Abstract – An improved procedure for the synthesis of diastereoenriched tetrasubstituted 4,5-dihydrofurans by using I\(_2\)-induced enolcyclization of \(\beta\)-keto esters is reported. The reactions using I\(_2\) in anhydrous MeCN are considered under thermodynamic control and the more stable \(\textit{trans}\) isomers are preferentially produced.

INTRODUCTION

Furan and dihydrofuran units are present in a wide variety of naturally occurring substances\(^1\) and studies directed towards their synthesis are of strategic importance for the preparation of natural or biologically interesting more complex compounds.

Prompted by an interest that these chemical units have roused in the scientific community,\(^2\) in the past we have investigated a new strategy for synthesizing tetrasubstituted furans and dihydrofurans\(^3\) from 2-allyl-\(\beta\)-dicarbonyl compounds, by using a cyclization process promoted by the I\(_2\)/Na\(_2\)CO\(_3\) system, of which we also investigated regiochemical aspects.\(^4\)

Using \(\beta\)-keto esters the reaction leads to mixtures of diastereoisomers and at time good selectivity in favour of \(\textit{cis}\)-isomers is seen.\(^5\)

We report now an improvement of this method to obtain very good diastereoselections in almost every case. Using I\(_2\) in anhydrous MeCN, and in the absence of bases, all steps of the process are in equilibrium and the most stable products are produced.
RESULTS AND DISCUSSION

As the first substrate we used 2-allylacetoacetate (1a) (Entry 1, Table 1) and the trans-4,5-dihydrofuran derivative was obtained in a highly stereoselective manner with a trans-cis ratio of 96:4. The same substrate gave a trans-cis ratio of 77:23 performing the reaction in the presence of Na₂CO₃. In Table 1 the results of iodoenolcyclizations performed by treating 2-allyl-β-keto esters with I₂ in anhydrous MeCN are summarized. Under standard conditions, using Na₂CO₃ as a base to enhance the enolisation of the active compound, low diastereoselectivities were observed.

Table 1. I₂-enolcyclization of 1,3-keto esters under thermodynamic conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound (I)</th>
<th>R</th>
<th>X</th>
<th>Y</th>
<th>Time</th>
<th>Yield (%)</th>
<th>2:3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>1 h</td>
<td>95</td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>Me</td>
<td>Ph</td>
<td>Et</td>
<td>1 h</td>
<td>77</td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>Me</td>
<td>t-Pr</td>
<td>Et</td>
<td>1 h</td>
<td>90</td>
<td>98:2</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>Me</td>
<td>n-Pr</td>
<td>Et</td>
<td>2 h</td>
<td>97</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>1 h</td>
<td>94</td>
<td>69:31</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>Ph</td>
<td>Ph</td>
<td>Et</td>
<td>1 h</td>
<td>82</td>
<td>95:5</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>Ph</td>
<td>t-Pr</td>
<td>Et</td>
<td>1 h</td>
<td>87</td>
<td>97:13</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>Ph</td>
<td>n-Pr</td>
<td>Et</td>
<td>1 h</td>
<td>91</td>
<td>75:25</td>
</tr>
</tbody>
</table>

We previously proposed a mechanism for the kinetically controlled process in which the presence of a base (Na₂CO₃) caused the precipitation of NaI in the reaction medium (CH₂Cl₂), making the ring closure an irreversible step. In the absence of a base, however, the I⁻ is the counterion of the intermediate and can remove I⁺ from the cyclization product thus transforming the ring closure into a reversible process. The reaction is thus under thermodynamic control and the more stable trans-isomer is preferentially produced. Reactions with acetoacetate derivatives having R=Ar, are an exception and less selective.

In kinetically controlled cyclization reactions the stereochemistry of the products depends on how I₂ approaches the double bond. In our case, the overall reaction is the result of a series of reversible steps with the thermodynamic stability of the products being the key factor determining the outcome. In contrast, the same method applied to β-diketones gave mainly the cis-isomers of the cyclized products.

To complete our research we investigated the role that the substituent on the allylic side chain of the acetoacetate derivatives had on the stereochemical course of the reaction. The results are summarized in Table 2 and are in agreement with the proposed mechanism, as shown in Scheme 1. In the case of Entry 5, where R=Ph, an interaction between the π system of the aromatic ring and the iodonium ion should be responsible for the less stereoselectivity.
Scheme 1. Diastereoselectivity in I₂-induced enolcyclization of 1,3-keto esters

\[
\text{YO OH} \quad \text{R} \quad \text{OXY} \quad + \quad \text{I}_2 \quad \text{O} \quad \text{O} \quad \text{OY X} \quad \text{R} \quad \text{H} \quad \text{I} 
\]

\[\text{cis-isomer} \quad \text{trans-isomer}\]

Table 2. I₂-induced heterocyclization of acetoacetate derivatives

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{MeO} & \quad \text{R} & \quad \text{I} \\
\text{1} & \quad \text{2} & \quad \text{3} & \quad \text{I}_2, \text{MeCN, 25°C} \\
\text{Entry} & \quad \text{Compound (1) R} & \text{Time} & \text{Yield (%)} & \text{5:6} \\
1 & \text{a} & \text{Me} & 1 \text{h} & 95 & 96:4 \\
2 & \text{i} & \text{Pr} & 1 \text{h} & 84 & 98:2 \\
3 & \text{l} & \text{i-Pr} & 3 \text{h} & 75 & 95:5 \\
4 & \text{m} & \text{i-Bu} & 2 \text{h} & 77 & 99:1 \\
5 & \text{n} & \text{Ph} & 1 \text{h} & 94 & 69:31 \\
\end{align*}
\]

In conclusion, the developed methodology constitutes an easy path to tetrasubstituted 4,5-dihydrofurans. The results obtained allow us to establish a correlation between the diastereoselection of the reaction and the conditions chosen for the cyclization process.

EXPERIMENTAL

\(^1\text{H-NMR} \quad \text{and} \quad \text{\textsuperscript{13}C-NMR} \quad \text{spectra \ were \ recorded \ in} \ \text{CDCl}_3 \quad \text{using \ either \ Varian \ XL-300 \ or \ Varian \ “Gemini”} \quad 200-\text{MHz} \quad \text{instruments, \ while} \ \text{IR} \quad \text{spectra \ were \ recorded \ in} \ \text{CCl}_4 \quad \text{and} \ \text{CHCl}_3 \quad \text{using \ a} \ \text{Shimadzu} \ \text{IR-740} \quad \text{instrument.} \ \text{MS} \quad \text{spectra \ were \ recorded \ by \ an} \ \text{HP5971A/MS} \quad \text{detector \ coupled \ with \ an} \ \text{HP5890} \quad \text{gas} \quad \text{chromatograph.} \ \text{The} \ \text{ratio \ of} \ \text{stereoselectivity \ was \ determined \ using} \ \text{HP \ 5880} \quad \text{and} \ \text{HP \ 5890} \quad \text{gas} \quad \text{chromatographs \ equipped \ with} \ \text{capillary} \quad \text{columns.} \ \text{CH}_2\text{Cl}_2 \quad \text{was \ dried \ by} \ \text{distillation \ on} \ \text{CaH}_2 \quad \text{and} \ \text{stored} \ \text{with} \ \text{molecular} \ \text{sieves.} \ \text{Column} \ \text{chromatography, \ unless \ otherwise \ stated, \ was \ carried \ out \ on} \ \text{Kieselgel}
Merck (70-230 mesh and 230-400 mesh). All reactions were carried out in amber-glass flasks under an argon atmosphere.

General procedure for the enolcyclization of β-dicarbonyl compounds. Iodine (1.27 g, 5 mmol) was added to a solution of the α-allyl-β-dicarbonyl compound (2 mmol) in dry MeCN (10 mL). The mixture was stirred at room temperature until the starting substrate disappeared (TLC and GC monitoring). Et₂O was added and the organic phase was repeatedly washed with sodium thiosulfate (2 M) and brine and finally dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude products were purified by flash column chromatography. Elution with a mixture of hexane/EtOAc 9:1 afforded pure 5-iodomethyl-4,5-dihydrofurans, as colorless oils.

All compounds obtained are known and their spectral properties were identical to those reported in the literature.⁷

REFERENCES

7. See ref. 5 and references reported therein.