Research Article

Synthesis of 1,4-Dihydropyridines Bearing a Carbamate Moiety on the 4-Position

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A good range of 1,4-dihydropyridines bearing a carbamate moiety on the 4-position were synthesized from the primary reaction of different hydroxyaldehydes with phenyl isocyanates and the subsequent reaction of the obtained carbamates with methyl acetoacetate in the presence of ammonium fluoride. When phenyl isothiocyanate was used in place of phenyl isocyanate in the same condition, the reaction did not take place.

1. Introduction

1,4-Dihydropyridines and their derivatives have gained considerable importance in the field of organic and medicinal chemistry since they have fascinating pharmacological properties [1–9]. The 1,4-dihydropyridine skeleton is common in many to be useful as calcium channel blockers [10, 11], and they are used most frequently as drugs such as nifedipine, nicardipine, and amlopidipine which have been found as cardiovascular agents for the treatment of hypertension [12]. Moreover, studies have discovered that 1,4-dihydropyridines exhibit diverse medical functions such as neuroprotectants, platelet antiaggregators, and chemosensitizers and are important in Alzheimer’s disease as anti ischaemic agents [13, 14]. However, preparation of new type of 1,4-dihydropyridines is an active ongoing research area, and there is scope for further improvement toward milder reaction conditions and improved yields. We demonstrated that the ammonium salt could be replaced with ammonia [15]. A number of improved methods have been reported in the literature for this condensation which involve the use of microwave, ionic liquids, reflux high temperature, AlCl₃·6H₂O [16], ultrasound irradiation [17], tetrabutylammonium hydrogen sulfate [18], cyanuric chloride [19], molecular iodine [20], silica gel-supported sodium bisulfate [21], TMSCI-NaI [22], scandium(III) triflate [23], CAN [24], iron(III) trifluoroacetate and trifluoromethanesulfonate [25], organocatalysed [26], silica gel/sulfonic acid [27], PTSSA [28], montmorillonite K10 clay [29], and phenylboronic acid [30]. Additionally, dihydropyridines are often produced in a synthetic sequence and have to be oxidized to pyridines [31].

The most interesting aspect of dihydropyridines can be attributed to the coenzyme reduced nicotinamide adenine dinucleotide (NADH) and the unique ability of these compounds in biological systems to reduce unsaturated functionalities and also strained ring systems (carbonyls, conjugated olefins, epoxides, etc.) [32]. Although 1,4-dihydropyridines with various aromatic, heteroaromatic [33], aliphatic, and sugar [34] substituents at C4 have been reported, there is no report of 1,4-dihydropyridines bearing carbamate substituent at C4.

2. Result and Discussion

We decided to develop the chemistry of this class of compounds and also provide a clean and easy work-up procedure. In continuation of our researches on the synthesis of heterocycles [35–41], we herein report a good range of 1,4-dihydropyridines which have a carbamate moiety on the 4-position. They were synthesized from a primary reaction of different hydroxyaldehydes with phenyl isocyanates and the subsequent reaction of the obtained carbamates with methyl acetoacetate in the presence of ammonium fluoride.
(Scheme I and Table I). The obtained carbamates (R\(^{\text{O}}\)CHO, 1a–f) will then react with methyl acetoacetate in the presence of ammonium fluoride to give different 1,4-dihydropyridines (2a–f, Scheme 2 and Table 2).

When phenyl isothiocyanate was used instead of phenyl isocyanate in the same condition, the reaction did not take place. Also, when ammonium carbonate was used instead of ammonium fluoride, the dihydropyridine which contains phenolic group at 4-position and phenylcarbamic acid were obtained. So dimethyl 2,6-dimethyl-4-(4-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2a) will be hydrolyzed to dimethyl 4-(4-hydroxy-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylate (3a, m.p. 224–226 \(^\circ\)C) and phenylcarbamic acid in the presence of ammonium carbonate (Scheme 3). Apparently, the released water from ammonium carbonate hydrolyzes the carbamate part of the dihydropyridines.

All compounds were characterized by \(^1\)H NMR and IR. In the \(^1\)H NMR spectrum of the 1,4-dihydropyridines a peak at 4.3–4.92 ppm belongs to the proton at C-4 position. In the IR spectrum, a strong absorbance peak for the N–H group of the corresponding 1,4-dihydropyridines appears at 3277–3336 cm\(^{-1}\) (Figure 1, see Supporting Information available online at http://dx.doi.org/10.1155/2013/495982).

### 3. Experimental

All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterized by spectroscopy data (FT-IR, \(^1\)H NMR spectra). The NMR spectra were recorded in CDCl\(_3\), acetone, and DMSO. \(^1\)H NMR spectra were recorded on a Bruker Avance DRX 90 MHz instrument. The chemical shifts (\(\delta\)) are reported in ppm relative to the TMS as internal standard. FT-IR (KBr) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. The elemental analysis was performed using Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel polygram SIL G/UV 254 plates.

#### 3.1. General Procedure for the Synthesis of Carbamates (1a–f)

A mixture of hydroxybenzaldehydes (1.0 mM) and phenyl isocyanate derivatives (1.0 mM) was stirred in ethyl acetate or
Scheme 2: Preparation of different 1,4-dihydropyridines from carbamates and methyl acetoacetate.

\[
\begin{align*}
\text{R''CHO} & \quad \text{(1a-f)} \quad \xrightarrow{\text{NH}_4\text{F}} \quad \text{NH}_4\text{F} \quad 80^\circ\text{C} \\
\text{H}_2\text{C} & \quad \text{O} \quad \text{O} \quad \text{CH}_3 \\
\end{align*}
\]

Scheme 3: Hydrolysis of 2a.

Figure 1: IR spectrum of dimethyl 2,6-dimethyl-4-(4-(phenylcarbamoyloxy)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2a).
Table 2: Synthesis of 1,4-dihydropyridine derivatives (2a–f).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbamates</th>
<th>Product</th>
<th>Yield %</th>
<th>Time (h)</th>
<th>M.p. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="1a" /></td>
<td><img src="image2.png" alt="2a" /></td>
<td>88</td>
<td>17</td>
<td>240–243</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="1b" /></td>
<td><img src="image4.png" alt="2b" /></td>
<td>91</td>
<td>24</td>
<td>233–238</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="1c" /></td>
<td><img src="image6.png" alt="2c" /></td>
<td>75</td>
<td>24</td>
<td>228–234</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="1d" /></td>
<td><img src="image8.png" alt="2d" /></td>
<td>53</td>
<td>24</td>
<td>225–230</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="1e" /></td>
<td><img src="image10.png" alt="2e" /></td>
<td>70</td>
<td>20</td>
<td>242–248</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="1f" /></td>
<td><img src="image12.png" alt="2f" /></td>
<td>69</td>
<td>20</td>
<td>232–244</td>
</tr>
</tbody>
</table>

*a* Isolated yield.

 solvent-free at 70°C in an appropriate time, and progress of the reaction was monitored by TLC (Scheme 1, Table 1). After completion, the suspension was cooled, ethyl acetate evaporated, the solid was crystallized in ethanol to get the pure carbamates, and the obtained crystals were characterized by ¹H NMR and IR.

3.2. Typical Procedure for the Synthesis of 1,4-Dihydropyridines (2a–f). A mixture of carbamate (1.0 mM), methyl acetoacetate (2.0 mM), and ammonium fluoride (2.0 mM) was stirred in ethyl acetate at 80°C for appropriate time, and progress of the reaction was monitored by TLC (Scheme 2, Table 2). After completion, the suspension was cooled, ethyl
acetate evaporated, and ethanol was added to dissolve any impurities since the 1,4-dihydropyridines donot dissolve in ethanol. The obtained solid was pure and characterized by \(^1\)H NMR and IR.

4. Conclusions

We demonstrated the synthesis of a good range of 1,4-dihydropyridines which have a carbamate moiety on the 4-position from the primary reaction of different aldehydes with phenyl isocyanate and the subsequent reaction of the obtained carboxamides with methyl acetoacetate in the presence of ammonium fluoride. As stated before, when phenyl isothiocyanate was used instead of phenyl isocyanate in the same condition, the reactions did not take place.

Disclosure

The authors of the paper do not have a direct financial relation with the commercial identities mentioned in this paper.

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