Microwave-assisted four-component reaction for the synthesis of a monothiohydantoin inhibitor of a fatty acid amide hydrolase

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Monothiohydantoin 3a is made in seven steps from 1,4-diiodobenzene and is shown to be an inhibitor of fatty acid amide hydrolase ($IC_{50} = 23.4 \pm 1.1 \mu M$). The key step in the sequence involves a microwave-assisted four-component reaction that makes the 5,5'-disubstituted hydantoin nucleus by the sequential formation of two C–C and two C–N bonds.

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The hydantoin nucleus 1 has many pharmacological effects\textsuperscript{1} and is found in several clinically important medicines (e.g., nilutamide,\textsuperscript{7} phenytoin\textsuperscript{3}). Hydantoins also serve as useful intermediates for the preparation of non-natural amino acids via chemical\textsuperscript{1} or enzymatic hydrolysis.\textsuperscript{4} Of existing methods to hydantoins,\textsuperscript{1,5} the Bucherer–Bergs reaction provides perhaps the best method for their preparation.\textsuperscript{6,7} It is a four-component reaction (4-CR) that involves the condensation of a ketone (or aldehyde) with cyanide, ammonia and carbon dioxide with the latter two reagents conveniently generated from ammonium carbonate (Scheme 1).

Recently, to enhance the scope of the Bucherer–Bergs reaction in drug discovery, Montagne et al. reported a modification of this 4-CR that uses nitriles and organometallic reagents as the starting materials.\textsuperscript{8} A key advantage of this method is that it creates two points of chemical diversity by combining the R and R\textsubscript{1} groups together in the same vessel as hydantoin assembly (Scheme 1). This reaction tolerates considerable variation in the structure of the organometallic reagent and the nitrile, and appears to have broad scope.\textsuperscript{9} To test its suitability for drug discovery, we sought to apply this new methodology to the synthesis of functionalised molecules that might serve as enzyme inhibitors. In this Letter, we report an efficient seven-step synthesis of a novel inhibitor of fatty acid amide hydrolase (FAAH) using this chemistry.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme1.png}
\caption{Synthesis of 5,5’-disubstituted hydantoins.}
\end{figure}

Fatty acid amide hydrolase (FAAH) is a membrane-bound enzyme, responsible for the hydrolysis of bioactive lipids, including endogenous ligands of the cannabinoid receptors such as anandamide.\textsuperscript{9} Effective inhibition of FAAH is widely recognised as a promising approach for the treatment of sleep disorders, anxiety, epilepsy, cancer and neurodegenerative disorders. Recently, a series of monothiohydantoins including 2 ($n = 5–13$) were identified by Muccioli et al. as reversible and competitive FAAH inhibitors, devoid of affinity for cannabinoid receptors (Fig. 1).\textsuperscript{10,11} Molecular modelling and docking studies by Michaux et al. using the active site of rat FAAH suggested that the introduction of a polar group at the 4-position of one of the aromatic rings might enhance FAAH
Next, selective monalkylation of hydantoin 5 at N-3 was achieved using bromoacetic acid to give 6 in 83% yield. The site of N-alkylation was deduced by the disappearance of the more downfield NH signal at 11.15 ppm in the $^1$H NMR spectrum, and is fully consistent with the literature precedent. Further, three-carbon homologation was effected by palladium-catalysed Heck coupling with methyl acrylate under microwave conditions to give ester 7 in 84% yield exclusively as the E-isomer. Hydrogenation to remove the alkene double bond followed by thionylation of the more nucleophilic C=O with Lawesson’s reagent gave monothiohydantoin 8 in 53% yield over the two steps. The chemoselectivity of this transformation was readily deduced from the downfield shift in the $^{13}$C NMR (DMSO-d$_6$) of the C-2 carbon (155.4–181.2 ppm). Finally, conversion of the methyl ester to the corresponding amide was achieved by hydrolysis to the carboxylic acid and amidation using PyBOP/HOBt/aqueous ammonia. This strategy provided the amide-functionalised monothiohydantoin 3a in seven steps and 17% overall yield from 1,4-diiodobenzene (Scheme 2).

Inhibition of rat recombinant FAAH by monothiohydantoin 3a was conducted in accordance to the method of Omeri et al. using labelled anandamide, [3H]-AEA. Whilst good inhibition was observed ($IC_{50} = 23.4 ± 1.1 \mu M$), this compound is four times less potent than the unsubstituted derivative 2 ($IC_{50} = 6.1 ± 0.3 \mu M$). Thus, in contradiction to in silico predictions, the introduction of the amide group at C-4 at one of the aromatic rings has no beneficial effect on rat FAAH inhibition.

To conclude, an efficient seven-step synthesis of amide-functionalised monothiohydantoin 3a has been achieved in 17% overall yield. The route exploits a microwave-assisted 4-CR to establish the 5,5′-hydantoin nucleus with formation of two C–C and two C–N bonds via a ‘one-pot’ process. Work to use this methodology to prepare further FAAH inhibitors is ongoing in our laboratories.

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Supplementary data

A supplementary data section is provided, which includes experimental procedures and characterisation data for 3a, 5–8 and the FAAH assay. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.100.

References and notes


14. For example, comparable yields are achieved in the synthesis of 5-buty1 5-phenylimidazolidine-2,4-dione 1 (R = Ph, R1 = Bu) from PhCN and n-Buli [THF, 0 °C, 30 min then KCN, (NH4)2CO3, aq EtOH] using MW conditions (70 °C, 50 W, 1 h: 73%) or a sealed tube (75 °C, 24 h: 79% or 75 °C, 1 h: 75%).


17. The weak inhibition of FAAH may, in part, be due to the fact that 3 was prepared as a racemate. However, this does not fully account for the poor inhibition in comparison to predictions from molecular modelling (Ref. 12).