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Continuous Synthesis of Hydantoins: Intensifying the Bucherer–Bergs Reaction

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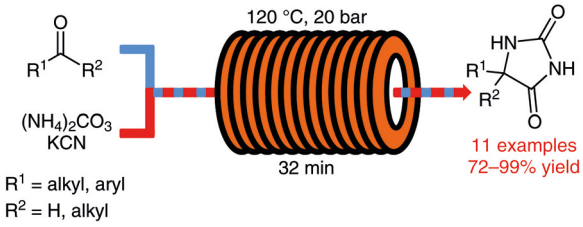
Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday



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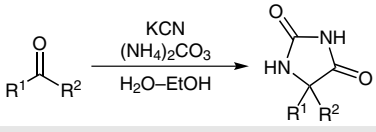
Abstract A continuous Bucherer–Bergs hydantoin synthesis utilizing intensified conditions is reported. The methodology is characterized by a two-feed flow approach to independently feed the organic substrate and the aqueous reagent solution. The increased interfacial area of the biphasic reaction mixture and the lack of headspace enabled almost quantitative conversions within ca. 30 minutes at 120 °C and 20 bar even for unpolar starting materials. In addition, a selective N(3)-monoalkylation of the resulting heterocycles under batch microwave conditions is reported yielding potential acetylcholinesterase inhibitors.

Key words continuous flow, process intensification, hydantoins, Bucherer–Bergs reaction, microwave-assisted organic synthesis

The hydantoin scaffold is an important structural motif with a broad range of biological activities.[1] Potential applications for medicinal purposes include the utilization as androgen receptor modulators,[2] anticonvulsant,[3] antidiabetic,[4] or anticancer agents.[5] From an industrial point of view, one of the simplest representatives of this compound class, 5,5-dimethylhydantoin (DMH), is a key intermediate in the synthesis of several commodity chemicals such as 1,3-dichloro-5,5-dimethylhydantoin, 1-bromo-3-chloro-5,5-dimethylhydantoin, and 1,3-dibromo-5,5-dimethylhydantoin. These N,N′-dihalogenated analogues of DMH are widely used as biocides for, for example, water treatment[6] and have also shown high potential as halogenation agents or oxidants in organic synthesis.[7]

A plethora of synthetic strategies are known to construct the heterocyclic core structure from a broad range of precursor molecules.[1,8,9] Among those, the Bucherer–Bergs reaction is presumably the most commonly used methodology to generate hydantoins from aldehydes or ketones (Scheme 1).[1,9] Mechanistically, the carbonyl compound initially reacts with ammonia and the cyanide anion forming an α-aminonitrile.[1,10] Nucleophilic addition of this intermediate to CO_2 generates a cyano-carbamic acid which undergoes a cyclization–rearrangement sequence to finally result in the hydantoin scaffold. From a practical point of view, the reaction is generally carried out by heating a mixture of the starting material, potassium cyanide, and ammonium carbonate – which thermally decomposes into ammonia and carbon dioxide – in a mixture of water and ethanol at reflux for several hours or even days.[1] It has to be stressed that significant amounts of ammonia and carbon dioxide are lost due to their volatility using traditional batch techniques. The highly polar reaction mixture can cause severe solubility problems for certain substrates resulting in a rather inefficient process.[8c] Moreover, heating an aqueous solution of potassium cyanide poses severe safety hazards especially on larger scales.



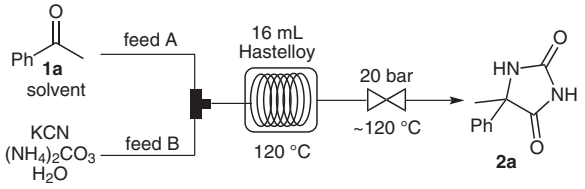
Scheme 1 Synthesis of hydantoins via the Bucherer–Bergs reaction

We hypothesized that a continuous process using microreactor technology can potentially overcome process limitations associated with this multicomponent reaction.[11–13] In continuous-flow mode, reactions can be easily conducted without any headspace at high temperatures, while working at high-pressure conditions to keep the gaseous reagents in solution (novel process windows).[11,14] Scaling is considerably easier for a continuous process than for a batch process by simply increasing the reactor volume (scale-up) keeping certain characteristics of the system constant ('smart dimensioning'). Moreover, numbering-up of flow devices or simply running a reactor for extended pe-

riods of time (scaling-out) are often acceptable strategies.[11] Biphasic liquid–liquid reactions can be efficiently carried out by generating a segmented flow pattern with significantly larger interfacial areas compared to traditional batch techniques.[15] Consequently, a modified Bucherer–Bergs reaction in continuous flow utilizing an aqueous solution of KCN and $(NH_4)_2CO_3$ in combination with an organic solution of the carbonyl compound would result in an efficient protocol even for highly unpolar starting materials which often suffer from low conversions in the traditional batch protocol.

To confirm these assumptions, a two-feed setup was assembled utilizing high-pressure syringe pumps for both the organic (feed A) and the aqueous stream (feed B) in order to precisely control reagent stoichiometry.[16] The solutions were merged in a T-shaped mixing unit, and the combined stream then entered a heated Hastelloy coil (16 mL) to perform the multicomponent hydantoin synthesis. The reaction mixture left the continuous-flow system through an adjustable stainless steel back-pressure regulator. For an initial process intensification study under continuous-flow conditions, acetophenone (**1a**) was chosen as starting material (Table 1).

Table 1 Optimization of the Bucherer–Bergs Reaction in Continuous Flow



Entry	Solvent (M)	Feed A/B (μL min^{-1})	t_{Res} (min)	KCN/$(NH_4)_2CO_3$ (equiv)	Conv. (%)[a]
1	–	166/834	16	1.2/3.0	clogging
2	EtOH (4)	166/834	16	1.2/3.0[b]	90
3	MeOH (4)	166/834	16	1.2/3.0[b]	93
4	i-PrOH (4)	166/834	16	1.2/3.0[b]	92
5	EtOAc (4)	166/834	16	1.2/3.0	72
6	EtOAc (4)	83/417	32	1.2/3.0	80
7[c]	EtOAc (4)	83/417	32	1.2/3.0	55
8[d]	EtOAc (4)	83/417	32	1.2/3.0	60
8	EtOAc (5)	83/417	32	1.2/3.0	88
9	EtOAc (5)	70/430	32	1.2/3.0	87
10	EtOAc (5)	70/430	32	1.5/3.5	96 (91)[e]
11	EtOAc (5)	70/490	29	1.5/4.0	95

[a] Determined as HPLC peak area percent at 215 nm.
[b] Accurate control of the stoichiometry was impossible. Due to the poorly defined (annular) flow pattern, a much higher excess is created during the process.
[c] Reaction was performed at 100 °C.
[d] Reaction was performed at 140 °C.
[e] Isolated yield in parentheses.

Since the liquid starting material can be easily pumped without the need of any organic solvent, the neat ketone was utilized for feed A (Table 1, entry 1). Unfortunately, the resulting heterocycle **2a** precipitated inside the flow system resulting in reactor clogging. Thus, various alcohols were tested for their applicability as suitable (co-)solvents (Table 1, entries 2–4). By additionally heating the back-pressure regulating unit to 100–120 °C on a standard hot plate blocking of the system could be avoided for all tested alcohols and promising conversions were obtained. However, we realized that mixing of the two phases led to a poorly defined (annular) flow pattern since the alcohol dissolves in the aqueous phase whereas the relatively unpolar starting material travels slowly on the channel wall.[17] Hence, different residence times (t_{Res}) for the aqueous and the organic phase were observed making a precise control of reagent stoichiometry impossible. Gratifyingly, by using ethyl acetate as organic solvent a well-defined segmented flow pattern was obtained allowing for accurate processing of the reaction mixture (Table 1, entry 5).[17] Systematic optimization of the reaction parameters resulted in an almost quantitative consumption of **1a** within 32 minutes, and excellent isolated yields were obtained for the corresponding hydantoin (**2a**, Table 1, entries 5–11). Notably, under the final conditions a saturated aqueous solution of KCN and $(NH_4)_2CO_3$ was utilized resulting in a productivity of ca. 19 mmol h^{-1}.

A batch control experiment employing a dedicated 10 mL microwave autoclave resulted in significantly lower conversions (ca. 40%) using a 3.5 mL reaction volume under identical conditions.[18–20] This is presumably resulting from the lower interfacial area of the biphasic mixture and the fact that a significant amount of $(NH_4)_2CO_3$ sublimed at the top of the 10 mL reaction vessel.[19] Reduction of the headspace by using a larger reaction volume (7 mL) gave even lower conversion (15%), likely due to inefficient stirring of the biphasic reaction mixture.[19] Utilization of an improved stir-bar design which was recently developed in our laboratories improved the hydantoin formation to 77% which is still significantly below the performance of the continuous-flow reactor (96%).[19,21]

Encouraged by these promising results, the applicability of the optimized protocol was further tested to demonstrate the versatility of the continuous strategy (Table 2).[22] Gratifyingly, various aromatic and aliphatic carbonyl compounds could be processed without the need for any re-optimization, and the desired hydantoins were obtained in good to excellent isolated yields (Table 2, entries 1–6). In the case of 3-methoxybenzaldehyde (**1h**), the low solubility of the resulting heterocycle required a less concentrated organic feed to avoid clogging of the reactor (Table 2, entry 7). The same issue necessitated even lower concentrations or a different solvent system for the synthesis of spirohydantoins **2i** and **2j** in almost quantitative yields (Table 2, entries 8 and 9). In contrast, for the industrially relevant DMH (**2k**) no organic solvent was required resulting in an efficient,

gram-scale continuous-flow process (Table 2, entry 10). It has to be pointed out that no segmented flow pattern was observed in this case since the starting material, acetone (**1k**), was completely soluble in the aqueous reagent mixture.[17] However, a quantitative multicomponent reaction was observed and DMH (**2k**) could be isolated in 60% by crystallization from the reaction mixture which is in good agreement with data reported in the literature.[23] By carefully extracting the mother liquor multiple times with EtOAc the yield could be further increased to 82% resulting in a productivity of 20 mmol h^{-1}.

Notably, it was recently reported that hydantoins can possibly be applied to treat neurodegenerative disorders such as Alzheimer's or Parkinsons's disease, by inhibition of acetylcholinesterase enzyme (AChE), which is mainly responsible for the regulation of the neurotransmitter acetylcholine (ACh).[24] In this context, preliminary unpublished results from our laboratories, employing an immobilized acetylcholinesterase capillary reactor,[25] indicated that the heterocyclic compounds **2a** and **2k** show moderate inhibition activity of AChE. We hypothesized that installing an aliphatic tertiary amine group mimicking the ACh scaffold increases the affinity to AChE, simultaneously improving their biological activity (Figure 1). Similar structural motifs were already demonstrated to exhibit significant antimicrobiological activity.[26]

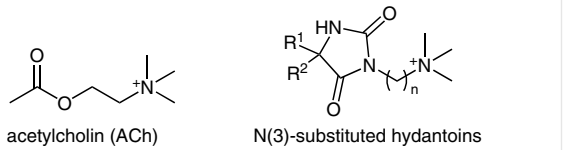
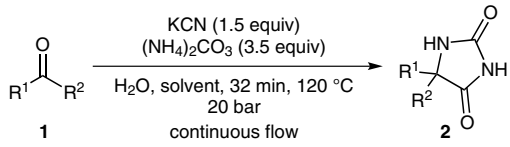
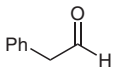
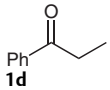
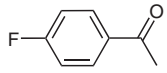
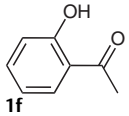
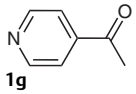
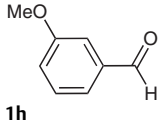
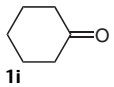
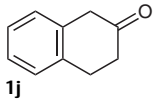


Figure 1 Structural modification of hydantoins to mimic acetylcholine (ACh)

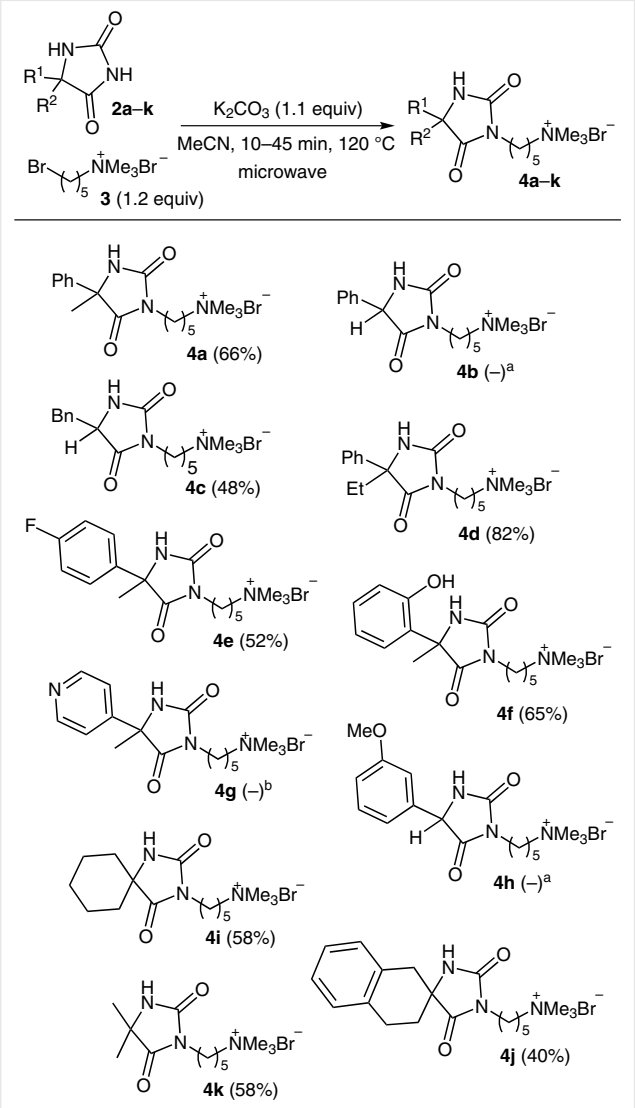
Initial experiments using (2-bromoethyl)trimethylammonium bromide (n = 2) suffered from extremely low conversions presumably due to steric hindrance of the brominated carbon atom.[27] However, by using (5-bromopentyl)trimethylammonium bromide (**3**, n = 5) satisfying conversions were determined by HPLC analysis.[27] A subsequent optimization study with the aid of microwave dielectric heating technology utilizing a dedicated batch reactor, resulted in an efficient, selective N(3)-monoalkylation of hydantoins **2a**–**k** (Scheme 2).[18,28] Depending on the starting material 10–45 minutes at 120 °C in acetonitrile were sufficient to synthesize several hitherto undisclosed hydantoins **4a**,**c**–**f**,**i**–**k** using 1.2 equivalents of **3** and 1.1 equivalents of K_2CO_3 as base. In case of **2g**, a complex reaction mixture was observed, and the corresponding ammonium salt **4g** could not be isolated. For the structurally similar hydantoins **4b** and **4h** an insoluble white solid was obtained which could not be characterized by NMR analysis.

Table 2 Scope of the Continuous Bucherer–Bergs Reaction[a]



Entry	Substrate	Solvent	*c* (M)[b]	Yield of **2** (%)[c]
1	 **1b**	EtOAc	5	**2b** 91
2	 **1c**	EtOAc	5	**2c** 72
3	 **1d**	EtOAc	5	**2d** 90
4	 **1e**	EtOAc	5	**2e** 78
5	 **1f**	EtOAc	5	**2f** 95
6	 **1g**	EtOAc	5	**2g** 88
7	 **1h**	EtOAc	3	**2h** 92
8	 **1i**	EtOAc	2	**2i** 99
9	 **1j**	DMF–EtOAc (2:1)	0.5	**2j** 96
10	 **1k**	neat	neat	**2k** 82

[a] Flow reactions were performed using two independent pumps for the aqueous and organic feed. All reactions were performed in a 16 mL Hastelloy coil. To avoid clogging the back pressure regulator was heated to ca. 120 °C.
[b] Substrate concentration in feed A.
[c] Isolated yields.



Scheme 2 Synthesis of N(3)-substituted hydantoins in batch. [a] An insoluble material was obtained. [b] Reaction resulted in a complex mixture.

In conclusion, a highly intensified continuous variant of the Bucherer–Bergs hydantoin synthesis was developed. Key to the success was the utilization of a well-defined segmented flow pattern to overcome solubility issues for unpolar starting materials and to significantly increase the interfacial areas compared to traditional batch techniques. The lack of gaseous headspace under high-pressure conditions avoids sublimation/volatilization of the in situ generated gaseous reagents (NH_3, CO_2). In addition, a microwave batch protocol for the selective N(3)-monoalkylation of the resulting hydantoin scaffolds is presented resulting in a series of potential acetylcholinesterase inhibitors. The biological activity of the final N-substituted hydantoins is currently under investigation in our laboratories.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560317.

References and Notes

(1) (a) Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int.* **2004**, *36*, 391. (b) Ware, E. *Chem. Rev.* **1950**, *46*, 403.
(2) (a) Nique, F.; Hebbe, S.; Peixoto, C.; Annoot, D.; Lefrancois, J.-M.; Duval, E.; Michoux, L.; Triballeau, N.; Lemoullec, J.-M.; Mollat, P.; Thauvin, M.; Prange, T.; Minet, D.; Clement-Lacroix, P.; Robin-Jagerschmidt, C.; Fleury, D.; Guedin, D.; Deprez, P. *J. Med. Chem.* **2012**, *55*, 8225. (b) Nique, F.; Hebbe, S.; Triballeau, N.; Peixoto, C.; Lefrancois, J.-M.; Jary, H.; Alvey, L.; Manioc, M.; Housseman, C.; Klaassen, H.; Van Beeck, K.; Guedin, D.; Namour, F.; Minet, D.; Van der Aar, E.; Feyen, J.; Fletcher, S.; Blanqué, R.; Robin-Jagerschmidt, C.; Deprez, P. *J. Med. Chem.* **2012**, *55*, 8236.
(3) (a) Dhanawat, M.; Banerjee, A. G. *Med. Chem. Res.* **2012**, *21*, 2807. (b) Thenmozhiyal, J. C.; Wong, P. T.-H.; Chui, W.-K. *J. Med. Chem.* **2004**, *47*, 1527.
(4) Iqbal, Z.; Ali, S.; Iqbal, J.; Abbas, Q.; Qureshi, I. Z.; Hameed, S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 488.
(5) (a) Sallam, A. A.; Mohyeldin, M. M.; Foudah, A. I.; Akl, M. R.; Nazzal, S.; Meyer, S. A.; Liu, Y.-Y.; El Sayed, K. A. *Org. Biomol. Chem.* **2014**, *12*, 5295. (b) Azizmohammadi, M.; Khoobi, M.; Ramazani, A.; Emami, S.; Zarrin, A.; Firuzi, O.; Miri, R.; Shafiee, A. *Eur. J. Med. Chem.* **2013**, *59*, 15.
(6) Ura, Y.; Sakata, G. *Chloroamines*, In *Ullmann's Enzyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, **2000**.
(7) For selected examples, see: (a) Xu, Z.; Zhang, D.; Zou, X. *Synth. Commun.* **2006**, *36*, 255. (b) Barnes, D. M.; Christesen, A. C.; Engstrom, K. M.; Haight, A. R.; Hsu, M. C.; Lee, E. C.; Peterson, M. J.; Plata, D. J.; Raje, P. S.; Stoner, E. J.; Tedrow, J. S.; Wagaw, S. *Org. Process Res. Dev.* **2006**, *10*, 803. (c) Hernández-Torres, G.; Tan, B.; Barbas, C. F. III. *Org. Lett.* **2012**, *14*, 1858. (d) Maegawa, T.; Koutani, Y.; Otake, K.; Fujioka, H. *J. Org. Chem.* **2013**, *78*, 3384.
(8) For recent illustrative examples, see: (a) Konnert, L.; Reneaud, B.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. *J. Org. Chem.* **2014**, *79*, 10132. (b) Hillier, M. C.; Gong, H.-H.; Clyne, D. S.; Babcock, M. J. *Tetrahedron* **2014**, *70*, 9413. (c) Safari, J.; Javadian, L. *RSC Adv.* **2014**, *4*, 48973. (d) Gore, S.; Chinthapally, K.; Baskaran, S.; König, B. *Chem. Commun.* **2013**, *49*, 5052. (e) Gao, M.; Yang, Y.; Wu, Y.-D.; Deng, C.; Shu, W.-M.; Zhang, D.-X.; Cao, L.-P.; She, N.-F.; Wu, A.-X. *Org. Lett.* **2010**, *12*, 4026. (f) Dumbris, S. M.; Díaz, D. J.; McElwee-White, L. *J. Org. Chem.* **2009**, *74*, 8862. (g) Zhao, B.; Du, H.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220. (h) Murray, R. G.; Whitehead, D. M.; Le Strat, F.; Conway, S. J. *Org. Biomol. Chem.* **2008**, *6*, 988. (i) Zhang, D.; Xing, X.; Cuny, G. D. *J. Org. Chem.* **2006**, *71*, 1750. (j) Montagne, C.; Shipman, M. *Synlett* **2006**, 2203.
(9) For selected recent applications of the Bucherer–Bergs reaction, see: (a) Hirata, T.; Ueda, A.; Oba, M.; Doi, M.; Demizu, Y.; Kurihara, M.; Nagano, M.; Suemune, H.; Tanaka, M. *Tetrahedron*

2015, *71*, 2409. (b) Matys, A.; Podlewska, S.; Witek, K.; Witek, J.; Bojarski, A. J.; Schabikowski, J.; Otrebska-Machaj, E.; Latacz, G.; Szymanska, W.; Kiec-Kononowicz, K.; Molnar, J.; Amaral, L.; Handzlik, J. *Eur. J. Med. Chem.* **2015**, *101*, 313. (c) Knizhnikov, V. O.; Voitenko, Z. V.; Golovko, V. B.; Gorichko, M. V. *Tetrahedron: Asymmetry* **2012**, *23*, 1080. (d) Anson, M. S.; Clark, H. F.; Evans, P.; Fox, M. E.; Graham, J. P.; Griffiths, N. N.; Meek, G.; Ramsden, J. A.; Roberts, A. J.; Simmonds, S.; Walker, M. D.; Willets, M. *Org. Process. Res. Dev.* **2011**, *15*, 389.

(10) Chubb, F. L.; Edward, J. T.; Wong, S. C. *J. Org. Chem.* **1980**, *45*, 2315.

(11) For recent reviews on flow chemistry, see: (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2015**, *54*, 6688. (b) Jensen, K. F.; Reizmana, B. J.; Newman, S. G. *Lab Chip* **2014**, *14*, 3206. (c) Wiles, C.; Watts, P. *Green Chem.* **2014**, *16*, 55. (d) Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15*, 1456. (e) Baxendale, I. R.; Brocken, L.; Mallia, C. J. *Green Process. Synth.* **2013**, *2*, 211. (f) McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384. (g) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849.

(12) For selected examples of multicomponent reactions in flow, see: (a) Salvador, C. E. M.; Pieber, B.; Neu, P. M.; Torvisco, A.; Andrade, C. K. Z.; Kappe, C. O. *J. Org. Chem.* **2015**, *80*, 4590. (b) Silva, G. C. O.; Correa, J. R.; Rodrigues, M. O.; Alvim, H. G. O.; Guido, B. C.; Gatto, C. C.; Wanderley, K. A.; Fioramonte, M.; Gozzo, F. C.; de Souza, R. O. M. A.; Neto, B. A. D. *RSC Adv.* **2015**, *5*, 48506. (c) Sharma, S.; Maurya, R. A.; Min, K.-I.; Jeong, G.-Y.; Kim, D.-P. *Angew. Chem. Int. Ed.* **2013**, *52*, 7564. (d) Pagano, N.; Herath, A.; Cosford, N. D. P. *J. Flow Chem.* **2011**, *1*, 28. (e) Baumann, M.; Baxendale, I. R.; Kirschning, A.; Ley, S. V.; Wegner, J. *Heterocycles* **2011**, *82*, 1297. (f) Herath, A.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 5182.

(13) For continuous-flow reactions involving cyanides, see: (a) Heugebaert, T. S. A.; Roman, B. I.; De Blieck, A.; Stevens, C. V. *Tetrahedron Lett.* **2010**, *51*, 4189. (b) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, 5597. (c) Wiles, C.; Watts, P. *Org. Process Res. Dev.* **2008**, *12*, 1001. (d) Acke, D. R. J.; Stevens, C. V. *Green Chem.* **2007**, *9*, 386.

(14) Hessel, V.; Kralisch, D.; Kockmann, N.; Noel, T.; Wang, Q. *ChemSusChem* **2013**, *6*, 746.

(15) For selected examples of biphasic liquid/liquid reactions in flow, see: (a) Van Waes, F. E. A.; Seghers, S.; Dermaut, W.; Cappuyns, B.; Stevens, C. V. *J. Flow Chem.* **2014**, *4*, 118. (b) Damm, M.; Gutmann, B.; Kappe, C. O. *ChemSusChem* **2013**, *6*, 978. (c) Mehenni, H.; Sinatra, L.; Mahfouz, R.; Katsiev, K.; Bakr, O. M. *RSC Adv.* **2013**, *3*, 22397. (d) Reichart, B.; Kappe, C. O.; Glasnov, T. *Synlett* **2013**, *24*, 2393.

(16) For details about the continuous-flow setup, see the Supporting Information.

(17) The flow regimes were monitored in a transparent perfluoroalkoxy tubing between the mixing unit and the Hastelloy coil.

(18) For a recent discussion on microwave assisted organic synthesis, see: Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 1088; and references cited therein.

(19) For details, see Table S1 and Figure S2 in the Supporting Information.

(20) In many cases microwave chemistry examples can be directly translated to continuous-flow applications: Glasnov, T. N.; Kappe, C. O. *Chem. Eur. J.* **2011**, *17*, 11956.

(21) Obermayer, D.; Damm, M.; Kappe, C. O. *Org. Biomol. Chem.* **2013**, *11*, 4949.

(22) **General Experimental Procedure for the Continuous Bucherer–Bergs Reaction**

Feed A consisting of the carbonyl compound **1a**–**k** dissolved in EtOAc was pumped with a flow rate of 70 μL min^{-1} and merged in a T-shaped mixing unit with a second feed (430 μL min^{-1}) containing an aqueous solution of $(NH_4)_2CO_3$ (3.5 equiv) and KCN (1.5 equiv). The combined mixture was passed through a coil reactor made out of Hastelloy (16 mL internal volume, 32 min residence time) at 120 °C and 20 bar back pressure. To avoid precipitation of the corresponding hydantoin, the back pressure regulating unit was heated to 120 °C. The reaction mixture was collected in a sealed flask and subsequently acidified with concentrated HCl. Workup by extraction with EtOAc or crystallization afforded the respective hydantoins **2a**–**k** in analytical purity.

Analytical Data for Compound 2a

Feed A: acetophenone (2.53 mmol, 5.0 M in EtOAc). Feed B: KCN (1.24 M), $(NH_4)_2CO_3$ (2.88 M) in H_2O. Isolation by extraction afforded the title compound in 91% yield (440 mg, 2.31 mmol) as a colorless solid; mp 197–199 °C. ^{1}H NMR (300 MHz, DMSO): δ = 10.77 (s, 1 H), 8.62 (s, 1 H), 7.50–7.46 (m, 2 H), 7.43–7.30 (m, 3 H), 1.66 (s, 3 H). ^{13}C NMR (75 MHz, DMSO): δ = 177.42, 156.69, 140.37, 128.93, 128.26, 125.77, 64.35, 25.39.

(23) The solubility of DMDH in water causes relatively low isolated yields and recovery rates: Wagner, E. C.; Baizer, M. *Org. Synth.* **1940**, *20*, 42.

(24) (a) Khanfar, M. A.; Asal, B. A.; Mudit, M.; Kaddoumi, A.; El Sayed, K. A. *Bioorg. Med. Chem.* **2009**, *17*, 6032. (b) Hamilton, G. S. US 20020058685, **2002**.

(25) Vanzolini, K.; Vieira, L. C. C.; Cardoso, C. L.; Correa, A. G.; Cass, Q. B. *J. Med. Chem.* **2013**, *56*, 2038.

(26) Jain, R. K.; Low, E.; Francavilla, C.; Shiau, T. P.; Kim, B.; Nair, S. K. WO 2010054009, **2010**.

(27) Very recently, a similar observation was reported for the N-alkylation of Riboflavin derivatives: Silva, A. V.; López-Sánchez, A.; Junqueira, H. C.; Rivas, L.; Baptista, M. S.; Orellana, G. *Tetrahedron* **2015**, *71*, 457.

(28) **General Experimental Procedure for the Selective N(3)-Monoalkylation of Hydantoins**

A sealed 10 mL microwave process vial containing a mixture of the respective hydantoin (0.5–1.0 mmol), K_2CO_3 (1.1 equiv), and (5-bromopenthyl)trimethylammonium bromide (1.2 equiv) in MeCN (2 mL) was heated for 10–45 min at 120 °C using a single-mode microwave reactor. After cooling to r.t. the reaction mixture was concentrated. The organic material was dissolved in MeCN, and the inorganic salts were separated by filtration. Evaporation of the solvent resulted in a solid material which was carefully washed with cold EtOH before drying affording the respective N-substituted hydantoins **4a**–**k** in analytical purity.

Analytical Data for Compound 4a

Reaction time: 10 min; yield: 66% (130 mg, 0.33 mmol) as colorless solid; mp 222–224 °C. ^{1}H NMR (300 MHz, DMSO): δ = 8.90 (s, 1 H), 7.49–7.31 (m, 5 H), 3.43–3.33 (m, 4 H), 3.25–3.19 (m, 2 H), 3.02 (s, 9 H), 1.68 (s, 3 H), 1.60–1.50 (m, 2 H), 1.25–1.15 (m, 2 H). ^{13}C NMR (75 MHz, DMSO): δ = 175.85, 156.11, 140.06, 129.05, 128.43, 125.81, 65.46, 63.14, 52.60, 52.56, 52.52, 37.94, 27.54, 25.40, 23.42, 22.03. HRMS (APCI): *m*/*z* calcd for $C_{18}H_{28}N_3O_2^+$ [M – Br^-]$^+$: 318.217604; found: 318.217459.