Facile one-pot synthesis of 5-substituted hydantoins†

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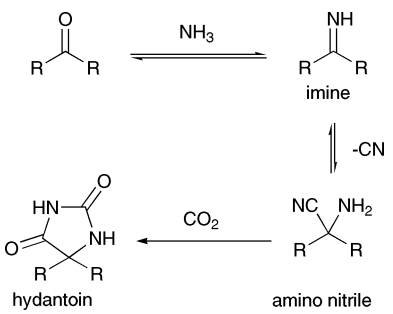
5-Substituted and 5,5-disubstituted hydantoins are synthesised from the corresponding aldehydes or ketones, using a one-pot, gallium(III) triflate-catalysed procedure that is compatible with a range of substrates and solvents.

The hydantoin scaffold is an important structural component that is present in a number of natural products[1–5] and pharmacologically important compounds.[1,6–12] More recently, hydantoin-derived guanine oxidation products have emerged as markers of oxidative cell damage. These hydantoins are significant DNA lesions that are targeted by repair enzymes and may be implicated in cancer, aging and neurological disorders.[13–17] Synthetically, hydantoins are important precursors to amino acids, *via* either acid-, base- or enzyme-catalysed hydrolysis. The Bucherer–Bergs reaction (Scheme 1) is the most commonly used method for the synthesis of hydantoins.[18] This multicomponent reaction commences from an aldehyde or a ketone and their ready availability makes the Bucherer–Bergs reaction an attractive method for the synthesis of hydantoins. However, the use of water and ethanol as solvents gives rise to solubility problems with a number of substrates, and the inclusion of ammonium carbonate can lead to problems with sublimation, causing the reaction to often be conducted within a sealed tube or acid digestion bomb. Other methods of furnishing hydantoins include the treatment of α-amino amides with triphosgene,[19] the reaction of amino acids with acetic anhydride and ammonium thiocyanate (to give the thiohydantoin),[20] combination of carbodiimides and α,β-unsaturated carboxylic acids, and the treatment of nitriles with organometallic reagents followed by potassium cyanide and ammonium carbonate.[21,22] Both microwave[23] and solid phase[24,25] technologies have been employed in the synthesis of hydantoins. There are also more esoteric syntheses of hydantoins that involve complex rearrangements.[1,26,27]



Scheme 1 Intermediates in the proposed mechanism of the Bucherer–Bergs reaction.[30,31]

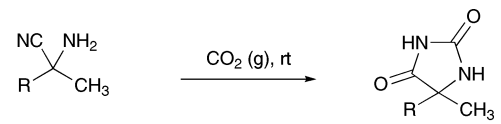
We have investigated a Lewis acid-catalysed variation of the Bucherer–Bergs reaction, which is compatible with a range of organic solvents and that commences from simple aldehyde or ketone starting materials. Lewis acid catalysis engenders the possibility of chiral catalysis and ultimately an enantioselective reaction. Herein, we report the development of a one-pot, Lewis acid-catalysed, hydantoin synthesis that is compatible with a range of substrates and organic solvents.

The mechanism of the Bucherer–Bergs reaction (Scheme 1) mirrors that of the Strecker synthesis until the formation of the amino nitrile. At this point, the Strecker synthesis is complete, whereas in the Bucherer–Bergs reactions, the amino nitrile goes on to react with carbon dioxide. As enantioselective Lewis acid-catalysed Strecker reactions are well documented,[28,29] our initial investigations focused on the conversion of amino nitriles to hydantoins by treatment with carbon dioxide.

Literature from 1934 details one example of the conversion of 2-amino-2-methylpropionitrile to 5,5-dimethylhydantoin by treatment with carbon dioxide in water.[32] In our hands, this reaction only proceeded in 9% yield, although this could be improved to 50% yield by conducting the reaction in a preformed solution of aqueous carbonic acid (Table 1).

To determine whether the volatility of amino nitrile **1** contributed to the poor yield, the reaction was repeated using the less volatile **2**. This reaction gave a yield of 50%, prompting us to consider whether two equivalents of the aminonitrile are required for the reaction to proceed. It was postulated that the amino

Table 1 Initial optimisation for the conversion of amino nitriles to hydantoins



1 R = CH_3
2 R = cyclopropyl
3 R = CH_3
4 R = cyclopropyl

Entry	R	Solvent	Time	Yield
1	CH_3	Water	15 h	9%
2	CH_3	Carbonic acid solution	24 h	50%
3	Cyclopropyl	Carbonic acid solution	12 h	50%
4	Cyclopropyl	Water & Hünig's base (3 eq)	6 h	77%
5	Cyclopropyl	CH_2Cl_2 & Hünig's base (3 eq)	12 h	90–94%

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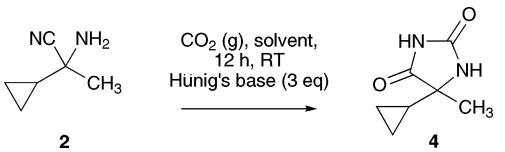
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data, ^1H and ^{13}C NMR spectra, and optimisation of the one-pot reaction. See DOI: 10.1039/b719675j

Table 2 Screening for the optimum solvent



Entry	Solvent	Yield
1	Dichloromethane	90–94% ($n = 2$)
2	Ethyl acetate	61–80% ($n = 2$)
3	Ethanol	71–75% ($n = 2$)
4	Diethyl ether	65%
5	Toluene	45%
6	Water	32–75%[a]

[a] Adding solid CO_2 gave 75% yield, bubbling $CO_{2(g)}$ gave 32% yield.

nitrile was hydrolysing to give the ketone, hydrogen cyanide and ammonia. The ammonia might then act as a base, either preventing further amino nitrile hydrolysis, or playing a role in the reaction itself. To investigate whether the addition of a base would improve the yield of hydantoin **4**, the reaction was repeated in the presence of Hünig's base (3 equivalents) and a yield of 77% was obtained. At this stage our working hypothesis was that the carbon dioxide was dissolving in the water to form carbonic acid and this was reacting with the amino nitrile. We were thus gratified to find that, when dichloromethane was employed as the solvent, **2** was converted to the corresponding hydantoin (**4**) in excellent (90–94%) yield. This high yield was maintained when strictly anhydrous conditions were employed. Failure to include Hünig's base resulted in no product formation, indicating that the base plays a vital role in the reaction when organic solvent is used.

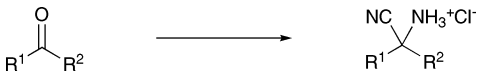
Using dichloromethane as the solvent, a range of bases was investigated. Both Hünig's base and triethylamine promoted the formation of **4** in excellent yield. Pyridine and DBU failed to promote hydantoin formation of **4**, indicating that those bases with a pK_b of approximately 11 are optimal. However, pK_b is not the only factor that affects the reaction, as the use of tributylamine ($pK_b = 10.9$) only afforded a 14–25% yield of the hydantoin **4**.

Having established that either triethylamine or Hünig's base would effectively promote hydantoin formation, a range of reaction solvents were investigated, but none was superior to dichloromethane (Table 2). The reaction proceeded in good yield when ethyl acetate, ethanol and diethyl ether were used as solvents. Moderate yields were obtained when toluene and water were used.

A range of amino nitriles (**1**, **2**, **5–10**) was then chosen so as to investigate the scope of the reaction. The amino nitriles were synthesised as shown in Table 3. Problems with solubility were encountered during the synthesis of the aromatic amino nitriles, hence DMSO or methanol was used as a co-solvent. The isolation of pure amino nitriles proved a challenge and we eventually found it convenient to purify the amino nitriles by crystallisation as their hydrochloride salts.

The amino nitrile salts were converted to the free amino nitriles, and these were transformed to hydantoins using the conditions described in Table 4. It can be seen that both aliphatic and aromatic methyl ketones can be converted to the corresponding hydantoins in good yield.

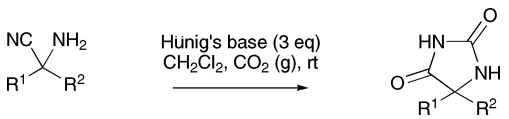
Table 3 The synthesis of amino nitriles



Amino nitrile	R^1	R^2	Reaction time	Yield
1[a]	CH_3	CH_3	20 h	30%
5[b]	C_5H_{11}	CH_3	20 h	82%
6[c]	^{t}Bu	CH_3	20 h	23%
2[c]	Cyclopropyl	CH_3	20 h	62%[e]/88%[f]
7[d]	Ph	CH_3	20 h	46%
8[d]	3-MeOPh	CH_3	40 h	41%
9[d]	Ph	C_2H_5	24 h	24%
10[c]	C_4H_9	C_4H_9	20 h	7%

[a] Conditions used: KCN, NH_4Cl, H_2O, rt.[33] [b] Conditions used: KCN, NH_4Cl, NH_4OH, H_2O, MeOH, 4 °C → rt.[34] [c] Conditions used: KCN, NH_4Cl, NH_4OH, H_2O, 4 °C → rt.[34] [d] Conditions used: KCN, NH_4Cl, DMSO, H_2O, rt.[35] [e] Isolated as HCl salt. [f] Isolated as the free amino nitrile.

Table 4 Scope of the amino nitrile to hydantoin reaction



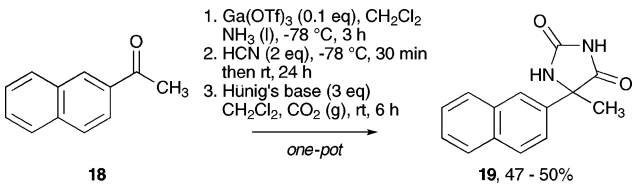
Hydantoin	R^1	R^2	Reaction time[a]	Yield
11	Ph	H	17 h	73%
12	C_5H_{11}	CH_3	9 h	87%
13[b]	^{t}Bu	CH_3	18 h	0%
13[b]	^{t}Bu	CH_3	17 h	62%
4	Cyclopropyl	CH_3	12 h	94%
14	Ph	CH_3	20 h	90%
15	3-MeOPh	CH_3	24 h	60%
16	Ph	C_2H_5	12 h	62%
17	C_4H_9	C_4H_9	14 h	47%

[a] Time of exposure to CO_2. [b] Ethanol was used as the solvent as pinacolone-derived amino nitrile is insoluble in dichloromethane.

The reaction times vary as each reaction was continued until no starting material was present by TLC analysis. In the case of **13**, successful reaction was only observed when using ethanol as a solvent, due to the insolubility of **6** (free amine) in dichloromethane. Both the steric and electronic nature of the amino nitrile affect the reaction, as lower yields were observed when **8** and **9** were subjected to the reaction conditions. In contrast, **7** was converted into the corresponding hydantoin in excellent yield (90%). It proved impossible to isolate 2-amino-2-phenylacetonitrile using the above conditions, however, commercially obtained material was used to evaluate the conversion of this amino nitrile to the corresponding hydantoin (**11**). Both *N*-allyl and *N*-benzyl substituted aminonitriles, derived from cyclopropyl methyl ketone and the corresponding primary amine, were submitted to our optimised conditions. In neither case was any hydantoin formed. This seems to indicate that *N*-substitution interferes with the formation of a hydantoin.

Although the above conversion of amino nitriles to hydantoins is useful, it is limited by the difficulty associated with the isolation and purification of the amino nitriles. It was therefore desirable to develop a one-pot synthesis of hydantoins from ketones or aldehydes. The formation of imines from aldehydes and amines is

often spontaneous. However, the formation of imines from amines and the less electrophilic ketones often requires the presence of a Brønsted or Lewis acid catalyst. The formation of an amino nitrile from an imine may also require the presence of a Brønsted or Lewis acid. In addition, it is possible that the addition of a Lewis acid may assist in the conversion of the amino nitrile to hydantoin, by interaction with carbon dioxide. Olah and co-workers have recently shown that a range of *N*-substituted amino nitriles can be formed from the corresponding amine, ketone and TMSCN using gallium(III) triflate as a Lewis acid catalyst.[36] We have extended these conditions to use ammonia, giving the free amino nitriles, which were then transformed *in situ* to the hydantoin. Optimisation studies (Scheme 2 and see ESI†) were conducted on 2-acetonaphthalene (**18**), as it had proved impossible to isolate a pure sample of the corresponding amino nitrile for use in the reaction described above.



Scheme 2 The optimised conditions for the conversion of 2-acetonaphthalene to its corresponding hydantoin.

The optimum conditions were found to involve the addition of liquid ammonia at −78 °C followed by stirring at this temperature for 3 h with gallium(III) triflate. The hydrogen cyanide solution in dichloromethane was added at −78 °C and the reaction solution allowed to warm to room temperature with stirring over 24 h, resulting in the evaporation of most of the liquid ammonia and leaving the dichloromethane solvent present. Hünig's base was added and the carbon dioxide bubbled through the reaction solution. When the gallium(III) triflate was excluded from the reaction solution no product was isolated, indicating that Lewis acid catalysis is required for either the formation of the imine or formation of both the imine and the amino nitrile. Although these conditions only gave modest yields (~50%), they were applied to a range of ketones in order to investigate the scope of the reaction. It can be seen from Fig. 1 (dark bars) that the conversion of aldehydes and ketones to the corresponding hydantoins was achieved in modest to excellent yield (25–98%). Benzaldehyde, heptan-2-one and cyclopropylmethyl ketone all underwent the transformation in excellent yield. Ketone-derived hydantoins with aromatic substituents were formed in more modest yields, presumably due to the less electrophilic nature of the ketone. The extended chain **17** was also formed in good yield. The yields for the two-pot reaction (Fig. 1, light bars) are obtained by combining the yields from Table 3 and Table 4. In all cases it can be seen that the yields of the one-pot reaction are equal to or higher than those of the two-pot reaction, demonstrating the advantages of the one-pot approach. It should be noted that the one- and two-pot procedures cannot be directly compared, as gallium(III) triflate is used in the one-pot procedure, but not the two-pot procedure and hence two different reactions are being considered. All compounds isolated displayed analytical and spectroscopic data consistent with the assigned structure.†

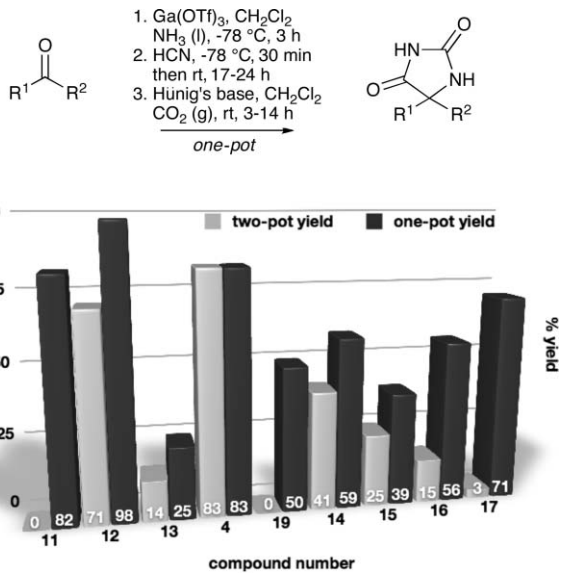


Fig. 1 Comparison of yields in the one- and two-pot conversions of ketones and aldehydes to hydantoins. **11**: R^1 = Ph, R^2 = H; **12**: R^1 = C_5H_{11}, R^2 = Me; **13**: R^1 = ^{t}Bu, R^2 = Me (EtOH is solvent); **4**: cyclopropyl, R^2 = Me; **19**: R^1 = naphthyl, R^2 = Me; **14**: R^1 = Ph, R^2 = Me; **15**: R^1 = 3-MeOPh, R^2 = Me; **16**: R^1 = Ph, R^2 = Et; **17**: R^1 = C_4H_9, R^2 = C_4H_9.

The methodology described herein represents a significant advance over the existing Bucherer–Bergs reaction for the synthesis of hydantoins. In the first instance we developed conditions for the synthesis of hydantoins from amino nitriles. Although one example of this transformation existed in the early literature,[31] we have demonstrated that the solvent can be changed from water to a range of organic solvents and discovered that the inclusion of Hünig's base or triethylamine is required for the reaction to progress in good yield. Despite these advances, however, we have found that the synthesis and purification of unsubstituted amino nitriles can be challenging, mainly resulting from the difficulty of isolating the amino nitriles or their salts. In order to address this problem, we have developed a one-pot, gallium(III) triflate-catalysed synthesis of hydantoins. Our methodology has a number of advantages over the existing Bucherer–Bergs reaction. Firstly, the use of organic, rather than aqueous, solvents makes the reaction applicable to a wide range of substrates. Secondly, the lower temperature at which the reaction is conducted avoids complications related to the volatility of the ammonium carbonate. In addition, it is operationally simple to carry out the one-pot reaction on both aldehydes and ketones.

In summary, we have synthesised a range of 5-substituted and 5,5-disubstituted hydantoins from the corresponding aldehydes and ketones in a one-pot procedure. We have demonstrated clearly that gallium(III) triflate catalysis is required for this reaction to progress.

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Notes and references

1 M. Meusel and M. Gutschow, *Org. Prep. Proced. Int.*, 2004, **36**, 391.
2 L. Chevolot, S. Padua, B. N. Ravi, P. C. Blyth and P. J. Scheuer, *Heterocycles*, 1977, **7**, 891.
3 R. Fathiafshar and T. M. Allen, *Can. J. Chem.*, 1988, **66**, 45.
4 C. Jimenez and P. Crews, *Tetrahedron Lett.*, 1994, **35**, 1375.
5 I. S. Chen, C. T. Chang, W. S. Sheen, C. M. Teng, I. L. Tsai, C. Y. Duh and F. N. Ko, *Phytochemistry*, 1996, **41**, 525.
6 K. Last-Barney, W. Davidson, M. Cardozo, L. L. Frye, C. A. Grygon, J. L. Hopkins, D. D. Jeanfavre, S. Pav, C. G. Qian, J. M. Stevenson, L. Tong, R. Zindell and T. A. Kelly, *J. Am. Chem. Soc.*, 2001, **123**, 5643.
7 M. Jansen, H. Potschka, C. Brandt, W. Loscher and G. Dannhardt, *J. Med. Chem.*, 2003, **46**, 64.
8 C. X. Zha, G. B. Brown and W. J. Brouillette, *J. Med. Chem.*, 2004, **47**, 6519.
9 J. C. Thenmozhiyal, P. T. H. Wong and W. K. Chui, *J. Med. Chem.*, 2004, **47**, 1527.
10 A. Balog, M. E. Salvati, W. F. Shan, A. Mathur, L. W. Leith, D. D. Wei, R. M. Attar, J. P. Geng, C. A. Rizzo, C. H. Wang, S. R. Krystek, J. S. Tokarski, J. T. Hunt, M. Gottardis and R. Weinmann, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 6107.
11 X. Q. Zhang, G. F. Allan, T. Sbriscia, O. Linton, S. G. Lundeen and Z. H. Sui, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5763.
12 G. G. Muccioli, D. Martin, G. K. E. Scriba, W. Poppitz, J. H. Poupaert, J. Wouters and D. M. Lambert, *J. Med. Chem.*, 2005, **48**, 2509.
13 S. S. David, V. L. O'Shea and S. Kundu, *Nature*, 2007, **447**, 941.
14 N. Krishnamurthy, J. G. Muller, C. J. Burrows and S. S. David, *Biochemistry*, 2007, **46**, 9355.
15 Y. Ye, J. G. Muller, W. C. Luo, C. L. Mayne, A. J. Shallop, R. A. Jones and C. J. Burrows, *J. Am. Chem. Soc.*, 2003, **125**, 13926.
16 W. Adam, M. A. Arnold, M. Grune, W. M. Nau, U. Pischel and C. R. Saha-Moller, *Org. Lett.*, 2002, **4**, 537.
17 W. C. Luo, J. G. Muller, E. M. Rachlin and C. J. Burrows, *Org. Lett.*, 2000, **2**, 613.
18 E. Ware, *Chem. Rev.*, 1950, **46**, 403.
19 D. Zhang, X. C. Xing and G. D. Cuny, *J. Org. Chem.*, 2006, **71**, 1750.
20 S. Reyes and K. Burgess, *J. Org. Chem.*, 2006, **71**, 2507.
21 C. Montagne and M. Shipman, *Synlett*, 2006, 2203.
22 C. Montagne, J. J. Shiers and M. Shipman, *Tetrahedron Lett.*, 2006, **47**, 9207.
23 M. J. Lee and C. M. Sun, *Tetrahedron Lett.*, 2004, **45**, 437.
24 J. J. Scicinski, R. D. Barker, P. J. Murray and E. M. Jarvie, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3609.
25 P. Y. Chong and P. A. Petillo, *Tetrahedron Lett.*, 1999, **40**, 2493.
26 N. Dieltiens, D. D. Claeys, V. V. Zhdankin, V. N. Nemykin, B. Allaert, F. Verpoort and C. V. Stevens, *Eur. J. Org. Chem.*, 2006, 2649.
27 M. Meusel, A. Ambrozak, T. K. Hecker and M. Gutschow, *J. Org. Chem.*, 2003, **68**, 4684.
28 H. Groger, *Chem. Rev.*, 2003, **103**, 2795.
29 D. Enders and J. P. Shilvock, *Chem. Soc. Rev.*, 2000, **29**, 359.
30 A. Rousset, M. Lasperas, J. Taillades and A. Commeyras, *Tetrahedron*, 1980, **36**, 2649.
31 J. Taillades, A. Rousset, M. Lasperas and A. Commeyras, *Bull. Soc. Chim. Fr.*, 1986, 650.
32 T. Bucherer and W. Steiner, *J. Prakt. Chem.*, 1934, **140**, 291.
33 J. Taillades and A. Commeyras, *Tetrahedron*, 1974, **30**, 3407.
34 J. L. Marco, S. T. Ingate and P. M. Chinchon, *Tetrahedron*, 1999, **55**, 7625.
35 W. L. Matier, D. A. Owens, W. T. Comer, D. Deitchman, H. C. Ferguson, R. J. Seidehamel and J. R. Young, *J. Med. Chem.*, 1973, **16**, 901.
36 G. K. S. Prakash, T. Mathew, C. Panja, S. Alconcel, H. Vaghoo, C. Do and G. A. Olah, *Proc. Natl. Acad. Sci. USA*, 2007, **104**, 3703.