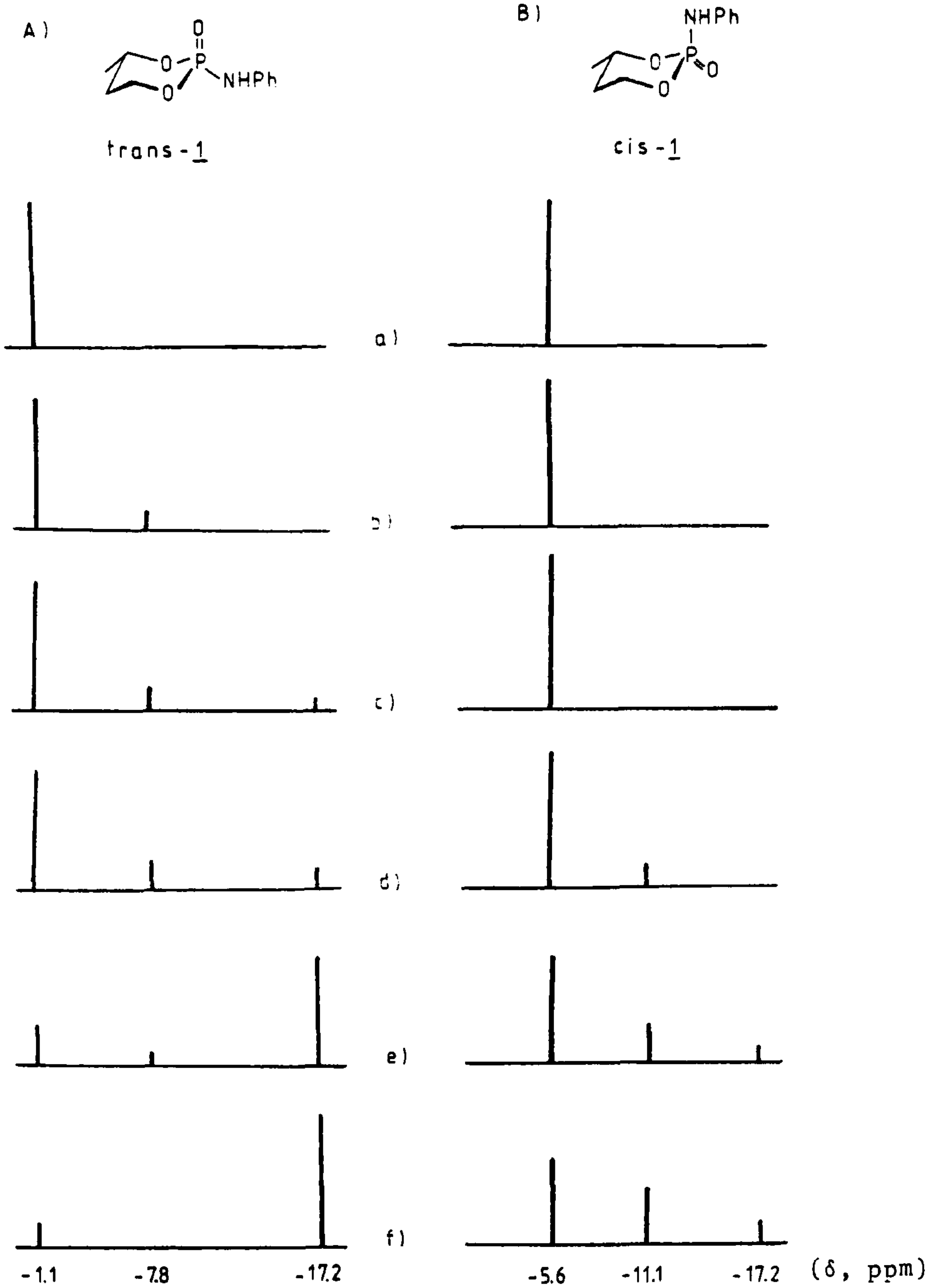
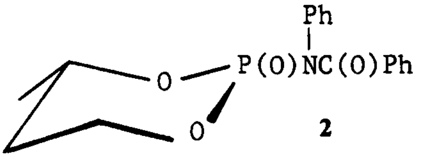
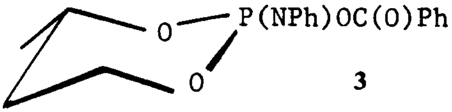


FIGURE 1. Schematic representation of ^{31}P NMR spectra of the reaction mixtures of pyridine solutions of A) *trans*-**1** and B) *cis*-**1** with benzoyl chloride, recorded: a) immediately after mixing of both components, b) after 0.5 hr of standing at room temperature, c) after 1 hr, d) after 2 hr, e) after 24 hr, h) after 48 hr.



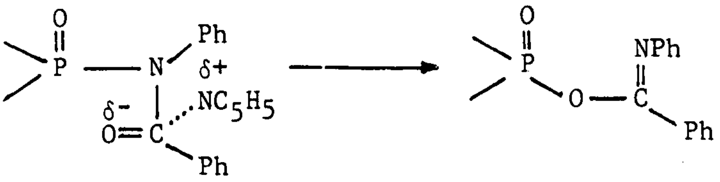
2



3

singlet and doublet centered at −11.1 ppm, with coupling constant of doublet $^1J_{^{31}P-^{15}N}$ 28 Hz. The slow disappearance of the signal at −11.1 ppm (see Figure 1) accompanied an increase in the −17.2 ppm signal. The −17.2 ppm resonance did not exhibit splitting resulting from the direct $^{31}P-^{15}N$ spin–spin interactions. The NMR results were crucial for assigning the structure *cis*-**2** for the species absorbing at −11.1 ppm (for *N*-benzoylated species derived from *trans*-**1** $\delta_{^{31}P(C_5H_5N)}$ − 7.8 ppm) and excluded the structure **3** for species absorbing at −17.2 ppm. Structure **3** derived from |^{15}N|-**1** should feature the doublet due to spin-spin interaction between directly bonded ^{31}P and ^{15}N.[8]

As an alternative structure for compound(s) absorbing at −17.2 ppm[7] we considered species **4** that may result from pyridine-catalysed rearrangement of **2** → **4** according to the mechanism common for Horner–Wadsworth–Emmons type reaction[9].



2 **4**

Compound of structure **4** should possess a ^{31}P NMR signal at ca. −15 ppm[10] like other anhydrides involving dialkyl phosphate group. Also the $^3J_{POC^{15}N}$ value should be negligible and the hydrolysis of compound of structure **4** should yield dialkyl phosphate via nucleophilic attack on either phosphorus or carbon.

To elucidate the structure of compound(s) absorbing at −17.2 ppm we treated **1** (1 mmole) with benzoyl chloride (5 mmoles) in pyridine (1.5 ml) and hydrolyzed the resulting products at 0°C with |^{18}O|H_2O (8 mmoles). The reaction mixture resulting from 48 hr exposure of *trans*-**1** on benzoyl chloride (signals at −1.1 ppm and −17.2 ppm) was treated with |^{18}O|H_2O (70% isotopic enrichment). The ^{31}P NMR spectrum of the reaction mixture showed the complete disappearance of the −17.2 ppm signal and showed only signals at −1.1 ppm (unchanged *trans*-**1**) and at −3.83 ppm characteristic for 2-hydroxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**5**). Isolation of both compounds and their mass-spectrometric examination had confirmed the structures of **1** and **5** and also indicated that compound **5** (analyzed after its *O*-benzylation[3]) did not contain any oxygen-18.

In a parallel experiment, *cis*-**1** was treated with benzoyl chloride in pyridine and the reaction mixture, including **1** and two products absorbing in ^{31}P NMR spectrum at −11.1 ppm and −17.2 ppm (intensities ratio 4:1) was hydrolyzed with |^{18}O|H_2O.

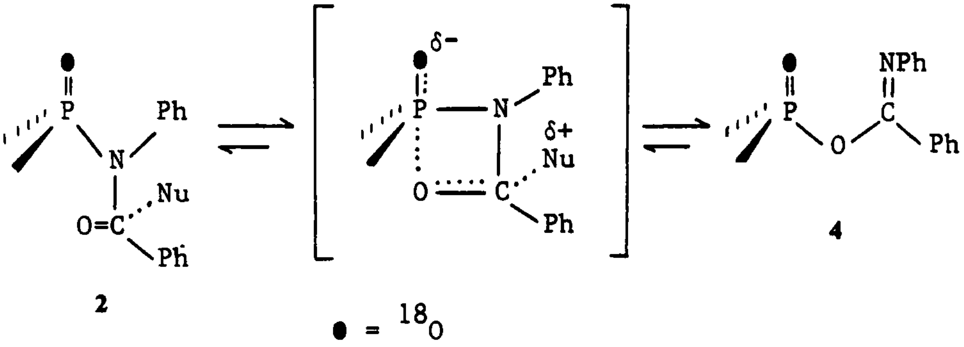
^{31}P NMR examination did show the disappearance of both signals at −11.1 ppm and −17.2 ppm. The isolated **5**, again, did not contain any oxygen-18. The lack of ^{18}O incorporation indicated that hydrolysis of **4** must occur via nucleophilic attack of water at *N*-phenylimino carbon.

However, these experiments did not allow us to draw any conclusions about stereochemistry of **2** → **4** rearrangement. Because the literature indicates that *N*-acylated phosphoramidates undergo neutral or acid-catalyzed hydrolysis with an attack of water at phosphoryl centre[11] the lack of incorporation of oxygen-18 in **5** resulting from hydrolysis of mixture *cis*-**2** and **4** was unexpected and required further elucidation.

Reaction of *trans*-1 with benzoyl chloride in pyridine was quenched with $|^{18}O|H_2O$ at the point, when ^{31}P NMR assay showed the presence of unchanged **1** and **2** ($\delta_{^{31}P(C_5H_5N)}$ −7.8 ppm) only. The isolated **5** was benzylated with phenyldiazomethane[12] and mass-spectral analysis had confirmed the lack of incorporation of oxygen-18 in **5**. An analogues experiment with *trans*-2-phenylamino-2-$|^{18}O|$ oxo-4-methyl-1,3,2-dioxaphosphorinane ($|^{18}O|$-**1**, 58% of oxygen-18 at phosphoryl terminal position) and hydrolysis of reaction mixture containing **1** and **2** only ($\delta_{^{31}P(C_5H_5N)}$ −1.1 ppm and −7.8 ppm) with H_2O, followed by isolation of **5**, its conversion to the mixture of *cis*- and *trans*-2-benzyloxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (**6**) according to published procedure[3] had indicated, that overall conversion **1** → **5** occurred with retention of isotope content and retention of configuration at phosphorus.

In summary we conclude that:

1. Benzoylation of dialkyl phosphoranilidates with benzoyl chloride in pyridine occurs with formation of dialkyl *N*-benzoyl phosphoranilidate, structure **2** (kinetic product). No reaction leading to *O*-benzoylated product of structure **3** occurs.
2. Compound **2** slowly isomerises into the thermodynamically more stable **4**. Hydrolysis of **4** in pyridine occurs with exclusive attack of water molecule on carbon atom of N-phenylimino group with formation of benzanilide and dialkyl phosphate (**5**, pyridinium salt).
3. Rearrangement **2** → **4**, most probably catalyzed by pyridine, is facilitated by water and occurs with retention of configuration at phosphorus (Scheme 1).



SCHEME 1

4. An equilibrium **2** ⇌ **4** depends on reaction medium as proved by results of attempted hydrolysis of **2**. Compound of structure **2** does not undergo hydrolysis in pyridine as a reaction medium prior rearrangement to **4**.
5. Under analogous conditions benzoylation of cyclic phosphoranilidate *trans*-**1** occurs more readily than that of *cis*-**1**. Also the product **2** resulting from benzoylation of *trans*-**1** undergoes isomerisation to *trans*-**4** more readily than rearrangement of *cis*-**2** to *cis*-**4**. These facts can be rationalized on the basis of steric hindrance accompanying these reactions if the *N*-phenylamino group occupies an axial position in 1,3,2-dioxaphosphorinanyl ring system.

The results obtained in presented studies illuminate the reactivity of dialkyl phosphoramidates towards acylating reagents[13] and demonstrate the different course of acylation of dialkyl phosphoramidates as compared with their alkylation.[14] They also demonstrate the different course of events accompanying the pyridine-catalyzed hydrolysis of N-benzoylated dialkyl phosphoramidates as compared with their acid- or neutral hydrolysis.[11] Moreover these results confirm the formerly observed diastereoselectivity of benzoylation of adenosine 3′,5′-cyclic phosphoranilidates and the course of events responsible for the formation of undesired $N^6,N^6,O^{2'}$-tribenzoyladenosine 3′,5′-cyclic phosphate.[1]

REFERENCES AND NOTES

1. J. Baraniak, K. Lesiak, W. J. Stec, Pol. J. Chem., **53**, 1387 (1978).
2. J. Baraniak, R. W. Kinas, K. Lesiak, W. J. Stec, J. Chem. Soc., Chem. Commun., 940, 1979.
3. J. Baraniak, K. Lesiak, M. Sochacki, W. J. Stec, J. Am. Chem. Soc., 4533 (1980) **102**.
4. W. J. Stec, A. Lopusinski, Tetrahedron, **29**, 547 (1973).
5. The term *cis* refers to diequatorial positions of 4-methyl and the senior exocyclic group on phosphorus, as determined by the sequence rule, while *trans* refers to equatorial -axial relationship between these two groups: J. Org. Chem., **35**, 2849 (1970).
6. ^{31}P NMR spectra were recorded on Jeol JNM FX-60 (24.2 MHz) instruments. Negative values were assigned for compounds absorbing upfield from 85% H_3PO_4.
7. The reaction of diastereomeric mixture of 2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes with sodium and benzanilide led to the mixture of products absorbing in ^{31}P NMR at −7.9 ppm, −11.8 ppm, −17.8 ppm, which proves that under applied spectroscopic conditions[6] diastereomers of **4** are indistinguishable.
8. G. J. Martin, M. Sanches, M.-R. Marre, Tetrahedron Lett., **24**, 4989 (1983).
9. N-dialkylphosphoryl *N*,N′-dialkyl(aryl)-ureas and -thioureas undergo base-catalyzed transformations into corresponding carbodiimides with concomitant formation of dialkyl phosphates or phosphorothioates, respectively (M. Mikolajczyk–personal communication).
10. S. Chandrasegaran, A. Murakami, L. Kan, J. Org. Chem., **49**, 4951 (1984); W. Dabkowski, J. Michalski, Z. Skrzypczynski, Chem. Ber., **118**, 1809 (1985).
11. V. Mizrahi, T. A. Modro, J. Org. Chem., **48**, 3030 (1983).
12. D. M. Brown, D. I. Magrath, A. R. Todd, J. Chem. Soc., 4396 (1955).
13. R. S. Edmundson, T. A. Moran, J. Chem. Soc.C., 3437 (1971).
14. B. C. Challis, J. A. Challis, J. Chem. Soc. Perkin II, 813 (1978).