Modified Bucherer–Bergs Reaction for the One-Pot Synthesis of 5,5′-Disubstituted Hydantoins from Nitriles and Organometallic Reagents

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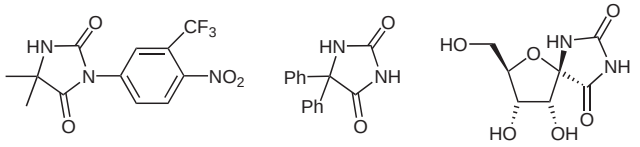
Received 21 April 2006

Abstract: Diverse sets of 5,5′-disubstituted hydantoins can conveniently be made in moderate to good yields (40–92%) by a one-pot process involving treatment of aromatic, heteroaromatic or aliphatic nitriles with an organometallic reagent (RLi or RMgX) followed by $KCN/(NH_4)_2CO_3$.

Key words: heterocycles, multicomponent reactions, combinatorial chemistry

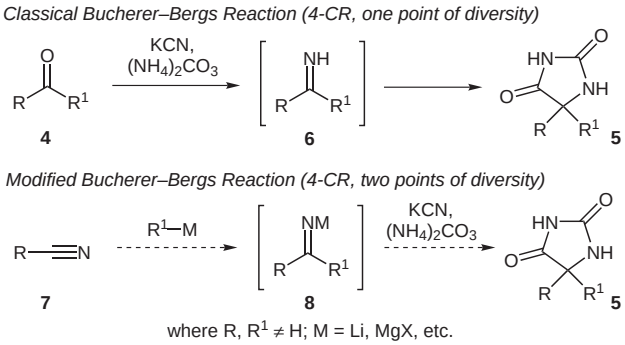
The hydantoin nucleus displays many important pharmacological effects[1] and is commonly used in drug discovery programmes. Indeed, several clinically important medicines including nilutamide (**1**)[2] (anticancer) and phenytoin (**2**)[3] (antiepileptic) are based upon this heterocyclic scaffold. Moreover, a number of hydantoin natural products are known, e.g. (+)-hydantocidin (**3**, Figure 1).[4] The hydantoin nucleus also serves as a precursor to nonnatural amino acids via chemical[1] or enzymatic hydrolysis.[5]



1, Nilutamide **2**, Phenytoin **3**, (+)-Hydantocidin

Figure 1

A number of methods exist for the synthesis of hydantoins.[1,6] Of these, the classical Bucherer–Bergs provides the one of the most direct methods.[7] It involves reaction of a ketone **4** (or aldehyde) with cyanide, ammonia and carbon dioxide (conveniently generated from ammonium carbonate) and directly produces the hydantoin **5** via the NH imine **6** (Scheme 1). It is highly practical and new applications of this reaction continue to be developed.[8] Despite the enormous scope and potential of this four-component reaction (4-CR), only changes in the structure of one component, namely **4**, leads to variation in the structure of the final hydantoin **5**. Thus, for every 5,5′-disubstituted hydantoin to be synthesized, the corresponding ketone with the correct R and R^1 groups has to be made or purchased. To increase the utility of this chemistry in drug discovery programmes, it would be desirable to generate the ketone **4** (or indeed the corresponding NH imine **6**), in the same vessel as the Bucherer–Bergs reaction by a process involving C–C bond formation. In this way, greater structural diversity in the compounds produced could be achieved. Of several possibilities, the reaction of a nitrile **7** with an organometallic reagent such as RMgX or RLi seemed attractive (Scheme 1).[9] Selection of this strategy was based on the following: (1) a very large number of nitriles are commercially available or readily accessible; (2) a variety of common organometallic reagents including RMgX[10] and RLi[11] add to alkyl-, aryl- and heteroaryl-substituted nitriles in high yields; (3) protonation of the intermediate metallated imine **8** directly leads to the NH imine, an intermediate in the Bucherer–Bergs reaction.[7] In this communication, we report the successful development of a practical, one-pot method for the synthesis of 5,5′-disubstituted hydantoins **5** based upon this approach.

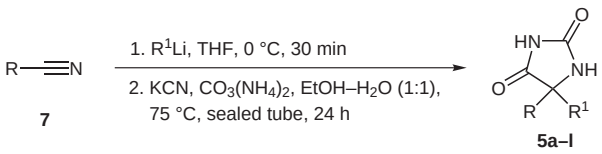


Scheme 1

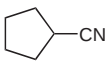
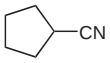
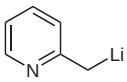
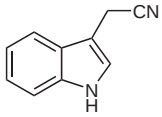
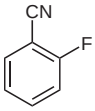
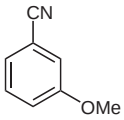
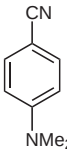
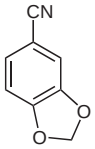
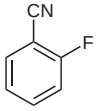
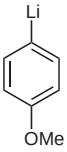
Initial studies were undertaken to ascertain whether Bucherer–Bergs reactions can be performed in solvent mixtures containing THF, an ideal solvent for organometallic additions to nitriles.[10,11] These experiments were performed on *n*-butyl phenyl ketone (1 mmol scale) under a standard set of reaction conditions [KCN (3 equiv), $CO_3(NH_4)_2$ (6 equiv), 75 °C, 24 h].[12] The reaction solvent was varied (total volume constant at 9 mL) and the extent of conversion to the corresponding hydantoin (**5a**, R = Ph, R^1 = Bu) monitored by ^{1}H NMR spectroscopy. In THF–H_2O (1:1), no appreciable conversion (<15%) to **5a** was observed. Similar results were obtained using the ternary solvent system, THF–H_2O–EtOH (2:1:1). However, reducing the amount of THF [THF–H_2O–EtOH, 1:4:4) did improve the conversion to 47%. Complete conversion (>95%) was achieved using these latter conditions when a

SYNLETT 2006, No. 14, pp 2203–2206
Advanced online publication: 24.08.2006
DOI: 10.1055/s-2006-949644; Art ID: D11506ST

Table 1 Selection of Hydantoins Made Using Organolithium Reagents



7 **5a–l**

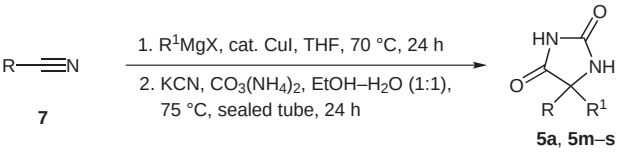
Entry	RCN	R^1Li	Hydantoin	Yield (%)[a]
1	PhCN	BuLi	**5a**	70
2	$Me(CH_2)_4CN$	MeLi	**5b**	64
3	$Me(CH_2)_4CN$	PhLi	**5c**	61
4		MeLi	**5d**	75
5			**5e**	50[b]
6	*t*-BuCN	MeLi	**5f**	75
7		MeLi	**5g**	45[c]
8		BuLi	**5h**	84
9		PhLi	**5i**	92
10		PhLi	**5j**	54
11		PhLi	**5k**	88
12			**5l**	53[d]

[a] Isolated yield of product. All reactions performed using the procedure described in ref. 13.
[b] Organolithium made by deprotonation of (2-methyl)pyridine using *n*-BuLi. This example was conducted in Et_2O.
[c] Conducted using MeLi (2.4 equiv).
[d] Organolithium prepared in situ by lithium–iodine exchange.

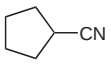
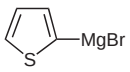
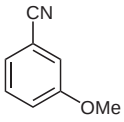
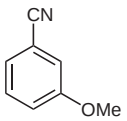
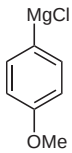
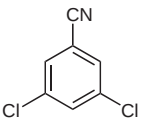
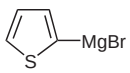
sealed tube was used to prevent release of the ammonia and carbon dioxide generated. In this way, hydantoin **5a** was isolated in 77% yield. Once it was established that THF is tolerated in Bucherer–Bergs reactions, albeit at low concentrations, the planned one-pot sequence was attempted. Gratifyingly, treatment of benzonitrile with *n*-BuLi at 0 °C in THF for 30 min smoothly generated the lithiated imine. Direct addition of EtOH (to quench the excess organolithium) then KCN, $CO_3(NH_4)_2$ and H_2O, and subsequent heating at 75 °C produced crystalline **5a** in 70% yield via this one-pot process (Table 1, entry 1).[13,14] The scope of this new 4-CR has been explored using a range of commercially available nitriles and easily accessible organolithiums (Table 1). Considerable variation in the nature of the nitrile (Table 1, entries 1, 2, 4, and 6–11) and the organolithium reagent (Table 1, entries 1–3, 5 and 12) can be achieved. The reaction shows good functional-group tolerance (Table 1, entries 5 and 7–11) and offers a simple, practical route to 5,5′-disubstituted hydantoins.

Grignard reagents can also be used in this modified Bucherer–Bergs process. In this instance, the organometallic addition to the nitrile is more sluggish and requires prolonged heating in the presence of catalytic amounts of copper(I) iodide[10] to facilitate complete conversion to the metallated imine **8** (M = MgX). However, under these conditions, good yields of a range of functionalised hydantoins can be produced (Table 2).[14,15] The results indicate that appreciable variation in the structure of the nitrile and Grignard reagent is possible.

Table 2 Selection of Hydantoins Made Using Grignard Reagents



7 **5a**, **5m–s**

Entry	RCN	R^1MgX	Hydantoin	Yield (%)[a]
1			**5m**	58
2	*t*-BuCN	$PhCH_2MgCl$	**5n**	74
3	*t*-BuCN	BuMgCl	**5o**	58
4	PhCN	BuMgCl	**5a**	57
5	PhCN	$PhCH_2MgCl$	**5p**	77
6		*t*-BuMgCl	**5q**	40
7			**5r**	65
8			**5s**	61

[a] Isolated yield of product. All reactions performed using the procedure described in ref. 15.

To conclude, this chemistry offers a simple, practical method for the synthesis of 5,5′-disubstituted hydantoins exploiting two points of diversity. Since all the heterocycles produced in these modified Bucherer–Bergs reactions are isolated in high purity without recourse to chromatography,[13,15] this chemistry seems well suited for the rapid generation of hydantoin chemical libraries.[16] Work in this direction continues in our laboratories.

Acknowledgment

The Engineering and Physical Sciences Research Council (GR/R82586/02) is gratefully acknowledged for financial support.

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(8) For recent applications, see: (a) Wermuth, U. D.; Jenkins, I. D.; Bott, R. C.; Byriel, K. A.; Smith, G. *Aust. J. Chem.* **2004**, *57*, 461. (b) Micová, J.; Steiner, B.; Koós, M.; Langer, V.; Gyepesová, D. *Carbohydr. Res.* **2003**, *338*, 1917. (c) Micová, J.; Steiner, B.; Koós, M.; Langer, V.; Gyepesová, D. *Synlett* **2002**, 1715.

(9) A similar approach has been used to improve and extend other multicomponent reactions, see: (a) Simoneau, C. A.; Ganem, B. *Tetrahedron* **2005**, *61*, 11374. (b) Simoneau, C. A.; George, E. A.; Ganem, B. *Tetrahedron Lett.* **2006**, *47*, 1205.

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(12) Lower conversion was observed when the quantities of KCN and $(NH_4)_2CO_3$ were reduced.

(13) **Experimental Method (Using RLi).**
In a flame dried ACE thick-walled pressure tube under nitrogen, are successively added THF (1 mL) and the organolithium reagent (1.2 mmol). The solution is cooled to 0 °C whereupon the nitrile (1.0 mmol) is added. The reaction mixture is stirred for 30 min at 0 °C then carefully quenched with EtOH (4 mL). Then, $(NH_4)_2CO_3$ (576 mg, 6 mmol), KCN (197 mg, 3 mmol; CAUTION) and H_2O (4 mL) are successively added and the tube is sealed. The heterogeneous solution is heated at 75 °C (preheated bath) for 24 h then allowed to cool to r.t. The mixture is poured into H_2O (50 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extract is washed with brine (25 mL), dried over $MgSO_4$ and evaporated to dryness. The resulting solid is washed with *n*-pentane (2 × 10 mL) and dried under high vacuum to yield the hydantoin in a high state of purity as judged by NMR analysis and microanalytical data.

(14) **Selected Data.**
Compound **5f**: mp 228–229 °C. IR (neat): 3169, 2961, 1750, 1717, 1430, 1370, 1108, 764 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 0.92 (s, 9 H), 1.24 (s, 3 H), 7.95 (s, 1 H), 10.50 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.8, 24.5, 36.1, 66.8, 156.7, 178.2. MS (ES): *m/z* = 169 [M – H]$^-$. HRMS (EI): *m/z* calcd for $C_8H_{12}N_2O_2$: 171.1134; found: 171.1128. Anal. Calcd for $C_8H_{14}N_2O_2$ (%): C, 56.45; H, 8.29; N, 16.46. Found: C, 56.52; H, 8.35; N, 16.35.
Compound **5h**: mp 181–182 °C. IR (neat): 3180, 3052, 2927, 1774, 1709, 1432, 1232, 813, 756 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 0.89 (t, *J* = 7.0 Hz, 3 H), 1.09–1.20 (m, 1 H), 1.24–1.41 (m, 3 H), 2.00–2.09 (m, 2 H), 7.21 (dt, *J* = 1.0, 7.0 Hz, 1 H), 7.23 (d, *J* = 7.5 Hz, 1 H), 7.38–7.45 (m, 1 H), 7.53 (dt, *J* = 1.5, 8.2 Hz, 1 H), 8.31 (s, 1 H), 10.87 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.9, 22.0, 24.8, 34.7, 64.9, 116.3 (d, *J* = 22 Hz), 124.4 (d, *J* = 3 Hz), 126.3 (d, *J* = 11 Hz), 128.1 (d, *J* = 3 Hz), 130.4 (d, *J* = 9 Hz), 156.7, 160.4 (d, *J* = 247 Hz), 176.1. MS (ES): *m/z* = 249 [M – H]$^-$. HRMS (EI): *m/z* calcd for $C_{13}H_{15}FN_2O_2$: 250.1118; found: 250.1114. Anal. Calcd for $C_{13}H_{15}FN_2O_2$ (%): C, 62.39; H, 6.04; N, 11.19. Found: C, 62.50; H, 6.11; N, 11.01.
Compound **5j**: mp 244–245 °C. IR (neat): 3304, 3191, 1775, 1759, 1728, 1710, 1411, 1023, 747, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.88 (s, 6 H), 6.70 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 8.8 Hz, 2 H), 7.29–7.40 (m, 5 H), 9.12 (s, 1 H), 10.9 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.0, 69.8, 111.9, 126.6, 127.1, 127.2, 127.7, 128.3, 140.4, 149.8, 156.0, 175.4. MS (ES): *m/z* = 294 [M – H]$^-$. HRMS (EI): *m/z* calcd for $C_{17}H_{17}N_3O_2$: 295.1321; found: 295.1317. Anal. Calcd for $C_{17}H_{17}N_3O_2$ (%): C, 69.14; H, 5.80; N, 14.23. Found: C, 68.80; H, 5.88; N, 13.96.
Compound **5m**: mp 199 °C (decomp.). IR (neat): 3227, 2958, 1767, 1736, 1713, 1396, 1232, 1006, 763, 710 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.14–1.32 (m, 2 H), 1.44–1.66 (m, 6 H), 2.63–2.73 (m, 1 H), 7.02 (dd, *J* = 3.8, 5.0 Hz, 1 H), 7.09 (dd, *J* = 1.3, 3.8 Hz, 1 H), 7.48 (dd, *J* = 1.3, 5.0 Hz, 1 H), 8.83 (s, 1 H), 10.83 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.0, 25.4, 26.2, 26.8, 46.6, 68.5, 124.5, 125.8, 127.0, 143.1, 156.9, 175.1. MS (ES): *m/z* = 249 [M – H]$^-$. HRMS (EI): *m/z* calcd for $C_{12}H_{14}N_2O_2S$: 250.0776; found: 250.0767. Anal. Calcd for $C_{12}H_{14}N_2O_2S$ (%): C, 57.58; H, 5.64; N, 11.19. Found: C, 57.91; H, 5.80; N, 11.04.
Compound **5q**: mp 244–245 °C. IR (neat): 3250, 3042, 1760, 1712, 1598, 1450, 1255, 758 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 0.92 (s, 9 H), 3.74 (s, 3 H), 6.88–6.92 (m, 1 H), 7.22–7.30 (m, 3 H), 8.91 (s, 1 H), 10.80 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.8, 37.8, 55.1, 71.9, 112.5, 113.8, 119.6, 128.3, 137.6, 156.3, 158.4, 175.3. MS (ES): *m/z* = 261 [M – H]$^-$. HRMS (EI): *m/z* calcd for $C_{14}H_{19}N_2O_3$: 263.1396; found: 263.1384. Anal. Calcd for $C_{14}H_{18}N_2O_3$ (%): C, 64.10; H, 6.92; N, 10.68. Found: C, 64.00; H, 6.95; N, 10.59.

(15) **Experimental Method (Using RMgX).**
In a flame-dried ACE pressure tube under nitrogen, are successively added copper iodide (9.5 mg, 0.05 mmol), THF (1 mL) and the organomagnesium reagent (1.2 mmol) immediately followed by the nitrile [1 mmol; either as liquid or in THF (1 mL) if solid]. The vessel is quickly heated to 70 °C (preheated bath) and maintained at this temperature for 24 h. Upon cooling to r.t., the reaction is carefully quenched with EtOH (4 mL). Then, $(NH_4)_2CO_3$ (576 mg, 6 mmol), KCN (197 mg, 3 mmol; CAUTION) and H_2O (4 mL) are successively added and the tube is sealed. The heterogeneous solution is heated at 75 °C (preheated bath) for 24 h then allowed to cool to r.t. The hydantoin is isolated using the same work-up and crystallisation protocol described in ref. 12.

(16) Shipman, M.; Montagne, C. GB 0603239.5, **2006**.