Reaction of imines with *N*-iodosuccinimide (NIS): unexpected formation of stable 1 : 1 complexes†

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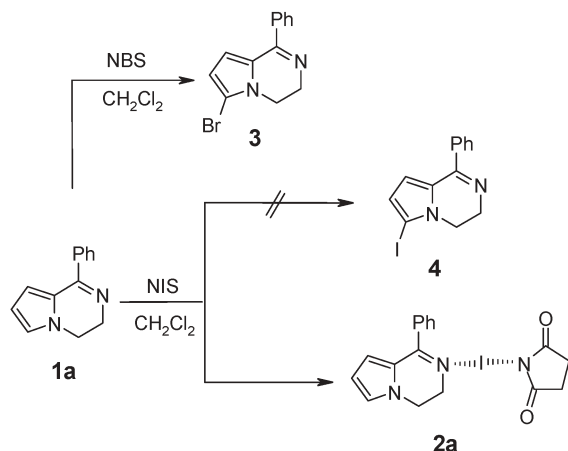
Imines react with *N*-iodosuccinimide (NIS) to afford unexpected 1 : 1 complexes and the structure of one of these was determined by single-crystal X-ray diffraction; the reaction seems to be very general for substituted cyclic imines with solid stable complexes obtained in high yields; this is the first reported example of a halogen bonding interaction involving the C=N bond and NIS.

As part of a project focussed on the preparation of a small library of derivatives of 1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine **1a** we needed to prepare either the 6-bromo or 6-iodo derivatives as appropriate substrates for the Stille and/or Suzuki reactions.[1] The reaction with NBS afforded the expected halogenated product **3** (Scheme 1) but under the same conditions, the reaction of **1a** with NIS gave a yellow solid compound, the structure of which incorporates the iodo atom and the full heterocyclic and succinimide moieties—as evidenced by NMR spectroscopy and elemental analysis. Further structural analysis allowed us to rule out the co-halogenation compound[2] and we therefore tried to confirm the structure of this apparently simple compound by X-ray analysis. However, all our initial attempts to obtain suitable crystals failed.

Scheme 1

It was shown that the iminic bond in **1a** seems to be critical for the formation of the unexpected reaction product with NIS, since 1-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine either does not react, or affords the 6-iodo derivative in the presence of NIS. For this reason, we decided to test the reaction with other imines in the hope that we could obtain an appropriate crystal for X-ray diffraction analysis. Fortunately, this aim was achieved in the reaction of 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline (**1h**) with NIS, which allowed us to establish structure **2a** for the reaction product between **1a** and NIS. We report here further details on the scope of this unprecedented reaction (Scheme 2).

First, substitution at the C-1 position of 3,4-dihydropyrrolo[1,2-*a*]pyrazine was explored with alkyl (methyl and *n*-propyl), aryl and heteroaryl substituents[3] (Table 1, entries 2–7). Other related bicyclic and tricyclic imines such as 1-substituted 3,4-dihydroisoquinolines (entries 8 and 9) and 2-substituted 3,4-dihydropyrazino[1,2-*a*]indoles (entries 10–12) were also employed as iminic substrates.[4] The results are summarised in Table 1 and show the reaction to be very general for all aryl (Table 1, entries 4–6, 8, 10 and 12) and heteroaryl (entries 7 and 13) substituted substrates, with complexes being formed in yields of up to 64% and reactions completed within 1 h. The behaviour of alkyl substituted substrates depends of the heterocyclic imine and the nature of the alkyl group. For example, the reaction of 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline **1i** (entry 9) and 2-methyl-3,4-dihydropyrazino[1,2-*a*]indole (**1k**) (entry 11) afforded the addition compounds **2i** and **2k** in excellent yields (86 and 89%, respectively). However, the methyl derivative **1b** gave a complex mixture of products and the *n*-propyl derivative **1c** was extensively iodinated on the *n*-propyl substituent.
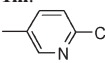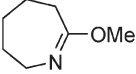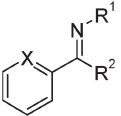
Further examples with monocyclic imines,[5] such as 2-substituted pyrrolines (entries 14–16), also showed similar behaviour to that found for 3,4-dihydropyrrolo[1,2-*a*]pyrazines, with 2-methylpyrroline **1o** also forming complex mixtures (entry 15) and 2-aryl-substituted derivatives leading to the expected compounds in good yields (entries 14 and 16). However, all of these complexes are less stable than those obtained from bicyclic imines. It is also worth

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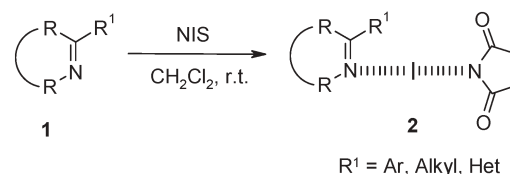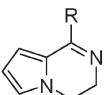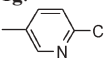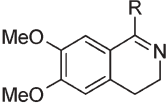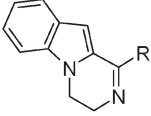[b]Departamento de Química Inorgánica, Universidad de Alcalá, 28871-Alcalá de Henares, Madrid, Spain

R[1] = Ar, Alkyl, Het

Scheme 2

Table 1 Complexes **2** from imines **1** and NIS

Entry	Imine (**1**)	Complex (**2**) yield (%)

1	**1a**: C_6H_5	64
2	**1b**: CH_3	—[a]
3	**1c**: $CH_2CH_2CH_3$	—[b]
4	**1d**: 2,4-$Me_2C_6H_3$	82
5	**1e**: 2,4-$(MeO)_2C_6H_3$	69
6	**1f**: 3,5-$(CF_3)_2C_6H_3$	67
7	**1g**:	70

8	**1h**: R = C_6H_5	92
9	**1i**: R = Me	86

10	**1j**: C_6H_5	81
11	**1k**: CH_3	89
12	**1l**: 2,4-$(MeO)_2C_6H_3$	80
13	**1m**:	77

14	**1n**: C_6H_5	81
15	**1o**: CH_3	—[a]
16	**1p**: 4-$MeOC_6H_4$	80
17	**1q**:	73[c,d]

18	**1r**: X = N; R^1 = $CHMe_2$; R^2 = 2-pyridyl	81[e]
19	**1s**: X = CH; R^1 = $CHMe_2$; R^2 = Ph	—[a]

[a] Complex mixture. [b] Iodination on the *n*-propyl substituent. [c] Reaction difficult to reproduce. [d] Unstable. [e] Unstable in solution.

noting the successful reaction with the 1-aza-2-methoxycyclohep-tene (entry 17), although the formation of this complex it is not easy to reproduce.[6]

The study was completed by testing different acyclic ketimines and aldimines.[7] The results show that only one of the ketimines tested (Table 1, entry 18) was reacted with NIS to afford the corresponding product, with a yield similar to those observed with cyclic imines.[8] In this case the reaction is quite sensitive to water
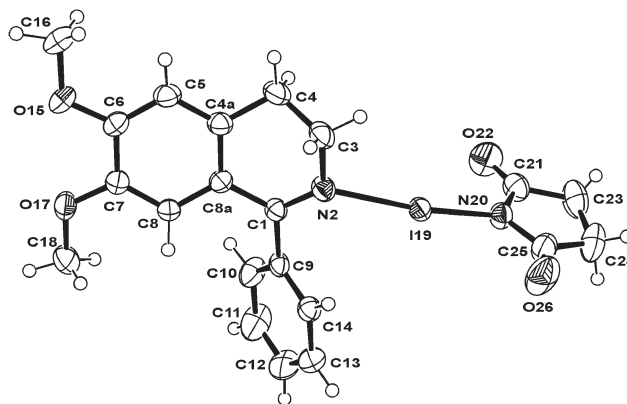
Fig. 1 X-Ray crystal structure of complex **2h**. Thermal ellipsoids at 50% level are shown.

and anhydrous conditions are necessary to ensure acceptable yields. Under non-anhydrous conditions the corresponding ketone was isolated as the main reaction product. The attempted reaction of representative aldimines did not afford the expected addition products and the starting materials were recovered unaltered. Moreover, unsubstituted cyclic imines were also unreactive towards NIS under analogous conditions to those used with the imines selected for this study.

Crystals obtained from **1h** and NIS allowed us to establish the structure of complexes **2** shown in Table 1. The X-ray crystal structure[9] of complex **2h** is shown in Fig. 1 and its solid structure is based on a non-covalent interaction between the iminic nitrogen and the iodine atom of the NIS. Only a few examples of this uncommon halogen bonding interaction[10] involving oxygen[11] and nitrogen atoms as donor atoms (Lewis base) and diiodo-perfluorocarbons[12] and 1,4-diiodotetrafluorobenzene[13] as acceptors have being reported previously. In this case the iodine atom of the NIS reagent seems to be a Lewis acid hard enough to be involved in the formation of these unexpected and unprecedented complexes.

The co-crystal **2h** shows bond lengths between the iodine and the iminic and succinic nitrogens being 2.486(2) and 2.120(2) Å, respectively,[14] and these three atoms have an almost linear disposition [173.0(1)° for the angle N(2)–I(19)–N(20)]. Contrary to previously reported data for melting points of other complexes involving halogen bonding interactions,[12,13] this complex (and all shown in Table 1) exhibits a lower melting point (112–114 °C) than those reported for the single components of the complex (200–202 °C for NIS and 121–125 °C for **1h**). Also, **2h** and the remainder of the complexes show a pale yellow colour, indicating a degree of change-transfer to the iminic chromophore.[15]

In general, IR and NMR spectra for these complexes show significant modifications when compared with those of the starting materials. As an example, in the ¹H NMR spectra of the imine **1h**, the aromatic protons for the phenyl substituent appear at δ 7.60 ppm (*ortho* hydrogens) and δ 7.42 ppm (*meta* and *para* hydrogens) while in the complex **2h** these aromatic signals collapse in a non-resolvable multiplet at δ 7.49 ppm. Furthermore, H5 and H8 aromatic protons in **1h** appear as a broad singlet centered at δ 6.76 ppm while the spectrum of **2h** show two well-differentiated singlets at δ 6.49 ppm and δ 6.72 ppm for the same hydrogens. Some changes are also observed in the aliphatic region of the ¹H

NMR spectra of the imine **1h** and NIS separately and in complex **2h**. For example, the signal assigned to the CH_2 in 3-position of **1h** is shifted 0.2 ppm downfield (3.79 ppm in **1h** and 3.98 in **2h**) and the signal of the methylenic hydrogens of the succinimide moiety in the complex also appears shifted 0.4 ppm when compared with the signal of these protons in NIS (δ 2.68 ppm and δ 3.01 ppm, respectively).

In the IR spectrum of **2h**, all relevant bands for NIS and **1h** are present along with some typical modifications[12] affecting both aliphatic and aromatic C–H stretching bands which are shifted to higher frequencies in the complex (selected bands at 3059, 2930 and 2830 cm^{-1} for **2h** and 3058, 2925 and 2828 cm^{-1} for **1h**).

In summary, a variety of substituted cyclic imines and some ketimines react with NIS to afford, in high yields, stable 1 : 1 complexes in which the iodine atom is linearly bonded to both iminic and succinic nitrogens. Ongoing work is aimed at demonstrating that such complexes based on a halogen bonding between the iminic nitrogen and the iodine of NIS could behave as better iodination reagents than NIS itself.

Notes and references

1 I. Castellote, PhD Thesis, University of Alcalá, 2001; I. Castellote, J. J. Vaquero, J. Fernández Gadea and J. Alvarez-Builla, *J. Org. Chem.*, 2004, **69**, 8668–8675.

2 J. Rodriguez and J. P. Dulcère, *Synthesis*, 1993, 1177–1205.

3 Preparation of substrates **1d–g** is detailed in the ESI† and ref. 1. The following imines were prepared according to literature procedures; **1a** and **1c**: A. M. Likhosherstov, V. P. Peresada, V. G. Vinokurov and A. P. Skoldinov, *Zh. Org. Khim.*, 1983, **22**, 2610–2614; **1b**: I. Jirkovsky and R. Baudy, *Synthesis*, 1981, 481–483.

4 Substrates **1h** and **1i** are commercially available. **1k**: M. P. Matía, J. Ezquerra, F. Sanchez-Ferrando, J. L. García-Navío, J. J. Vaquero and J. Alvarez-Builla, *Tetrahedron*, 1991, **47**, 7329–7342. Compounds **1j** and **1l,m** are unknown and are described in the ESI†.

5 Imines **1o,q** are commercially available and **1n,p** were prepared according to the literature procedure: N. de Kimpe, K. A. Tehrani, C. Stevens and P. de Cooman, *Tetrahedron*, 1997, **53**, 3693–3706.

6 In different experiments using commercially available imine **1q** and NIS the corresponding complex **2q** was not formed or was formed in low yields under the same conditions that had previously afforded this complex in 73% yield (Table 1, entry 17).

7 I. Moretti and G. Torre, *Synthesis*, 1970, 141.

8 *General procedure for compounds* **2**: A solution of *N*-iodosuccinimide (1 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise under an argon atmosphere to a stirred solution of the corresponding imine **1** (1 mmol) for compounds **1e,h–s** or imine salt for compounds **1a–d,f,g**, in dry CH_2Cl_2 (4 mL) at room temperature. The reaction mixture was stirred for 1 h at this temperature, concentrated *in vacuo* and the residue triturated with Et_2O. Compounds **2** are yellow solids and were isolated by filtration.

9 *Crystal data* for **2h**: $C_{21}H_{21}IN_2O_4$, $M = 492.3$, monoclinic, $P2_1/c$, $a = 8.9590(2)$, $b = 12.0504(4)$, $c = 19.2674(11)$ Å, $\beta = 96.661(4)°$, $Z = 4$, $V = 2066.1(1)$ Å^3, $T = 293$ K, μ(Mo-Kα) = 1.579 mm^{-1}. Of 46 207 total reflections ($5 \leqslant \theta \leqslant 25°$), 3594 were independent ($R_{int} = 0.02$). A multi-scan absorption correction was performed. Direct methods were used to solve the structure. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were found in the difference Fourier map and refined isotropically. Largest minimum and maximum in the final difference Fourier synthesis: -0.465 and 0.31 e Å^{-3}. $R1 = 0.020$ (for 3260 reflections with $F > 4\sigma(F)$) and $wR2 = 0.024$ (all data). The values of $R1$ and $wR2$ are defined as $R1 = \sum\|F_o| - |F_c\|/[\sum|F_o|]$; $wR2 = \{[\sum w(F_o^2 - F_c^2)^2]/[\sum w(F_o^2)^2]\}^{1/2}$. CCDC 207325. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b615183c.

10 P. Metrangolo and G. Resnati, *Chem. Eur. J.*, 2001, **7**, 2511–2519, and references therein.

11 P. Auffinger, F. A. Hays, E. Westhof and P. S. Ho, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 16789–16794.

12 For some examples, see: P. L. Wash, S. Ma, U. Obst and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1999, **121**, 7973–7974; F. Fontana, A. Forni, P. Metrangolo, W. Panzeri, T. Pilati and G. Resnati, *Supramol. Chem.*, 2002, **14**, 47–55; D. D. Burton, F. Fontana, P. Metrangolo, T. Pilati and G. Resnati, *Tetrahedron Lett.*, 2003, **44**, 645–648; M. Amati, F. Lelj, R. Liantonio, P. Metrangolo, S. Luzzati, T. Pilati and G. Resnati, *J. Fluorine Chem.*, 2004, **125**, 629–640; P. Metrangolo, C. Präsang, G. Resnati, R. Liantonio, A. C. Whitwood and D. W. Bruce, *Chem. Commun.*, 2006, 3290–3292.

13 J. L. Syssa-Magalé, K. Boubekeur, P. Palvadeau, A. Meerschaut and B. Schöllhorn, *J. Mol. Struct.*, 2004, **691**, 79–84.

14 The N–I bond length in NIS is 2.059 Å, see: K. Padmanabhan, I. C. Paul and D. Y. Curtin, *Acta Crystallogr., Sect. C*, 1990, **46**, 88–92.

15 D. J. Price, T. Richardson and D. W. Bruce, *J. Chem. Soc., Chem. Commun.*, 1995, 1911–1912.