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

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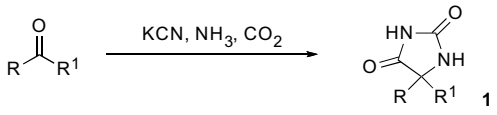
ABSTRACT

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 ± 1.1 μM). 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.

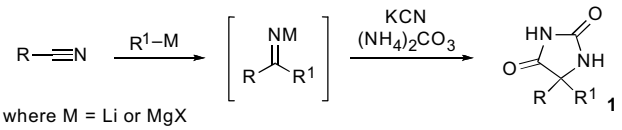
The hydantoin nucleus **1** has many pharmacological effects[1] and is found in several clinically important medicines (e.g., nilutamide,[2] phenytoin[3]). Hydantoins also serve as useful intermediates for the preparation of non-natural amino acids via chemical[1] or enzymatic hydrolysis.[4] Of existing methods to hydantoins,[1,5] the Bucherer–Bergs reaction provides perhaps the best method for their preparation.[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.[8] A key advantage of this method is that it creates two points of chemical diversity by combining the R and R^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.[8] 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.

Bucherer–Bergs reaction (4-CR, one point of diversity):



Modified Bucherer–Bergs reaction (4-CR, two points of diversity):



where M = Li or MgX

Scheme 1. Synthesis of 5,5′-disubstituted hydantoins.

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.[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).[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

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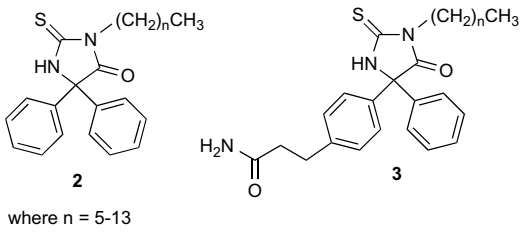
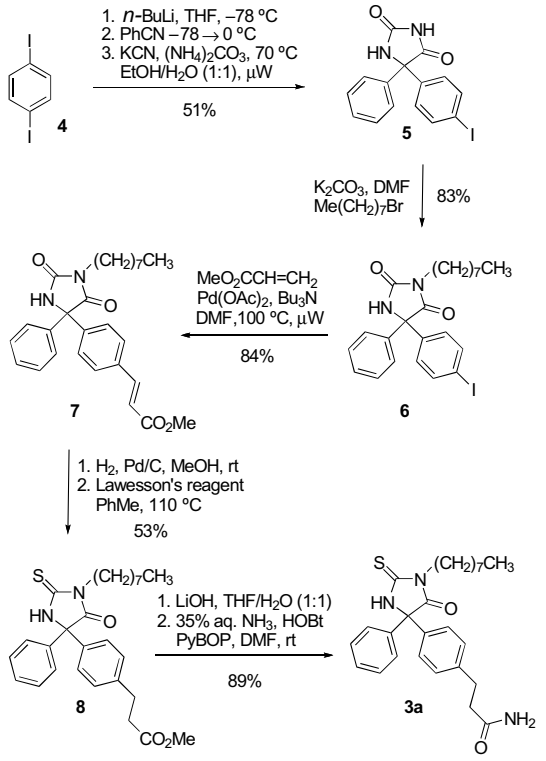


Figure 1. Monothiohydantoin FAAH inhibitors.

binding through hydrogen bonding to residues of the catalytic triad (Ser241, Ser217 and Lys142).[12] Specifically, monothiohydantoin **3** ($n = 5$) was calculated to bind with a higher affinity than **2** ($n = 5$) within the active site of rat FAAH by 7.0 kcal/mol.

To test the validity of this binding model, we decided to construct monothiohydantoin **3** and measure its inhibition of FAAH. Based upon early data for **2** ($n = 5$–13),[10] we targetted **3a** bearing an octyl side chain at *N*-3 to maximise inhibition. Our synthesis of **3a** began with the preparation of 5,5′-disubstituted hydantoin **5** using the new 4-CR (Scheme 2). Thus, treatment of 1,4-diiodobenzene (**4**) with *n*-BuLi at −78 °C in THF gave the presumed monolithiated species, to which was added benzonitrile. Upon warming to 0 °C, EtOH, $(NH_4)_2CO_3$, KCN and water were successively added, then the mixture was irradiated in a CEM Discover® microwave (50 W) for 1 h.[13] After work-up and purification, hydantoin **5** was isolated in 51% yield (see Supplementary data). Microwave irradiation is not essential and similar results can be achieved in a resealable glass pressure tube as reported in the original study.[8,14] However, the microwave procedure allows the process to be conducted with better control of vessel pressure and temperature, as well as enhanced reaction containment and safety. For these reasons, we recommend the use of these new microwave-based conditions.



Scheme 2. Synthesis of monothiohydantoin **3a** from 1,4-diiodobenzene.

Next, selective monoalkylation of hydantoin **5** at *N*-3 was achieved using bromooctane/K_2CO_3 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.[1] Further, three-carbon homologation was effected by palladium-catalysed Heck coupling with methyl acrylate under microwave conditions[15] 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 Omeir et al.[16] using labelled anandamide, [3H]-AEA. Whilst good inhibition was observed ($IC_{50} = 23.4 \pm 1.1$ μM), this compound is four times less potent than the unsubstituted derivative **2** ($n = 7$) ($IC_{50} = 6.1 \pm 0.3$ μM). 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.[17]

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.

Acknowledgements

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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

1. (a) Ware, E. *Chem. Rev.* **1950**, *46*, 403–470; (b) López, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177–228; (c) Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int.* **2004**, *36*, 391–443.
2. Nakabayashi, M.; Regan, M. M.; Lifsey, D.; Kantoff, P. W.; Taplin, M.-E.; Sartor, O.; Oh, W. K. *BJU Int.* **2005**, *96*, 783–786.
3. Bazil, C. W. *Curr. Treat. Options Neurol.* **2004**, *6*, 339–345.
4. Burton, S. G.; Dorrington, R. A. *Tetrahedron: Asymmetry* **2004**, *15*, 2737–2741.
5. For recent examples, see: Zhao, B. G.; Du, H. F.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220–7221; Kumar, V.; Kaushik, M. P.; Mazumdar, A. *Eur. J. Org. Chem.* **2008**, 1910–1916; Shih, H. W.; Cheng, W. C. *Tetrahedron Lett.* **2008**, *49*, 1008–1011; Yeh, W. P.; Chang, W. J.; Sun, M. L.; Sun, C. M. *Tetrahedron* **2007**, *63*, 11809–11816;; Brouillette, Y.; Lisowski, V.; Guillon, J.; Massip, S.; Martinez, J. *Tetrahedron* **2007**, *63*, 7538–7544; Colacino, E.; Lamaty, F.; Martinez, J.; Parrot, I. *Tetrahedron Lett.* **2007**, *48*, 5317–5320; Alizadeh, A.; Sheikhi, E. *Tetrahedron*

Lett. **2007**, *48*, 4887–4890; Zhang, D.; Xing, X. C.; Cuny, G. D. *J. Org. Chem.* **2006**, *71*, 1750–1753.
6. Bergs, H. Ger. Pat. Appl., 1929, 566094; *Chem. Abstr.*, *27*, 10154; Bucherer, H. T.; Brandt, W. *J. Prakt. Chem.* **1934**, *140*, 129–150; Bucherer, H. T.; Steiner, W. *J. Prakt. Chem.* **1934**, *140*, 291–316; Bucherer, H. T.; Lieb, V. A. *J. Prakt. Chem.* **1934**, *141*, 5–43. See also Ref. 1a.
7. For recent applications, see: Murray, R. G.; Whitehead, D. M.; Le Strat, F.; Conway, S. J. *Org. Biomol. Chem.* **2008**, *6*, 988–991; Montagne, C.; Shiers, J. J.; Shipman, M. *Tetrahedron Lett.* **2006**, *47*, 9207–9209; Wermuth, U. D.; Jenkins, I. D.; Bott, R. C.; Byriel, K. A.; Smith, G. *Aust. J. Chem.* **2004**, *57*, 461–465; Micová, J.; Steiner, B.; Koós, M.; Langer, V.; Gyepesová, D. *Carbohydr. Res.* **2003**, *338*, 1917–1924; Micová, J.; Steiner, B.; Koós, M.; Langer, V.; Gyepesová, D. *Synlett* **2002**, 1715–1717.
8. Montagne, C.; Shipman, M. *Synlett* **2006**, 2203–2206.
9. For a recent review, see: Labar, G.; Michaux, C. *Chem. Biodiversity* **2007**, *4*, 1882–1902.
10. Muccioli, G. G.; Fazio, N.; Scriba, G. K. E.; Poppitz, W.; Cannata, F.; Poupaert, J. H.; Wouters, J.; Lambert, D. M. *J. Med. Chem.* **2006**, *49*, 417–425.
11. For a survey of FAAH inhibitor classes, see: Vandevoorde, S. *Curr. Top. Med. Chem.* **2008**, *8*, 247–267.
12. Michaux, C.; Muccioli, G. G.; Lambert, D. M.; Wouters, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4772–4776.
13. Microwave induced Bucherer–Bergs reactions have been reported. Faghihi, K.; Zamani, K.; Mobinikhaledi, A. *Turk. J. Chem.* **2004**, *28*, 345–350.
14. For example, comparable yields are achieved in the synthesis of 5-butyl-5-phenylimidazolidine-2,4-dione **1** (R = Ph, R^1 = Bu) from PhCN and *n*-BuLi [THF, 0 °C, 30 min then KCN, $(NH_4)_2CO_3$, 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%).
15. Larhead, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584.
16. Omeir, R. L.; Chin, S.; Hong, Y.; Ahern, D. G.; Deutsch, D. G. *Life Sci.* **1995**, *56*, 1999–2005; Labar, G.; Vliet, F. V.; Wouters, J.; Lambert, D. M. *Amino Acids* **2008**, *34*, 127–133.
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).