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# Electrophilic substitution as a convenient approach to functionalized *N*-benzyl-1,4-dihydropyridines

Aleksandr N. Kostyuk,* Dmitriy M. Volochnyuk, Larisa N. Lupiha, Aleksandr M. Pinchuk and Andrei A. Tolmachev

*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya 5, 02094 Kyiv-94, Ukraine*

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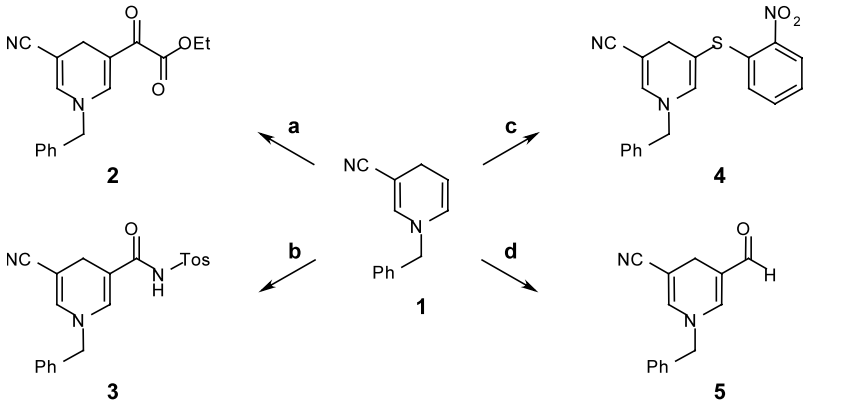
**Abstract**—The reactivity of 1-benzyl-3-cyano-1,4-dihydropyridine was studied in reactions with electrophilic reagents based on structural analogy of 1,4-dihydropyridines with enamines. Different 5-functionalized derivatives were obtained by direct electrophilic substitution. 

1,4-Dihydropyridines play a key role in biological Red–Ox systems,[1] in treatment and prophylaxis of cardiovascular diseases[2] and are also convenient building blocks in the synthesis of alkaloids.[3] Thus the search for new methods of synthesizing functionalized derivatives of 1,4-dihydropyridines is a useful exercise. Electrophilic substitution is a promising method for functionalization of 1,4-dihydropyridines as they are cyclic enamines. The results of several investigations reported recently support this.[4]

In this paper we report the results of a study of the reactions of *N*-benzyl-3-cyano-1,4-dihydropyridine **1**[5] with various types of electrophilic reagent (Scheme 1).

1-Benzyl-3-cyano-1,4-dihydropyridine **1** was regioselectively acylated with ethyl oxalyl chloride and tosyl isocyanate affording the corresponding acyl derivatives **2** and **3**.[6,7] Also, **1** was sulfenylated with 2-nitrophenylsulphenyl chloride giving **4**.[8]




**a**: ClCOCOOEt, $Et_3N$; **b**: TosNCO; **c**: *o*-$NO_2$-$C_6H_4$-SCl, $Et_3N$; **d**: $POCl_3$, $Me_2NCHO$, then aq. $NaHCO_3$

**Scheme 1.**

*Keywords*: 1,4-dihydropyridine; electrophilic substitution.

* Corresponding author. Fax: 380 44 269 67 94; e-mail: dov@fosfor.kiev.ua

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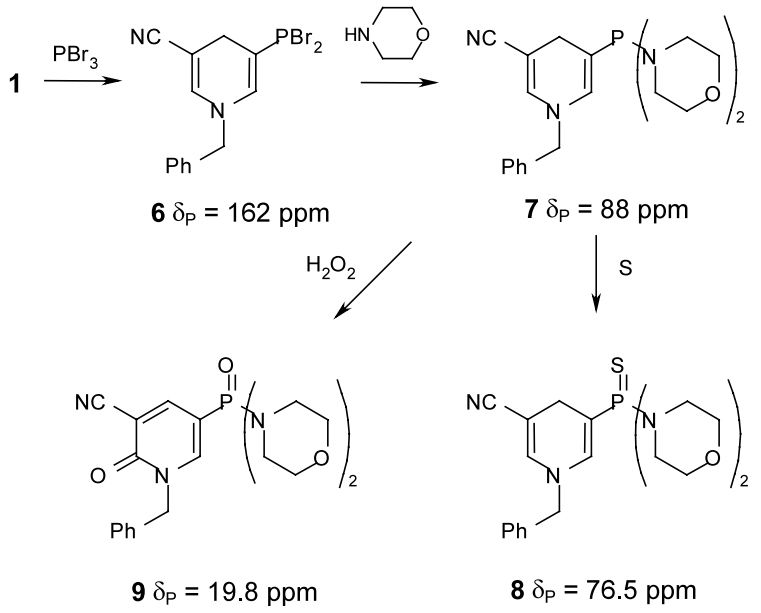


**Scheme 2.**

Vilsmeier–Haak formylation of dihydropyridine **1** also occurred easily affording **5**.[9]

There are reports of unsuccessful attempts to phosphorylate 1,4-dihydropyridines with phosphorous halides (III and V).[4a,10] However, we have found that 1-benzyl-3-cyano-1,4-dihydropyridine **1** can be phosphorylated with $PBr_3$, like other enamines with phosphorus halides.[11] Dibromophosphine **6** was not obtained in a pure state because of its low stability and high reactivity (Scheme 2). However, its formation was proved by $^{31}P$ NMR spectroscopy and its further transformation into stable thiophosphonamide **8**.[12] In an attempt to obtain the analogous phosphonate by oxidation of **7** with $H_2O_2$, oxygenation of the dihydropyridine ring occurred and the bismorpholide of 1-benzyl-2-oxo-3-cyano-1,2-dihydro-5-pyridinylphosphonic acid **9** was obtained.[13]

As is known, the introduction of the second electron-withdrawing substituent leads to an increase in stability of dihydropyridines. In fact, unlike the starting dihydropyridine **1** bearing one electron-acceptor group, substances **2**–**5** and **8**, with two electron-acceptor groups are quite stable substances with a long shelf-life in air (Table 1).

**Table 1.** Yields and melting points of compounds **2**–**5** and **8**

| Product | Electrophile | Yield (%)[a] | Mp (°C)[b] |
|---|---|---|---|
| **2** | $EtO_2CCOCl$ | 60 | 105–108 |
| **3** | TosN=C=O | 78 | 184–186 |
| **4** | 2-$NO_2$-$C_6H_4$-SCl | 61 | 125–127 |
| **5** | DMF, $POCl_3$ | 52 | 122–124 |
| **8** | $PBr_3$ | 47 | 145–147 |

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.

The structures of compounds **2**–**5**, **8** and **9** were confirmed by $^1H$ NMR spectroscopy, and the structures of compounds **5**, **8** and **9** were also confirmed by $^{13}C$ NMR spectroscopy.[14]

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5. The starting material, 1-benzyl-3-cyano-1,4-dihydropyridine was obtained by reduction of *N*-benzyl-3-cyanopyridinium chloride with $Na_2S_2O_4$. See: Dittmer, D. C.; Lombardo, A.; Batzold, F. H.; Greene, C. S. *J. Org. Chem.* **1976**, *41*, 2976–2981.
6. To a stirred solution of 10 mmol of **1** in 40 ml of dry toluene, 10 mmol of triethylamine was added. Then a solution of 10 mmol of ethyl oxalyl chloride in 10 ml of

toluene was added. After 5 h, triethylamine hydrochloride was removed by filtration and the toluene was evaporated in vacuo. The residue was triturated with petroleum and crystallized from 2-propyl alcohol to give **2**. $^1$H NMR (300 MHz, $CDCl_3$): 1.34 (3H, t, $^3J=7.1$ Hz, -C$H_3$), 3.25 (2H, s, -C$H_2$-), 4.29 (2H, q, $^3J=7.1$ Hz, -O-C$H_2$-), 4.48 (2H, s, N-C$H_2$-), 6.51 (1H, d, $^4J=1.5$ Hz, N-C$^6H$=), 7.23 (2H, dd, $^3J=7.8$ Hz, $^4J=2.1$ Hz, C$H^{o\text{-Ph}}$), 7.38–7.47 (3H, m, C$H^{m,p\text{-Ph}}$), 7.63 (1H, d, $^4J=1.5$ Hz, N-C$^2H$=).

7. To a stirred solution of 10 mmol of **1** in 15 ml of dry benzene a solution of 10 mmol of tosyl isocyanate in 15 ml of dry benzene was added. The precipitated solid was crystallized from acetonitrile to give **3**. $^1$H NMR (300 MHz, DMSO-$d_6$): 2.39 (3H, s, -C$H_3$), 2.97 (2H, s, -C$H_2$-), 4.49 (2H, s, N-C$H_2$-), 7.14 (1H, s, N-C$^6H$=), 7.28–7.48 (8H, m, C$H$), 7.79 (2H, d, $^3J=7.9$ Hz, C$^{2'}H$), 11.55 (1H, s, -N$H$-).
8. To a stirred solution of 10 mmol of **1** in 15 ml of dry benzene a solution of 10 mmol of 2-nitrophenylsulphenyl chloride in 15 ml of dry benzene was added. After 24 h, triethylamine hydrochloride was removed by filtration and the toluene was evaporated in vacuo to give **4**. The residue was crystallized from a mixture of methanol–acetonitrile (1:1). $^1$H NMR (300 MHz, $CDCl_3$): 3.14 (2H, s, -C$H_2$-), 4.40 (2H, s, N-C$H_2$-), 6.48 (1H, s, N-C$^6H$=), 6.62 (1H, s N-C$^2H$=), 7.23–7.49 (7H, m, C$H$), 7.60 (1H, t, $^3J=7.6$ Hz, C$^{5'}H$), 8.21 (1H, d, $^3J=8.1$ Hz, C$^{3'}H$).
9. To a solution of 6 mmol of **1** in 5 ml of dry DMF, 2 ml of $POCl_3$ was added at 0°C. The mixture was maintained at 50°C for 90 min, then cooled and poured onto ice and neutralized with a solution of $NaHCO_3$. The precipitated solid was crystallized from a mixture of ethanol–water (2:1) to give **5**. $^1$H NMR (300 MHz, DMSO-$d_6$): 3.02 (2H, s, -C$H_2$-), 4.59 (2H, s, N-C$H_2$-), 7.25 (1H, s, N-C$^6H$=), 7.32–7.47 (6H, m, C$H$), 9.21 (1H, s, C$H$O). 2,4-Dinitrophenylhydrazone derivative: mp 210–212°C; $^1$H NMR (300 MHz, DMSO-$d_6$): 3.23 (2H, s, -C$H_2$-), 4.58 (2H, s, N-C$H_2$-), 6.79 (1H, s, N-C$^6H$=), 7.28 (1H, s, N-C$^2H$=), 7.32–7.47 (5H, m, C$H^{\text{Ph}}$), 7.88 (1H, d, $^3J=10.2$ Hz, C$^{6'}H$), 8.24 (1H, s, C$H$=N), 8.29 (1H, dd, $^3J=10.2$ Hz, $^4J=2.3$ Hz, C$^{5'}H$), 8.83 (1H, d, $^4J=2.3$ Hz, C$^{3'}H$), 11.48 (1H, s, -N$H$-).
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12. To a stirred solution of 2.5 mmol of **1** and 30 mmol of triethylamine in 20 ml of dry benzene, a solution of 2.5 mmol of phosphorus tribromide in 5 ml of dry benzene was added. A solution of 10 mmol of morpholine in 5 ml of dry benzene was then added. After 2 h, 2.5 mmol of finely ground elemental sulfur was added. After the sulfur had dissolved, the precipitated solid was filtered and benzene was evaporated in vacuo. The residue was triturated with octane and crystallized from ethanol to give **8**. $^1$H NMR (300 MHz, $CDCl_3$): 3.07 (8H, t, $^3J=4.5$ Hz, -N(C$H_2$-C$H_2$)$_2$O), 3.17 (2H, d, $^3J_{PH}=3.5$ Hz, -C$H_2$-), 3.65 (8H, t, $^3J=4.5$ Hz, -N(CH$_2$-C$H_2$)$_2$O), 4.39 (2H, s, N-C$H_2$-), 6.55 (1H, s, N-C$^2H$=), 6.85 (1H, d, $^3J_{PH}=15.6$ Hz, N-C$^6H$=), 7.22 (2H, dd, $^3J=7.8$ Hz, $^4J=2.1$ Hz, C$H^{o\text{-Ph}}$), 7.35–7.45 (3H, m, C$H^{m,p\text{-Ph}}$).
13. The product was prepared according to the procedure applied to the substance **8**,[12] but instead of sulfur, 0.35 ml 50% $H_2O_2$ was added. The precipitated solid was filtered and the benzene was evaporated in vacuo. The residue was crystallized from ethanol to give **9**. Compound **9**: yield 12%; mp 228–229°C; $^1$H NMR (300 MHz, $CDCl_3$): 3.00–3.12 (8H, m, -N(C$H_2$-CH$_2$)$_2$O), 3.64 (8H, t, $^3J=4.2$ Hz, -N(CH$_2$-C$H_2$)$_2$O), 5.19 (2H, s, N-C$H_2$-), 7.37–7.42 (5H, m, C$H^{\text{Ph}}$), 7.81 (1H, dd, $^3J_{PH}=8.7$ Hz, $^4J_{HH}=1.8$ Hz, C$^4H$), 8.18 (1H, dd, $^3J_{PH}=9.3$ Hz, $^4J_{HH}=1.8$ Hz, C$^6H$).
14. Compound **5**: $^{13}$C NMR (75 MHz, DMSO-$d_6$): 24.3 *C*(4), 60.3 N-*C*H$_2$-, 89.6 *C*(3)-CN, 117.7 *C*N, 123.3 *C*(5)-CHO, 131.4 *C*(*o*-Ph), 131.9 *C*(*p*-Ph), 132.7 *C*(*m*-Ph), 140.5 *C*(*ipso*-Ph), 146.6 *C*(2), 152.5 *C*(6), 192.8 *C*HO. Compound **8**: $^{13}$C NMR (75 MHz, $CDCl_3$): 24.2 ($^2J_{PC}=8.0$ Hz) *C*(4), 45.1 -N(*C*H$_2$-CH$_2$)$_2$O, 57.97 N-*C*H$_2$-, 66.8 ($^3J_{PC}=7.2$ Hz) -N(CH$_2$-*C*H$_2$)$_2$O, 82.3 ($^3J_{PC}=11.8$ Hz) *C*(3)-CN, 102.0 ($^1J_{PC}=129.0$ Hz) *C*(5)-P, 119.6 *C*N, 127.4 *C*(*o*-Ph), 128.7 *C*(*p*-Ph), 129.2 *C*(*m*-Ph), 135.3 *C*(*ipso*-Ph), 141.2 ($^2J_{PC}=21.6$ Hz) *C*(6), 142.0 *C*(2). Compound **9**: $^{13}$C NMR (75 MHz, $CDCl_3$): 44.5 -N(*C*H$_2$-CH$_2$)$_2$O, 53.8 N-*C*H$_2$-, 66.9 ($^3J_{PC}=3.5$ Hz) -N(CH$_2$-*C*H$_2$)$_2$O, 106.1 ($^3J_{PC}=20.3$ Hz) C(3)-CN, 107.3 ($^1J_{PC}=130.6$ Hz) *C*(5)-P, 114.8 *C*N, 128.7 *C*(*o*-Ph), 129.1 *C*(*p*-Ph), 129.4 *C*(*m*-Ph), 134.3 *C*(*ipso*-Ph), 147.1 *C*(4), 149.3 ($^2J_{PC}=16.4$ Hz) *C*(6), 159.0 *C*(2)=O.