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Addition of some aminoheterocycles to *N*-benzyl-3-cyanopyridinium chloride

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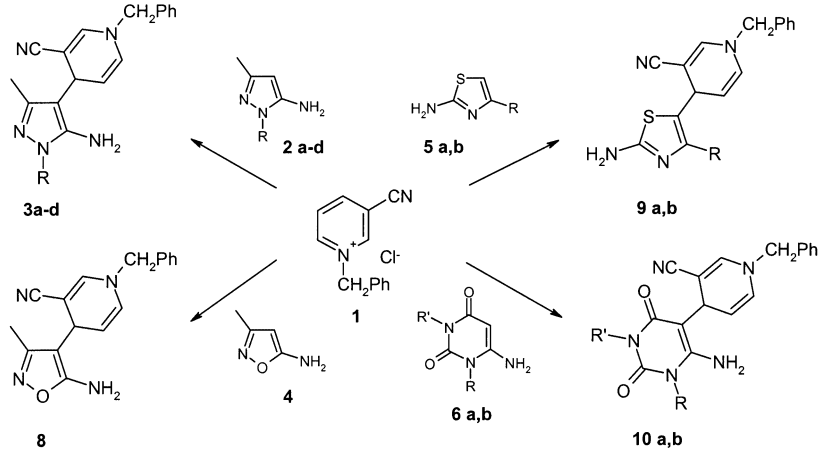
Abstract—5-Aminopyrazoles react with *N*-benzyl-3-cyanopyridinium chloride giving 1-benzyl-3-cyano-4-(5-aminopyrazol-4-yl)-1,4-dihydropyridines with high regioselectivity. 5-Aminoisoxazole, 2-aminothiazole and 6-aminouracil react analogously.

1,4-Dihydropyridines have a recognized place both in medicinal[1,2] and in synthetic[3] chemistry due to their unique properties. Considerable efforts have been directed at the introduction of substituents in the ring, especially at the 4-position. One of the main methods for synthesis of 1,4-dihydropyridines is nucleophilic addition to *N*-acylpyridinium salts.[1,4,5] At the same time addition of *C*-nucleophiles to *N*-alkylpyridinium salts has not been widely studied due to the low regioselectivity of the reaction and the low stability of 1,2- and 1,4-dihydropyridines having an alkyl substituent on the N atom.[6] The sole successful example of heterocyclic addition with good regioselectivity affording 1,4-dihydropyridines has been described for indole derivatives.[6c] In this work, we report our study of the regioselective reaction of *N*-benzyl-3-cyanopyridinium chloride with reactive *C*-nucleophiles including some aminoheterocycles. This approach allowed us to prepare previously unknown 4-heteroaryl- (bearing an unsubstituted amino group) *N*-alkyl-1,4-dihydropyridines.

5-Aminopyrazole is known to be a highly reactive heterocyclic *C*-nucleophile.[7,8] It was found that 5-aminopyrazoles react regioselectively with *N*-benzyl-3-



Scheme 1.

Keywords: 1,4-dihydropyridine; pyridinium salts; aminoheterocycles; nucleophilic addition.

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cyanopyridinium chloride to give *N*-benzyl-3-cyano-4-(5-aminopyrazol-4-yl)-1,4-dihydropyridines **3** (Scheme 1).

The reaction goes to completion at 4°C in methanol over 24–72 h (Table 1) in the presence of triethylamine as a base.[9] Along with alcohols, DMSO can be used as the solvent for the reaction. An attempt to use two-phase systems such as aq. NaOH–toluene, and aq. NaOH–CH_2Cl_2[6c] gave no positive results.

Like 5-aminopyrazole, other electron-rich aminoheterocycles, namely 5-aminoisoxazoles **4**,[7a,c,9] 2-aminothiazoles **5**,[9,10] and 6-aminouracils **6**[11] enter the reaction affording the corresponding *N*-benzyl-3-cyano-4-hetaryl-1,4-dihydropyridines **8**–**10** (Scheme 1). Although 2-amino-5-carbethoxyfuran[7c] also enters the reaction, due to the low stability of the final product, we failed to separate it in analytically pure form.

At the same time under analogous conditions, the reaction of *N*-benzyl-3-cyanopyridinium chloride **1** with 2-amino-5-carbethoxy-3-methylthiophene[7c] did not give the expected 4-thienyl-1,4-dihydropyridine. It should be noted that isomeric 1-phenyl-3-aminopyrazole and 3-amino-5-methylisooxazoles, unlike **2** and **4**, did not give the targeted dihydropyridines.

1,4-Dihydropyridines **3**, **8**–**10** are stable substances at −20°C under an inert atmosphere; at ambient temperature in air they decomposed. The structural integrity of the 1,4-dihydropyridines was confirmed by ^1H, ^{13}C NMR and mass spectroscopy.[12–14] (Tables 2 and 3).[6c] Also these compounds exhibit a strong dependence of chemical shifts on the solvent in their PMR spectra.

The synthesis of stable derivatives of the *N*-benzyl-3-cyano-4-heteroaryl-1,4-dihydropyridines proved to be difficult. Both attempts to reduce them with $NaBH_4$ or

Table 1. Yields, melting points, solvent for crystallization and time of reaction of the 1-benzyl-3-cyano-4-heteroaryl-1,4-dihydropyridines **3** and **8**–**10**

	R	R′	Mp (°C)[a,b]	Solvent	Time (h)	Yield (%)[c]
3a	H	–	123–125	MeOH/H_2O ~ 1:3	24	52
3b	CH_2CH_2CN	–	87–91	MeOH/H_2O ~ 1:3	24	79
3c	Ph	–	74–76	MeOH/H_2O ~ 1:5	72	56
3d	4-MeC_6H_4-	–	76–79	MeOH/H_2O ~ 1:5	72	59
8	–	–	121–123	MeOH/H_2O ~ 1:5	24	25
9a	Me	–	193–196	MeCN	24	32
9b	Ph	–	136–139	MeCN	48	60
10a	CH_2Ph	H	196	MeCN	12	57
10b	Me	Me	112–115	MeCN	12	51

[a] Melting points are uncorrected.
[b] Melt with decomposition.
[c] Yields refer to pure isolated products.

Table 2. Significant ^1H NMR data for dihydropyridines **3a**, **3d**, **8**, **9a** and **10b**

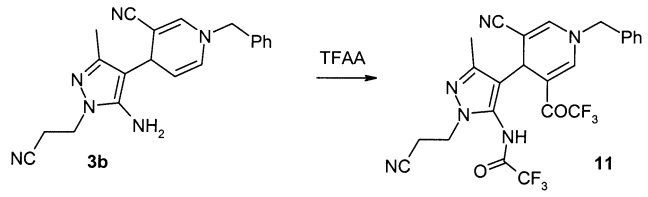
	H(2)	H(4)	H(5)	H(6)	N-CH_2	$^4J_{H(2)H(4)}$	$^3J_{H(4)H(5)}$	$^3J_{H(5)H(6)}$
3a[a]	7.09 d	4.17 dd	4.50 dd	6.02 d	4.42 s	1.2	3.6	8.1
3d[b]	6.71 s	4.35 d	4.71 dd	5.95 d	4.35 s	–	3.6	8.1
8[b]	6.72 d	4.16 dd	4.64 dd	5.99 d	4.35 s	0.9	3.9	8.1
9a[a]	7.14 s	4.47 d	4.71 dd	6.06 d	4.47 s	–	3.3	8.7
9a[b]	6.64 s	4.56 d	4.81 dd	5.86 d	4.37 s	–	3.3	8.7
10b[a]	7.13 s	4.39 d	4.72 bs	6.04 d	4.44 s	–	3.3	7.8

[a] DMSO-d_6.
[b] $CDCl_3$.

Table 3. Significant ^{13}C NMR data for dihydropyridines **3a**, **3d**, **8**, **9a** and **10b**

	C(2)	C(3)	C(4)	C(5)	C(6)	NCH_2	CN
3a[a]	141.7	80.6	27.2	104.2	126.8	56.2	121.0
3d[b]	141.4	82.4	29.0	104.5	128.6	58.0	121.1
8[b]	141.4	81.6	27.7	103.2	128.1	58.0	120.4
9a[a]	140.6	81.5	30.7	104.8	127.2	56.1	120.5
10b[a]	143.0	79.6	27.2	103.4	128.6	56.0	120.2

[a] DMSO-d_6.
[b] $CDCl_3$.



Scheme 2.

functionalize the electrophilic 1,4-dihydropyridine nucleus failed.[15] Nevertheless, bis-trifluoroacetylation with an excess of trifluoroacetic anhydride was successful. Thus, the bis-trifluoroacetylated derivative **11**, which is stable in air, was obtained by this method (Scheme 2).[6a,16]

References

1. Lyle, R. E. In *Pyridine and its Derivatives*, Supplement; Abramovich, R. A., Ed.; Wiley: New York, 1974; Vol. 1, p. 137.
2. (a) Goldman, S.; Stoltefuss, J. *Angew. Chem., Int. Ed.* **1991**, *30*, 1559–1578; (b) Sunkel, C.-E.; Fau de Casa-Juana, M.; Santos, L.; Gomes, M.-M.; Villarroya, M.; Gonzalez-Morales, M.-A.; Priego, J.-G.; Ortega, M.-P. *J. Med. Chem.* **1990**, *33*, 3205–3210; (c) Jiang, J. L.; Li, A.-H.; Jang, S.-Y.; Chang, L.; Melman, N.; Moro, S.; Ji, X.; Lobkovsky, E.; Clardy, J.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 3055–3065.
3. (a) Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press: London, 1996; Vol. 2, pp. 251–294; (b) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182–8187; (c) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184–2185; (d) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855–857; (e) Pays, C.; Mangeney, P. *Tetrahedron Lett.* **2001**, *42*, 589–592.
4. For reviews see (a) Comins, D. L.; O'Connor, S. *Adv. Heterocyclic. Chem.* **1988**, *44*, 199; (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223.
5. (a) Deubel, H.; Wolkenstein, D.; Jokisch, H.; Messerschmitt, T.; Brodka, S.; von Dobeneck, H. *Chem. Ber.* **1971**, *104*, 705; (b) Naito, T.; Iida, N.; Ninomiya, I. *J. Chem. Soc., Chem. Commun.* **1981**, 44; (c) Piers, E.; Soucy, M. *Can. J. Chem.* **1974**, *52*, 3563–3564; (d) Comins, D. L.; Stroudd, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151–157; (e) Akiba, K.; Iseki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994–1999; (f) Shiao, M. J.; Liu, K. H.; Lin, L. G. *Synlett* **1992**, 655–656; (g) Mangeney, P.; Gosmini, R.; Raussou, S.; Commercon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877–1888.
6. (a) Bennasar, M.-L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, *27*, 789; (b) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1995**, *60*, 4280–4286; (c) Lavilla, R.; Gotsens, T.; Guerrero, M.; Masdeu, C.; Santano, C.; Minguillon, C.; Bosch, J. *Tetrahedron* **1997**, *53*, 13959–13968; (d) Bennasar, M.-L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **2001**, *42*, 585–588; (e) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141–1156.
7. (a) Winters, G.; Sala, A.; De Paoli, A.; Conti, M. *Synthesis* **1984**, *12*, 1050–1052; (b) Esteves-Souza, A.; Echevarria, A.; Vencato, I.; Jimeno, M. L.; Elguero, J. *Tetrahedron* **2001**, *57*, 6147–6153; (c) Pushechnikov, A. O.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2002**, *7*, 1140–1142.
8. One example of 5-aminopyrazole addition to an *N*-mesylpyridinium salt has been disclosed: Szilagyi, G.; Dvortsak, P. *Monatsh. Chem.* **1989**, *120*, 131–137.
9. Typical procedure: To a solution of 2 mmol *N*-benzyl-3-cyanopyridinium chloride **1** and 2 mmol triethylamine in 15 mL methanol was added 2 mmol of 5-aminopyrazole **2a** in 5 mL methanol. The reaction mixture was maintained at 4°C under argon until completion of the reaction monitored by TLC EtOAc/SiO_2, and then it was poured into 80 mL water. The colloidal solution thus formed was destroyed by sodium sulfate. The precipitated solid was filtered and crystallized from the corresponding solvent. Recrystallization was carried out as follows. The substance was dissolved in a minimum volume of solvent at 30°C (at higher temperature decomposition is high) and left at 0°C under argon for 10–12 h.
10. One example of 2-aminothiazole addition to an *N*-acylpyridinium salt has been disclosed: Somei, M.; Yamada, Y.; Kitagava, K.; Sugaya, K.; Tomita, Y.; Yamada, F.; Nakagava, K. *Heterocycles* **1997**, *45*, 435–438.
11. Typical procedure: To a solution of *N*-benzyl-3-cyanopyridinium chloride **1** and 2 mmol of triethylamine in DMSO 3 mL was added a solution of 6-aminouracil **6** in DMSO 5 mL. The reaction mixture was maintained under argon at 4°C for 12 h, and then poured into 50 mL of water. The precipitated solid was collected by filtration and recrystallized from acetonitrile.
12. Typical ^{1}H NMR spectrum of 1-benzyl-3-cyano-4-(hetaryl)-1,4-dihydropyridines. **3b**: (300 MHz, DMSO-d_6): 1.90 (3H, s, CH_3), 2.81 (2H, t, ^3J=6.9 Hz, CH_2CH_2CN), 4.04 (2H, t, ^3J=6.9 Hz, CH_2CH_2CN), 4.21 (1H, dd, ^3J=3.6 Hz, ^4J=1.8 Hz, C^4H), 4.41 (2H, s, N-CH_2-Ph), 4.47 (1H, dd, ^3J=8.1 Hz, ^3J=3.6 Hz, C^5H), 4.86 (2H, s, ex. with D_2O, NH_2), 6.02 (1H, d, ^3J=8.1 Hz, C^6H), 7.09 (1H, d, ^4J=1.8 Hz, C^2H), 7.30–7.40 (5H, m, Ph). **8**: (300 MHz, $CDCl_3$): 2.15 (3H, s, CH_3), 4.16 (1H, d, ^3J=3.9 Hz, C^4H), 4.30 (2H, s, ex. with D_2O, NH_2), 4.35 (2H, s, N-CH_2), 4.64 (1H, dd, ^3J=8.1 Hz, ^3J=3.9 Hz, C^5H), 5.99 (1H, d, ^3J=8.1 Hz, C^6H), 6.73 (1H, s, C^2H), 7.20–7.40 (5H, m, Ph). **9a**: (300 MHz, $CDCl_3$): 2.18 (3H, s, CH_3), 4.37 (2H, s, N-CH_2), 4.56 (1H, d, ^3J=3.3 Hz, C^4H), 4.81 (1H, dd, ^3J=8.7 Hz, ^3J=3.3 Hz, C^5H), 4.81 (2H, s, ex. with D_2O, NH_2), 5.86 (1H, d, ^3J=8.7 Hz, C^6H), 6.64 (1H, s, C^2H), 7.20–7.40 (5H, m, Ph). **10b**: (300 MHz, DMSO-d_6): 3.14 (3H, s, N-CH_3), 3.33 (3H, s, N-CH_3), 4.37–4.44 (3H, m, N-CH_2 and C^5H), 4.73 (1H, bs, C^4H), 6.03 (1H, d, ^3J=7.8 Hz, C^6H), 6.21 (2H, bs, ex. with D_2O, NH_2), 7.14 (1H, s, C^2H), 7.30–7.40 (5H, m, Ph).
13. Typical ^{13}C NMR spectrum of 1-benzyl-3-cyano-4-(hetaryl)-1,4-dihydropyridines. **3a**: (75 MHz, DMSO-d_6): 10.0 (*C*H_3), 27.2 (*C*(4)), 56.2 (N-*C*H_2Ph), 80.6 (*C*(3)), 104.2 (*C*(5)), 105.9 (*C*(4′, azole)), 121.0 (*C*N), 126.8 (*C*(6)), 127.3 (*C*(*o*-Ph)), 128.4 (*C*(*p*-Ph) and *C*(*m*-Ph)), 137.4 (*C*(*ipso*-Ph)), 138.2 (*C*(5′, azole)), 141.7 (*C*(2)), 160.0 (*C*(3′, azole)). **8**: (75 MHz, $CDCl_3$): 10.4 (*C*H_3), 27.7 (*C*(4)), 58.0 (N-*C*H_2Ph), 81.6 (*C*(3)), 95.9 (*C*(4′, azole)), 103.2 (*C*(5)), 120.4 (*C*N), 127.5 (*C*(*o*-Ph)), 128.1 (*C*(6)), 128.6 (*C*(*p*-Ph)), 129.3 (*C*(*m*-Ph)), 136.0 (*C*(*ipso*-Ph)),

141.4 (*C*(2)), 159.6 (*C*(3′, azole)), 166.2 (*C*(5′, azole)). **9a**: (75 MHz, DMSO-d_6): 14.4 (CH_3), 30.7 (*C*(4)), 56.1 (N-CH_2Ph), 81.5 (*C*(3)), 104.8 (*C*(5)), 120.5 (*C*N), 125.3 (*C*(4′, azole)), 127.0 (*C*(*o*-Ph)), 127.2 (*C*(6)), 127.3 (*C*(*p*-Ph)), 128.4 (*C*(*m*-Ph)), 137.3 (*C*(*ipso*-Ph)), 140.9 (*C*(5′, azole)), 141.7 (*C*(2)), 166.3 (*C*(2′, azole)). **10b**: (75 MHz, DMSO-d_6): 27.2 (*C*(4)), 28.1 (N-CH_3), 29.3 (N-CH_3), 56.0 (N-CH_2Ph), 79.6 (*C*(3)), 89.3 (*C*(5′, ur.)), 103.4 (*C*(5)), 120.2 (*C*N), 127.1 (*C*(*o*-Ph)), 127.3 (*C*(*p*-Ph)), 128.4 (*C*(*m*-Ph)), 128.6 (*C*(6)), 137.1 (*C*(*ipso*-Ph)), 143.3 (*C*(2)), 150.5 (*C*(6′, ur.)), 152.4 (*C*(4′, ur.)), 160.6 (*C*(2′, ur.)).

14. MS (EI) (*m*/*z* (%)): **3a**: 291 (M^+, 16), 200 (81), 134 (6), 106 (11), 97 (54), 91 (100), 65 (13), 39 (8); **8**: 292 (M^+, 8), 201 (3), 195 (6), 91 (100), 65 (9); **9a**: 308 (M^+, 31), 217 (26), 195 (9), 91 (100), 65 (10); **10b**: 349 (M^+, 3), 347 (27), 242 (5), 155 (17), 106 (11), 91 (100), 82 (10), 65 (10).
15. (a) Lavilla, R.; Kumar, R.; Coll, O.; Masdeu, C.; Spada, A.; Bosh, J.; Espinosa, E.; Molins, E. *Chem. Eur. J.* **2000**, *6*, 1763–1772; (b) Kostyuk, A. N.; Volochnyuk, D. M.; Lupiha, L. N.; Pinchuk, A. N.; Tolmachev, A. A. *Tetrahedron Lett.* **2002**, *43*, 5423–5425.
16. 4-(5-Amino-1-(2-cyanoethyl)-3-methyl-1*H*-pyrazol-4-yl)-1-benzyl-3-cyano-5-(2,2,2-trifluoroacetyl)-1,4-dihydropyridine **11**. After cooling a solution of 1.5 mmol **3b** and 3 mmol of triethylamine in 20 mL of dioxane to a solid state, 6 mmol of TFAA was added in one portion. The reaction mixture was allowed to warm to ambient temperature and kept for 3 h. Dioxane was removed by distillation under reduced pressure. The residue was triturated with water and recrystallized from isopropanol. Yield: 12%. mp = 103°C. ^{1}H NMR (300 MHz, DMSO-d_6, signals are broad and structurally unresolved due to hampered revolution around C^4_{DHP}–$C^{4'}_{azole}$ bond): 2.07 (3H, s, CH_3), 2.92 (2H, bs, CH_2CH_2CN), 4.04 (2H, bs, CH_2CH_2CN), 4.53 (1H, s, C^4H), 4.78 (2H, badly resolved AB-system, N-CH_2), 7.3–7.4 (6H, m, Ph and C^2H), 7.62 (1H, s, C^6H), 11.34 (1H, s, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6): 11.9 (CH_3), 17.2 (CH_2CH_2CN), 26.9 (*C*(4)), 42.9 (CH_2CH_2CN), 57.1 (N-CH_2Ph), 90.6 (*C*(3)), 106.3 (*C*(5) and *C*(4′, azole)), 115.5 (q, $^1J_{CF}$ = 292.5 Hz) (CF_3), 115.9 (*C*N), 116.4 (q, $^1J_{CF}$ = 292.5 Hz) (CF_3), 117.7 (*C*N), 127.8 (*C*(*o*-Ph)), 128.1 (*C*(*p*-Ph)), 128.7 (*C*(*m*-Ph)), 131.2 (*C*(5′, azole)), 135.5 (*C*(*ipso*-Ph)), 139.6 (*C*(2)), 143.9 (*C*(6)), 146.0 (*C*(3′, azole)), 156.0 (q, $^2J_{CF}$ = 37.5 Hz) (C^5COCF_3), 175.8 (q, $^2J_{CF}$ = 33.8 Hz) (NH*C*OCF_3). ^{19}F NMR (282 MHz, DMSO): −74.4 (3F, s, CF_3), −69.2 (3F, s, CF_3). MS (EI) (*m*/*z* (%)): 536 (M^+, 18), 445 (24), 392 (23), 91 (100).