SELECTIVE MONO BROMINATION OF 1,4-DIHYDROPYRIDINES

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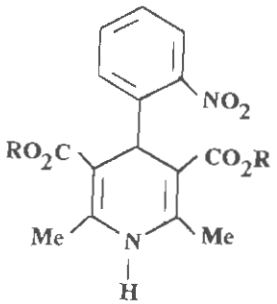
ABSTRACT: *2-monobromomethyl 1,4-dihydropyridines is selectively synthesized by bromination of the parent compound by 1.1 equivalents of pyridinium bromide perbromide in dichloromethane/pyridine at -20 °C. The same reagent in dichloromethane at 0 °C produce the 2,6-bis(bromomethyl) 1,4-dihydropyridines.*

KEY WORDS: *Nifedipine analogues, Calcium channel antagonist, 1,4-Dihydropyridines, Bromomethyl-1,4-dihydropyridines.*

INTRODUCTION

As a class of chemical compounds, 1,4-dihydropyridine-3,5-dicarboxylates have been known since 1882 when *Hantzsch* discovered them as stable intermediates in the pyridine synthesis which bears his name [1,2]. In spite of their ready accessibility and the significance of dihydropyridines as coenzymes of numerous dehydrogenases, this class of compounds found little interest until mid-sixties [3]. Then, the vasodilating properties and hence the pharmacological activities of numerous 4-aryldihydropyridine-3,5-dicarboxylates first beacme known and were widely investigated. Among many derivatives, nifedipine **1a**, the prototype of 1,4-dihydropyridine calcium antagonists, has dramatically improved the therapeutic standard in the treatment of coronary heart diseases [4].

Synthesis and biological activity of isoxazolyl-1,4-dihydropyridines (IDHPs) is reported [5]. A rapid



1

Nifedipine **a: R=Me**

b: R=Et

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entry into 1,4-dihydropyridine-3,5-dicarboxylic acid diesters was required in which 2-methyl group could be substituted by various groups.

EXPERIMENTAL

Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. 1H NMR spectra were recorded on Bruker AC-80 (80 MHz) and Bruker 400 MHz spectrometers using $CDCl_3$ as the solvent. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer. Mass spectra were taken on Finnigan-Mat 8430 and Shimadzu QP1000A. Solvents prior to being used were distilled under N_2 atm., THF was freshly distilled from Na/benzophenone; CH_2Cl_2 , DMF were distilled from CaH_2 and stored over 4 Å molecular sieves; pyridine was dried over molecular sieves.

Unless otherwise noted, all extracts were dried over anhydrous Na_2SO_4 and the solvent was removed by rotary evaporation under reduced pressure. All new compounds are homogenous on TLC and their purities were further verified by ^1H NMR. For column chromatography silica gel 60 (*Merck* 70-230 mesh) or neutral alumina (70-230 mesh) was used, for TLC and PTLC, silica gel $HF60_{(254+366)}$ was used. All reactions involving air or moisture sensitive compounds were performed under N_2 atm.

All solvents and reagents were of reagnet grade, all reagents were purchased from *Aldrich, Merck* and *Fluka* unless otherwise indicated.

Preparation of 2,6-dimethyl- 3,5-dicarboethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine (5)

A mixture of 3-nitrobenzaldehyde (10.0 g, 64.8 mmol), ethylacetoacetate (16.7 mL, 64.8 mmol), 25% ammonia (40.0 mL, 260 mmol) and ethanol (220.0 mL) was heated to reflux (75 °C) for 72 hours. The reaction mixture was cooled and the yellow solid which precipitated was filtered. Recrystallization from ethylacetate-hexane gave **6** as a yellow solid (57%, m.p. 169 °C). δ_H(400 MHz, $CDCl_3$): 1.24(6H, t, J=6.5, ester $2\times CH_3$), 2.36(6H, s, allylic $2\times CH_3$), 4.1(4H, m, ester $2\times CH_2$), 5.1(1H, s, CH), 6.1(1H, s, NH), 7.4-8.15(4H, m, ArH); $\bar{\nu}_{max}$(KBr)/cm^{-1} 3350 (NH), 3080(ArH), 1707(C=O ester), 1640 (C=C), 1520(NO_2), 1370, 1345(NO_2); m/z(%) 372(2), 251 (74), 224(20), 196(44), 170(100), 151(36), 70(71), 28(82); Anal. Calcd. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.91, N, 7.48. Found: C, 60.89; H, 5.84; N, 7.54.

Preparation of 2- bromomethyl-6- methyl-3,5-dicarboethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine (6)

To a solution of **5** (0.3 g, 0.96 mmol) in CH_2Cl_2 (20.0 mL) at –10 °C was added pyridine (0.08 mL, 1mmol) and pyridinium bromide perbromide (0.34 g, 1 mmol). The solution was stirred for 45 minutes (–10 °C) and after completion of the reaction, it was diluted with CH_2Cl_2 (20.0 mL) and washed with hydrochloric acid (20.0 mL of 2M). The solution was then dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The bromides (66% of **6**, and 20% of **7**) were obtained by column chromatography over silica gel 60(2% EtOAc/CH_2Cl_2, m.p. 143-44 °C). δ_H(80 MHz, $CDCl_3$): 1.3(6H, dt, ester $2\times CH_3$), 2.4(3H, s, allylic CH_3), 4.15(4H, dq, 2 CH_2O), 4.75(2H, dd, J=11 Hz, allylic CH_2Br), 5.15 (1H, s, CH), 6.2(1H, broad s, NH), 7.3-8.2(4H, m, ArH); $\bar{\nu}_{max}$(KBr)/cm^{-1} 3300 (NH), 3100(ArH), 3050 (CH_2Br), 1705(ester C=O), 1675(C=C), 1525, 1350 (NO_2), 1290(C-N).

Preparation of 2,6-bis(bromomethyl)-3,5- dicarboethoxy-4-(3-nitrophenyl)-1,4- dihydropyridine (7)

To a solution of **5** (0.60 g, 1.6 mmol) in CH_2Cl_2 (20.0 mL) at 0 °C (ice-bath) pyridinium bromide perbromide (1.126 g, 3.5 mmol) was added. The solution was stirred for 45 minutes and diluted with CH_2Cl_2 (30.0 mL) and was washed with hydrochloric acid (30.0 mL of 2M) and brine (2×30.0 mL), the solution was then dried over anhydrous sodium sulfate and the solvent was removed in vacuo. The bromide (95%) was obtained by flash chromatography over silica gel 60(10% EtOAc/CH_2Cl_2). There was no obvious change on heating up to 149 °C, after which it was converted to the corresponding lactone by loss of C_2H_5Br (as indicated by IR). δ_H(80 MHz, $CDCl_3$): 1.25(6H, t, J= 7.2 Hz ester $2\times CH_3$), 4.17 (4H, q, J= 7.2 Hz ester $2\times CH_2$), 4.8

(4H, dd, J= 11 Hz, 2×CH_2Br), 5.15(1H, s, CH), 6.6 (1H, broad s, NH), 7.4-8.3(4H, m, ArH); $\bar{\nu}_{max}$(KBr)/ cm^{-1} 3300 (N-H), 3100(ArH), 2970-2800, 1705(ester, C=O), 1670(C=C), 1525, 1350(NO_2).

RESULTS AND DISCUSSION

Young [6] reported that reaction of the 1,4-dihydropyridines **2** with pyridinium bromide perbromide in chloroform solution at 0 °C gave an unstable brominated species which on heating yielded lactones **4** (Scheme 1).

Reaction of **5** with 1.1 equivalents of pyridinium bromide perbromide in dichloromethane at 0 °C followed by rapid work-up afforded 2-bromomethyl derivative **6** (23%) and 2,6-dibromomethyl derivative **7** (40%).

The method was not suitable for obtaining monobromide **6** regioselectively.

It was found that, reaction of **5** with 2 equivalents of pyridinium bromide perbromide in dichloromethane at 0 °C produces **7** (>90%) and with 1.1 equivalents of the same brominating agent in dichloromethane/pyridine at −20 °C gives **6** (>98%) (Scheme 2), (Table 1).

Since elimination of bromoethane from brominated compounds **6** or **7** in contrast to the elimination of bromomethane from compound **3** (reported by *Young* [6]) occurs much slower, so brominated compounds **6** and **7** were relatively stable and ^{1}H NMR spectrum of the recrystallized compound (ethylacetate/hexane) **6** shows no change after 2 weeks of standing at room temperature.

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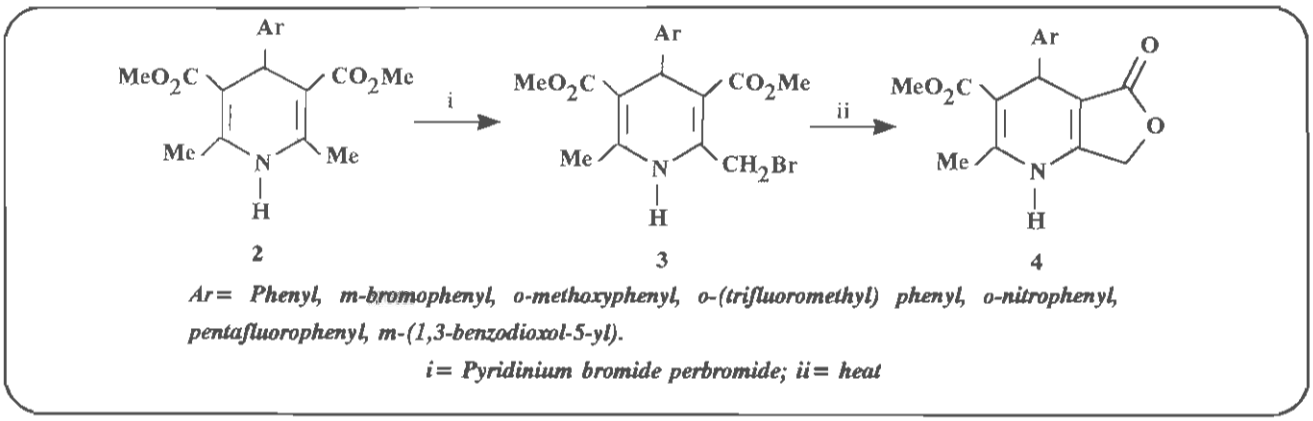
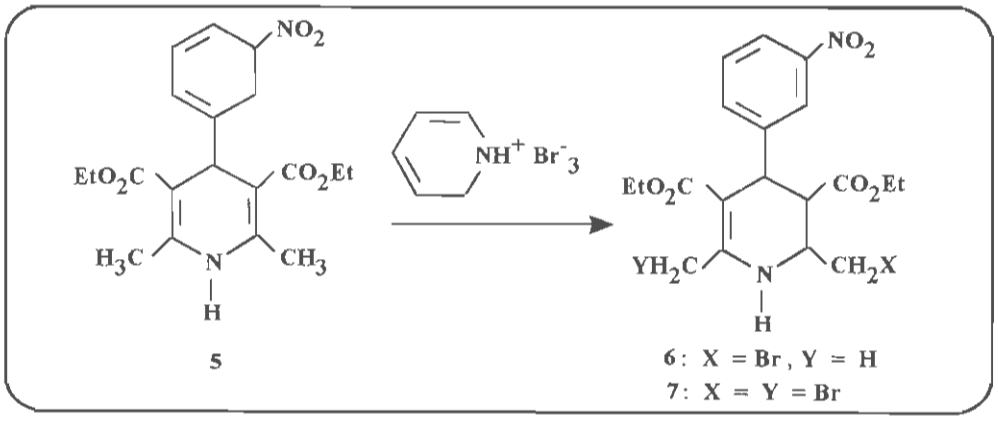


2 **3** **4**

Ar= Phenyl, m-bromophenyl, o-methoxyphenyl, o-(trifluoromethyl) phenyl, o-nitrophenyl, pentafluorophenyl, m-(1,3-benzodioxol-5-yl).

i= Pyridinium bromide perbromide; ii= heat

Scheme 1



5

6: X = Br , Y = H

7: X = Y = Br

Scheme 2

Table 1 :

Solvent system	Reaction temperature °C	% Yield of monobromide product **6**	% Yield of dibromide product **7**	Unreacted[a] starting material **5**	Ratio of brominating agent to **5**
dichloromethane	0	23	40	31	1.1
dichloromethane	−10	23	32	40	1.1
dichloromethane/ pyridine	−10	66	20	—	1.1
dichloromethane/ pyridine	−20	>98	—	—	1.1
dichloromethane	0	—	>90	—	2

[a] *Separated by chromatography over silica gel*

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