Regioselective Raction of 1-(Arylimino)-1*H*-isoindol-3-amines with Aryl isocyanates

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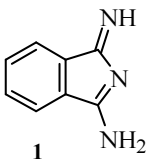
Aryl isocyanates were found to react regioselectively with 1-(arylimino)-1*H*-isoindol-3-amines by exocyclic nitrogen atom of amino group to form *N*-phenyl-*N'*-[3-(arylimino)-2,3-dihydro-1*H*-isoindol-1-ylidene]ureas in high yields. The structure of compounds formed was surely confirmed by ^{1}H NMR spectra and NOE experiments.

Introduction

N-Substituted derivatives of 3-imino-1*H*-isoindol-1-amine (**1**) represent an important class of heterocycles due to the different biological activities [1–3] demonstrated by compounds of this series.

The structure of 1-(arylimino)-1*H*-isoindol-3-amines (**2**) as potential tautomeric systems has been studied in detail in solution [4] and crystal state [5, 6]. At the same time only few examples of chemical transformations of these compounds have been described in the literature. Among them the nuclephilic substitution with primary and secondary amines has been studied [4, 7, 8]. Electophilic substitution for this class of isoindol derivatives was described only for 1-(phenylimino)-1*H*-isoindol-3-amine (**2**, Ar^1 = Ph) with bifunctional 3-bromopropan-1-amine that led to the formation of the compound **3** in 52% yield [4]. Reaction of **1** with electrophilic reagents such as isocyanates has not been studied until recently. According to patent data [9, 10] isoindole **1** and its analogs react with aryl isocyanates to form *N1,N3*-bis(arylurea) derivatives **4**.

Compounds of type **2** have two nucleophilic centers that differ in their reactivity: the endocyclic nitrogen atom and amino group. Such structural characteristics open two possible reaction pathways of **2** with isocyanates. It is difficult to predict the structural features of the reaction products **5** considering the possibility of the existence of these compounds in various tautomeric and stereoisomeric forms.



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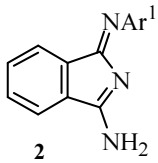

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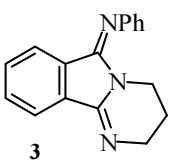

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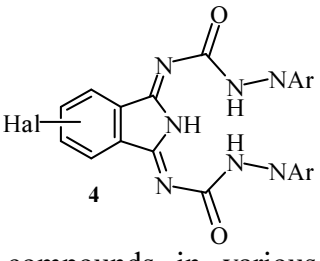

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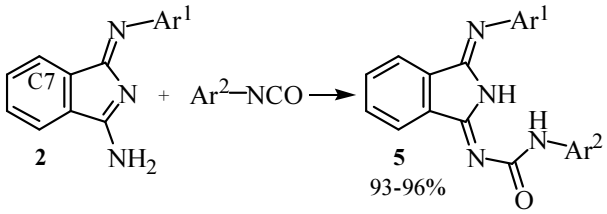
Results and discussion

The reaction of **2,** as binucleophilic cyclic amidine system, with 1-chlorobenzyl-isocyanates we have shown previously to be a suitable approach towards 1,3,5-triazino[2,1-*a*]isoindol-2-one derivatives [6, 11]. In continuation of this research, we present here, that aryl isocyanates react regioselectively at the exocyclic nitrogen atom of the amino group to form *N*-aryl-*N*'-[3-(arylimino)-2,3-dihydro-1*H*-isoindol-1-ylidene]ureas (**5**) in high yields (Scheme 1).

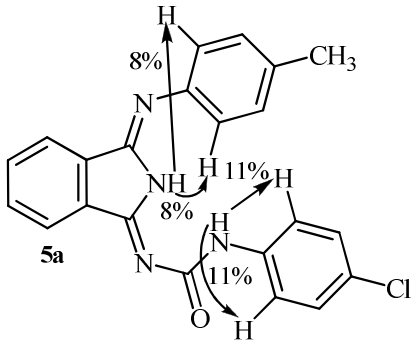


Ar^1 = 4-MeC_6H_4, Ar^2 = 4-ClC_6H_4 (a);
Ar^1 = 2-MeC_6H_4, Ar^2 = 4-ClC_6H_4 (b);
Ar^1 = 2-FC_6H_4, Ar^2 = 4-ClC_6H_4 (c);
Ar^1 = 3-$CF_3C_6H_4$, Ar^2 = C_6H_5 (d);
Ar^1 = 2-Me-4-ClC_6H_3, Ar^2 = 3-$CF_3C_6H_4$ (e)

Scheme 1.

The direction of the nucleophilic attack at one of the *N*-atoms was studied on the basis of ^{1}H NMR spectra analysis. It is known that [4, 6, 11] substituents like Ar^1 at the exocyclic C=N bond will adopt *E*-orientation upon nucleophilic attack at the endocyclic nitrogen atom, due to arising steric hindrance. This would lead to an upfield shift of the signal of H7 in the isoindole unit to 6.5 ppm. In the case of compounds **5** the signals of H4 and H7 protons are observed at 7.90–8.10 ppm, indicating a *Z*-orientation of the Ar^1 substituent and therefore, it can be concluded that reaction did not take place at the endocyclic nitrogen atom.

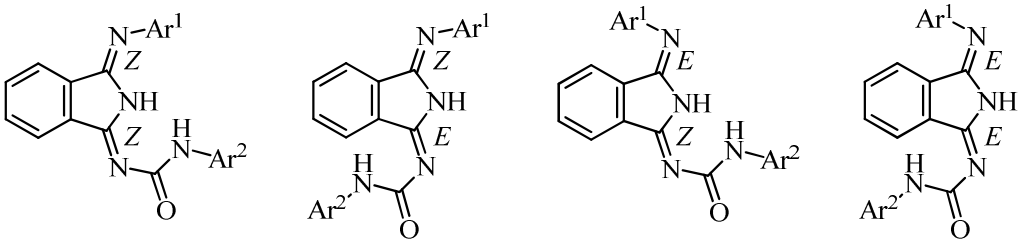
The predominant tautomeric form of ureas **5** was determined by NOE experiments for derivative **5a** (Scheme 2).



Scheme 2.

It was found that the endocyclic NH proton (δ = 10.87 ppm) is situated in a close proximity to the *ortho*-protons of the 4-mehtyl-phenyl substituent. In addition, the *ortho*-protons of 4-chlorophenyl residue shows NOE coupling with the carbamide NH proton (δ = 10.48 ppm). These structural features are only possible if the compounds **5** have the diimino tautomeric form depicted in Scheme 2.

Furthermore, in the ^{1}H NMR spectra of derivatives **5** several additional signals were observed. At least, three additional isomeric forms (in total 20% in the mixture) were identified based on low intensity signals of CH_3 groups between 2.25–2.38 ppm. The fact that there are no regioisomers, arising from an attack



Scheme 3.

at the endocyclic *N*-atom, was proven by means of TLC and LC/MS data. The isomeric ratio also did not change after recrystallization of compounds **5**. Most probably these isomers adopt altering *Z*- or *E*-orientation of the Ar-substituents at the exocyclic C=N bonds (Scheme 3). Finally all isomers are in a dynamic equilibrium as signals at the ^{1}H NMR spectrum of compound **5a** start coalesce in DMSO[D_6] at 80 °C.

Conclusions

The regioselective reaction of 1-(aryl-imino)-1*H*-isoindol-3-amines with aryl isocyanates has been studied. The structure of the obtained products was surely confirmed by ^{1}H NMR spectra and NOE experiments. According to their ^{1}H NMR spectra in DMSO[D_6], ureas **5** exist as a mixture of *Z*-, *E*-isomers at the exocyclic C=N bonds with the *Z,Z*-isomer being predominant (about 80%).

Experimental part

1-(Arylimino)-1*H*-isoindol-3-amines (**2**) were prepared starting from phthalonitrile and corresponding amines [4]. Melting points were measured on a Boetius microscope hot plate apparatus. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI). ^{1}H NMR and ^{13}C NMR spectra were measured on Mercury (Varian) 400 spectrometer (400 MHz ^{1}H and 100 MHz for ^{13}C) in DMSO[D_6] solutions with TMS as internal standard. ^{1}H NMR spectra of derivatives **5** are shown for the predominant *Z,Z*-isomeric form.

General Procedure for the Synthesis of *N*-aryl-*N*'-[3-(arylimino)-2,3-dihydro-1*H*-isoindol-1-ylidene]ureas (5). The mixture of 3 mmol of corresponding 1-(arylimino)-1*H*-isoindol-3-amine (**2**) and 3 mmol of aryl isocyanate was heated to reflux with stirring in 30 mL of dry dioxane during 2-3 h. The reaction mixture was cooled. Precipitate formed was filtered, washed with hexane and dried on air.

***N*-(4-chlorophenyl)-*N*'-{3-[(4-methylphenyl)imino]-2,3-dihydro-1*H*-isoindol-1-ylidene}urea (5a).** Yield 95%, mp 213–214 ºC. MS (CI): m/z = 390 $[M + H]^+$. NMR ^{1}H: δ = 2.41 (s, 3H, CH_3), 6.99 (d, 2H, J = 8.4 Hz), 7.23 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.70 (d, 2H, J = 8.0 Hz), 7.80–7.94 (m, 3H), 8.05 (d, 1H, J = 7.6 Hz), 10.47 (s, 1H, NH), 10.87 (s, 1H, NH) ppm. NMR ^{13}C: δ = 20.9, 119.9, 120.8, 121.4, 122.9, 123.6, 127.1, 128.9, 129.5, 130.2, 130.5, 132.8, 133.8, 134.3, 134.9, 138.6, 145.4, 149.5, 160.2, 161.5 ppm.

***N*-(4-chlorophenyl)-*N*'-{3-[(2-methylphenyl)imino]-2,3-dihydro-1*H*-isoindol-1-ylidene}urea (5b).** Yield 96%, mp 243–244 ºC.

MS (CI): m/z = 390 $[M + H]^+$. NMR ^1H: δ = 2.21 (s, 3H, CH_3), 6.99 (d, 1H, J = 6.8 Hz), 7.13 (t, 1H, J = 6.8 Hz), 7.25–7.28 (m, 2H), 7.31 (d, 2H, J = 8.0 Hz), 7.66 (d, 2H, J = 8.0 Hz), 7.81–7.86 (m, 2H), 7.94 (d, 1H, J = 7.6 Hz), 8.09 (d, 1H, J = 7.6 Hz), 10.46 (s, 1H, NH), 10.65 (s, 1H, NH). NMR ^{13}C: δ = 17.9, 119.9, 120.8, 123.0, 125.1, 127.1, 127.3, 128.8, 129.7, 130.8, 131.1, 132.8, 133.9, 138.6, 139.0, 146.9, 149.4, 159.9, 161.5 ppm.

***N*-(4-chlorophenyl)-*N*'-{3-[(2-fluorophenyl)imino]-2,3-dihydro-1*H*-isoindol-1-ylidene}urea (5c).** Yield 96%, mp 222–223 ºC. MS (CI): m/z = 394 $[M + H]^+$. NMR ^1H: δ = 7.25–7.38 (m, 6H), 7.73 (d, 2H, J = 8 Hz), 7.84–7.96 (m, 3H), 8.10 (d, 1H, J = 7.6 Hz), 10.54 (br. s, 1H, NH), 10.86 (br. s, 1H, NH) ppm. NMR ^{13}C: δ = 116.7, 116.9, 120.6, 120.9, 123.2, 123.7, 124.8, 125.6, 126.6, 127.1, 128.9, 129.2, 132.0, 133.1, 133.9, 134.9, 135.7, 138.5, 138.9, 151.5, 152.3, 153.9, 154.7, 159.3, 161.2 ppm.

***N*-phenyl-*N*'-(3-{[3-(trifluoromethyl)-phenyl]imino}-2,3-dihydro-1*H*-isoindol-1-ylidene)urea (5d).** Yield 95%, mp 202–203 ºC. MS (CI): m/z = 409 $[M + H]^+$. NMR ^1H: 7.02 (t, 1H, J = 8.0 Hz), 7.28 (t, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.64–7.70 (m, 3H), 7.79–7.85 (m, 2H), 7.94 (d, 1H, J = 7.6 Hz), 8.05 (d, 1H, J = 7.6 Hz), 10.32 (br. s, 1H, NH), 10.87 (s, 1H, NH) ppm. NMR ^{13}C: δ = 118.4, 119.0, 119.3, 121.0, 121.4, 122.8, 123.1, 123.5, 124.0, 124.5, 125.2, 125.4, 126.7, 129.0, 129.2, 130.1, 131.1, 132.0, 132.7, 133.0, 133.6, 137.5, 137.9, 139.6, 140.0, 149.2, 149.2, 151.0, 151.1, 159.2, 161.2, 163.1 ppm.

***N*-{3-[(4-chloro-2-methylphenyl)imino]-2,3-dihydro-1*H*-isoindol-1-ylidene}-*N*'-[3-(trifluoromethyl)phenyl]urea (5e).** Yield 93%, mp 199–200 ºC. MS (CI): m/z = 458 $[M + H]^+$. NMR ^1H: δ = 2.18 (s, 3H, CH_3), 7.03 (d, 1H, J = 8 Hz), 7.32 (d, 1H, J = 8 Hz), 7.37–7.40 (m, 2H), 7.54 (t, 1H, J = 8.0 Hz), 7.82–7.94 (m, 4H), 8.07–8.09 (m, 2H), 10.59 (br. s, 1H, NH), 10.63 (br. s, 1H, NH). NMR ^{13}C: δ = 17.8, 115.2, 119.3, 119.7, 121.4, 121.7, 122.9, 123.1, 123.5, 124.9, 127.0, 128.6, 129.3, 129.5, 130.3, 130.5, 130.6, 133.0, 133.4, 133.9, 140.4, 140.9, 145.8, 149.8, 152.4, 161.5 ppm.

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