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Efficient preparation of *N*′,*N*″-1*H*-isoindole-1,3-diylidenedicarbohydrazides via 1,1,3-trichloro-1*H*-isoindole, and their characterization

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ABSTRACT

N′,*N*″-1*H*-Isoindole-1,3-diylidenedialkyl(aryl,heteroaryl)carbohydrazides were prepared in good yields via 1,1,3-trichloro-1*H*-isoindole, which was shown to be a versatile reagent for their synthesis. Tautomeric structure and conformational behaviour of dicarbohydrazides in solid state as well as in solution have been studied by X-ray crystallography, NMR spectroscopy and quantum calculations. The dependence of *Z*/*E* amide-type isomerism upon steric effects and solvent polarity is discussed.

1. Introduction

Carboxylic acid hydrazides are known to possess a wide range of pharmacological activities, among them antitubercular and antibacterial properties.[1] Recently, adamantane and norbornane carboxylic acid hydrazides were reported as HIV inhibitors.[2] At the same time, little data has been reported on 1-imino-1*H*-isoindole-3-amine activities, among them a series of 1,3-disubstituted 1,3-diiminoisoindolines were described as potential C3a antagonists.[3] From the other hand, a previously described disubstituted hydrazone derivative—phthalimide dithiosemicarbazone was found to be useful as an analytical reagent for spectrophotometric determination of metals by means of complex formation.[4]

In pursuance of our work[5] on the synthesis of 1*H*-isoindole carbohydrazide derivatives we set out to study the preparation and structure elucidation of compounds in which two hydrazide moieties are present in the molecule possessing an isoindole skeleton. Of the methodologies that were described in the literature for the synthesis of 1-imino-1*H*-isoindole-3-amine derivatives, two approaches are particularly widely explored. One of them includes reamination of 1-imino-1*H*-isoindole-3-amine with *N*-nucleophiles.[6] Another commonly used method relies on the base catalyzed addition of *N*-nucleophiles, including amines, hydrazine and its derivatives, to phthalonitrile.[7,8] A series of *N*′-(3-amino-1*H*-isoindol-1-ylidene)alkyl(aryl,heteroaryl)carbohydrazides bearing one *N*-acyl hydrazone residue were synthesized by us in good yields by this method.[5] Unfortunately, in our hands, this cyclization reaction did not allow synthesis of dicarbohydrazide 1*H*-isoindole derivatives, contrary to the published data,[8] most probably due to reduced electophilicity of *N*′-(3-amino-1*H*-isoindol-1-ylidene)carbohydrazides. Known *N*′,*N*″-1*H*-isoindole-1,3-diylidenedicarbohydrazide—phthalimide dithiosemicarbazone was synthesized by exchange reaction from phthalimide dioxime and thiosemicarbazide.[9]

3-Amino-1-imino-1*H*-isoindole and its *N*-alkyl(aryl) derivatives are known to demonstrate amino–imino type tautomerism.[10,11] The equilibrium between two tautomeric forms of 3-amino-1-imino-1*H*-isoindole and 1,3-diimino-1*H*-isoindole depends on the nature of the substituents at nitrogen atoms as well as on solvent polarity and the temperature (Scheme 1).

N′-(3-amino-1*H*-isoindol-1-ylidene)alkyl(aryl,heteroaryl)carbohydrazides A studied earlier were shown to exist predominantly in the amino–imino form both in crystal and in the solvents studied and confirmed by quantum calculations.[5] Besides this, carbohydrazides A derived from aliphatic carboxylic acids demonstrate amide-type isomerism in solutions at the *N*-acyl hydrazone chain, and the

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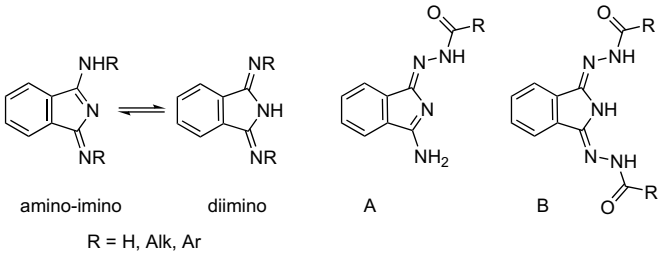


Scheme 1. Possible tautomeric forms of 3-amino-1-imino-1*H*-isoindole and 1,3-diimino-1*H*-isoindole.

equilibrium was shown to be determined by solvent polarity and the nature of the substituent R in favour of *Z* isomer, being totally predominant for aryl and bulky adamantyl derivatives.[5,12]

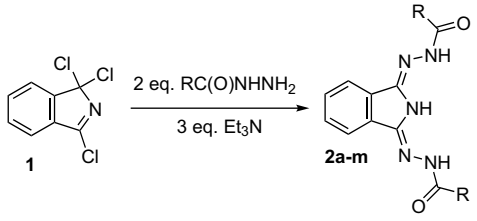
In this paper we describe an efficient synthesis of 1,3-disubstituted 1*H*-isoindoles B containing two hydrazide acid moieties, via the nucleophilic substitution reaction between 1,1,3-trichloro-1*H*-isoindole **1** and carboxylic acid hydrazides, and their structural elucidation.

2. Results and discussion

Highly reactive 1,1,3-trichloro-1*H*-isoindole[13] **1** can serve as a versatile reagent for preparation of variety of 1,3-disubstituted 1*H*-isoindoles that are hardly available or even sometimes could not be synthesized by other methods.[10,14] In this case, reactions usually proceed through nucleophilic substitution of chlorine atoms in the 1,1,3-trichloro-1*H*-isoindole **1** under treatment with amines, as well as sometimes in the presence of a tertiary amine as the HCl scavenger.

To prepare *N*′,*N*″-1*H*-isoindole-1,3-diylidenedicarbohydrazides according to the strategy outlined in Table 1, equimolar amounts of **1** and the corresponding carbohydrazide were reacted in dry solvents to give the substitution products **2a**–**m** in good yields. Triethylamine was found to be a good scavenger of the HCl. Notably, synthetically useful Boc-protected hydrazine derivative **2m** was also synthesized by this methodology.

Table 1
Synthesis of *N*′,*N*″-1*H*-isoindole-1,3-diylidenedicarbohydrazides **2a**–**m**[a]



Entry	Compound **2**	R	Yield of **2** (%)
1	**a**	Me	76
2	**b**	*i*-Pr	93
3	**c**	1-Adamantyl	71
4	**d**	Ph	86
5	**e**	4-MeC_6H_4	70
6	**f**	4-BrC_6H_4	87
7	**g**	4-FC_6H_4	83
8	**h**	2-Pyridyl	79
9	**i**	2-BrC_6H_4	76
10	**j**	2-ClC_6H_4	90
11	**k**	2-IC_6H_4	68
12	**l**	2-Thiophenyl	62
13	**m**	O-*t*-Bu	77

[a] Reaction conditions: carbohydrazide (20 mmol), triethylamine (30 mmol), **1** (2.205 g, 10 mmol), dry toluene (50 mL) at 60–70 °C for 1 h.

The advantage of this methodology is the fast nucleophilic substitution of all three chlorine atoms at both positions of 1,1,3-trichloro-1*H*-isoindole **1** by two carbohydrazide residues.

The reactions were carried out in dry aprotic solvents (toluene, DCM, dioxane) by heating the reaction mixture at 40–70 °C for 1 h until the precipitation of the solid products finishes. The best solvent for the reaction is toluene—it was found to be a good alternative to polar solvents. The resulting carbohydrazides **2a**–**m** were obtained in 62–93% yields and were purified by recrystallization.

The structural assignment of the synthesized compounds is complicated due to their possible existence in different isomeric and tautomeric forms: two amidrazone fragments, C=N double bonds and amide-type bonds can contribute to this ambiguity. From the structural investigations presented herein, the desired products have the symmetrical form of type B resulting from a tautomeric shift.

2.1. Crystal structure determination of *N*′,*N*″-1*H*-isoindole-1,3-diylidenebis(2-methylpropanohydrazide) 2b

An X-ray diffraction study showed that the dihydrazide **2b** (R=*i*-Pr) in crystal form exists in the symmetrical tautomeric form B (Fig. 1) in contrast to *N*′-(3-amino-1*H*-isoindol-1-ylidene)carbohydrazides A.[5]

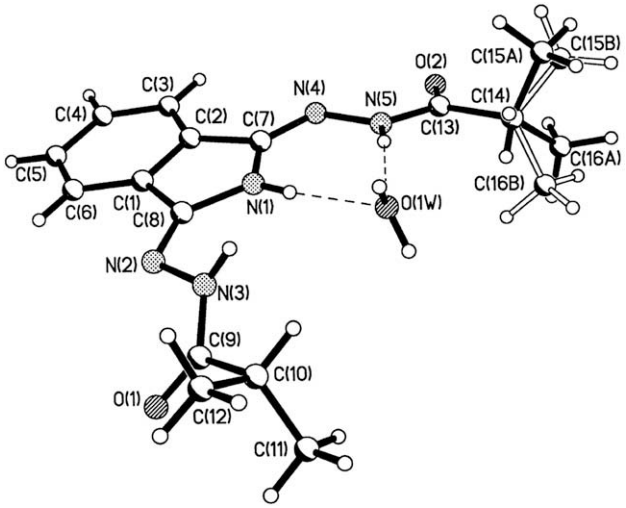


Figure 1. Molecular structure of **2b** according to X-ray diffraction study.

This is confirmed by quantum calculations. Tautomeric form B is 5 kcal mol^{-1} more stable than the amino–imino form for compound **2b**. Both substiutents have the similar *Z* conformation at the amide bonds and orientation relative to isoindole heterocycle. The values of the N–C–N–N, C–N–N–C and N–N–C–C torsion angles are −0.3(3)°, 168.2(2)° and 179.2(2)° for the substituent at C(7) and 4.6(3)°, −152.5(2)° and −173.1(2)° for the substituent at C(8). Thus, the N–H bonds are orientated inside a cavity formed by the substituents (Fig. 2). In the crystal a water molecule resides within this cavity. However, it forms only two hydrogen bonds with the NH groups of parent molecule: N(1)–H(1N)···O(1W) (H···O 1.94 Å, O–H···O 168°) and N(5)–H(5N)···O(1W) (H···O 2.04 Å, O–H…O 169°). The N(3)–H(3N) bond is oriented slightly outside the pocket and it forms H-bond with carbonyl group of adjacent molecule: N(3)–H(3N)···O(2′) [*x*−*y*, −1+*x*, 1−*z*] (H···O 2.03 Å, N–H···O 169°). This cavity is completed (Fig. 2) by two neighbouring molecules bonded by hydrogen bonds to a water molecule as a proton donor O(1W)–H(1W)···O(1′) [1(1/3)−*x*+*y*, (2/3)−*x*, −(1/3)+*z*] (H···O 1.87 Å, O–

H···O 153°), O(1W)–H(2W)···O(2′) [$x-y$, $-1+x$, $1-z$] (H···O 2.19 Å, O–H···O 133°) and O(1W)–H(2W)···N(4′) [$x-y$, $-1+x$, $1-z$] (H···N 2.23 Å, O–H···N 151°). It is interesting to note that in the crystal very large channels are formed along the $\overline{3}$ axes (Fig. 3), with a radius of about 4.5 Å. Very probably these cavities contain disordered solvent molecules.

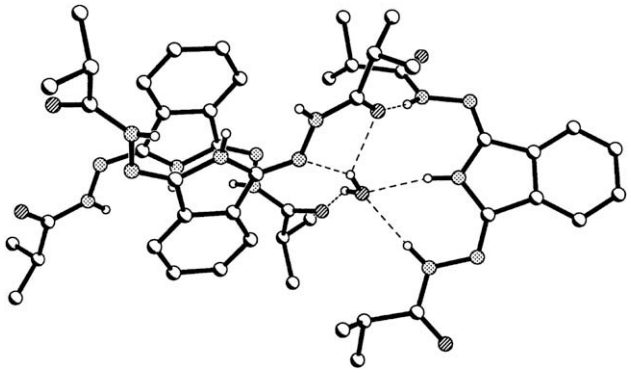


Figure 2. A cavity formed in crystals of **2b** containing hydrogen-bonded water molecule.

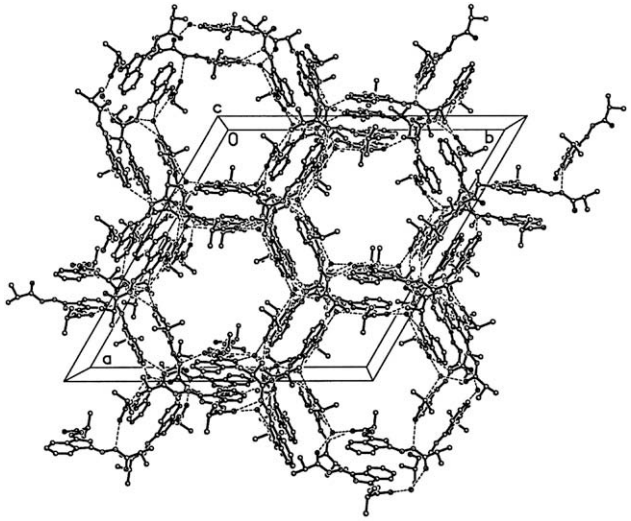


Figure 3. View of crystal packing of **2b** showing void channels along *c* axis.

2.2. Spectroscopic studies

It is very likely that the tautomeric form B observed in crystals is stabilized due to the formation of intermolecular H-bonds. However, the behaviour of dicarbohydrazide **2b** (R=*i*-Pr) in solution is much more complex. Thus, ^{1}H NMR spectrum of **2b** in DMSO-d_6 solution reveals up to seven NH proton signals of relative intensity 0.2H, 0.6H, 0.6H, 0.6H, 0.6H, 0.3H, 0.3H. Upon heating to 80 °C they coalesce and transform into a broad signal at 9.9 ppm. Such behaviour indicates that several interconverting forms of **2b** exist in the solution. This conclusion is confirmed by ^{13}C NMR data that reveal several signals for all carbons.

In principle, there are two structural elements responsible for appearance of isomers (rotamers). First, *Z*/*E* isomers at the exocyclic C=N double bonds can be expected. However, interconversion of the isomeric forms is not probable in this case due to the high energetic barrier. Therefore, we suggest the existence of the three amide conformers in the solution (Scheme 2), which are present due to the hindered rotation at the hydrazide residues. Such effects were observed for simpler *N*′-(3-amino-1*H*-isoindol-1-ylidene)-carbohydrazides A.[5]

Two symmetrical rotamers and one unsymmetrical might be present in the solution. The symmetrical one should reveal two NH proton peaks with the ratio 1:2 that belong to one heterocyclic and two hydrazide NH. The unsymmetrical conformer should demonstrate three nonequivalent NH proton signals of equal intensity. Analysis of the ^{1}H NMR spectrum of **2b** showed that the symmetrical forms are minor in the mixture (15% and about 25%). Most likely, signals at 10.52 ppm (0.19H) and 9.58 ppm (0.34H) belong to the minor rotamers. As a matter of fact, for both compounds **2b** (R=*i*-Pr) and **2a** (R=Me), quantum calculations reveal that the most stable conformation in vacuo is the *EE* conformer, followed by the *EZ* one (2.1 kcal mol^{-1} above for **2b**, 2.2 kcal mol^{-1} for **2a**) and the *ZZ* one (4.5 kcal mol^{-1} above *EE* for compound **2b**, 4.8 kcal mol^{-1} above *EE* for compound **2a**). It is thus plausible that they coexist in solution, even though the X-ray results only show the *ZZ* conformer.

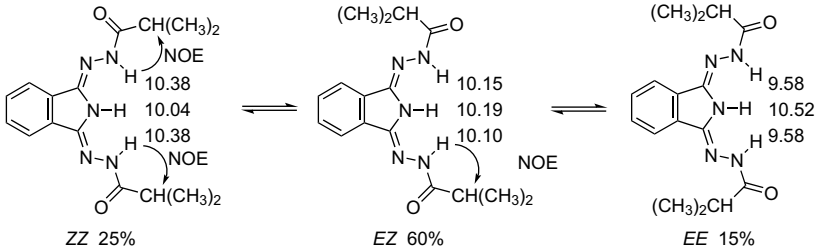
Additional information was obtained from the NOESY experiment. Correlation peaks between NH resonances at 10.38 and 10.10 ppm and isopropyl CH resonance were found. They indicate that both NH signals are hydrazide type at the exocyclic residues possessing *Z* configuration. Such residues are characteristic of the unsymmetrical and one of the symmetrical rotamers.

The ^{1}H NMR spectrum of compound **2b** shows also two sets of CH isopropyl proton multiplets of similar intensity observed at 2.50 and 3.38 ppm. Their appearance can be explained by the presence of three *Z*/*E* conformers described above suggesting that one of the multiplets corresponds to the overall signal of *Z* fragments of isomeric mixture and the second one—to the total signal of *E* conformers (Scheme 2).

This conclusion is in an agreement with the ^{13}C NMR spectrum of **2b** that reveals three isopropyl C–H peaks at 29.8, 33.7 and 33.8 ppm. The latter peaks could be observed as two due to some chemical shift difference of both symmetrical *EE* and unsymmetrical *ZE* isomers.

Full assignment in the ^{13}C NMR was done using HMQC and HMBC experiments. The result is shown in Table 2 and Figure 4.

Dynamic NMR experiments were applied for the study of amide-type isomerism in solution of other aliphatic carbohydrazide derivative **2a** (R=Me) which, in principle, could exist as three amide



Scheme 2. NH signals assignment of three amide conformers of **2b** according to HMQC, HMBC and NOESY data (400 and 100 MHz, DMSO-d_6).

Table 2
Heteronuclear $^{1}H–^{13}C$ correlations found for compound **2b**

δ, ppm	HMQC	HMBC
1.11	19.3; 20.2	29.8; 33.7; 33.8; 173.3; 173.5; 178.4; 178.8
2.50	33.7; 33.8	20.2; 173.3; 173.5
3.38	29.8	19.3; 178.4; 178.8
7.61	131.4; 131.7	121.6; 122.1; 133.2; 133.6
7.78	122.1; 121.6	131.4; 131.7; 133.2; 133.6
9.58	—	29.8; 141.0; 178.4
10.04	—	133.2; 133.6; 145.1
10.10	—	146.3; 173.3; 173.5
10.15	—	29.8; 140.4; 178.8
10.19	—	133.2; 133.6; 140.4; 146.3
10.38	—	145.1; 173.5
10.52	—	133.2; 141.0

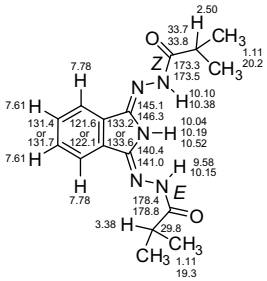


Figure 4. Signals assignment of ^{1}H and ^{13}C spectra for **2b** according to HMQC, HMBC and NOESY data (400 and 100 MHz, DMSO-d_6).

conformers with *ZZ*, *ZE* and *EE* configuration at C(O)–NH bond analogously to compound **2b**.

Protons of the methyl groups of each *ZZ* or *EE* conformers due to their chemical equivalence should appear as one signal, contrary to the methyl proton signals of *ZE* form that should appear as two peaks. Indeed, in the ^{1}H NMR spectrum of **2a** in DMSO-d_6 at room temperature there is a set of four signals of similar intensity: two pairs of singlets with 0.21 ppm shift difference (Fig. 5).

On increase of the temperature from 291 to 313 K the pairs of 1, 2 and 3, 4 signals coalesce (Fig. 5), and the further coalescence of two broad singlets leads to a broad signal at ca. 2.2 ppm detected at 353 K. It is reasonable to assign the ^{1}H chemical shift pairs of 1.99, 2.01 and 2.20, 2.22 ppm, respectively, to the methyl protons of *Z* and *E* amide conformers, presented in all three forms: *ZZ*, *ZE* and *EE*. Thus, the major signals at 2.2 ppm

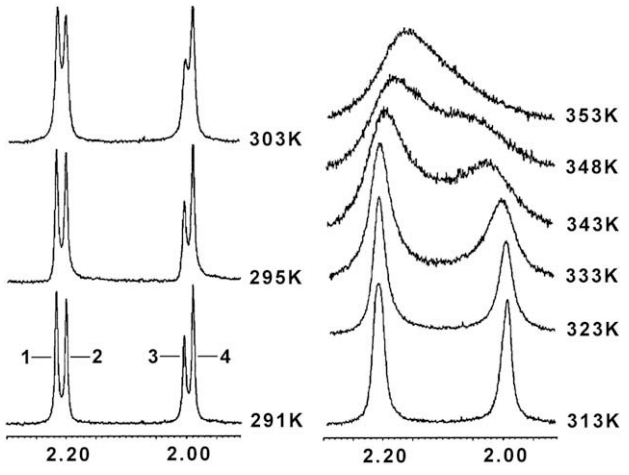


Figure 5. Temperature-dependent ^{1}H NMR (400 MHz, DMSO-d_6) spectra of compound **2a** (signals of methyl protons shown only).

correspond to the *E* form and the minor set at 2.0 ppm to the *Z* form because of the chemical shifts of the C–H protons of *E* carbohydrazide conformers are known to be shifted downfield while those for the corresponding *Z* conformers are shifted upfield.[5,12] It should be noted that *E* form for compound **2a** slightly predominates (*E*/*Z* 10:9) as in the case of corresponding monohydrazide derivative.[5]

The above conclusions can be confirmed by the analysis of the NH resonances of **2a**. Seven NH protons singlets at 9.7–10.5 ppm appear in the spectrum of **2a** in DMSO-d_6 (see Supplementary data): three of pyrroline NH[a] from *ZZ*, *ZE* and *EE* forms, and four hydrazide NH—from three conformers as in the case of methyl groups. Heating the sample causes rapid interconversion of isomers and at the temperature 343 K the spectrum exhibits one broad signal at ca. 10 ppm. The reversibility of the spectral changes was also confirmed.

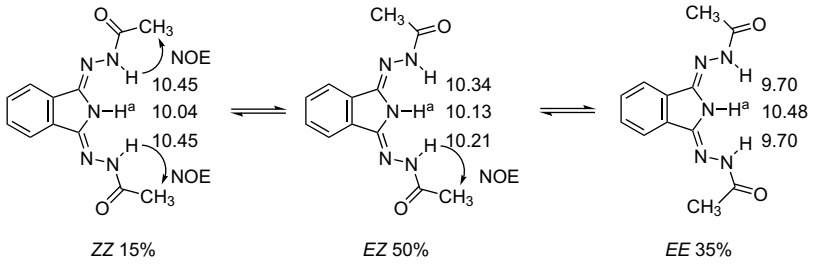
Full assignment of signals for **2a** in DMSO-d_6 based on HMQC, HMBC (Table 3) and NOESY experiments is proposed on Scheme 3 and Figure 6.

In Table 4 are given the proportions of the three stereoisomers in function of the polarity of the solvent found from ^{1}H NMR experiment (Fig. 7). A decrease of the polarity of the medium shifts the equilibrium toward *E* forms with disappearance of the *ZZ* form and in DMSO-d_6/$CDCl_3$ 1:3 the ratio of *E*/*Z* conformers is about 2:1. This observation is not in complete agreement with correlations obtained earlier for monoacyl hydrazones A when decrease of the solvent polarity shifted the equilibrium towards the *E* form with less dipole moment. Though the *EZ* form of **2a** is dramatically less polar (1.2 D), *EE* and *ZZ* forms possess much higher similar dipole moments—3.7 D and 3.6 D, respectively, as calculated by quantum calculations. It could be suggested that the key feature of such difference is the relative orientation of both C=O bonds in two *N*-acyl hydrazone residues. On the contrary, by comparison with the ratios observed for compound **2b** in DMSO-d_6, it appears that with increasing size of the alkyl group, the proportion of the *E* forms decreases, the *Z* form being favoured by a lower steric repulsion as previously demonstrated.

It was of interest to inspect the influence of different substituents at the hydrazide residue on *Z*/*E* amide isomerism. Carbohydrazides **2c–l** with bulky aliphatic, aromatic and heteroaromatic groups were synthesized. ^{1}H NMR spectra of **2c** (R=Ad), **2d** (R=Ph), **2e** (R=4-MeC_6H_4), **2f** (R=4-BrC_6H_4), **2g** (R=4-FC_6H_4), and **2h** (R=2-Py) in DMSO-d_6 demonstrate only one set of signals: a symmetrical AA′BB′ system of 4–7 isoindole protons, one-proton singlet of pyrroline NH, two-proton singlet of NH–C(O)R moieties and signals from the substituent R. Hence, at room temperature, exclusive predominance of the symmetrical diimino tautomeric form B can be observed for **2c**–

Table 3
Heteronuclear $^{1}H–^{13}C$ correlations found for compound **2a**

δ, ppm	HMQC	HMBC
1.99; 2.01	22.33; 22.39	166.06; 166.26
2.20; 2.22	20.67	172.49; 172.81
7.61	131.40; 131.70; 131.77	121.58; 121.67; 122.02; 122.14; 133.09; 133.20; 133.54; 133.62
7.78	121.58; 121.67; 122.02; 122.14	131.40; 131.70; 131.77; 133.09; 133.20; 133.54; 133.62; 139.88; 147.49
9.70	—	20.67; 140.91; 172.49
10.04	—	133.09; 133.20; 133.54; 133.62; 145.27
10.13	—	133.09; 133.20; 133.54; 133.62; 139.88; 147.49
10.21	—	147.49; 166.06
10.34	—	20.67; 139.88; 172.81
10.45	—	145.27; 166.26
10.48	—	133.09; 133.20; 133.54; 133.62; 140.91



Scheme 3. NH signals assignment of three amide conformers of **2a** according to HMQC, HMBC and NOESY data (400 and 100 MHz, DMSO-d_6).

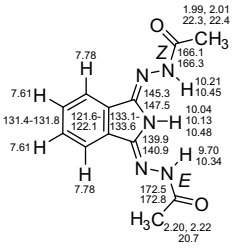


Figure 6. Signals assignment of ^{1}H and ^{13}C spectra for **2a** according to HMQC, HMBC and NOESY data (400 and 100 MHz, DMSO-d_6).

Table 4
Influence of solvent polarity on the *Z*/*E* isomeric ratio of compound **2a**

DMSO-d_6/$CDCl_3$	*ZZ*	*EZ*	*EE*
1:0	15	50	35
1:1	0	63	37
1:3	0	60	40

h, as well as only one amide conformer being dominant in solution, with the most probable *Z* configuration at C–N amide bond, as it could be extrapolated from their monohydrazide derivatives A.[5] Boc-hydrazono derivative **2m**, as evidenced from its NMR spectra, also exhibits symmetrical diimino tautomeric form B.

Amide-type isomerism of other derivatives of aromatic or heteroaromatic carboxylic acids **2i–l** was studied only by analysis of their NH protons signals, as the aromatic region appears as a quite complex superposition of signals. Thus, it might be suggested that *o*-substituted carbohydrazides **2i–l** could demonstrate all three possible amide conformers. Their equilibrium depends on conditions such as solvent polarity and temperature. At least, the appearance of sets of six NH proton signals for **2i** (R=2-BrC_6H_4), seven for **2j** (R=2-ClC_6H_4), seven for **2k** (R=2-IC_6H_4) and six signals for thiophencarboxylic acid derivative **2l**, respectively, could be observed in DMSO-d_6/CCl_4 (1:1) solution, and fewer signals in pure DMSO-d_6 are detected.

3. Conclusions

The present study has established an efficient synthesis of *N*′,*N*″-1*H*-isoindole-1,3-diylidenedicarbohydrazides via the nucleophilic substitution of chlorine atoms of highly reactive 1,1,3-trichloro-1*H*-isoindole **1** by appropriate carbohydrazides in the presence of triethylamine as the HCl scavenger, and that are not available by the common route from phthalonitrile or 3-amino-1-imino-1*H*-isoindole.

The predominant symmetrical tautomeric form derived from 1*H*-isoindole-1,3(2*H*)-dione for *N*′,*N*″-1*H*-isoindole-1,3-diylidenedicarbohydrazides has been determined in the solid state as well as in solution, and amide-type isomerism in *N*-acyl hydrazone residues of the molecules with aliphatic and *o*-substituted aromatic carbohydrazide derivatives was observed. The *Z* amide rotamer predominates in all of the studied compounds whereas the *E* conformation is favoured in solution for the less hindered *N*′,*N*″-1*H*-isoindole-1,3-diylidenediacetohydrazide. Due to their tautomeric and conformational behaviour these compounds can be considered as good candidates to be applied as analytical reagent for spectrophotometric determination of metals by means of complex formation.

4. Experimental section

4.1. Materials and instrumentation

^{1}H NMR spectra (in DMSO-d_6, 20 °C) were measured on a Bruker Avance 300 (300 MHz for ^{1}H), and Mercury Varian-400 (400 MHz for ^{1}H) instruments, with tetramethylsilane as an internal reference. ^{13}C NMR spectra in DMSO-d_6 were measured on a Mercury Varian-400 (100 MHz for ^{13}C) and Bruker Avance 300 (75 MHz for ^{13}C), with tetramethylsilane residual peak as a standard.

The heteronuclear HMQC and HMBC correlation spectra were measured on a Varian Mercury-400 instrument (400 and 100 MHz, respectively). All chemical shifts were referenced to the tetramethylsilane residual peak as internal standard. HMQC and HMBC experiments were carried out with the method of indirect detection of carbon signals and gradient selection of useful signals. The mixing times in the pulse sequences were $^1J_{CH}$=140 Hz and $^{2-3}J_{CH}$=8 Hz, respectively. The number of increments in the HMQC

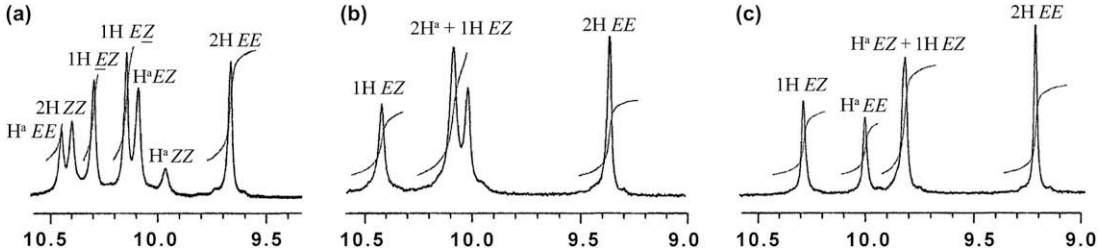


Figure 7. NH resonance assignment (300 MHz) of compound **2a** in (a) DMSO-d_6, (b) DMSO-d_6/$CDCl_3$ 1:1, (c) DMSO-d_6/$CDCl_3$ 1:3.

spectra was 128 and in the HMBC it was 400. For each increment 32 scans were collected.

The COSY-90 spectra were carried out with gradient selection of useful signals. For gradient NOESY spectra the mixing time was 200 ms. The temperature was maintained at 293 K. IR spectra were recorded with a Nicolet Nexus 470 instrument as KBr pellets. TLC analyses were carried out on silica gel coated aluminium plates (Silufol UV-254) in $CHCl_3$/MeOH 9:1 and spots were visualized with UV light. Melting points were determined with a Boetius microscope hot plate apparatus. Toluene was distilled from phosphorus pentoxide. 1,1,3-Trichloro-1*H*-isoindole **1** was prepared by phthalimide chlorination with phosphorus pentachloride in *o*-dichlorobenzene solution.[13]

4.2. General procedure for the preparation of *N*′-(3-(2-acylhydrazono)-1*H*-isoindol-1(2*H*)-ylidene)-carbohydrazides 2a–m

To a vigorously stirred suspension of the appropriate carbohydrazide (20 mmol) and triethylamine (4.15 mL, 30 mmol) in dry toluene (30 mL) was added dropwise a solution of 1,1,3-trichloro-1*H*-isoindole **1** (2.205 g, 10 mmol) in toluene (20 mL). Stirring of the resulting mixture was continued at 60–70 °C for 1 h to complete solid precipitation. The precipitate was filtered off and washed once with hexane, then with water to remove triethylamine hydrochloride and recrystallized. Aliphatic carbohydrazide derivatives were recrystallized from ethanol, and aromatic carbohydrazides—from aqueous DMF or acetic acid to yield after drying the carbohydrazides **2a**–**m** as coloured crystalline solids.

4.2.1. *N*′,*N*″-1H-Isoindole-1,3-diylidenediacetohydrazide (**2a**)

Yield: 1.97 g (76%) as a white solid, mp 280–282 °C (lit. Mp 235–236 °C[8]). IR (KBr disk, cm^{-1}): 1701 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C): δ 1.99, 2.01, 2.20, 2.22 (4×s, 6H, CH_3), 7.60–7.62 (m, 2H), 7.77–7.79 (m, 2H), 9.71, 10.04, 10.13, 10.21, 10.35, 10.45, 10.48 (3H, 7×s, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C) δ 20.67, 22.33, 22.39, 121.58, 121.67, 122.02, 122.14, 131.40, 131.70, 131.77, 133.09, 133.20, 133.54, 133.62, 139.88, 140.91, 145.27, 147.49, 166.06, 166.26, 172.49, 172.81. Anal. Calcd for $C_{12}H_{13}N_5O_2$ (259.26): C, 55.59; H, 5.05; N, 27.01. Found: C, 55.68; H, 5.14; N, 27.12.

4.2.2. *N*′,*N*″-1H-Isoindole-1,3-diylidenebis(2-methylpropanohydrazide) (**2b**)

Yield: 2.93 g (93%) as light yellow crystals, mp 190–191 °C. IR (KBr disk, cm^{-1}): 1664 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C): δ 1.11 (br s, 12H, 4×CH_3), 2.50–2.53 (m, 1H, CH), 3.40–3.50 (m, 1H, CH), 7.61 (br s, 2H), 7.78 (br s, 2H), 9.58, 10.04, 10.10, 10.15, 10.19, 10.38, 10.52 (7×s, 3H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ 19.32, 20.22, 29.83, 33.67, 33.82, 121.57, 122.09, 131.42, 131.65, 133.21, 133.59, 140.41, 140.97, 145.06, 146.30, 173.28, 173.54, 178.41, 178.77. Anal. Calcd for $C_{16}H_{21}N_5O_2$ (315.37): C, 60.94; H, 6.71; N, 22.21. Found: C, 61.08; H, 6.80; N, 22.14.

4.2.3. *N*′,*N*″-1H-Isoindole-1,3-diylidenediadamantane-1-carbohydrazide (**2c**)

Yield: 3.54 g (71%) as a light yellow solid, mp 203–205 °C. IR (KBr disk, cm^{-1}): 1655 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 1.71 (br s, 12H), 1.99 (br s, 18H), 7.56–7.59 (m, 2H), 7.77 (br s, 2H), 9.16 (br s, 1H, NH), 10.16 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6, 20 °C): δ 27.74, 35.91, 38.23, 40.02, 121.10, 130.41, 173.54. Anal. Calcd for $C_{30}H_{37}N_5O_2$ (499.65): C, 72.12; H, 7.46; N, 14.02. Found: C, 72.10; H, 7.54; N, 13.98.

4.2.4. *N*′,*N*″-1H-Isoindole-1,3-diylidenedibenzohydrazide (**2d**)

Yield: 3.29 g (86%) as a yellow solid, mp 226–227 °C. IR (KBr disk, cm^{-1}): 1716 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.46–7.57 (m, 8H), 7.82 (br s, 2H), 7.92 (d, J=8.8 Hz, 4H), 10.25 (br s, 3H, NH); ^{13}C NMR (75 MHz, DMSO-d_6, 20 °C): δ 121.19, 127.40, 128.54, 130.27, 131.16, 134.24, 163.03. Anal. Calcd for $C_{22}H_{17}N_5O_2$ (383.40): C, 68.92; H, 4.47; N, 18.27. Found: C, 69.03; H, 4.51; N, 18.32.

4.2.5. *N*′,*N*″-1H-Isoindole-1,3-diylidenebis(4-methylbenzohydrazide) (**2e**)

Yield: 2.87 g (70%) as a light brown solid, mp 290–291 °C. IR (KBr disk, cm^{-1}): 1684 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 2.38 (s, 6H, CH_3), 7.35 (d, J=10.4 Hz, 4H), 7.67–7.69 (m, 2H), 7.83–7.88 (m, 6H), 10.53 (br s, 1H, NH), 10.80 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6, 20 °C): δ 21.05, 121.45, 127.65, 128.90, 130.85, 131.20, 133.04, 141.63, 145.87, 163.25. Anal. Calcd for $C_{24}H_{21}N_5O_2$ (411.46): C, 70.06; H, 5.14; N, 17.02. Found: C, 70.15; H, 5.15; N, 16.94.

4.2.6. *N*′,*N*″-1H-Isoindole-1,3-diylidenebis(4-bromobenzohydrazide) (**2f**)

Yield: 4.70 g (87%) as a light yellow solid, mp>300 °C. IR (KBr disk, cm^{-1}): 1655 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.68–7.89 (m, 12H), 10.53 (br s, 1H, NH), 10.98 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6, 20 °C): δ 121.54, 125.37, 129.85, 131.32, 131.52, 132.68, 132.94, 146.35, 162.43. Anal. Calcd for $C_{22}H_{15}Br_2N_5O_2$ (541.20): C, 48.82; H, 2.7; Br, 29.53; N, 12.94. Found: C, 48.90; H, 2.81; Br, 29.60; N, 12.91.

4.2.7. *N*′,*N*″-1H-Isoindole-1,3-diylidenebis(4-fluorobenzohydrazide) (**2g**)

Yield: 3.47 g (83%) as a light green solid, mp 287–289 °C. IR (KBr disk, cm^{-1}): 1654 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.31 (t, J=11.6 Hz, 4H), 7.61–7.63 (m, 2H), 7.84–7.86 (m, 2H), 7.97–8.01 (m, 4H), 10.21 (br s, 3H, NH); ^{13}C NMR (75 MHz, DMSO-d_6, 20 °C): δ 115.36, 115.64, 121.45, 130.28, 130.94, 133.70, 162.39, 165.71. Anal. Calcd for $C_{22}H_{15}F_2N_5O_2$ (419.38): C, 63.01; H, 3.61; N, 16.70. Found: C, 62.92; H, 3.55; N, 16.73.

4.2.8. *N*′,*N*″-1H-Isoindole-1,3-diylidenedipyridine-2-carbohydrazide (**2h**)

Yield: 3.04 g (79%) as a light yellow solid, mp>300 °C. IR (KBr disk, cm^{-1}): 1691 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.67–7.69 (m, 4H), 7.89 (br s, 2H), 8.05–8.16 (m, 4H), 8.76–8.77 (m, 2H), 11.26 (s, 2H, NH), 11.36 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ 122.17, 123.47, 127.69, 131.83, 133.89, 138.81, 145.82, 149.13, 149.20, 150.35, 161.28. Anal. Calcd for $C_{20}H_{15}N_7O_2$ (385.38): C, 62.33; H, 3.92; N, 25.44. Found: C, 62.41; H, 3.90; N, 25.59.

4.2.9. *N*′,*N*″-1H-Isoindole-1,3-diylidenebis(2-bromobenzohydrazide) (**2i**)

Yield: 4.10 g (76%) as a light yellow solid, mp 189–190 °C. IR (KBr disk, cm^{-1}): 1658 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.30–7.95 (m, 12H), 10.14, 10.30, 10.83, 10.97 (4×s, 3H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ 119.85, 120.39, 120.48, 121.54, 122.26, 128.01, 128.35, 128.41, 129.63, 130.14, 130.20, 131.39, 131.78, 131.90, 132.03, 132.30, 132.78, 133.23, 133.46, 133.63, 133.69, 137.81, 137.87, 138.41, 142.30, 145.63, 146.40, 162.99, 164.03, 164.18, 169.98. Anal. Calcd for $C_{22}H_{15}Br_2N_5O_2$ (541.20): C, 48.82; H, 2.79; Br, 29.53; N, 12.94. Found: C, 48.77; H, 2.80; Br, 29.55; N, 12.81.

4.2.10. *N*′,*N*″-1H-Isoindole-1,3-diylidenebis(2-chlorobenzohydrazide) (**2j**)

Yield: 4.06 g (90%) as a light yellow solid, mp 196–198 °C. IR (KBr disk, cm^{-1}): 1661 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.31–7.89 (m, 12H), 10.16, 10.31, 10.86, 10.99 (4×s, 3H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ 121.53, 122.26, 127.57, 127.90, 127.95, 129.60, 129.70, 130.14, 130.21, 130.52,

130.58, 130.70, 131.37, 131.78, 131.91, 132.04, 132.19, 133.20, 133.24, 133.48, 135.72, 136.24, 142.39, 145.72, 146.49, 161.52, 163.17, 163.31, 169.32. Anal. Calcd for $C_{22}H_{15}Cl_2N_5O_2$ (452.29): C, 58.42; H, 3.34; Cl, 15.68; N, 15.48. Found: C, 58.39; H, 3.33; Cl, 15.58; N, 15.41.

*4.2.11. N′,N″-1H-Isoindole-1,3-diylidenebis-(2-iodobenzohydrazide) (**2k**)*

Yield: 4.31 g (68%) as a light yellow solid, mp 193–194 °C. IR (KBr disk, cm^{-1}): 1655 (C=O); ^1H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.20–7.36 (m, 3H), 7.46–7.70 (m, 5H), 7.84–8.00 (m, 4H), 10.20, 10.33, 10.75, 10.91 (4×s, 3H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ 94.53, 95.05, 95.26, 121.55, 122.17, 122.25, 128.39, 128.76, 128.82, 129.13, 129.46, 131.15, 131.75, 131.88, 132.01, 132.16, 133.26, 133.46, 139.08, 140.04, 140.11, 141.56, 141.63, 142.01, 142.49, 145.54, 146.32, 162.99, 165.61, 165.75, 171.35. Anal. Calcd for $C_{22}H_{15}I_2N_5O_2$ (635.196): C, 41.60; H, 2.38; N, 11.03. Found: C, 41.67; H, 2.42; N, 11.11.

*4.2.12. N′,N″-1H-Isoindole-1,3-diylidenedithiophene-2-carbohydrazide (**2l**)*

Yield: 2.45 g (62%) as a yellow solid, mp 294–295 °C. IR (KBr disk, cm^{-1}): 1622 (C=O); ^1H NMR (300 MHz, DMSO-d_6, 20 °C): δ 7.25 (t, J=6.0 Hz, 2H), 7.71 (br s, 2H), 7.89–8.12 (m, 6H), 10.49, 10.94, 11.09 (3×br s, 3H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ 122.22, 122.49, 127.35, 128.74, 129.44, 129.57, 131.75, 132.12, 132.19, 132.96, 133.61, 133.82, 135.70, 135.85, 139.19, 139.91, 146.72, 150.42, 158.69, 162.10. Anal. Calcd for $C_{18}H_{13}N_5O_2S_2$ (395.46): C, 54.67; H, 3.31; N, 17.71; S, 16.22. Found: C, 54.61; H, 3.28; N, 17.82; S, 16.15.

*4.2.13. Di-tert-butyl 2,2′-(1H-isoindole-1,3-diylidene)-dihydrazinecarboxylate (**2m**)*

Yield: 2.88 g (77%) as a flesh-coloured solid, mp 201–202 °C decomp.; ^1H NMR (400 MHz, DMSO-d_6, 20 °C): δ 1.47 (s, 18H), 7.56–7.59 (m, 2H), 7.71–7.73 (m, 2H), 9.47 (br s, 2H), 10.26 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ 28.47, 79.89, 121.35, 130.93, 132.18, 142.60, 153.27. Anal. Calcd for $C_{18}H_{25}N_5O_4$ (375.42): C, 57.59; H, 6.71; N, 18.65. Found: C, 57.69; H, 6.68; N, 18.72.

4.3. X-ray crystallographic studies

Crystals of **2b** ($C_{16}H_{21}N_5O_2\cdot H_2O$, M_r=333.39) are hexagonal, at 100 K. a=27.750(4) Å, c=16.430(2) Å, V=10,958(3) Å^3, space group $R\bar{3}$, Z=18, d_{calcd}=0.909 g cm^{-1}, F(000)=3204, μ(Mo Kα)=0.065 mm^{-1}, 28,790 reflections were measured at 'Xcalibur 3' diffractometer (graphite monochromated Mo Kα, ω-scans, CCD detector) of which 4454 were unique (R_{int}=0.040). Structure was solved by direct methods and refined in anisotropic approximation for all non-hydrogen atoms using SHELX-97 package.[15] Hydrogen atoms were placed in calculated positions and refined in riding model with $U_{iso}(H)=nU_{eq}$ of the carrier atom (n=1.5 for methyl groups and water and n=1.2 for remaining H-atoms). During refinement the C–C bond lengths in disordered isopropyl group were restrained to 1.53(1) Å. The crystal structure contains very large intermolecular voids located along $\bar{3}$ axes (three per unit cell) each of 1155 Å^3 volume, presumably containing disordered solvent molecules. Integrated electron number is 36 per void. In the final stages of refinement the contribution from this electron density was eliminated using SQUEEZE procedure implemented in Platon.[16] The contribution from disordered solvent was not accounted in calculations of molecular weight, crystal density, F(000) etc. Final R-values: R_1=0.049 (for 2131 reflections with $F>4\sigma(F)$), wR_2=0.129 (all data), S=0.996.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 691478. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.4. Computational details

All calculations have been performed at the CINES calculation centre with the Gaussian 03 version B5 package,[17] with default conditions. The geometry optimization of compound **2b** has been performed in two tautomeric forms. For compounds **2a** and **2b** three (*EE*, *EZ* and *ZZ*) conformations have been optimized using the B3LYP/6-31G(d,p)[18,19] density functional level of theory. Minima were checked successfully for consistent positive vibration frequencies.

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Supplementary data

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