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A Double Protection Strategy for the Synthesis of 3,5-Disubstituted Dihydropyridines

Mohammad R. Marzabadi,* Xingfang Hong, and Charles Gluchowski
The Department of Chemistry, Synaptic Pharmaceutical Corporation, 215 College Road, Paramus, New Jersey, 07652.

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Abstract A double protection strategy for the synthesis of the biologically important dihydropyridines is described. Deprotection followed by independent chemical manipulation of the C_3- and C_5-substituents allows one to access a variety of derivatives not readily available using traditional routes.

Introduction Dihydropyridines (DHP's) comprise a large family of medicinally active compounds with precedence as Ca^{++} and K^+ channel blockers, platelet activating factor antagonists, and thromboxane A_2 synthase inhibitors. Our interest in this area stems from the finding that DHP's such as **2** are also potent α_{1a} (formerly α_{1c})[1] antagonists with potential as agents for the treatment of BPH (Benign Prostatic Hyperplasia).[2] The development of methodology to synthesize 3,5-dicarboxylic acid derivatives was very important to our understanding of the SAR of such compounds.[3] Herein, we describe a double protection strategy that uses **1** as a useful common intermediate. The protecting groups of **1** (P_1 and P_2) can be selectively cleaved followed by attachment of the appropriate substituents at C_3 and C_5. The flexibility of this approach is exemplified by the preparation of **2** from the protected intermediate **1** (Figure 1).

The synthesis of dihydropyridine rings was first reported by Hantzsch[4] more than one hundred years ago. Although used extensively in the past, the original Hantzsch synthesis is not suitable for unsymmetrical DHP's. There are different modifications reported for the Hantzsch reaction,[5] but they generally involve the placement of the C_3- and/or C_5-substituents prior to cyclization to form the dihydropyridine ring. One such method, developed by Fax,[5] uses preformed benzylidines (**4**, Scheme 1) for the synthesis of the unsymmetrical DHP's.

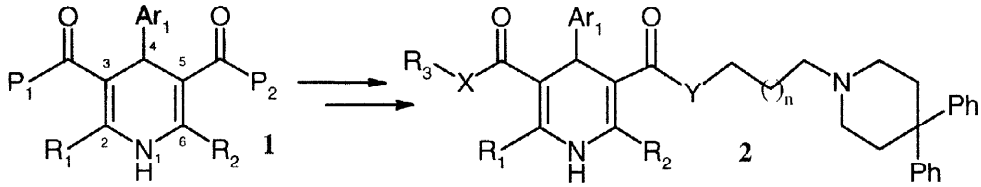

Figure 1: Double Protection in the Synthesis of Dihydropyridines

Double Protection Strategy The C_3- and C_5-esters of DHP's are resistant to basic hydrolysis as compared with other esters. We examined the feasibility of using several protecting groups that did not require "nucleophilic" attack at the C_3- and C_5-carbonyl groups for deprotection. Recently, single protection strategies were described in which the Hantzsch reaction gave a dihydropyridine with one protected cyanoethyl,[6] t-butyl,[7] or trimethylsilylethyl [8] ester. In each case, a subsequent deprotection yielded mono-carboxylic acids which were further manipulated. For our purposes, it was apparent that a double protection strategy would be a useful method to efficiently synthesize a variety of suitably functionalized compounds for our SAR studies. We also anticipated that the use of double protection offers more synthetic opportunities to explore SAR by allowing one to independently elaborate the C_3 and C_5 positions.

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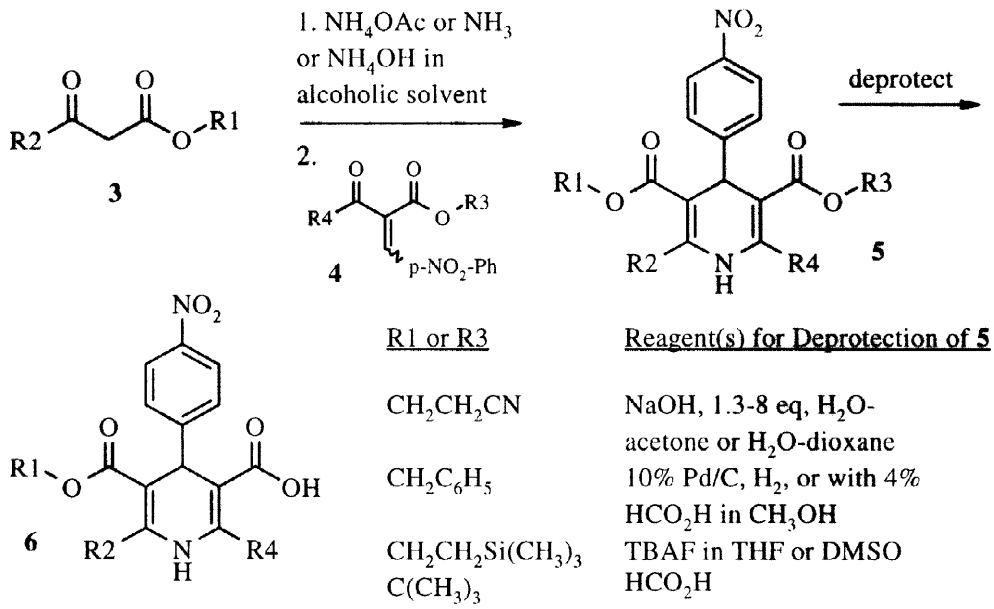


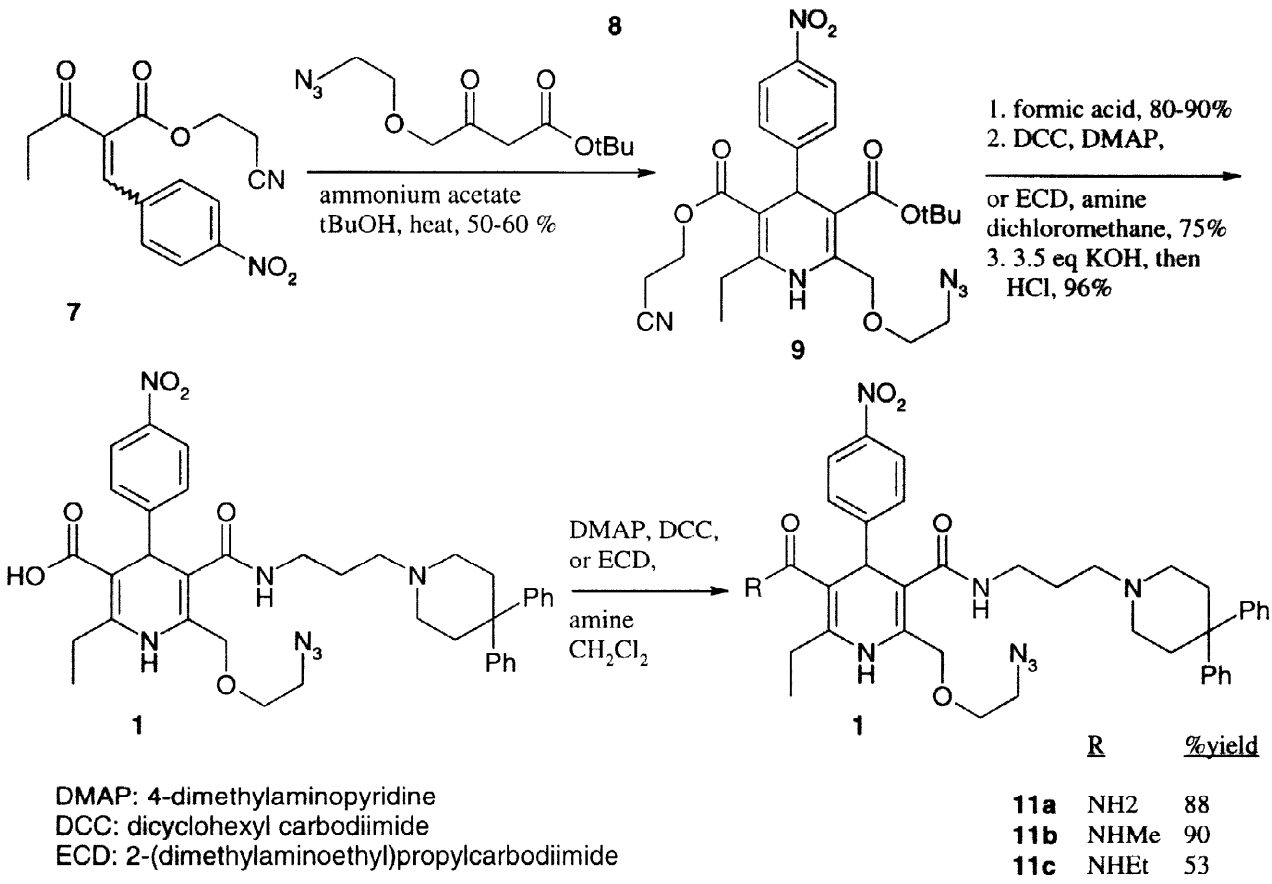
Scheme 1: Synthesis of the Doubly Protected Dihydropyridines

Results Our ability to synthesize various DHP's was dependent on the ease of the synthesis of the ketoesters **3** (Scheme 1). Transesterification at high temperatures was used to synthesize the protected commercially available β-ketoesters. Meldrum's acid route[9] was used to synthesize the protected noncommercial β-ketoesters. The formation of benzylidines **4** from ketoesters and aldehydes proceeded well using catalytic (5-10%) piperidinium acetate in alcoholic solvents at room temperature or benzene under Dean-Stark conditions. The enamides were produced *in situ* using ammonia (THF, 30-50 °C, molecular sieves 4A) or ammonium acetate (ethanol, reflux, 30 minutes). The Hantzsch reaction was performed with benzylidines and enamides in an alcoholic solvent to produce the required doubly protected $C_{3,5}$-diesters (**5**, Scheme 1). Various combinations of the protecting groups were examined and found to be compatible with subsequent chemical reactions: cyanoethyl with t-butyl esters and TMS-ethyl esters, t-butyl esters with benzyl esters. The corresponding deprotection conditions to give the carboxylic acids **6** from esters **5** are summarized in Scheme 1. It is interesting to note that benzyl ester deprotection can occur in the presence of an aromatic nitro group using 4% HCO_2H in MeOH and catalytic 10% Pd/C for 15-30 minutes at room temperature. In the case of t-butyl esters, we found that the t-butyl ester has to be cleaved first because the placement of an amide at C_3/C_5 deactivates the t-butyl ester toward acidic cleavage. In the case of trimethylsilylethyl esters, the use of TBAF (tetrabutylammonium fluoride) in DMSO (vs. THF) as the solvent increases the rate of the deprotection. The use of DMSO as the solvent or with added acid (HCl) as a buffer in the reaction mixture minimizes the formation of side products. We found that TBAF in THF deprotects cyanoethyl esters, probably due to the pH of the reaction medium (a wet pH paper gives a 9-10 value).

A variety of groups were coupled with the carboxylic acids resulting from the double protection methodology, using standard DCC type coupling conditions. A typical amide formation route is depicted in Scheme 2. Manipulation of the doubly protected intermediates such as **9** allowed us to selectively modify C_3- and C_5-substituents of the dihydropyridine ring. The versatility of synthetic intermediates such as **6**, **9** and **10** enabled the expeditious development of the analog program by a parallel synthesis paradigm.

We have described a useful method for the synthesis of $C_{3,5}$-substituted DHP's. The double protection offers alternative synthetic approaches to functionalize both C_3 and C_5 positions of a dihydropyridine selectively. This methodology allowed us to rapidly synthesize a variety of DHP's resulting in a better understanding of the SAR of

this class of compounds. The SAR of the synthesized compounds will be described in due course.



Scheme 2: Double Protection Using t-Butyl and Cyanoethyl esters

Experimental Section:

2-Cyanoethyl 3-Oxopentanoate: A mixture of 143 g of ethyl 3-oxopentanoate ((0.989 mol) and 70.3 g of 3-hydroxypropionitrile (0.989 mol) were placed in a round bottom flask equipped with a short distillation head. The mixture was heated at 180 °C (± 10 °C, bath temperature) for 8 hrs or until no more ethanol could be collected. The reaction mixture was cooled and the product was distilled under reduced pressure to give 110 g (66%) of product as a light yellow oil: bp 120-124 °C (0.4 mmHg).

3-(*tert*-Butyl) 5-(2-Cyanoethyl) 2-[(2-Azidoethoxy)methyl]-6-ethyl-4-(4-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate, 9: A mixture of 1.00 g of t-butyl 4-(2-azidoethoxy)-3-oxopentanoate[10] **8** (4.10 mmol) and concentrated ammonia (0.800 g, 24.6 mmol) in 1.5 mL of t-BuOH was stirred at room temperature for 17 hrs. The solvent was removed *in vacuo* to give a yellow viscous oil. A mixture of the resulting enamide and 850 mg of **7** in 15 mL of t-BuOH was heated at reflux temperature for 5 hrs, concentrated, chromatographed on silica (EtOAc-hexane, 1:3) to give 836 mg the desired product (56%) as a yellow viscous oil.

2-[(2-Azidoethoxy)methyl]-5-[(2-Cyanoethoxy)carbonyl]-6-ethyl-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylic Acid: A mixture of 1.03 g of **9** (1.96 mmol) in 15 mL of formic acid was stirred for 1.25 hrs, and the solvent was removed *in vacuo*. The crude product was triturated with EtOAc and a small amount of hexane and the resulting precipitated yellow product was collected (520 mg, 58%): mp 150 °C (decomp.). More product could be obtained by concentration and trituration of the filtrate. The product was used in the following steps after

spectral characterization.

2-Cyanoethyl 6-[(2-Azidoethoxy)methyl]-5-([3-(4,4-diphenylpiperidino)propyl]aminocarbonyl)-2-ethyl-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate: A solution of 2.10 g of 2-[(2-azidoethoxy)methyl]-5-[(2-cyanoethoxy)carbonyl]-6-ethyl-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylic acid (4.46 mmol), 1.47 g of DCC (7.14 mmol), and 440 mg of DMAP (3.57 mmol) in 30 mL of dry dichloromethane were stirred at room temperature for 40 min. The reaction mixture was charged with 1.71 g of N-(3-aminopropyl)-4,4-diphenylpiperidine[2b] (5.80 mmol), and the reaction mixture was stirred for 2 days and concentrated. Flash chromatography (silica, MeOH-EtOAc 5% to 10%) gave 2.65 g of the desired product (80%) as a yellow foamy solid: mp 63-67 °C. **6-[(2-Azidoethoxy)methyl]-5-([3-(4,4-diphenylpiperidino)propyl]aminocarbonyl)-2-ethyl-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylic Acid, 10**: A solution of sodium hydroxide (200 mg) in 4 mL of water was added to a solution of 2.50 g of 2-cyanoethyl 6-[(2-azidoethoxy)methyl]-5-([3-(4,4-diphenylpiperidino)propyl]aminocarbonyl)-2-ethyl-4-(4-nitrophenyl)-1,4-dihydro-3-pyridinecarboxylate (3.35 mmol) in 10 mL of dioxane. The resulting mixture was stirred at room temperature for 1.5 hrs, and the solvent was removed in vacuo. The residue was dissolved in 250 mL of water, acidified to pH 4 (concentrated HCl), the precipitated yellow solid was collected to give 2.22 g of **10** (96%): mp 118 °C (decomp.). **11a-c**: A mixture of **10** (1 equivalent), DCC (1.5-2 equivalents), DMAP (1 equivalent) in dry dichloromethane were stirred at room temperature for 1-2 hours (monitor by TLC). An aqueous solution of the amine (excess) was added to the reaction mixture and stirred at room temperature (**11a** and **11b**) or heated at reflux (**11c**) for a specified time. The reaction mixture was concentrated, charged with ethyl acetate (drops of dichloromethane were added to make the solution homogeneous), washed with saturated ammonium chloride solution, dried with sodium sulfate, solvent removed and chromatographed on silica (MeOH-EtOAc) to give **11a-c**: **11a**: (88%) as a yellow solid, mp 88-93 °C; Anal. Calcd. for $C_{38}H_{44}N_8O_5$+0.5H_2O: C, 65.03; H, 6.46; N, 15.97. Found: C, 64.80; H, 5.96; N, 15.88; **11b**: (90%) as a yellow solid: mp 95 °C (decomp.); Anal. Calcd. for $C_{39}H_{46}8_8O_5$+1.7H_2O: C, 63.52; H, 6.75; N, 15.19. Found: C, 63.46; H, 6.32; N, 14.82; **11c**: (53%) as a yellow solid, mp 82-87 °C; Anal. Calcd. for $C_{40}H_{48}N_8O_5$+2.0H_2O: C, 63.47; H, 6.92; N, 14.80. Found: C, 63.49; H, 6.24; N, 14.78.

References:

1. Hieble, J.P.; Bylund, D.B.; Clarke, D.E.; Eikenberg, D.C.; Langer, S.Z.; Lefkowitz, R.J.; Minneman, K.P.; Ruffolo, Jr., R.R. *Pharmacol. Rev.* **1995**, *47*, 267-270.
2. a. Forray, C.; Bard, J.A.; Wetzel, J.M.; Chiu, G.; Shapiro, E.; Tang, R.; Lepor, H.; Hartig, P.R.; Weinshank, R.L.; Branchek, T.A.; Gluchowski, C. *Mol. Pharmacol.* **1994**, *45*, 703-708; b. Wetzel, J.M.; Miao, S.W.; Forray, C.; Borden, L.A.; Branchek, T.A.; Gluchowski, C. *J. Med Chem.* **1995**, *38*, 1579-1581.
3. For a preliminary SAR report, See Wong, W.; Marzabadi, M.R.; Wetzel, J.; Chiu, G.; Nagarathnam, D.; Wang, D.; Hong, X.; Miao, S.W.; Fang, J.; Forray, C.; Vaysse, P.J.-J.; Branchek, T.A.; Gluchowski, C. *210th American Chemical Society National Meeting*, Chicago, IL, August 20-24, **1995**, MEDI #43
4. Hantzsch, A. *Liebigs Ann. Chem.* **1882**, *215*, 1.
5. Fax, H.H.; Lewis, J.I.; Wenner, W. *J. Org. Chem.* **1951**, *16*, 1259-1270.
6. See, e.g., Ashimori, A.; Ushida, T.; Ohtaki, Y.; Tanaka, M.; Ohe, K.; Fukaya, C.; Watanabe, M.; Kagitani, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1991**, *39*, 108-111; Shibanuma, T.; Iwanami, M.; Okuda, K. Takenaka T.; Murakami, M. *Chem. Pharm. Bull.* **1980**, *28*, 2809.
7. Ramesh, M.; Matowe, W.C.; Wolowyk, M.W.; Knaus, E.E. *Drug Design and Delivery* **1988**, *3*, 337-341; Enders, D.; Muller, S.; Demir, A.S. *Tetrahedron Lett.* **1988**, *29*, 6437-6440.
8. Tacke, R.; Bentlage, A.; Towart, R.; Moeller, E. Eur. *J. Med. Chem.* **1983**, *18(2)*, 155-161.
9. Oikawa, Y.; Sugano, K.; Yonemitsu, O.; *J. Org. Chem.* **1978**, *43*, 2087-2088.
10. For the synthesis of the ethyl ester, See, Arrowsmith, J.E.; Campbell, S.E.; Cross, P.E.; Stubbs, J.K.; Burges, R.A.; Gardiner, D.G.; Blackburn, K.J. *J. Med. Chem.* **1986**, *29*, 1696-1702.