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METALATION OF 1,4-DIHYDROPYRIDINE ESTERS

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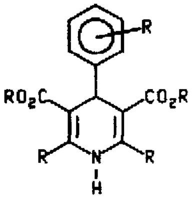
Summary: 4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic esters are metalated at the NH and the C-2 methyl positions via treatment with two equivalents of n-butyl lithium. The resulting dilithio species can be treated with a variety of electrophiles to furnish C-2 methyl functionalized dihydropyridine esters.

Over the past several years, we have been interested in the preparation of novel 4-aryl-2,6-dialkyl-1,4-dihydro-3,5-pyridinedicarboxylic esters (Hantzsch esters) **1** for *potential therapeutic applications*[1]. *These general types of dihydropyridines, as* exemplified by amlodipine (**2**)[2], represent a potent structural class of agents collectively known as "calcium antagonists"[3]. Our interest in this area has focused on the preparation of unsymmetrical dihydropyridine adducts not easily prepared by classical Hantzsch condensation routes[4]. We wish to report our preliminary results on the chemical elaboration of readily available, symmetrically substituted, dihydropyridine esters via vinylogous metalation methodology [5,6].



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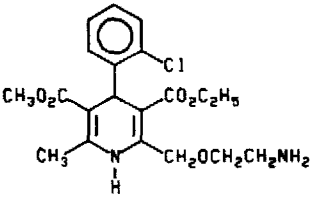

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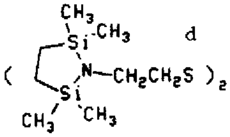
A tetrahydrofuran (THF) solution of dihydropyridine **3**[7] was treated with 2.1 equivalents of n-butyl lithium at -78°C. Metalation of **3** to the dilithio species **4**[9] was judged complete after 30 minutes by quenching the intense yellow solution at low temperature with excess CH_3OD. Workup and crystallization furnished **5** (95% yield, mp 139-141°C) which on ^1H NMR analysis revealed complete monodeuterium incorporation at the C-2 methyl position[10].

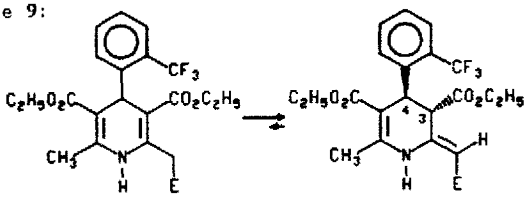
The utility of the metalation pathway was subsequently explored using other electrophiles[11]. Complex distributions of products similar to those reported by Patterson[6] were generally observed when alkyl halides, acid chlorides, or chloroformates were employed as electrophiles. However good yields of products could be obtained using other electrophiles. The results from these experiments are summarized in the Table.

Table. **Products and Yields From the Reaction of Dilithio Species 4 with Various Electrophiles.**[a,b]

Entry	Electrophile	Product, E	% Yield[c]	mp (°C)
1	$(CH_3S)_2$	**6a**, SCH_3	83	100-102
2	 [d]	**6b**, $SCH_2CH_2NH_2$	70	oil
3	$(CH_3)_3SiCN$	**6c**, $Si(CH_3)_3$	69	145-146
4	$(C_2H_5O)_2POCl$	**6d**, $PO(OC_2H_5)_2$	87	96-97
5	n-C_4H_9NCO	**6e**, CONHn-C_4H_9	61	oil
6	CH_3SO_2Cl	**6f**, SO_2CH_3	29	156-157
7	$HCON(CH_3)_2$	**6g**, CHO[e]	71	82-85
8	$CH_3CON(OCH_3)CH_3$	**6h**, $COCH_3$[e]	70	87-88
9	$C_2H_5O_2CCN$	**6i**, $CO_2C_2H_5$[e]	29	79-91[f]
10	CO_2	**6j**, CO_2Na[g]	52	154-165 (dec)

a. All reactions carried out at -78°C with 10 mmol of 3 using 2.1 equivalents of n-butyl lithium as base. b. All reported dihydropyridines displayed spectral characteristics (IR, MS, ^1H- and ^{13}C-NMR) which were consistent with their assigned structure. All new compounds gave satisfactory analytical data (0.4% for C, H, and N). c. Isolated yields. d. STABASE[12] derivative of cystamine. e. Isolated as the 3α, 4β-substituted tetrahydropyridine 9:

f. Lit.[15]: glass. g. The carboxylic acid ($E=CO_2H$) slowly decarboxylates to 3 on standing at room temperature. The sodium salt was obtained on crystallization after treatment of the crude reaction mixture with brine.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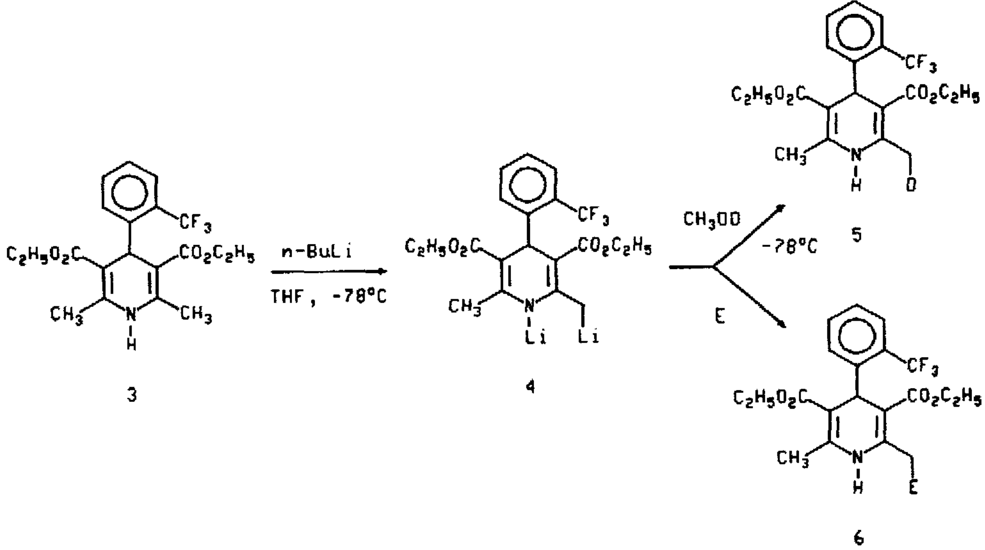
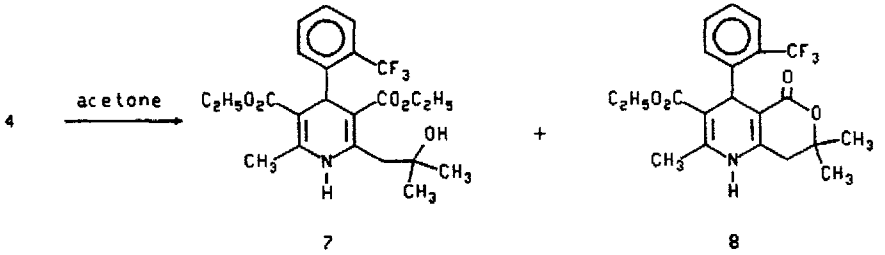
Use of alkyl disulfides, trimethylsilyl cyanide, diethyl chlorophosphonate, butyl isocyanate, and carbon dioxide gave the functionalized dihydropyridines **6a**-**6e** and **6j** in moderate to excellent yields.



Treatment of **4** with methanesulfonyl chloride furnished sulfone **6f** in low yield due to the formation of N-substituted products. Alternatively, **6f** could be obtained in higher yield (71%) by OXONE®[16] oxidation of sulfide **6a**. No ring oxidation to the aromatic species was observed under these conditions.

Formyl and acetyl adducts **6g** and **6h** were isolated in moderate yield from reaction of **4** with either N,N-dimethylformamide or the Weinreb reagent[13]. Similarly, ester adduct **6i** was obtained after treatment of **4** with ethyl cyanoformate (Mander's reagent[14]).

A mixture of hydroxy ester **7** (oil) and lactone **8** (mp 194-195°C) was isolated after treatment of **4** with acetone. Higher yields of the lactone (69%) could be realized by the use of longer reaction periods at ambient temperature before quenching.



In summary Hantzsch dihydropyridine esters can be readily metalated at low temperatures and allowed to react with a variety of electrophiles to afford C-2 methyl functionalized dihydropyridines which are not readily accessible by classical Hantzsch condensation routes.

References and Notes

1. For recent reviews on the preparation and chemistry of dihydropyridines, see: D.M. Stout and A.I. Meyers, *Chem. Rev.*, **82**, 223 (1982); A. Sausins and G. Duburs, *Heterocycles*, **27**, 269 (1988); and A. Sausins and G. Duburs, *ibid.*, **27**, 291 (1988).

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4. Other routes have also been developed to circumvent this problem: I. Sircar, K.R. Anderson, and L. Bonadies, *Tetrahedron Lett.*, **29**, 6835 (1988).

5. A.D. Adams, R.H. Schlessinger, J.R. Tata, and J.J. Venit, *J. Org. Chem.*, **51**, 3068 (1986); and T.A. Bryson and R.B. Gammill, *Tetrahedron Lett.*, 3963 (1974).

6. For an earlier report on the low-temperature metalation of N-methyl dihydropyridines using lithium diisopropylamide followed by non-selective alkylation with alkyl halides, see: J.W. Patterson, *J. Heterocyclic Chem.*, **23**, 1689 (1986).

7. Prepared and purified in a 68% yield by Hantzsch condensation: mp 142-143°C. Lit.[8]: mp 140-142.5°C.

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9. Although myriad dilithio species may be envisioned, for simplicity and clarity **4** is depicted as the N,C-localized dianion.

10. Deuterium incorporation into the vinylogous carbamate group of **5** (the N-D bond) was negligible due to proton exchange with water on workup.

11. Typical experimental procedure: A solution of **3** (10 mmol) in 100 mL of dry, O_2-free tetrahydrofuran is cooled under nitrogen in a dry-ice/2-propanol cold bath (-78°C). A solution of 8.5 mL of n-butyl lithium (21 mmol, 2.5 *M* in n-hexane, Aldrich Chemical Co.) is slowly added via syringe. After stirring the yellow solution for 30 min at -78°C, 1.25 eq of the requisite electrophile is added and the solution is allowed to warm to room temperature. The reaction is quenched by the addition of a saturated aqueous ammonium chloride solution. The layers are separated and the organic portion is washed with water and brine and then dried over anhydrous magnesium sulfate. After filtration the solution is concentrated *in vacuo* and the resulting products purified by either recrystallization or flash chromatography (silica gel, ethyl acetate/ hexanes).

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