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 became 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 isoxazoly-1,4-dihydropyridines (IDHPs) is reported [5]. A rapid
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 Electro-
thermal 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\(_2\)Cl\(_2\), 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\(_2\)SO\(_4\) 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 reagent grade,
all reagents were purchased from Aldrich, Merck and
Fluka unless otherwise indicated.

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

A mixture of 3-nitrobenzaldehyde (10.0 g, 64.8
mmol), ethylacetocetate (16.7 mL, 64.8 mmol), 25%
nitric acid (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). \( \delta_H \) (400 MHz, CDCl\(_3\)): 1.24(6H, t,
J=6.5, ester 2×CH\(_3\)), 2.36(6H, s, alllic 2×CH\(_3\)),
4.1(4H, m, ester 2×CH\(_2\)), 5.1(1H, s, CH), 6.1(1H, s,
N=H), 7.4-8.15(4H, m, ArH); \( \nu_{\text{max}} \) (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. Caled. for C\(_9\)H\(_{12}\)N\(_2\)O\(_2\): 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-
dicarboxethoxy-4-(3-nitrophenyl)-1,4-dihydropy-
ridine (6)

To a solution of 5 (0.3 g, 0.96 mmol) in CH\(_2\)Cl\(_2\)
(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\(_2\)Cl\(_2\) (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 chromato-
graphy over silica gel 60(2% EtOAc/CH\(_2\)Cl\(_2\), m.p.
143-44 °C). \( \delta_H \) (80 MHz, CDCl\(_3\)): 1.3(6H, dt, ester
2×CH\(_3\)), 2.4(3H, s, allicylic CH\(_3\)), 4.15(4H, dq, 2
CH\(_2\)O), 4.75(2H, dd, J=11 Hz, allicylic CH\(_2\)Br), 5.15
(1H, s, CH), 6.2(1H, broad s, N=H), 7.3-8.2(4H, m,
ArH); \( \nu_{\text{max}} \) (KBr) cm\(^{-1}\) 3300 (NH), 3100(ArH), 3050
(CH\(_2\)Br), 1705(esterr C=O), 1675(C=C), 1525, 1350
(NO\(_2\)), 1290(C-N).

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

To a solution of 5 (0.60 g, 1.6 mmol) in CH\(_2\)Cl\(_2\)
(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\(_2\)Cl\(_2\) (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 chromato-
graphy over silica gel 60(10% EtOAc/CH\(_2\)Cl\(_2\)).
There was no obvious change on heating up to
149 °C, after which it was converted to the corre-
sponding lactone by loss of C\(_2\)H\(_2\)Br (as indicated
by IR). \( \delta_H \) (80 MHz, CDCl\(_3\)): 1.25(6H, t, J= 7.2 Hz ester
2×CH\(_3\)), 4.17 (4H, q, J= 7.2 Hz ester 2×CH\(_2\)), 4.8
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 mono-bromide 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 ¹H NMR spectrum of the recrystallized compound (ethyl-acetate/hexane) 6 shows no change after 2 weeks of standing at room temperature.

ACKNOWLEDGMENTS

This work was financially supported by Tabriz University. One of the authors (Y.R.M) is grateful to Professor N. R. Natale for providing some chemicals and Professor Y. Ipakchi for ¹H NMR measurements.

Received, 18th July 1996; Accepted, 17th December 1996
Table 1:

<table>
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<th>Solvent system</th>
<th>Reaction temperature °C</th>
<th>% Yield of monobromide product 6</th>
<th>% Yield of dibromide product 7</th>
<th>Unreacted* starting material 5</th>
<th>Ratio of brominating agent to 5</th>
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* Separated by chromatography over silica gel

REFERENCES