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THE FIRST 4-DIALKYLAMINO-1,2-DIHYDROPYRIDINE DERIVATIVES: SYNTHESIS AND BASIC REACTIONS

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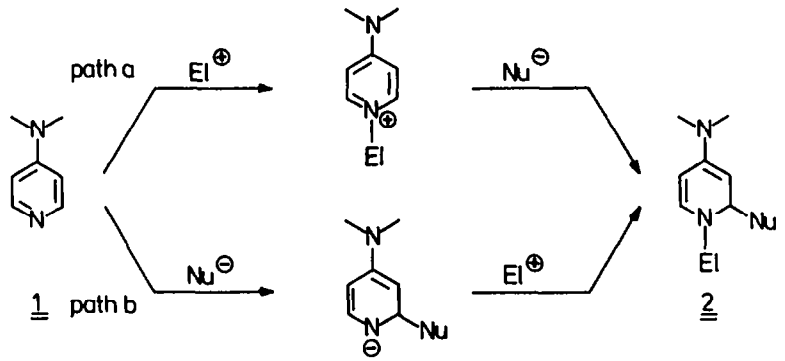
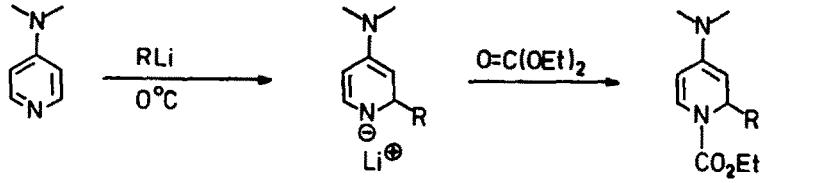
Summary: The first two 4-dialkylamino-1,2-dihydropyridine derivatives **4a** and **4b** are prepared in good yield by addition of n-butyllithium or t-butyllithium to 4-dimethylaminopyridine **1** followed by quench with diethylcarbonate. Compound **4a** can be hydrolyzed under mild conditions providing 4-dihydropyridone **5**, an interesting acceptor building block. On the other hand reaction of **4a** with dimethyl acetylene dicarboxylate gives benzene derivative **7** via a cycloaddition-cycloreversion path.

4-Dimethylaminopyridine (DMAP) **1** has found extensive use as a super catalyst for acylations and related reactions [2]. Although commercially available and inexpensive, its potential to serve as a functionalized building block in stoichiometric amounts for organic synthesis has so far been neglected [3]. We were attracted by the possibility to convert DMAP **1** into 1,2-dihydropyridines of type **2**, which should display enamine reactivity and might act as very eletronrich cyclic dienes in Diels-Alder as well as other cycloadditions opening the way to interesting products.

Scheme I



Two principle alternatives to transform **1** into **2** are depicted in Scheme I: addition of an electrophile - usually an acylating agent - followed by treatment with an appropriate nucleophilic component (path a) is the most common method for dihydropyridine preparations [4]. Not surprisingly, however, a broad spectrum of reagent combinations under largely varied reaction conditions applied with DMAP **1** at best delivered traces of 1,2-dihydropyridines **2** [5]. We therefore turned to path b interchanging the sequence of reagent additions. To our delight n-butyllithium (1.25 equivalents) adds smoothly to DMAP **1** in tetrahydrofuran (THF) at 0 °C as ascertained by ^{1}H NMR control. The orangered solution formed under these conditions after one hour shows a doublet at 6.20 ppm (J = 7.0 Hz) as the only low field signal which is assigned to H-6 of adduct **3a** [6]. Addition of diethylcarbonate at -78 °C, warming to room temperature, aqueous work up, and distillation afford the urethane **4a** in 77 % yield. To our best knowledge **4a** is the first 4-dialkylamino-1,2-dihydropyridine [4)7)].



1 R = n-C_4H_9 3a 4a 77%

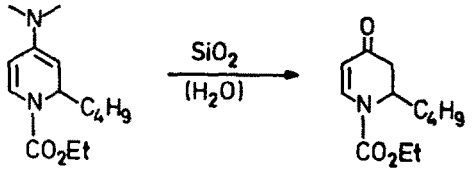
R = t-C_4H_9 3b 4b 46%

4a is rather labile at room temperature and moderately stable at -30 °C. Therefore immediate use after preparation is recommended. All spectral data are in accord with its proposed structure (see experimental part). Due to the hindered rotation around the N-CO_2Et bond the ^{1}H NMR spectrum at 60 MHz exhibits two broad doublets for 6-H and 5-H at 6.67 and 5.30 ppm (J = 7 Hz) [8]. At 400 MHz, four sharp doublets show up for these protons (6.80, 6.68, 5.39 and 5.30 ppm, J = 7.5 Hz) according to the two rotamers of **4a**.

Other electrophiles ($ClCO_2Et$, $ClSiMe_3$, H_2O and MeI) added to **3a** did not provide definite reaction products although the crude product obtained after methyl iodide quench might contain the corresponding 2,5-dihydropyridine derivative [9].

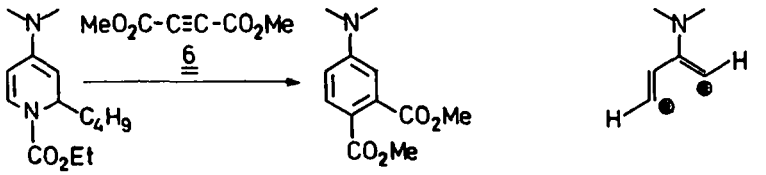
Monoaddition of t-butyllithium to **1** can best be performed at 0 °C in diethylether instead of THF delivering a solution of **3b** (^{1}H NMR: 6.48 ppm, d, J = 7.0 Hz, 6-H). Trapping this anion with diethylcarbonate and usual work up delivers **4b** in unoptimized 46 % yield. So far, synthesis of **4a** and **4b** analogues via path b (Scheme I) was not successful employing various hydride reagents or methyl-, phenyl- or trimethylsilyllithium; thus, only the most nucleophilic organolithiums add to the electronrich pyridine **1**.

Despite these current limitations adducts **4** can serve as versatile building blocks. Mild hydrolysis of **4a** with wet silica gel affords the 4-dihydropyridone **5** in 77 % yield. The conversion of **1** → **5** without purification of the intermediate **4a** occurs with a satisfying 58 % overall yield. Substituted 4-dihydropyridones of type **5** are compounds of actual pharmacological [10] and synthetic [11] interest.



4a 5 77%

Reaction of **4a** with dimethyl acetylenedicarboxylate **6** at room temperature gives the crystalline phthalic acid derivative **7** [12] in 44 %. Presumably, the Diels-Alder addition of **6** to **4a** affording a (non detectable) bicyclic intermediate is followed by fast cycloreversion of an imine to the aromatic compound **7**. Further experiments have to establish whether diene **4a** generally behaves as synthon **8** in cycloadditions [13].



4a 7 8

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Experimental Part

IR spectra were recorded on a Beckman-Acculab 4 spectrometer, UV spectra on a Beckman DB-GT spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian T-60 or Bruker WH 400 in $CDCl_3$ with tetramethylsilane as the internal standard. Boiling points (bp) reported correspond to the oven temperature of a Büchi-Kugelrohr apparatus. Melting points are not corrected. 4-Dimethylaminopyridine was dissolved in methanol filtered through a pad of charcoal and recrystallized from ethyl acetate. THF was distilled from K/benzophenone, diethyl ether from NaH just before use.

Ethyl 4-Dimethylamino-2-n-butyl-1,2-dihydropyridine-1-carboxylate (**4a**): 30.0 ml of a 2.09 M solution (62.7 mmol) n-butyllithium in hexane are added to a suspension of 6.10 g (50.0 mmol) **1** in 40 ml THF under dry nitrogen at 0 °C within 15 min. After 30 min the red solution is cooled to -78 °C and treated with 7.09 g (60.0 mmol) diethyl carbonate for 30 min at this temperature, plus 1 h at room temperature. After addition of 50 ml saturated $NaHCO_3$ solution and 50 ml t-butylmethyl ether (MTB), the aqueous phase is extracted twice with 30 ml MTB and the organic phases are dried over Na_2SO_4. Concentration delivers 12.2 g (97%) crude product which after distillation at 110-130 °C/0.02 mm affords 9.70 g (77%) **4a** as yellow oil. - ^{1}H NMR ($CDCl_3$), 60 MHz): δ=6.67 (bd, J = 7 Hz, 1H, 6-H), 5.30 (bd, J = 7 Hz, 1H, 5-H), 5.0-4.2 (m, 2H, 2-H, 3-H), 4.16 (q, J = 7.0 Hz, 2H, OCH_2), 2.58 (s, 6H, NMe_2), 1.7-0.5 (m, 12H, C_4H_9, $OCH_2\underline{CH_3}$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ=6.80, 6.68 (2d, J = 7.5 Hz, 1H, 6-H), 5.39, 5.30 (2d, J = 7.5 Hz, 1H, 5-H), 4.8-4.6 (m, 1H, 2-H), 4.5-4.4 (m, 1H, 3-H), 4.23 (q, J = 7.0 Hz, 2H, OCH_2), 2.32 (s, 6H, NMe_2), 1.7-1.2 [m, 6H, $-(CH_2)_3-$], 1.30 (t, J = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 0.88 (t, J = 7.0 Hz, 3H, $-C_3H_6-\underline{CH_3}$). - ^{13}C NMR ($CDCl_3$): δ=142.9, 142.5 (2s, C=O, C-4), 126.1, 125.3 (2d, C-6, C-5), 104.1 (d, C-3), 61.5 (t, OCH_2), 52.3 (d, C-2), 40.3 (q, NMe_2), 34.0, 26.6, 22.4 (3t, $-C_3H_6-$), 14.2, 13.7 (2q, 2x CH_3).
IR (CCl_4): 3080-2790 (C-H), 1720 (C=O), 1655 cm^{-1} (C=C). - UV (hexane): λ_{max}(log ε)=253 (3.92), 299 nm (3.37). - $C_{14}H_{24}N_2O_2$ (252.4) Calc. C, 66.63; H, 9.59; N, 11.10. Found C, 66.44; H, 9.95; N, 11.05%.

Ethyl 4-Dimethylamino-2-t-butyl-1,2-dihydropyridine-1-carboxylate (**4b**): 15.5 ml of a 1.55 M solution (24.0 mmol) t-butyllithium in pentane are added to a suspension of 2.44 g (20.0 mmol) **1** in 20 ml diethyl ether under dry nitrogen at 0 °C. After one hour the red solution is cooled to -78 °C and treated with 2.83 g (24.0 mmol) diethyl carbonate for one hour. Five minutes after removing the cooling bath, 20 ml of MTB and 20 ml of saturated $NaHCO_3$ solution are added. The aqueous phase is extracted twice with 20 ml MTB and the organic phases are dried with Na_2SO_4. Concentration and distillation (120 °C/0.02 mm) deliver 2.34 g (46%) **4b** as yellow oil (ca. 90% pure). - ^{1}H NMR ($CDCl_3$, 60 MHz): δ=7.0-6.5 (m, 1H, 6-H), 5.5-5.1 (m, 1H, 5-H), 4.7-4.3 (m, 2H, 2-H, 3-H), 4.18 (q, J = 7.0 Hz, 2H, OCH_2), 2.58 (s, 6H, NMe_2),

1.27 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.82 (s, 9H, C_4H_9). - IR (CCl_4): 3080-2800 (C-H), 1720 (C=O), 1655 cm^{-1} (C=C). - $C_{14}H_{24}N_2O_2$ (252.4) Calc. C, 66.63; H, 9.59; N, 11.10. Found C, 66.58; H, 9.98; N, 11.46%.

Ethyl 2-n-Butyl-4-oxo-1,2,3,4-tetrahydropyridine-1-carboxylate (5): 1.26 g (5.00 mmol) **4a** in 30 ml MTB are stirred with 12 g wet silica gel (obtained by mixing 10 g silica gel 0.2-0.5 mm, Merck, with 2 g of water) for 16 h at room temperature. Filtration and careful elution with MTB, concentration and distillation at 100 °C/0.02 mm afford 866 mg (77%) **5** as colorless oil. - ^1H NMR ($CDCl_3$): δ=7.75 (bd, J = 8.0 Hz, 1H, 6-H), 5.30 (bd, J = 8.0 Hz, 1H, 5-H), 4.8-4.4 (m, 1H, 2-H),4.38 (q, J = 7.5 Hz, 2H, OCH_2) 2.9-2.3 (m, 2H, 3-H), 1.42 (t, J = 7.5 Hz, 3H, OCH_2CH_3), 1.9-0.7 (m, 9H, C_4H_9). - IR (CCl_4): 3000-2850 (C-H), 1730 (N-CO_2Et), 1685 (C=O), 1610 cm^{-1} (C=C). - $C_{12}H_{19}NO_3$(225.3) Calc. C, 63.98; H, 8.50; N, 6.22 Found C, 64.21; H, 8.83; N, 6.54%.

Dimethyl 4-Dimethylaminophthalate (7): 0.71 g (5.00 mmol) dimethyl acetylene dicarboxylate **6** in 2.5 ml THF are added to 1.26 g (5.00 mmol) **4a** in 2.5 ml THF at -78 °C. After one hour at this temperature the resulting red solution is stirred for 5 d at room temperature. Filtration through a pad of aluminum oxide (activity III) and low temperature crystallization from ether/petrol ether at -78 °C provide 0.52 g (44%) **7** as colorless needles (m.p. 58-60 °C; ref. 12: m.p. 59 °C). - ^1H NMR ($CDCl_3$): δ=7.75 (d, J = 9.0 Hz, 1H), 6.8-6.4 (m, 2H), 3.92, 3.88 (2s, 2x3H, OCH_3), 3.04 (s, 6H, NMe_2). IR (CCl_4):3000-2800 (C-H), 1730 (C=O), 1620 cm^{-1} (C=C).

References

1) Part of the Diploma Thesis, Universität Würzburg, 1984.

2) a) H. Vorbrüggen, G. Höfle and W. Steglich, Angew. Chem. **90**, 602 (1978); Angew. Chem. Int. Ed. Engl. **17**, 569 (1978); b) E. F. V. Scriven, Chem. Soc. Rev. **12**, 129 (1983).

3) For the very few known reactions of DMAP see ref. 2a.

4) a) U. Eisner and J. Kuthan, Chem. Rev. **72**, 1 (1972); b) D. M. Stout and A. I. Meyers, Chem. Rev. **82**, 223 (1982).

5) In most cases DMAP **1** demonstrates its super acylating/alkylating quality impressively.

6) G. Illuminati and F. Stegel, Advances in Heterocyclic Chemistry (Ed. A. R. Katritzky), Vol. 34, p. 306, Academic Press, New York 1983.

7) 4-Methoxy-1,2-dihydropyridine has been synthesized only recently: S. Raucher and J. E. Macdonald, Synth. Commun. **10**, 325 (1980).

8) L. M. Jackman and F. A. Cotton, Dynamic Nuclear Magnetic Resonance Spectroscopy, p. 203, Academic Press, New York 1975.

9) ^1H NMR doublets at 7.42 (J = 7 Hz) and 4.98 ppm (J = 7 Hz) beside a broad multiplet (4.0-0.7 ppm) might arise from 4-dimethylamino-2-n-butyl-5-methyl-2,5-dihydropyridine: for formation of 2,5-dihydropyridines see: R. F. Francis, C.D. Crews and B. Scott, J. Org. Chem. **43**, 3227 (1978).

10) J.-P. Roduit and Hugo Wyler, Helv. Chim. Acta **68**, 403 (1985).

11) a) A. P. Kozikowski and P. Park, J. Org. Chem. **49**, 1974 (1984); b) P. Guerry and R. Neier, Synthesis **1984**, 485 and references cited.

12) a) H. Neunhöffer and G. Werner, Liebigs Ann. Chem. **1973**, 128; b) R. Gompper and U. Heinemann, Angew. Chem. **92**, 207 (1980); Angew. Chem. Int. Ed. Engl. **19**, 216 (1980).

13) For cycloadditions with 1,2-dihydropyridines see: B. Weinstein, L. C. Lin and F. W. Fowler, J. Org. Chem. **45**, 1675 (1980) and ref. 4b.