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AN IMPROVED AND EFFICIENT SYNTHESIS OF 2-SUBSTITUTED 1,4-DIHYDROPYRIDINE DERIVATIVES VIA REGIOSPECIFIC BROMINATION

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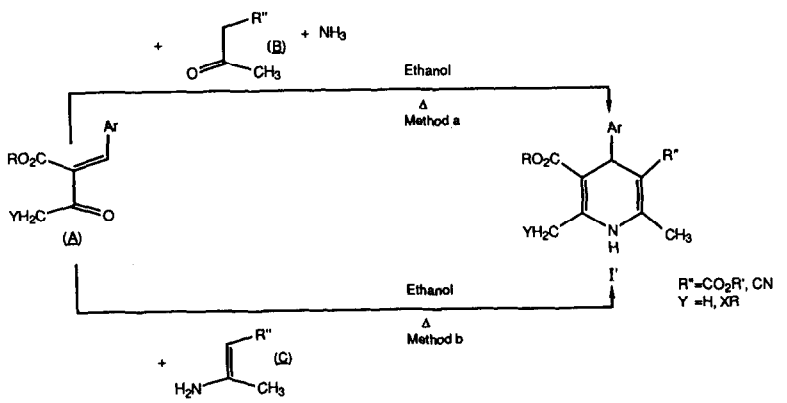
Abstract. A highly regioselective conversion of DHP I to DHP II has been achieved for the first time in high yield. Treatment of the bromide II with different nucleophiles under basic conditions produced 2-substituted 1,4-dihydropyridines in high yields and purity.

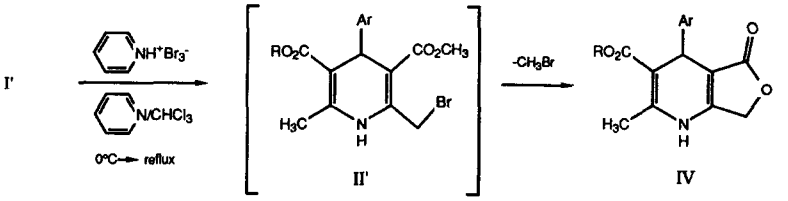
The conventional method of synthesis of 1,4-dihydropyridine (DHP) derivatives I' is via the Hantzsch procedure employing all the components in different combinations (Scheme 1, R"=CO_2R' and Y=H). A typical procedure involves the condensation of the benzylidene A with either (i) the requisite β-ketoester B and ammonia (method a) or (ii) the enamine C thereof (method b).[1]

Scheme 1



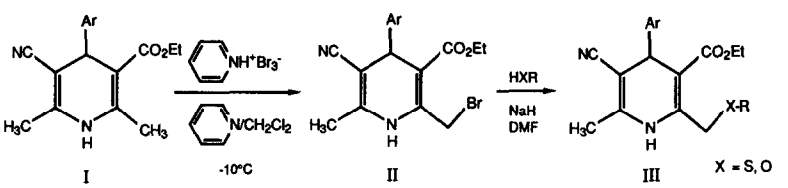
These procedures work moderately well for symmetrical dihydropyridines, but the yields of the desired products decrease very rapidly for asymmetrically substituted dihydropyridines. In an attempt to prepare dihydropyridine analogs III using the typical procedure, we obtained a complex mixture from which target compounds were isolated in yields anywhere between 10-30% after extensive chromatography. Thus, it was necessary to find an alternative procedure, and if possible, utilize a common intermediate for analog synthesis. Young[2] has reported the synthesis of lactone IV via an unstable bromide II' (Scheme 2).

Scheme 2



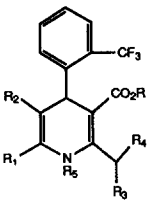
We investigated this bromination reaction in depth to evaluate the suitability of the brominated species II' as an intermediate for a variety of 2-substituted dihydropyridines which are otherwise difficult to access. Bromination of dihydropyridine I[3] with pyridinium bromide perbromide in CH_2Cl_2 at -10°C gave the regiospecific bromide II which was isolated by flash chromatography in 70-90% yield. The bromide was obtained as a pale yellow foam which can be stored for several weeks under vacuum. The compound was characterized by ^1H NMR and elemental analysis. The chemical shift for CH_2Br ($CDCl_3$) appears as a doublet of doublets centered around 4.6 ppm. The bromine was then displaced with a variety of nucleophiles in the presence of sodium hydride yielding target compounds of general structure III in high yields (Scheme 3, Table II).

Scheme 3



Structures of these 2-substituted dihydropyridines were proven from the spectral data, elemental analysis, and by comparison with authentic compounds prepared previously by the conventional procedure (Scheme 1, R"=CN and Y=XR). In Young's case the ease of elimination of methyl bromide made the bromide II' rather unstable, but we were able to purify 2, Table I) via flash chromatography, and convert 2 to the desired dihydropyridine (13, Table II) by following same procedure employed for the ethyl ester. Excess brominating agent provided bisbrominated species which were characterized only in few cases. To expand the scope of the bromination reaction effects of i) different functional groups at the 5-position, ii) different ester functions at the 3-position, iii) substitution at the dihydropyridine nitrogen, and iv) substitution at the 2-methyl position of the DHP ring were also studied. The data in the Table I indicate the versatility of this method.

TABLE I. Brominated Dihydropyridine Derivatives



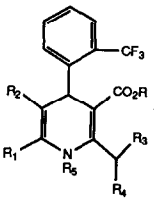
Compound Number	R	R_1	R_2	R_3	R_4	R_5	Yield[a]	^{1}HNMR($CDCl_3$) (ppm, CH R_3 R_4)
1	Et	Me	CN	H	Br	H	90	4.6 (dd)
2	Me	Me	CN	H	Br	H	72	4.6 (dd)
3	CH_2CH_2CN	Me	CN	H	Br	H	73	4.6 (dd)
4	Me	Me	CN	SO_2Ph	Br	H	66	6.9 (s)
5	Et			H	Br	H	71	4.6 (dd) ($DMSO-d_6$)
6	Et			H	Br	H	85	4.6 (dd)
7	Et			Br	Br	H	14	7.3 (s) ($DMSO-d_6$)
8	Et	Me	CN	Me	Br	H	75	4.6 (s)
9	Et	Me	CN	H	Br	Me	76	4.6 (dd)

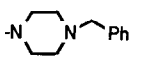
[a]Isolated yield by chromatography.

Typical Procedure: Bromination of DHP I. General Procedure. To a solution of 5 g (14.3 mmol) of I in 100 mL of $CHCl_3$ containing pyridine (1.2 mL, 15.2 mmol) at -10°C was added in one portion 5.2 g (16.2 mmol) of 90% pyridinium bromide perbromide. The solution was stirred for 45 min and evaporated under reduced pressure at 30°C. The bromide (6 g, 1, Table I) was obtained by flash chromatography over silica gel (10% EtOAc/CH_2Cl_2).

Preparation of DHP III. General Procedure. To an ice cold solution of the sodium salt of 4-mercaptopyridine (derived from 1.5 g of 4-mercaptopyridine and 0.5 g of (60%) NaH) in 50 mL of THF/DMF was added a solution of the above bromide in 30 mL of THF and the mixture was stirred for 1 h. The solution was allowed to come to room temperature for an additional hour to complete the reaction. Water (100 mL) was added, and the oil was extracted with CH_2Cl_2, and the extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from EtOAc to give 5.1 g of the desired product (11, Table II).

TABLE II. 2-Substituted Dihydropyridine Derivatives



Compound Number	R	R_1	R_2	R_3	R_4	R_5	Yield[a]	mp °C
10	Et	Me	CN	H	SPh	H	60	112-114
11	Et	Me	CN	H	S-Py(4)	H	80	222-224
12	Et	Me	CN	H	S-Ph-CO_2Me(2)	H	21	181-182
15	Et	Me	CN	H	S-Py(4)	CH_3	58	168-170
16	Et	Me	CN	Me	S-Py(4)	H	50	133-135
17	Et			H	S-Py(4)	H	60	Foam
18	Et			H	S-Py(4)	H	40	178-180
19	Et	Me	CN	H		H	83	179-180.5
20	Et	Me	CN	H		H	75	174-175
21	Et	Me	CN	H		H	35	216-218

[a]Yields refer to the overall yield from dihydropyridines.

In conclusion, we have developed a general, efficient, high yield, and operationally simple procedure for the synthesis of a wide variety of 2-substituted dihydropyridines having different functionality at the 3- and 5- positions.

Acknowledgment. We thank F. A. Mackellar and his associates for spectral determinations and microanalyses.

References.

[1]D. M. Stout and A. I. Meyers, Chem. Rev, J. Med. Chem., 1982, 82, 223.

[2]S. D. Young, Synthesis, 1984, 617.

[3]Prepared via the conventional procedure.

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