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Complementary regioselectivity in the synthesis of iminohydantoins: remarkable effect of amide substitution on the cyclization†‡

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Complementary regioselective synthesis of iminohydantoins from isocyanoacetamides controlled by the substituent on the amide group has been described. 4-Iminohydantoins were the major products when the starting materials were *N*-alkyl isocyanoamides, whereas 2-iminohydantoins were the major products with *N*-aryl isocyanoamides.

Apart from the interest in isocyanoacetamides for their high antimicrobial activity,[1] a number of works have reported their usefulness as starting materials in the synthesis of a wide variety of nitrogen-containing heterocycles.[2] Besides the characteristic chemistry of isocyanides with a formally divalent carbon,[3] two different approaches have been employed for the cyclization, the use of the active methylene[4] and the use of the amide group, either through the oxygen[5] or nitrogen atom.[6] Several factors have a significant influence on the course of these cyclizations such as the substitution at the α-carbon of the isocyanoacetamides,[7] the nucleophilicity of the isocyanide group[8] or the reaction conditions.[7] However, although the importance of the degree of the amide substitution[9] in these reactions has also been studied,[10] the significance of the nature of *N*-substituents on the amide group has not been reported.

In previous papers we have reported the outcome of the 3-component reaction of isocyanides with chloramines and aromatic amines[11] and exploited it in the synthesis of nitrogen heterocycles such as quinazolines[12] and imidazoles[13] by two-step one-pot reactions. As a part of our efforts directed towards the synthesis of heterocyclic compounds from isocyanides, this paper deals with a novel application of α-isocyanoacetamides in the regioselective synthesis of iminohydantoins. These heterocycles have been described as potential drugs for the treatment of Alzheimer's disease acting as β-secretase inhibitors with good potential for brain penetration.[14]

We have studied the three centers-two component reaction (3C-2CR) of chloramines with isocyanoacetamides, where the amide moiety was expected to be chlorinated and then interact as an electrophile with the isocyanide divalent carbon, leading directly to interesting heterocyclic structures. In this way, we attempted the reaction between *N*-alkyl- and *N*-aryl isocyanoacetamides[15] (**1**) and chloramines (**2**) to synthesize aminoimidazolidinones from a simple reaction under phase transfer conditions. Therefore, a small amount of TEBA (benzyltriethylammonium chloride) was added to a stirred suspension of isocyanoacetamide **1a–i** (1 equiv.) and dry chloramine (B, **2a**, or T, **2b**) (1 equiv.) in dry chloroform at room temperature for 4 days. Aqueous work-up, extraction with chloroform and recrystallization gave iminohydantoin derivatives **3–4** in fair yields (Table 1).

The cyclization was expected to be regioselective, producing 2-iminohydantoins **4** as single regioisomers. However, although all the α-isocyanocarboxamides tested afforded iminohydantoins, two different regioisomers were obtained depending on the nature of the *N*-substituent in the amide group (Table 1). 4-Iminohydantoins **3** were predominantly obtained when *N*-alkyl α-isocyanocarboxamide derivatives were used as starting materials (Table 1, entries 1–8), while 2-iminohydantoins **4** were the major products with *N*-aryl derivatives (Table 1, entries 9–12). As far as we know this is the first reported example of a complementary regioselective cyclization controlled by the substituents on an amide group.

These experimental data suggest that the observed regioselectivity might be correlated to the electron density on the nitrogen of the amide group. Thus, while the *N*-phenylisocyanocarboxamides **1h** and **1i** afford 2-iminohydantoin derivatives **4j–l** as the overwhelming product (Table 1, entries 10–12),

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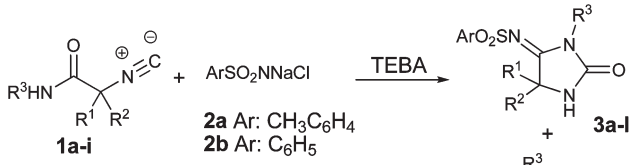
†This paper is dedicated to the memory of Stefano Marcaccini.

‡Electronic supplementary information (ESI) available: Experimental details, synthesis and characterization of products. CCDC 907949 and 907950. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob27098f

Table 1 Synthesis of iminohydantoins



1a: R^1= H, R^2= H, R^3= -cC$_6$H$_{11}$
1b: R^1= H, R^2= H, R^3= -CH(CH$_3$)$_2$
1c: R^1, R^2= -(CH$_2$)$_4$-, R^3= -cC$_6$H$_{11}$
1d: R^1, R^2= -(CH$_2$)$_5$-, R^3= -cC$_6$H$_{11}$
1e: R^1, R^2= -(CH$_2$)$_6$-, R^3= -CH$_2$C$_6$H$_5$
1f: R^1, R^2= -(CH$_2$)$_2$O(CH$_2$)$_2$-, R^3= -cC$_6$H$_{11}$
1g: R^1, R^2= -(CH$_2$)$_5$-, R^3= pCH$_3$OC$_6$H$_4$-
1h: R^1, R^2= -CH$_2$CH(CH$_3$)(CH$_2$)$_3$-, R^3= -C$_6$H$_5$
1i: R^1, R^2= -(CH$_2$)$_2$CH(CH$_3$)(CH$_2$)$_2$-, R^3= -C$_6$H$_5$

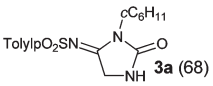
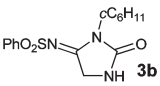
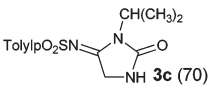
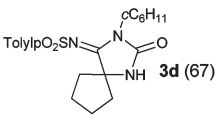
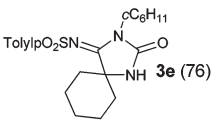
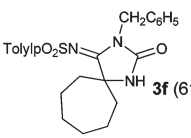
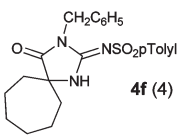
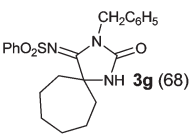
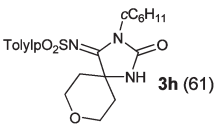
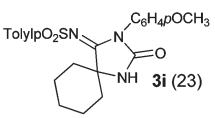
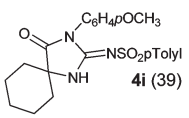
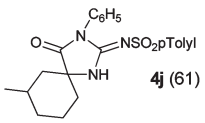
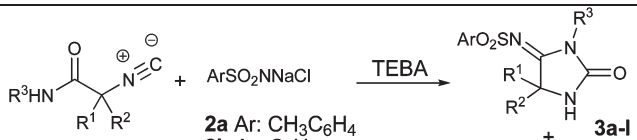
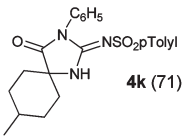
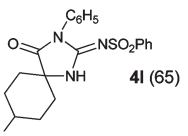
Entry	1	2	3[a] (%)	4[a] (%)	3 : 4[b]
1	**1a**	**2a**	 **3a** (68)	—	>95 : <5
2	**1a**	**2b**	 **3b** (61)	—	>95 : <5
3	**1b**	**2a**	 **3c** (70)	—	>95 : <5
4	**1c**	**2a**	 **3d** (67)	—	>95 : <5
5	**1d**	**2a**	 **3e** (76)	—	>95 : <5
6	**1e**	**2a**	 **3f** (61)	 **4f** (4)	85 : 15
7	**1e**	**2b**	 **3g** (68)	—	>95 : <5
8	**1f**	**2a**	 **3h** (61)	—	>95 : <5
9	**1g**	**2a**	 **3i** (23)	 **4i** (39)	36 : 64
10	**1h**	**2a**	—	 **4j** (61)	6 : 94

Table 1 *(Contd.)*



1a: R^1= H, R^2= H, R^3= -*c*C_6H_{11}
1b: R^1= H, R^2= H, R^3= -$CH(CH_3)_2$
1c: R^1, R^2= -$(CH_2)_4$-, R^3= -*c*C_6H_{11}
1d: R^1, R^2= -$(CH_2)_5$-, R^3= -*c*C_6H_{11}
1e: R^1, R^2= -$(CH_2)_6$-, R^3= -$CH_2C_6H_5$
1f: R^1, R^2= -$(CH_2)_2O(CH_2)_2$-, R^3= -*c*C_6H_{11}
1g: R^1, R^2= -$(CH_2)_5$-, R^3= *p*$CH_3OC_6H_4$-
1h: R^1, R^2= -$CH_2CH(CH_3)(CH_2)_3$-, R^3= -C_6H_5
1i: R^1, R^2= -$(CH_2)_2CH(CH_3)(CH_2)_2$-, R^3= -C_6H_5

Entry	1	2	3[a] (%)	4[a] (%)	3 : 4[b]
11	**1i**	**2a**	—	 **4k** (71)	7 : 93
12	**1i**	**2b**	—	 **4l** (65)	9 : 91

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

when the *N*-phenyl group on the amide is bearing an electron-donating substituent the 4-iminohydantoin **3i** was obtained in fair yield (Table 1, entry 9).

The structures of compounds **3** and **4** were assigned on the basis of different NMR studies. The most deshielded signal in the ^{13}C NMR spectra for compounds **3** is around 166 ppm corresponding to the C=N carbon while the ^{13}C NMR spectra of compounds **4** displayed the most deshielded signal around 177 ppm corresponding to the C=O group. These structures were confirmed by single-crystal X-ray diffraction analysis performed on iminohydantoin derivatives **3c** and **4f** as shown in Fig. 1. The tautomeric structures of the compounds synthesized were established by ^{13}C–^{1}H HMBC spectra analysis. The NH proton in **3** and **4** regioisomers only shows cross peaks with the carbons on the heterocycles (C2, C4 and C5) showing that the iminohydantoin, and not the 1*H*-imidazole, is the tautomer form preferred.

To explain the above results, some considerations on the reaction mechanism should be made. Although the formation of the carbodiimide intermediate has been discussed as the key to the reaction of isocyanides with chloramine T,[11,16] the different results obtained from *N*-alkyl and *N*-aryl isocyanoacetamides in these reactions are not in agreement with the formation of such an intermediate, because this would lead in both cases to 2-iminohydantoins as the only product.[17] We believe that the answer to the complementary regioselectivity observed could be found in the different ability of *N*-alkyl and *N*-aryl amides to undergo *N*-chlorination.

The ionic character of chloramine[18] favors the hydrogen bond between the amido hydrogen and the sulfonamide anion. The rate of reaction of chlorination depends upon the ease of formation of such a bond, that is, the reaction is faster when there is lower electron density on the amide *N* atom.[19] In this way, the reaction with *N*-aryl isocyanoacetamides presumably starts with the *N*-chlorination of the amide to yield the *N*-chlorinated amide **5**. The α-addition on the isocyanide from the sulfonylamide anion and the *N*-chloroamide explains the ring closure to give 2-arylsulfonylamino-3-arylimidazolone derivatives, tautomers of the corresponding 2-iminohydantoin derivatives **4** (Scheme 1).

The higher electron density on the nitrogen and oxygen in *N*-alkyl amides could explain the different regiochemistry obtained when *N*-alkyl isocyanoacetamides are used as starting compounds. The slower rate of chlorination on the amide group[19] would allow the competitive reaction of α-addition on the isocyanide group from the chloronium cation[20] and the amide oxygen atom to give 2-chlorooxazoline **6** as the intermediate. The addition of the sulfonamide anion to the imidic group in **6** would induce the ring opening of oxazoline with the formation of isocyanate **7** and the subsequent intramolecular attack by the most nucleophilic nitrogen atom in the amidine group yielding 4-arylsulfonyliminoimidazolidin-2-one **3** as the major product as shown in Scheme 2.

The synthesis of 4-sulfonyliminoimidazolidin-2-one has been previously described by the sequential treatment of

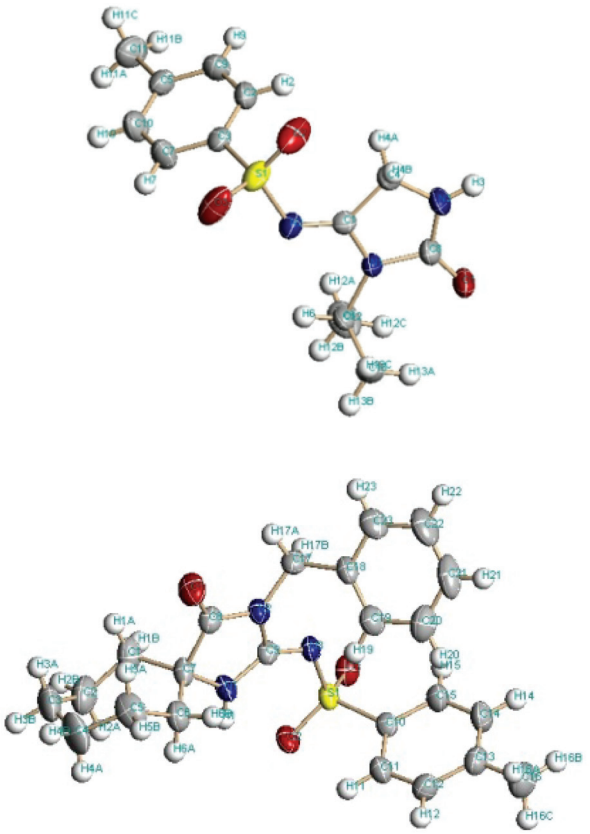
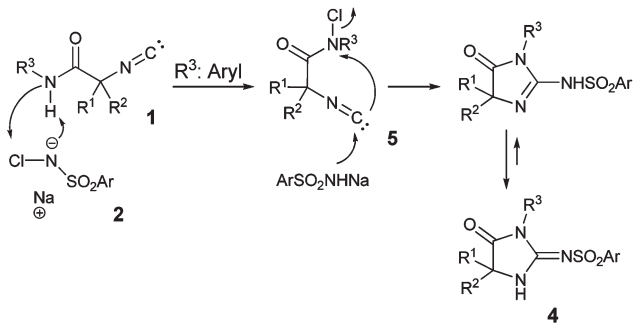


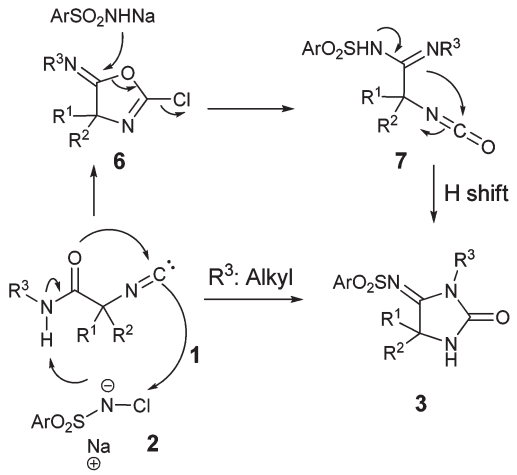
Fig. 1 X-ray diffraction structures of 4-iminohydantoin **3c** (above) and 2-iminohydantoin **4f** (below).



Scheme 1 Proposed mechanism to explain the formation of 2-iminohydantoins.

α-azido esters with triphenylphosphine, tosyl isocyanate and primary amines at room temperature,[21] the drawbacks of this sequence as the use of azides and the generation of triphenylphosphine oxide are overcome in this new synthesis. On the other hand, examples in the synthesis of 3-alkyl-2-sulfonyliminoimidazolidin-4-one are scarce and with low yields.[22]

In conclusion, a highly efficient synthesis of iminohydantoin derivatives by means of a very simple and general reaction between α-isocyanoacetamides and chloramines T and B has been described. This reaction, which can be regarded as a new isocyanide-based reaction, is the first example of a



Scheme 2 Proposed mechanism to explain the formation of 4-iminohydantoins.

complementary regioselective cyclization controlled by the substitution on an amide group. The ability of the amide group to undergo *N*-chlorination has been proposed as being key to the regioselectivity observed.

Acknowledgements

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Notes and references

1 (*a*) R. Bossio, S. Marcaccini, R. Pepino, G. Pellegrini and M. Polsinelli, *Farmaco*, 1992, **47**, 1173; (*b*) R. Bossio, S. Marcaccini, G. Pellegrini and R. Pepino, *Arzneim.-Forsch./Drug Res.*, 1992, **42**, 1494.

2 A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru and V. G. Nenajdenko, *Chem. Rev.*, 2010, **110**, 5235.

3 J. Campo, M. García-Valverde, S. Marcaccini, M. J. Rojo and T. Torroba, *Org. Biomol. Chem.*, 2006, **4**, 757.

4 (*a*) K.-I. Nunami, M. Suzuki and N. Yoneda, *J. Org. Chem.*, 1979, **44**, 1887; (*b*) S. Kamijo, C. Kanazawa and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9260; (*c*) C. Kanazawa, S. Kamijo and Y. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 10662; (*d*) D. Monge, K. L. Jensen, I. Marín and K. A. Jørgensen, *Org. Lett.*, 2011, **13**, 328.

5 (*a*) J. P. Chupp and K. L. Leschinsky, *J. Heterocycl. Chem.*, 1980, **17**, 705; (*b*) R. Bossio, S. Marcaccini, R. Pepino, C. Polo and T. Torroba, *Heterocycles*, 1989, **29**, 1829; (*c*) X. Sun, P. Janvier, G. Zhao, H. Bienaymé and J. Zhu, *Org.*

Lett., 2001, **3**, 877; (*d*) Q. Wang, Q. Xia and B. Ganem, *Tetrahedron Lett.*, 2003, **44**, 6825.

6 (*a*) U. Schöllkopf, H.-H. Hausberg, M. Segal, U. Reiter, I. Hoppe, W. Saenger and K. Lindner, *Liebigs Ann. Chem.*, 1981, 439; (*b*) R. Bossio, S. Marcaccini, S. Papaleo and R. Pepino, *J. Heterocycl. Chem.*, 1994, **31**, 397.

7 N. Elders, E. Ruijter, F. J. J. de Kanter, M. B. Groen and R. V. A. Orru, *Chem.–Eur. J.*, 2008, **14**, 4961.

8 X.-T. Zhou, Y.-R. Lin, L.-X. Dai and J. Sun, *Tetrahedron*, 1998, **54**, 12445.

9 For a survey on the preparation of *N*-substituted- and *N*,*N*-disubstituted α-isocyanoamides and their synthetic applications see: A. Dömling, B. Beck, T. Fuchs and A. Yazbak, *J. Comb. Chem.*, 2006, **8**, 872.

10 N. Elders, E. Ruijter, F. J. J. de Kanter, E. Janssen, M. Lutz, A. L. Spek and R. V. A. Orru, *Chem.–Eur. J.*, 2009, **15**, 6096.

11 R. Bossio, S. Marcaccini and R. Pepino, *Tetrahedron Lett.*, 1995, **36**, 2325.

12 R. Bossio, S. Marcaccini and R. Pepino, *J. Heterocycl. Chem.*, 1995, **32**, 1115.

13 R. Bossio, S. Marcaccini, R. Pepino and T. Torroba, *J. Org. Chem.*, 1996, **61**, 2202.

14 (*a*) J. C. Barrow, J. C. S. R. Stauffer, K. E. Rittle, P. L. Ngo, Z.-Q. Yang, H. G. Selnick, S. L. Graham, S. Munshi, G. B. McGaughey, M. K. Holloway, A. J. Simon, E. A. Price, S. Sankaranarayanan, D. Colussi, K. Tugusheva, M.-T. Lai, A. S. Espeseth, M. Xu, Q. Huang, A. Wolfe, B. Pietrak, P. Zuck, D. A. Levorse, D. Hazuda and J. P. Vacca, *J. Med. Chem.*, 2008, **51**, 6259; (*b*) J. N. Cumming, E. M. Smith, L. Wang, J. Misiaszek, J. Durkin, J. Pan, U. Iserloh, Y. Wu, Z. Zhu, C. Strickland, J. Voigt, X. Chen, M. E. Kennedy, R. Kuvelkar, L. A. Hyde, K. Cox, L. Favreau, M. F. Czarniecki, W. J. Greenlee, B. A. McKittrick, E. M. Parker and A. W. Stamford, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2444.

15 Isocyanocarboxamides were prepared according to the literature. (*a*) K. Matsumoto, M. Suzuki, N. Yoneda and M. Miyoshi, *Synthesis*, 1977, 249; (*b*) R. Bossio, S. Marcaccini and R. Pepino, *Liebigs Ann. Chem.*, 1990, 935.

16 W. Aumüller, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 616.

17 S. Bepary, I. K. Youn, H.-J. Lim and G. H. Lee, *Eur. J. Org. Chem.*, 2012, 2542.

18 S. Minakata, *Acc. Chem. Res.*, 2009, **42**, 1172.

19 E. W. C. W. Thomm and M. Wayman, *Can. J. Chem.*, 1969, **47**, 3289.

20 (*a*) R. Bossio, S. Marcaccini and R. Pepino, *Heterocycles*, 1986, **24**, 2003; (*b*) T. Mitamura, A. Nomoto, M. Sonoda and A. Ogawa, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 822.

21 P. Molina, P. M. Fresneda and M. A. Sanz, *J. Org. Chem.*, 1999, **64**, 2540.

22 (*a*) E. Schaumann and S. Grabley, *Chem. Ber.*, 1980, **113**, 934; (*b*) G. A. Orekhova, O. V. Lebedev, Y. A. Strelenko and A. N. Kravchenko, *Mendeleev Commun.*, 1996, 68.