**Synthesis of substituted hydantoin derivatives**

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A novel domino synthesis of 1,3,5-trisubstituted hydantoin derivatives has been developed in low melting L-(+)-tartaric acid–DMU melt mixtures. The functionalized hydantoins are obtained in good yields from β,γ-unsaturated ketoacids and urea under environmentally benign and simple reaction conditions.

The hydantoin moiety is an important structural scaffold found in a number of biologically active compounds. Many hydantoin derivatives have been identified as anticonvulsant, antidiabetes, antiarrhythmic, antimuscarinic, antiviral and antidiabetic agents. Moreover, hydantoin derivatives have also been used as antidepressants as well as platelet aggregation inhibitors. Aplysinopsin 1, isolated from the sponge Aplysinopsis reticulata (Dictyoceartida), exhibits cytotoxicity against cancer cells and shows ability to affect neurotransmitters (Fig. 1). The spirocyclic hydantoin 2 is a small molecule antagonist of LFA-1 (lymphocyte function-associated antigen-1). Phenyltoin 3 is used in the treatment of epilepsy, whereas nitrofurantoin is an antimicrobial agent. Very recently, GLPG0492 4 has been found to be a potent partial agonist of the human androgen receptor. In addition, hydantoin dantrolene 5 is a skeletal muscle relaxant. Herbicides, such as (+)-hydantocidin, also contain the hydantoin moiety as an integral part of their structure. Moreover, substituted hydantoin derivatives are valuable intermediates for the synthesis of enantiomerically pure aminoacids through dynamic kinetic resolution.

**Scheme 1** Synthesis of a 1,3,5-trisubstituted hydantoin derivative.

**Fig. 1** Biologically active hydantoins.
A variety of synthetic methods exist in the literature for the preparation of hydantoins from diverse starting materials.\textsuperscript{1} The classic methods for the synthesis of hydantoins include the Bucherer–Bergs synthesis and the reaction of urea with carbonyl compounds.\textsuperscript{12} In particular, the synthesis of highly substituted hydantoins is accomplished by reacting N-substituted \(\alpha\)-amino acids or their esters with isocyanates.\textsuperscript{13}

Alternative strategies for the synthesis of substituted hydantoins use transition metal catalyzed reactions,\textsuperscript{14} Ugi condensation,\textsuperscript{15a} reaction of \(\alpha,\beta\)-unsaturated carboxylic acids with carbodiimide,\textsuperscript{15b} as well as the reaction of \(\alpha\)-amino amides with phosgene.\textsuperscript{15c}

We have established low melting mixtures\textsuperscript{16a,b} based on renewable resources as alternative reaction media for carrying out organic transformations.\textsuperscript{16c–f} Recently, we reported the synthesis of dihydropyrimidinones (DHPM), pyrimidopyrimidinediones and indoles in L-(+)-tartaric acid–urea melts.\textsuperscript{17}

Herein, we report the first domino synthesis of 1,3,5-trisubstituted hydantoin from a \(\beta,\gamma\)-unsaturated ketoacid in low melting mixtures. Thus, \(\beta,\gamma\)-unsaturated ketoacid 6 reacts in a surprising transformation, upon exposure to L-(+)-tartaric acid–dimethylurea (DMU) melt conditions, to 1,3,5-trisubstituted hydantoin derivative 7 in excellent yield with good diastereoselectivity (Scheme 1).

The hydantoin derivative was obtained as a mixture of \textit{syn}- and \textit{anti}-diastereomers and the relative stereochemistry of the aryl and the hydantoin group was found to be \textit{anti} to each other (major distereomer). The relative stereochemistry of the major \textit{anti}-hydantoin derivative 13 was established using NOE experiments.\textsuperscript{18} Structure and relative stereochemistry of the major \textit{anti}-6,7 isomer were confirmed using single crystal X-ray analysis (Fig. 2).\textsuperscript{19}

Various \(\beta,\gamma\)-unsaturated ketoacids derived from electron rich as well as electron deficient aldehydes were found to react readily under the melt conditions to furnish the corresponding substituted hydantoin derivatives in good to excellent yields.\textsuperscript{19} The \(\beta,\gamma\)-unsaturated ketoacid 10 derived from piperonal furnished the corresponding hydantoin derivative 11 in very good yield. Similarly, the \(\beta,\gamma\)-unsaturated ketoacid 16 derived from sterically demanding aldehydes, such as 2,4-dichlorobenzaldehyde, smoothly gave the corresponding hydantoin derivative 17 in excellent yield (Table 1).\textsuperscript{20} A plausible mechanism for the formation of trisubstituted hydantoin derivatives is depicted in Scheme 2.

Surprisingly, exposure of \(\beta,\gamma\)-unsaturated ketoacid 18, derived from furfural, to L-(+)-tartaric acid–DMU melt resulted in the formation of a novel bicyclic alkylidine hydantoin derivative.

\begin{table*}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Entry} & \textbf{Substrate} & \textbf{Time (h)} & \textbf{Major anti-isomer Yield} & \textbf{dr anti/syn} \\
\hline
1 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image1}};
\end{tikzpicture} & 7 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image2}};
\end{tikzpicture} & 2:1 84
\hline
2 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image3}};
\end{tikzpicture} & 9 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image4}};
\end{tikzpicture} & 2.8:1 86
\hline
3 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image5}};
\end{tikzpicture} & 10 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image6}};
\end{tikzpicture} & 2.8:1 85
\hline
4 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image7}};
\end{tikzpicture} & 6 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image8}};
\end{tikzpicture} & 2:1 87
\hline
5 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image9}};
\end{tikzpicture} & 5 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image10}};
\end{tikzpicture} & 2.4:1 92
\hline
6 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image11}};
\end{tikzpicture} & 2.5 & \begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.3\textwidth]{image12}};
\end{tikzpicture} & 2.7:1 85
\hline
\hline
\end{tabular}
\caption{Synthesis of 1,3,5-trisubstituted hydantoins in melt\textsuperscript{a}

\textsuperscript{a} Reaction conditions: \(\beta,\gamma\)-unsaturated ketoacid (1 mmol) in L-tartaric acid–DMU melt (1.5 g) at 70 °C. Isolated yield.
}
\end{table*}

\begin{scheme}
\begin{tikzpicture}
\draw (0,0) node {\includegraphics[width=0.4\textwidth]{image13}};
\end{tikzpicture}
\caption{Plausible mechanism for the domino synthesis of a novel 1,3,5-trisubstituted hydantoin derivative.}
\end{scheme}
The structure and relative stereochemistry of the bicyclic alkylidine hydantoin derivative 19 were confirmed using single crystal X-ray analysis (Fig. 3). This example is of particular interest, since a similar alkylidine hydantoin derivative has been used in the synthesis of the spirocyclic hydantoin antagonist 2 (Fig. 1).

In conclusion, we have developed an efficient domino synthesis of 1,3,5-trisubstituted hydantoin in low melting mixtures. The substituted hydantoin were obtained in good yields under mild and environmentally benign reaction conditions. The melt medium serves simultaneously as a solvent, a catalyst and a reactant. The facile construction of functionalized hydantion makes it a suitable protocol for the synthesis of potentially bioactive compounds.

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Notes and references
5 The irradiation of H2 proton resulted in the enhancement of signal intensities of H4 and H5 protons by 1.4 and 2.2%, respectively, indicating that these protons are in close proximity to H6. See ESI† for details. A mechanistic proposal for the formation of compound 19 is given in the ESI†. All obtained compounds were racemic.
6 CCDC 907117 (7) and 907118 (19). Compound 7: C13H16N4O5, M = 341.37, crystal system, space group monoclinic, P21/c; unit cell dimensions a = 10.7255(5) Å, b = 18.0150(9) Å, c = 116.632(3) Å, A = 10.8800(6) Å, γ = 90°, volume 1800.49(16) Å3, Z = 4, reflections collected/unique 11 735/4167 [R(int) = 0.0217]; final R indices (I > 2σ(I)): R1 = 0.0501, wR2 = 0.1265; R indices (all data), R1 = 0.0534, wR2 = 0.1459. Compound 19: C17H19N5O3, M = 306.32, crystal system, space group monoclinic, P21/c; unit cell dimensions a = 6.6929(3) Å, b = 90°, c = 9.8842(6) Å, β = 97.236(4)°, γ = 82.36(4)°, volume 848.36(17) Å3, Z = 4; final R indices (I > 2σ(I)): R1 = 0.0442, wR2 = 0.1058; R indices (all data) R1 = 0.0773, wR2 = 0.1204.
7 The melt medium is readily recovered and recycled up to three cycles without any significant loss of activity or yield.