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## LETTERS TO THE EDITOR

*Dedicated to the 115th anniversary of B.A. Arbuzov's birth*

# Phosphorylation of Betti Base with Bis(diethylamino)phosphoryl Chloride

**K. E. Metlushka[a], D. N. Sadkova[a], K. A. Nikitina[a], Z. R. Yamaleeva[a], K. A. Ivshin[a,b], O. N. Kataeva[a], and V. A. Alfonsov[a]***

[a] *A.E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, ul. Akademika Arbuzova 8, Kazan, Tatarstan, 420088 Russia*
**e-mail: alfonsov@yandex.ru*

[b] *Butlerov Chemical Institute, Kazan (Volga Region) Federal University, Kazan, Tatarstan, Russia*

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**Abstract**—The reaction of bis(diethylamino)phosphoryl chloride with *N*-Boc-protected 1-(α-aminobenzyl)-2-naphthol (Betti base) proceeded via *O*-phosphorylation of the phenolic OH group to form the target product as trifluoroacetate salt. The latter reacted with *O*,*O*-diethyl thiophosphorylisothiocyanate to give thiourea bearing a chiral Betti base fragment.

**Keywords:** Betti base, phosphorylation, thiourea

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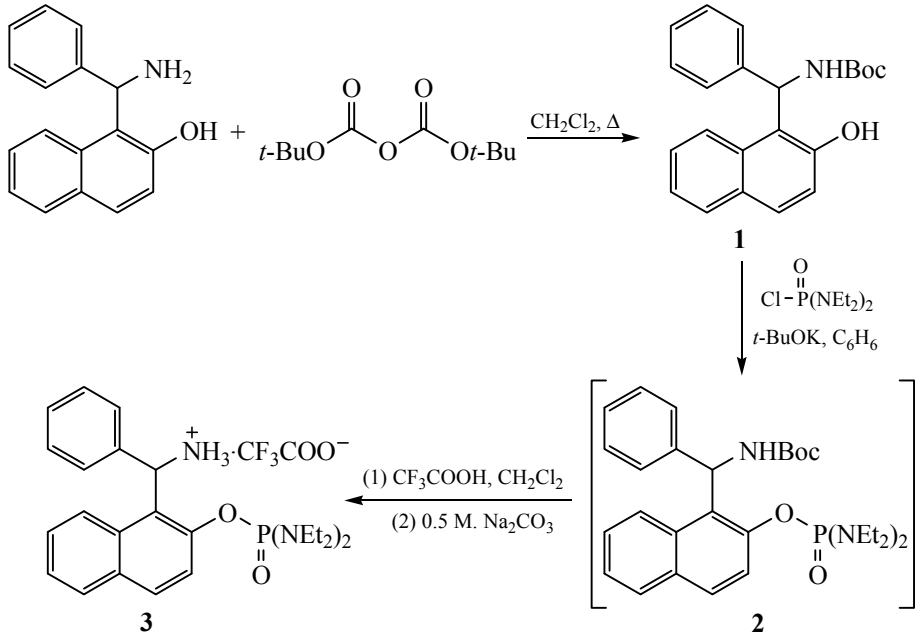
Chiral organophosphorus compounds are widely used in modern asymmetric synthesis both as organocatalysts or chiral ligands, and as building blocks for the production of biologically active substances [1–5]. In this regard, the search for methods for synthesizing new specimens of this class of compounds is an urgent task.

In continuation of our work on the study of the possibility of phosphorylation of the Betti base and its derivatives [6–9] with the aim of further application in the asymmetric synthesis of phosphorus compounds, we chose bis(diethylamino)phosphoryl chloride as the phosphorylating agent. The introduction of additional active groups into the chiral Betti base molecule increases its functionality. In particular, the bis (diethylamino)phosphoryl group having pronounced basic properties can provide the molecule with additional activity when binding proton donors.

Direct phosphorylation of the Betti base is difficult due to the presence of two active nucleophilic proton-containing centers in the 1-(α-aminobenzyl)-2-naphthol molecule that can compete in reaction with electrophilic phosphorylating agents [7]. For selective *O*-phosphorylation, we carried out preliminary Boc-protection of the amino group of the Betti base by reacting with di-*tert*-butyl dicarbonate (Scheme 1). As a result, the product **1** was obtained, which reacted with tetraethyl diamidochlorophosphate in the presence of potassium *tert*-butylate to form compound **2** ($\delta_P$ = 13.68 ppm, Scheme 1). To remove the Boc-protecting group, compound **2** without isolation was treated with trifluoroacetic acid to form trifluoroacetate **3**.

It should be noted that the free base cannot be isolated from the salt with trifluoroacetic acid even when treated with an aqueous solution of sodium carbonate. In the IR spectrum of **3**, the absorption band at 1686 $cm^{-1}$ characteristic of the trifluoroacetate anion and the broad band of the ammonium group at 2933 $cm^{-1}$ are retained. The reason for the high stability of compound **3** with respect to an aqueous solution of sodium carbonate was made clear by studying its structure by X-ray diffraction method (Fig. 1). It can be seen from the obtained data that all three protons of the ammonium group form strong hydrogen bonds: two with trifluoroacetic acid anions, and the third with strongly basic phosphoryl oxygen of

**Scheme 1.**




the neighboring molecule. In this case, structure of the hydrogen-bonded dimer is realized.

The $^{1}H$, $^{31}P$ NMR and mass spectrometry data confirm also the proposed structure of compound **3**.

It is interesting to note that for carrying out the reaction of salt **3** with *O*,*O*-diethyl phosphorylisothiocyanate, it is not necessary to isolate the free base. The reaction readily proceeded with trifluoroacetate **3** to form compound **4**, which is a double phosphorylated thiourea containing a chiral Betti base fragment (Scheme 2). Structure of compound **4** was established using IR, NMR spectroscopy, mass spectrometry and X-ray diffraction data (Fig. 2).

In summary, we obtained new products of the Betti base phosphorylation, promising polyfunctional polydentate chiral derivatives.

*tert*-Butyl (2-hydroxynaphth-1-yl)(phenyl)methylcarbamate **1** was synthesized according to the method described in [7].

**[2-(Tetraethyldiamidophosphoryloxy)naphth-1-yl](phenyl)methylammonium trifluoroacetate (3).** A

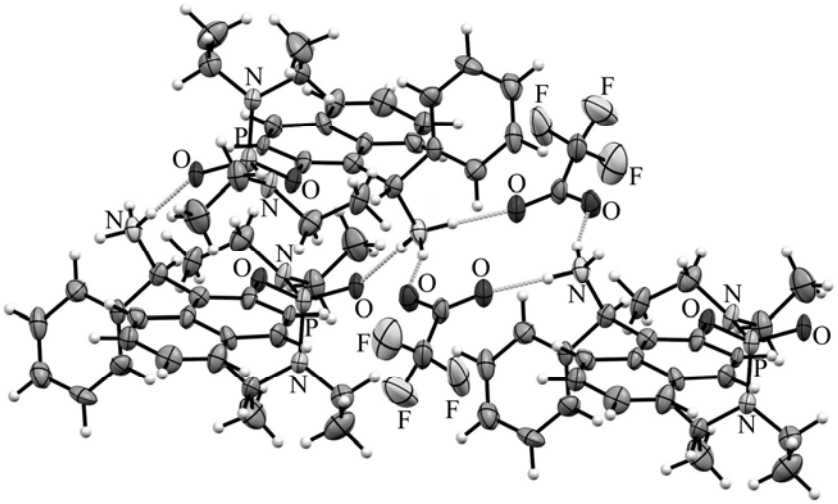
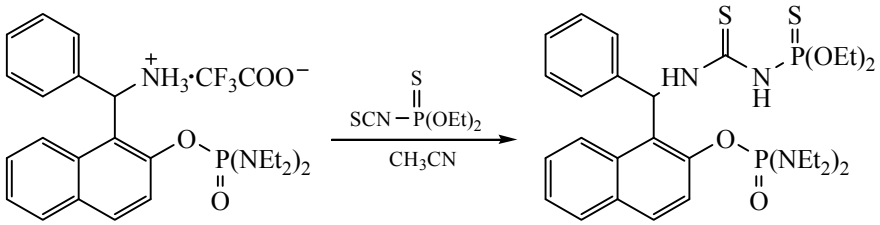


**Fig. 1.** A fragment of the crystal packing of compound **3**. Intermolecular hydrogen bonds are marked by a dotted line.

**Scheme 2.**




**3** **4**

mixture of 15 mL of anhydrous benzene, 0.6 g (1.72 mmol) of compound **1**, and 0.21 g (1.89 mmol) of potassium *t*-butoxide was stirred for 30 min, and then cooled to 5°C. A solution of 0.41 g (1.81 mmol) of bis(diethylamino)phosphoryl chloride in 2 mL of anhydrous benzene was added. The resulting mixture was kept at room temperature in an argon atmosphere for 24 h, then the precipitate was filtered off. The solvent was removed at a reduced pressure. A mixture of 3 mL of trifluoroacetic acid and 6 mL of methylene chloride was added to the residue. After stirring for 1.5 h at room temperature, the volatiles were removed at a reduced pressure. The residue was dissolved in 10 mL of methylene chloride, and 10 mL of 0.5 M. aqueous solution of sodium carbonate was added. The resulting mixture was stirred for 1 h at room temperature, then the organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 5 mL). The organic layers were combined and dried with $Na_2SO_4$. The solvent was removed at a reduced pressure, and the residue was crystallized from acetonitrile. Yield 0.64 g (67.4%), mp 198–199°C ($CH_3CN$). IR spectrum, ν, $cm^{-1}$: 1225 s (P=O), 1599 w (C=$C_{Ar}$), 1628 w (C=$C_{Ar}$), 1686 s (C=O), 2933 br ($NH_3^+$). $^1H$ NMR spectrum, δ, ppm: 1.03 t and 1.07 t (12H, $NCH_2C\underline{H}_3$, $^3J_{HH}$ = 7.1 Hz), 2.88–3.21 m (8H, $NC\underline{H}_2CH_3$), 6.65 s (1H, PhCH), 7.25–7.41 m (8H, $H_{Ar}$), 7.84–8.01 m (3H, $H_{Ar}$). $^{31}P$ NMR spectrum: $\delta_P$ 15.08 ppm. Mass spectrum ($ESI^+$), *m*/*z*: 367.3 $[M - NEt_2]^+$, 440.2 $[M + H]^+$, 879.5 $[2M + H]^+$. Found, %: C 58.75; H 6.56; N 7.40; P 5.43. $C_{27}H_{35}F_3N_3O_4P$. Calculated, %: C 58.58; H 6.37; N 7.59; P 5.60.

**1-[(2-Tetraethyldiamidothiophosphatoxynaphth-1-yl)methyl]-3-(*O*,*O*-diethylthiophosphoryl)thiourea (4).** To a solution of 0.39 g (0.7 mmol) of compound **3** in 12 mL of $CH_3CN$, a solution of 0.163 g (0.77 mmol) of *O*,*O*-diethyl thiophosphorylisothio-cyanate in 3 mL of $CH_3CN$ was added at room temperature. The mixture was stirred at room tem-perature for 4 h, and then kept for 1 day at 10°C. The crystals were filtered off, washed with cold aceto-nitrile, and dried in a vacuum. Yield 0.32 g (69.8%), mp 164–166°C ($CH_3CN$). IR spectrum, ν, $cm^{-1}$: 1007 s (P–O–$C_{Alk}$), 1026 s (P–O–$C_{Alk}$), 1243 s (P=O), 1350 s (S=C–NH), 1546 s (S=C–NH), 1598 w (C=$C_{Ar}$), 1625 w (C=$C_{Ar}$), 3080 br (NH). $^1H$ NMR spectrum, δ, ppm: 0.78 t and 1.32 t (6H, $OCH_2C\underline{H}_3$, $^3J_{HH}$ = 7.1 Hz), 1.04 t and 1.08 t (12H, $NCH_2C\underline{H}_3$, $^3J_{HH}$ = 7.1 Hz), 3.04–3.32 m (8H, $NC\underline{H}_2CH_3$), 3.85–3.93 m (2H, $OC\underline{H}_2CH_3$, $H_A$), 4.11–4.19 m (2H, $OC\underline{H}_2CH_3$, $H_B$), 7.08 d (1H, NH, $^3J_{HP}$ = 13.4 Hz), 7.21–8.06 m (12H, PhCH + $H_{Ar}$), 8.84 br. s (1H, NH). $^{31}P$ NMR spectrum, $\delta_P$, ppm: 14.27, 56.83. Mass spectrum ($ESI^+$), *m*/*z*: 651.3 $[M + H]^+$, 1323.4 $[2M + Na]^+$. Found, %: C 55.52; H 6.61; N 8.42; P 9.40; S 9.87. $C_{30}H_{44}N_4O_4P_2S_2$. Calculated, %: 55.37; H 6.81; N 8.61; P 9.52; S 9.85.

$^{31}P$ NMR spectra were recorded on a Bruker Avance-400 instrument (161.98 MHz), relative to the external standard (85% $H_3PO_4$). $^1H$ NMR spectra were recorded on a Bruker Avance-400 instrument (400.13 MHz) relative to the signals of residual protons of $CDCl_3$. IR spectra were recorded on a Bruker Tensor 27 spectrometer from KBr pellets. Mass spectrometry was performed on an AmazonX instrument. Melting points were measured on a Boetius melting point microscope.

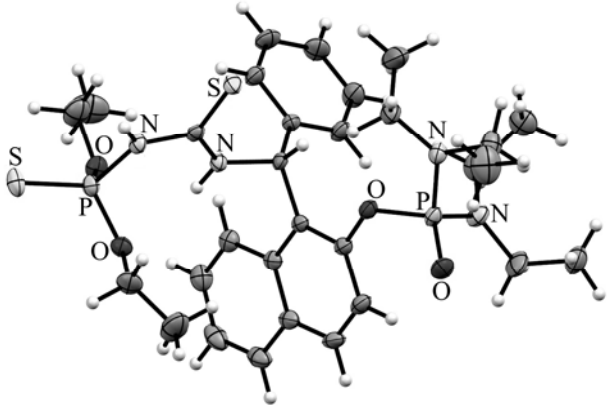



**Fig. 2.** General view of the molecule of compound **4** in the crystal.

**X-Ray diffraction study** of the crystals of compounds **3** and **4** was carried out on a Bruker AXS Kappa APEX Duo diffractometer with Mo$K_\alpha$-radiation ($\lambda$ = 0.71073 Å) at 150(2) K using APEX3 [10] and SAINT [11] programs. The absorption correction was taken into account using SADABS software [12]. Structure was solved and refined using the least squares method using SHELXS97 [13] and SHELXL-2014 [13] programs.

The crystals of compounds **3** are monoclinic, $C_{27}H_{35}F_3N_3O_4P$, 0.036 × 0.051 × 0.224 mm$^3$, $M$ = 553.55 g/mol, space group P$2_1/n$, $Z$ = 4, $a$ = 13.073(6) Å, $b$ = 11.834(6) Å, $c$ = 17.792(8) Å, $\beta$ = 92.536(9)°, $V$ = 2750(2) Å$^3$, $d_{calc}$ = 1.337 g/cm$^3$, $\mu$ = 0.158 mm$^{-1}$, 28051 reflection were measured ($-16 \le h \le 16$, $-14 \le k \le 14$, $-21 \le l \le 21$), in the range of $\theta$ from 1.89° to 26.00°, 5392 independent ($R_{int}$ = 0.5393) and 1540 observed reflections [$I > 2\sigma(I)$] were measured, 357 refinement parameters, $R_1$ = 0.1051, $wR^2$ = 0.1671. The maximum and minimum residual electron density peaks are 0.307 and –0.353 $e$/Å$^3$.

The crystals of compounds **4** are triclinic $C_{30}H_{44}N_4O_4P_2S_2$, 0.101 × 0.211 × 0.315 mm$^3$, $M$ = 650.75 g/mol, space group $P$-1, $Z$ = 2, $a$ = 8.6379(8) Å, $b$ = 11.6272(11) Å, $c$ = 17.4633(17) Å, $\alpha$ = 79.662(2)°, $\beta$ = 87.055(2)°, $\gamma$ = 80.189(2)°, $V$ = 1699.8(2) Å$^3$, $d_{calc}$ = 1.271 g/cm$^3$, $\mu$ = 0.290 mm$^{-1}$, 25861 reflection were measured ($-11 \le h \le 11$, $-15 \le k \le 15$, $-22 \le l \le 23$), in the range of $\theta$ from 1.80° to 28.00°, 8132 independent ($R_{int}$ = 0.0454) and 6320 observed reflections [$I > 2\sigma(I)$] were measured, 393 refinement parameters, $R_1$ = 0.0444, $wR^2$ = 0.1039. The maximum and minimum residual electron density peaks are 0.665 and –0.352 $e$/Å$^3$.

The crystallographic data obtained were deposited in Cambridge Crystallographic Data Center [CCDC 1849405 (**3**), 1849404 (**4**)].

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## CONFLICT OF INTERESTS

No conflict of interests was declared by the authors.

## REFERENCES

1. Zhang, J. and Li, W., *Chem. Soc. Rev*., 2016, vol. 45, p. 1657. doi 10.1039/c5cs00469a
2. Chen, X.-S., Hou, C.-J., and Hu, X.-P., *Synth. Commun*., 2016, vol. 46, no. 11, p. 917. doi 10.1080/00397911.2016.1171362
3. Terada, M., *Synthesis*, 2010, no. 12, p. 1929. doi 10.1055/s-0029-1218801
4. *Amino Acids, Peptides and Proteins in Organic Chemistry*, Hughes, A.B., Ed., Weinheim: Wiley-VCH Verlag GmbH, 2009, vol. 2, p. 189.
5. Mikolajczyk, M. and Balczewski, P., *Top. Curr. Chem*., 2003, vol. 223, p. 161. doi 10.1007/3-540-46100-0
6. Nikitina, K.A., Metlushka, K.E., Sadkova, D.N., Shaimardanova, L.N., and Alfonsov, V.A., *Mendeleev Commun*., 2016, vol. 26, p. 395. doi 10.1016/j.mencom.2016.09.009
7. Metlushka, K.E., Sadkova, D.N., Nikitina, K.A., Shaimardanova, L.N., Kataeva, O.N., and Alfonsov, V.A., *Russ. J. Gen. Chem*., 2016, vol. 86, no. 3, p. 515. doi 10.1134/S107036321603004X
8. Metlushka, K.E., Sadkova, D.N., Shaimardanova, L.N., Nikitina, K.A., Tufatullin, A.I., Kataeva, O.N., and Alfonsov V.A., *Russ. Chem. Bull*., 2014, no. 6, p. 1390. doi 10.1007/s11172-014-0608-5
9. Metlushka, K.E., Kashemirov, B.A., Zheltukhin, V.F., Sadkova, D.N., Büchner, B., Hess, C., Kataeva, O.N., McKenna, Ch.E., and Alfonsov, V.A., *Chem. Eur. J*., 2009, vol. 15, no. 27, p. 6718. doi 10.1002/chem.200802540
10. *Bruker*. APEX3 Crystallography Software Suite, Bruker AXS, Inc., Madison, USA, 2016.
11. *Bruker*. SAINT. Crystallography Software Suite, Bruker AXS, Inc., Madison, USA, 2016.
12. Krause, L., Herbst-Irmer, R., Sheldrick, G.M., and Stalke, D., *J. Appl. Crystallogr*., 2015, vol. 48, p. 3. doi 10.1107/S1600576714022985
13. Sheldrick, G.M., *Acta Crystallogr. (A)*, 2008, vol. 64, no. 1, p. 112. doi 10.1107/S0108767307043930