Tetrahedron Letters 55 (2014) 6615–6618

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An atypical easy reductive cleavage of the conjugated C=C bond in 1,1′-disubstituted isoindigos under the action of aqueous hydrazine hydrate

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ARTICLE INFO

Article history:
Received 22 August 2014
Revised 29 September 2014
Accepted 14 October 2014
Available online 22 October 2014

Keywords:
Isoindigo
Reduction cleavage
Hydrazones
Single-crystal
Oxindoles

ABSTRACT

The reaction of diverse symmetrically-substituted isoindigo derivatives with 80% aqueous hydrazine hydrate is described. The influence of the structure of the substituent on either oxindole or isatin-3-hydrazone formation is discussed.

Isoindigo is one of three bis-indoles (indigo, indirubin, and isoindigo), which is closely connected with various pharmaceutical and material applications. Recent data show that numerous substances bearing the indolin-2-on-3-ylidene motif possess strong potencies in anticancer drug design.[1] Important examples include isoindigo derivatives such as meisoindigo and natura which are already used in leukemia treatment (Fig. 1).[2]

Being a bis-heterocycle incorporating two lactam moieties joined via a carbon–carbon double bond, isoindigo represents a highly reactive conjugated system. Such structures allow these molecules to behave as electron-acceptor materials in organic electronics such as in organic photovoltaics (OPVs) and organic field effect transistors (OFETs).[3] However, the utilization of these compounds in organic reactions is limited to the synthesis of oligo- or polymeric structures with an isoindigo unit for OPV and OFETs under Stille or Suzuki reaction conditions.[4]

In the present work we disclose novel aspects of the chemistry of these bis-heterocycles, namely their unusual reaction with hydrazine hydrate. Thus, initially we were trying to obtain the dihydrazide **2** with an isoindigo core from the corresponding diester **1** using a standard organic synthetic approach. However, treatment of isoindigo **1** with a fivefold excess of hydrazine hydrate in EtOH at reflux temperature resulted in a discoloration of the reaction mixture that could indicate a disruption of the conjugated double bond system. Indeed, the ^{1}H and ^{13}C NMR spectral data showed presence of two reaction products, **3** and **4**, as an inseparable mixture, but not compound **2** (Scheme 1).

Thus in this case, besides hydrolysis and hydrazinolysis of the ester units, cleavage of the central C=C double bond had occurred. It should be noted here that the reactions of α,β-unsaturated car-

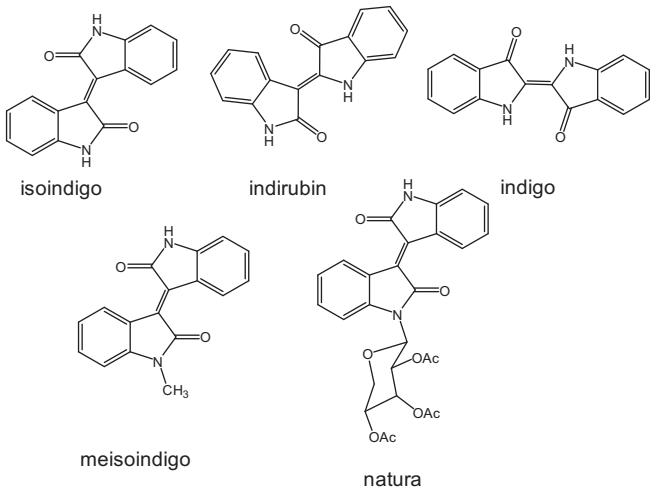

Figure 1. Examples of compounds containing the bis-indole moiety.

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http://dx.doi.org/10.1016/j.tetlet.2014.10.088
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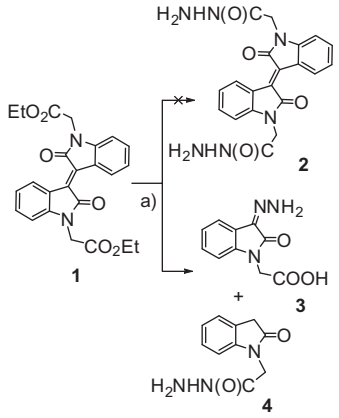
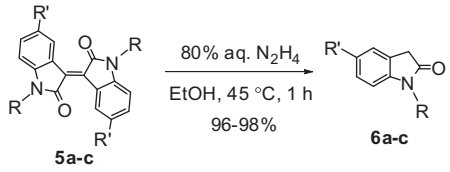


Scheme 1. Hydrazinolysis of ester-containing isoindigo **1**. Reagents and condition: (a) aqueous N_2H_4 (85%), EtOH, reflux.



R' = H, R = Me (**a**); R' = H, R = 4-$FC_6H_4CH_2$ (**b**);
R' = Br, R = Me (**c**)

Scheme 2. Substituted oxindoles from the corresponding isoindigos.

bonyl compounds with N_2H_4 are characterized by the formation of either the corresponding pyrazolidinones or the products of C=C bond reduction.[5,6]

Keeping in mind such an unexpected result, we decided to examine the behavior of other symmetrically substituted isoindigos **5**–**7** toward hydrazine hydrate.[7,8] Compounds **5a**–**c** were found to undergo facile C=C bond cleavage to give oxindoles **6a**–**c** (Scheme 2) as the main reaction products under conditions much milder than those used in the above reaction.

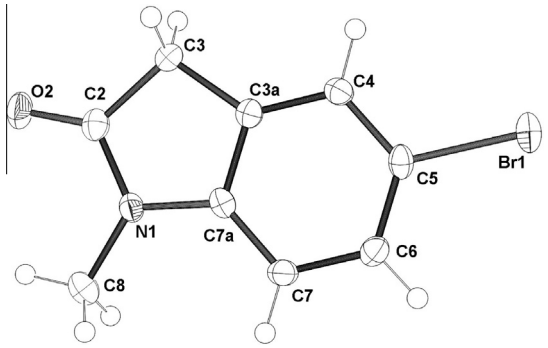


Figure 3. ORTEP view (thermal ellipsoids at the 50% probability level) of 5-bromo-1-methylindolin-2-one (**6c**). Selected bond lengths [Å] and angles [°]: C2–O2 1.215(4), C5–Br1 1.902(3), N1–C2 1.379(4), C7a–N1 1.393(5), C2–C3 1.528(5), C3–C3a 1.499(4), O2–C2–N1 125.1(3), C2–N1–C7a 111.3(3), C3a–C3–C2 103.5(3), C3a–C7a–N1 110.1(3), C3–C3a–C7a 107.3(3), O2–C2–C3 127.5(3).

The fact that the double bond underwent reduction-cleavage was proved from the ^1H and ^{13}C NMR data that showed the presence of the methylene and amide carbonyl fragments in the molecule. Exemplifying on **6a**, the signal corresponding to the C3 methylene appeared in a characteristic high-field region (δ = 26.1) in the ^{13}C NMR spectrum while C2 appeared at δ 175.1, being consistent with an amide carbonyl (Fig. 2).

Finally, the structure of one of the reaction products (**6c**) was unequivocally confirmed by X-ray crystallographic analysis (Fig. 3).[9]

A plausible reaction mechanism for the formation of **6a**–**c** shown in Scheme 3 may be presented to rationalize the reaction outcome. In the first stage of the reaction a conjugate addition of hydrazine to the C=C bond to form intermediate **A** takes place.

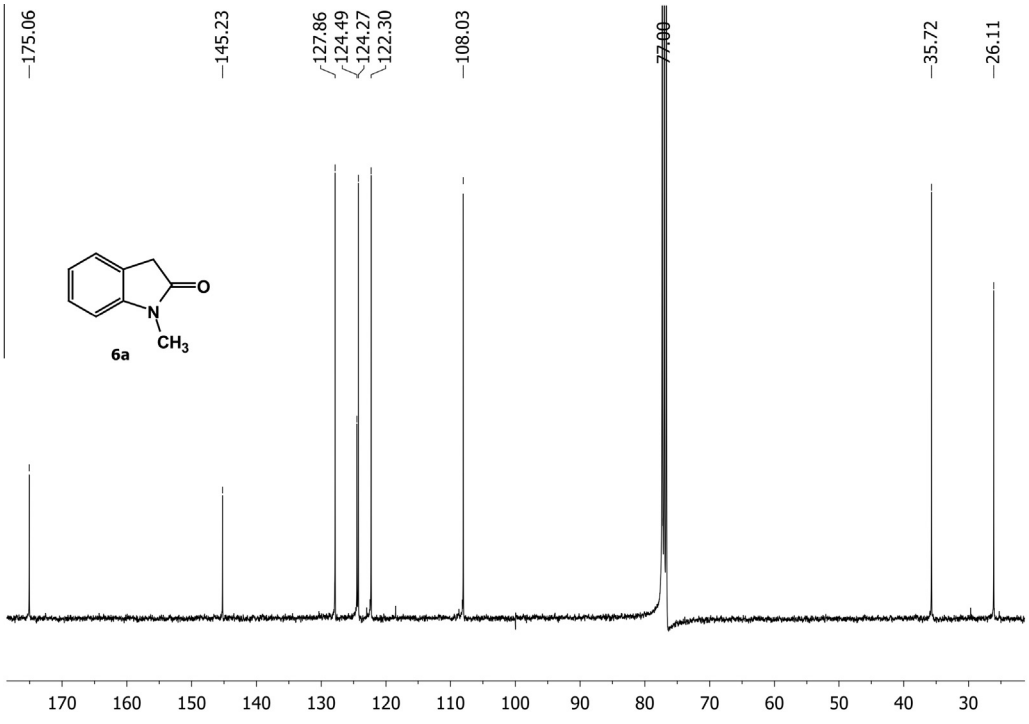
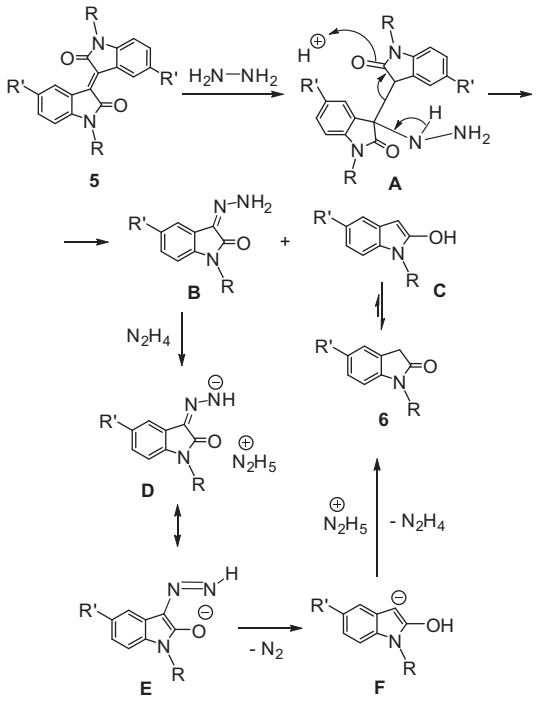
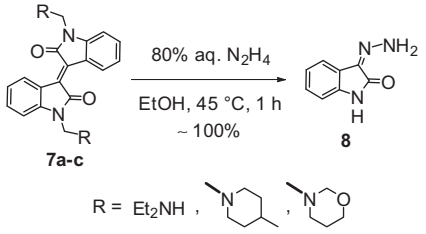


Figure 2. ^{13}C–{^1H} NMR spectrum of 1-methyloxindole **6a** in $CDCl_3$.



Scheme 3. A plausible mechanism of the formation of **6a–c**.



Scheme 4. Substituted oxindoles from the corresponding isoindigos.

Then redistribution of electron density and the C–C bond cleavage lead to the formation of hydrazone **B** and enol **C**. Further, hydrazone **B** under the action of hydrazine generates anionic intermediate **D**, which tautomerizes to N=N containing species **E**. This intermediate eliminates dinitrogen to form an anionic enolate, which undergoes protonation with hydrazinium to give the second molecule of final product **6**.

A distinctive feature of this reaction is the sensitivity of the synthetic result to the structure of the substituent at the nitrogen atom of the bis-indole. It was found that aminomethyl-containing isoindigos **7a–c** (the so-called isoindigo *N*-Mannich bases) reacted with aqueous N_2H_4 to afford isatin-3-hydrazone **8** in almost quantitative yield (Scheme 4). In this reaction, besides the formation of a hydrazone function and C=C bond cleavage, an elimination of an aminomethyl moiety occured.

At 25 °C in DMSO-d_6 (c = 20% w/w), the ^{1}H NMR spectrum of compound **8** exhibited four signals in the aromatic region (δ = 6.86–7.35) and two broad signals due to the NH_2-group (δ = 9.50 and 10.52). It is interesting that the exchangeable signal of the lactam proton appeared as a singlet at δ 8.04 only at a lower solution concentration (c = 5% w/w) (Fig. 4).

The absence of doubling of the signals in these spectra indicated the formation of only one *Z*-isomer. Its structure was finally established by XRD analysis which data were in good agreement with those reported earlier.[10]

In summary, the reaction of isoindigo derivatives with aqueous hydrazine hydrate has been studied. It was found that in all cases, reductive cleavage of the central C=C bond took place under mild conditions. It was revealed that 1,1′-dialkylisoindigos in this reaction afforded the corresponding oxindoles, whereas aminomethyl examples gave isatin-3-hydrazone. Furthermore, this reaction may serve as a promising approach for the synthesis of difficult to prepare 1-substituted oxindoles.

Acknowledgement

We are grateful for the financial support of the Russian Foundation for Basic Research (Grant no. 14-03-31717-mol_a).

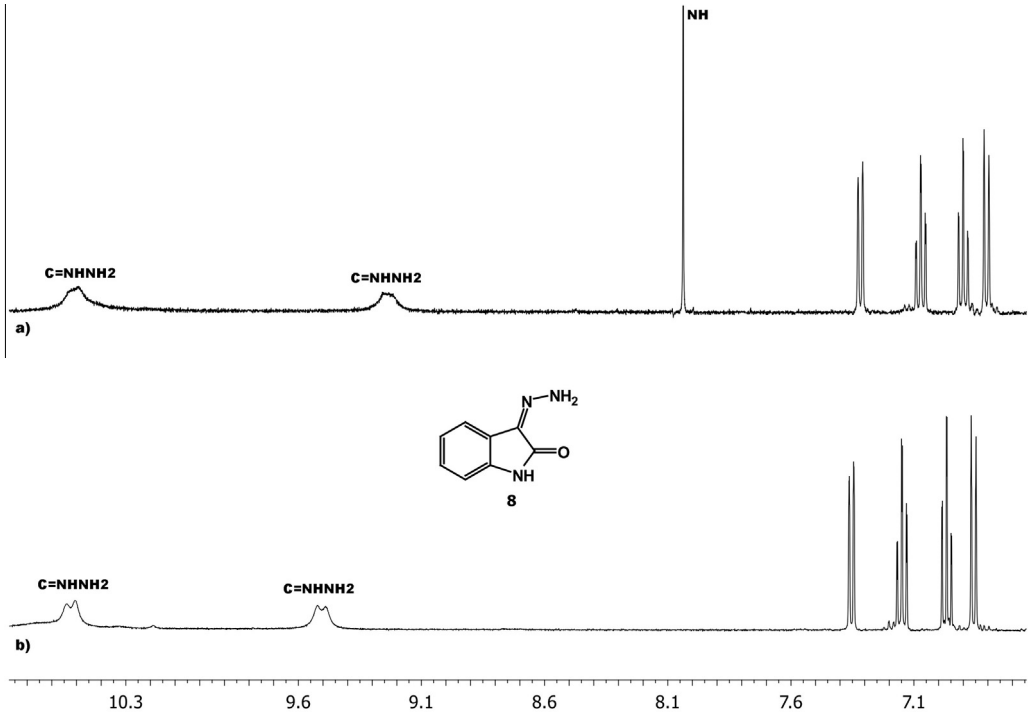


Figure 4. Low-field fragments of the ^{1}H spectra of isatin-3-hydrazone **8** in DMSO-d_6 at 25 °C: (a) c = 5% w/w; (b) c = 20% w/w.

Supplementary data

Supplementary data (detailed experimental procedures, NMR spectra and X-ray analysis (CIF-files)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.088.

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7. *General procedure for the synthesis of products* ***6a–c***: A mixture of substituted isoindigo (0.2 mmol) and hydrazine hydrate (3 ml) in freshly distilled EtOH (3 ml) was heated at 45 °C for 10 min. The solvent and volatiles were evaporated to afford pure products as white solids which did not need to be specially purified.
8. *1-(4-Fluorobenzyl)indolin-2-one* (***6b***): Yellow solid; (yield 96%); mp 67 °C; IR (Nujol) (ν_{max}, cm^{-1}): 1689 (C=O), 1610 (C=C), 1509 (C—N); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, 2H, J = 8.7 Hz, J = 5.3 Hz, Ar-H), 7.25 (d, 1H, J = 7.1 Hz, Ar-H), 6.98–7.03 (m, 3H, Ar-H), 7.18 (d, 1H, J = 7.7 Hz, J = 7.5 Hz, Ar-H), 6.71 (d, 1H, J = 7.9 Hz, Ar-H), 4.88 (s, 2H, CH_2), 3.61 (s, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): 35.65, 42.99, 108.82, 115.59 (d, J = 21.6 Hz), 122.42, 124.44, 127.75, 129.01, 129.09, 131.66 (d, J = 2.9 Hz), 144.06, 162.17 (d, J = 246.1 Hz, C–F), 175.02; MS (m/z): 241.1. Anal. Calcd for $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; N, 5.81. Found: C 74.05, H 4.38, N 5.77.
9. Crystallographic data for compound **6c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1008769. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).
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