Tetrahedron 66 (2010) 8214–8222

Contents lists available at ScienceDirect

Tetrahedron

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

On the reactivity of isoindolo[2,1-*a*]quinazoline-5-ones☆

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ARTICLE INFO

Article history:
Received 17 June 2010
Received in revised form 29 July 2010
Accepted 5 August 2010
Available online 12 August 2010

Keywords:
Acceptor–donor–acceptor chromophores
Aldol condensation
Aromatic aldehydes
Dibenzoylacetylene
Isoindoles
Isoindolo[2,1-*a*]quinazolines
Maleimides
Michael addition
Quadratic hyperpolarizability

ABSTRACT

Base- and acid-catalyzed nucleophilic addition of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one to aromatic aldehydes and maleimides was investigated. The aldol adducts and condensation products were obtained stereoselectively. Main diastereomers of the Michael adducts were isolated in 74–89% yield, and converted by *N*-methylation to new stable α-substituted isoindole derivatives, for which 6-methylisoindolo[2,1-*a*]]quinazoline-5-one stands as the unsubstituted reference. The stability of the latter was monitored in moist aerated $CDCl_3$ solution, and one of the oxidative hydrolysis product was characterized by X-ray diffraction analysis as the corresponding *N*-arylphthalimide. The reactivity of the unsubstituted 6-methylisoindolo[2,1-*a*]]quinazoline-5-one was also investigated with acetylenic Michael acceptors. Fully conjugated isoindole derivatives possessing an original pull–push–pull structure were obtained. The conformations and molecular orbitals of the dibenzoylacetylene adduct were studied at the DFT level of theory. Its static quadratic hyperpolarizabilty β_0 was also calculated at the ZINDO level.
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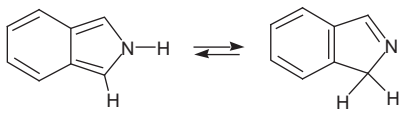
1. Introduction

The influence of aromaticity on tautomeric equilibria[1] is well illustrated by the isoindole case where the bicyclic *o*-quinodimethane motif is stabilized with respect to the unicyclic isoindolenine tautomeric form by the topological aromaticity (quantified by topological resonance energy, TRE) of both the 6-π electron rings and the 10-π electron peripheral macrocycle (TRE (isoindole)=0.323>TRE(isoindolenine)=0.233) (Scheme 1).[2]



Scheme 1. Isoindole/insoindolenine tautomeric equilibrium and corresponding topological resonance energy values (in units of a uniform resonance integral β between adjacent p_z orbitals).[2]

N-substitution and exocyclic conjugation at C-1 with a more acidic N–H tautomeric source allows for a relative stabilization of the isoindolenine form. The isoindole form is however not suppressed provided that its 10-π-electron system is part of a more extended π-system. This is exemplified with the 20-π-electron tetracycle **1**, exhibiting an equilibrium between the isoindolenine form **1a** and the isoindole form **1b** (Scheme 2). Assuming a C^+–O^- polarization of the amide carbonyl group, **1b** contains a 18-π electron peripheral macrocycle,[3] but its reactivity is similar to that of other 1,2-disubstituted isoindoles.[4,5] In the presence of maleic imides, 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** is indeed capable to generate new rearrangement products,[6] or give classical Michael: Diels–Alder adducts in a 1:2 ratio.[7] In the presence of other substrates possessing activated double or triple bonds, **1** reacts in a different manner, which has not been reported before.

Derivatives of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** exhibit biological activities,[8] which were shown to strongly depend on the nature of the α-substituent at the imidazo[2,1-*a*]isoindole core.[8,9] Several reports have dealt with electrophilic functionalization of annelated isoindoles with an activated methylene group.[9] The acidic character of the benzylic methylene group of the imido main form **1a** of **1** is illustrated by the tautomerism with the amido form

☆ Investigations performed within the framework of the GDRI 'Groupement Franco-Ukrainien en Chimie Moleculaire'.

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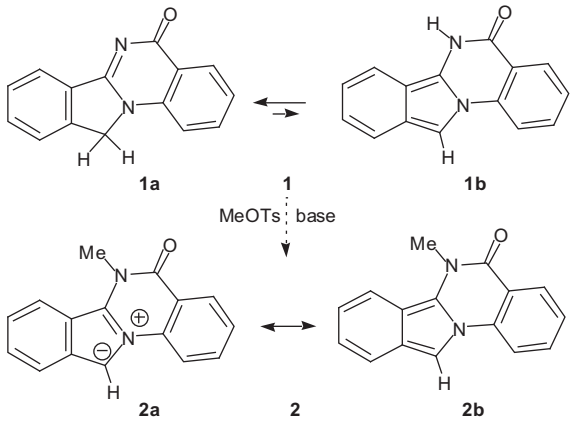
0040-4020/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tet.2010.08.013



Scheme 2. 11*H*-Isoindolo[2,1-*a*]quinazoline-5-one **1**, its major and minor tautomeric forms **1a** and **1b**, and its *N*-methyl derivative **2** described by mesomeric forms **2a** and **2b**.

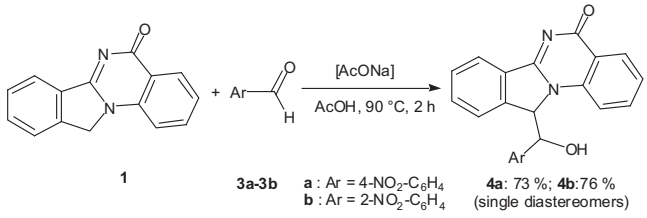
1b (Scheme 2), which is similar to that observed for thieno[3′,2′:5,6]pyrimido[2,1-*a*]isoindol-4-(10*H*)one.[10] Both mesomeric and tautomeric flexibility thus suggest that **1** behaves as an ambident nucleophile (Scheme 2). The *N*-nucleophilicity of **1** was revealed in its reaction with a hard electrophile, i.e., methyl tosylate, locking the isoindole form **1b** in the methyl derivative **2**, which can be described by the mesomeric forms **2a** and **2b**.[11]

1.1. *C*-Nucleophilicity of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one 1

By analogy with a recently reported study in the thieno-fused series,[12] two kinds of quite soft *C*-electrophiles were first investigated, namely aromatic aldehydes and maleimides.

1.2. Addition and condensation with aromatic aldehydes

Condensation of **1** with aromatic aldehydes bearing electron-withdrawing or -donating substituents was first considered. Standard base-catalyzed conditions lead to mixtures of products, which were difficult to separate and identify. In acetic acidic medium however, the electron-poor aldehydes **3a** and **3b** produced the aldol products **4a** and **4b** in 73% and 76% yield, respectively (Scheme 3).



Scheme 3. Aldol reaction of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one with nitro-aromatic aldehydes in acetic acid medium, in the presence of a catalytic amount of sodium acetate.

The presence of the O*H* groups in **4a**–**b** was checked by IR (νO–H=3300–3000 cm^{-1}) and by ^{1}H NMR (deuterium exchange with D_2O), and their structure was confirmed by other spectroscopic and elemental analyses. The isomeric purity of **4a** and **4b** was suggested by TLC and checked by ^{1}H NMR analysis (only traces of a second diastereomer could be detected). The elimination products were not obtained, likely because of the relative mesomeric destabilization of the benzylic carbenium ion through the influence of nitro substituent of **4a** and **4b** in *para*- and *ortho*-positions, respectively. Under prolonged reflux in acetic anhydride however, the electron-rich *p*-dimethylaminobenzaldehyde **3c** lead to the condensation product **5c** in 58% yield (*E*-isomer in Scheme 4).

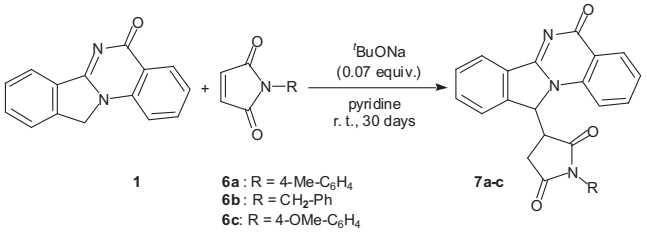
The structure of **5c** was established by elemental and spectroscopic analyses. Its isomeric purity was controlled by TLC and checked by ^{1}H NMR analysis (only traces of a second isomer could be detected). Considering that the thermodynamic conditions used (refluxing Ac_2O, 6 h) should favor the formation of the most stable isomer, it is reasonably assumed that **5c** is formed in the less strained (*E*)-configuration. The donor *p*-dimethylamino group should indeed favor a *E*1 process by stabilizing the carbenium ion resulting from the dissociation of the intermediate acetate **4c**.

1.3. Addition to Michael acceptors and subsequent deproto-N-methylation

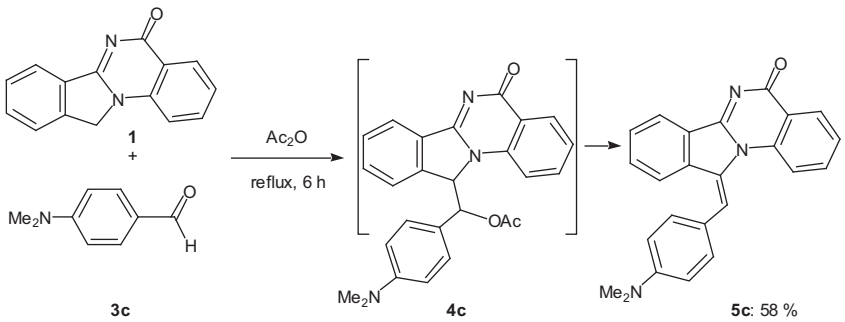
Previous experiments showed that **1** could behave as an active methylene reactant. On the other hand, maleimides are classical dienophiles or Michael electrophiles, and many of their derivatives possess useful biological properties.[13] The reaction between both kinds of compounds was thus naturally envisioned.

1.3.1. Michael addition to maleimides. Under base-catalyzed conditions, reaction of maleimide **6a**–**c** with **1** afforded the thermodynamic adduct **7a**–**c** in good yield (Scheme 5).

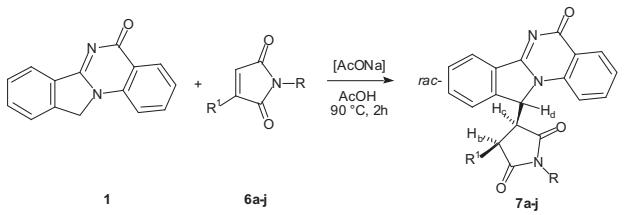
In order to shorten the reaction times, other conditions were then attempted. In acetic acid (Scheme 4), maleimides **6a**–**i** afforded mixtures of diastereomers of **7a**–**i**, from which a main diastereomer (out of two possible) could be isolated in 74–89% yield (Scheme 6). Although the exact *threo* or *threo* configuration could



Scheme 5. Michael addition of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** to maleic imides under strongly basic conditions.



Scheme 4. Aldol condensation of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** with an electron-rich aldehyde in acetic anhydride medium.



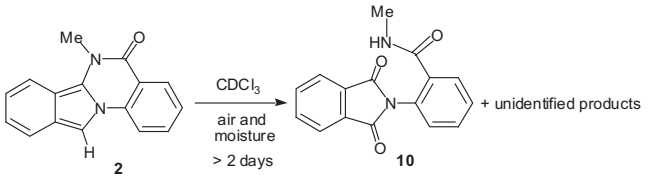
Scheme 6. Michael addition of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one to maleimide derivatives under acidic conditions. Yields are given for the main diastereomers.

not be assigned, it might be the same for the adducts **7a**–**i** displaying almost isochronous ^1H_d resonances in the range 6.05–6.21 ppm (in DMSO-d_6) and small $^3J_{HcHd}$ coupling constants (in the range 0–4 Hz for **7a**–**e** and **7g**–**i**).[14] In the case of the 3-methylmaleimide substrate **6j**, two diastereomers of the adduct **7j** (out of four possible) could be isolated in 80% and 11% yield, respectively. The relative stereochemistry could not be assigned, but it is noteworthy that for both the isomers, the ^1H_d resonances (6.21 ppm and 6.09 ppm) and $^3J_{HcHd}$ coupling constants (2.9 Hz and <1 Hz) are in the same range as for the non-substituted representatives **7a**–**i**.[15]

The proposed structures **7a**–**j** were otherwise confirmed by elemental analysis and ^1H and ^{13}C NMR spectroscopy. Additional evidence for structure **7b** was provided by its ^1H–^1H COSY spectrum.

1.3.2. N-Methylation of Michael adducts to α-substituted isoindoles. Alkylation of **1** by maleimides takes place at the C-11 position exclusively (no N-alkylation was observed). The resulting steric hindrance of the C-11 center in **7** rules out the possibility of a second C-alkylation, while the soft character of the maleimide electrophile disfavors N-alkylation. Nevertheless the possibility of a second alkylation was investigated using a hard and small electrophile, such as methyl tosylate. The Michael adducts **7a**,**b** were thus found to undergo N-methylation to **8a**,**b**. The isoindoleninium salt **8a** was then readily deprotonated to the isoindole **9a**, while the Michael adduct **7j** was directly N-methylated/deprotonated to the isoindole **9j** (without characterization of the intermediate salt **8j**). The original C-11 methylene center of **7** is no longer stereogenic in **9**, and pure diastereomers of **9a** and **9j** were isolated in 79% and 98% yield, respectively (Scheme 7).

Although the behavior of the isoindole framework under oxidative treatment can be remarkably selective,[16] it is noteworthy that the isoindoles **2** (Scheme 2) and **9** are quite stable in the solid state and in the air with respect to possible polymerization or oxidative degradation. The stability of the parent isoindole **2** in moist non-deaerated $CDCl_3$ solution was thus monitored at r. t by ^1H NMR. New unidentified signals started to appear after 6 h, but it took more than 2 days before **2** became a minor component of the decomposition mixture. Although most of the degradation products could not be isolated, crystals of one of them deposited and could be characterized by X-ray diffraction analysis as the phthalimide derivative **10** resulting from hydrolysis of the amidine C–NC(O) bond and complete oxidation of the C-11 carbon atom (Scheme 8, Fig. 1). Although the yield in **10** could not be determined from the sample of the in situ NMR monitoring, the latter process is anyway not possible for α-substituted isoindoles **9a** and **9j**, which are therefore expected to be more stable than **2** with this respect. It must be mentioned that several examples of pyrrole ring oxidation to isoindolo[2,1-*a*]quinazoline-5,11-diones under acidic conditions have been reported, and that isoindolo[2,1-*a*]quinazoline-5,11-diones give phtalimidines under basic conditions, and give products with two rings opened after a prolonged treatment.[17–19]



Scheme 8. Oxidative hydrolysis of the 6-methylisoindolo[2,1-*a*]quinazoline-5-one **2** (unsubstituted at C-11) to phthalimide **10** (Fig. 1).

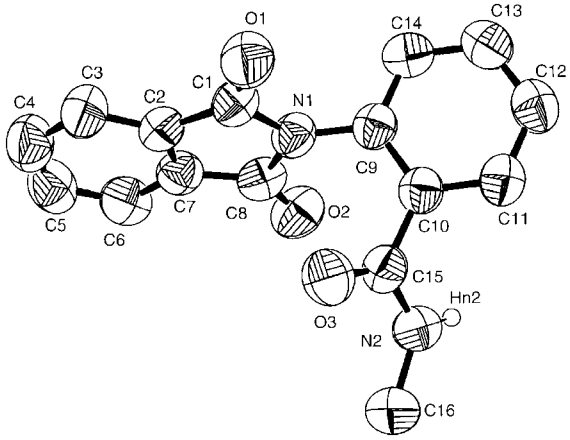
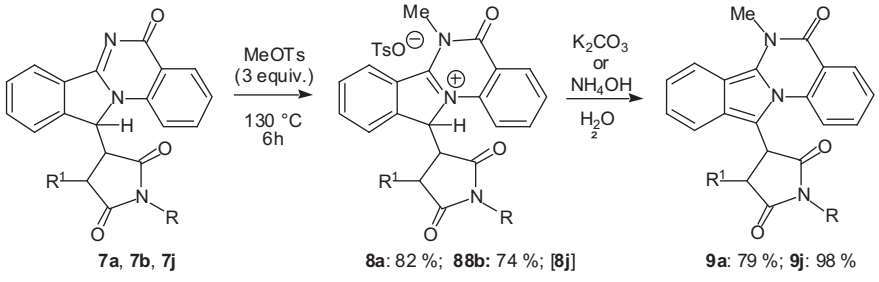


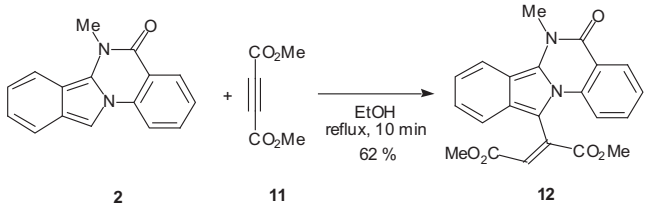
Figure 1. ORTEP view of the X-ray crystal structure of phthalimide **10** (Scheme 8), with 50% probability displacement ellipsoids for non-hydrogen atoms (R_1=4.26%). Selected bond lengths in Å: N(1)–C(8)=1.397(3); N(1)–C(1)=1.398(3); N(1)–C(9)=1.424(3); O(1)–C(1)=1.215(3); O(2)–C(8)=1.207(3); C(1)–C(2)=1.469(4); C(7)–C(8)=1.477(4); N(2)–C(15)=1.335(3); C(10)–C(15)=1.487(4); O(3)–C(15)=1.227(3). Selected bond angles in degrees: C(1)–N(1)–C(9)=124.4(2); C(8)–N(1)–C(9)=124.6(2); C(1)–N(1)–C(9)=124.4(2); O(1)–C(1)–N(1)=124.0(2); O(1)–C(1)–C(2)=129.7(2); N(1)–C(1)–C(2)=106.3(2); O(2)–C(8)–N(1)=124.0(2); O(2)–C(8)–C(7)=129.9(2); N(1)–C(8)–C(7)=106.1(2).



Scheme 7. N-Methylation/deprotonation of maleimide adducts of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one to the corresponding isoindoles.

1.4. *C*-nucleophilicity of 6-methylisoindolo[2,1-*a*] quinazoline-5-one 2

As shown in Section 1, the 'masked isoindole' **1** reacts as a C-nucleophile with activated electrophiles, such as nitro-aromatic aldehydes and maleimides to give primary adducts **4** or **7**, which may then undergo N-methylation (Scheme 7). Reverting the C-alkylation/N-methylation sequence,[11] the 'locked isoindole' **2** was found to react as a C-nucleophile with dimethyl acetylenedicarboxylate **11** (DMAD) to give the Michael adduct **12** in 62% yield (Scheme 9), instead of the possibly competing Diels–Alder cycloadduct.[20] The structure of **12** was assigned to the (*E*)-configuration by a 2D NMR NOESY experiment (Fig. 2).



Scheme 9. Reaction of 6-methylisoindolo[2,1-*a*]quinazoline-5-one with a strongly activated acetylenic electrophile.

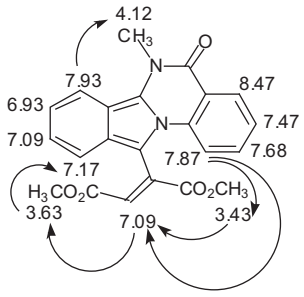
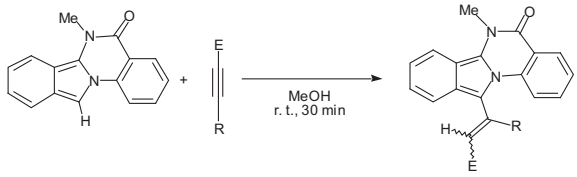


Figure 2. Chemical shifts and NOESY correlations (400 MHz, $CDCl_3$) of the *E* adduct **12** (Scheme 9).

Other acetylenic Michael acceptors were then investigated. Reaction of **2** with methyl propiolate **13a** thus afforded the isoindoloacrylate **14a** in 68% yield as a 1:1 mixture of *E* and *Z* isomers (Scheme 10).



Scheme 10. Reaction of 6-methylisoindolo[2,1-*a*]quinazoline-5-one with acetylenic Michael acceptors.

Beyond monocarbonylacetylenes,[21] dibenzoylacetylene **13b** is a diketonic alternative to the diester **11**,[22] which has been widely used as a C4 synthon for making the edges of *N*-oxy-[*N*]pericyclynes (*N*=5, 6).[23] Reaction of **13b** with **2** afforded the Michael adduct **14b** in 93% yield and 90:10 *E*/*Z* stereoselectively (according to ^1H NMR). The isoindolylenedione **14b** was also tested as Michael acceptor in the presence of a second equivalent of **2**, but no further reaction was observed.

The chromophores **14a** and **14b** exhibit an extended 'acceptor–donor–acceptor' conjugation path, which might induce particular optical properties, such as two-photon absorption ability.[24] The structure of (*E*)-**14b** was investigated in detail. In the absence of suitable X-ray diffraction data, the gas phase geometry of **14b** was calculated at the B3LYP/6-31G* level of theory.[25] This level of calculation indeed proved to be suitable for the structural and electronic description of indole analogues.[26] The calculated structure of the most stable conformer exhibits a *cisoid*/*cisoid* conformation of the O=C–C=C–C=O side chain (Fig. 3), but the *cisoid*/*transoid* and *transoid*/*transoid* conformations are found only 1.9 and 3.0 kcal/mol higher in energy, respectively. A mixture of these conformers is therefore expected in the experimental product. The isoindole core of **14b** is planar, but the quinazoline moiety is slightly distorted in order to minimize van der Waals repulsion between O-1 and H-1 while preserving residual π-conjugation between the isoindole system and the the C=O-2 bond (Fig. 3).

The near-frontier orbitals of **14b** (Fig. 4) highlight the donor ability of the isoindole core (HOMO), and the acceptor ability of both the α-ene-dione side chain (LUMO) and the quinazoline-5-one moiety (LUMO+1).

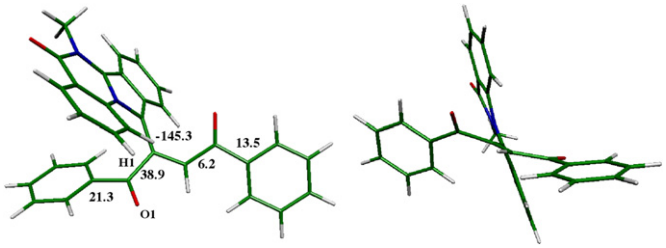


Figure 3. Front and side views of the most stable conformer of **14b** calculated at the B3LYP/6-31G** level. On the left view, torsion angles are given in degrees.

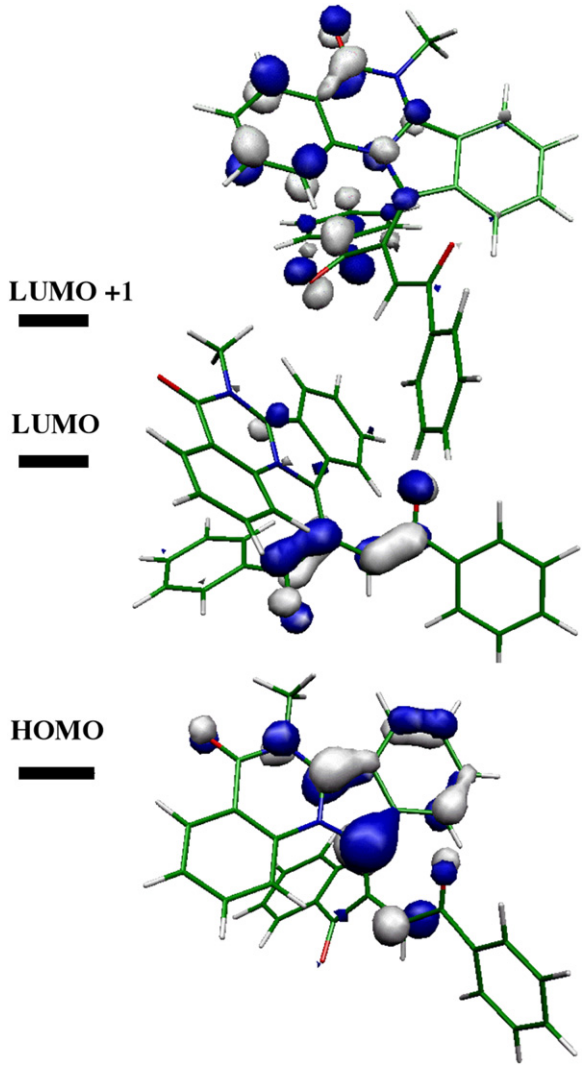


Figure 4. Frontier and near-frontier orbitals of the most stable conformer of **14b** calculated at the B3LYP/6-31G** level.

Efficient push–pull nonlinear optical chromophores containing indole cores have been reported recently.[27] Indole nuclei may are also encountered as side groups in chromophoric polymers.[28] In the isoindole series, the gas phase static quadratic hyperpolarizability β_0 of the various conformers of **14b** has been calculated using the sum-over-states method implemented in ZINDO.[29] The highest value is obtained for the most stable *cisoid*/*cisoid* conformer (Fig. 3), but it remains however quite low: β_0=14.2 10−30 esu units.

2. Summary and conclusion

The nucleophilic reactivity and selectivity of isoindolo[2,1-*a*]-quinazoline-5-ones **1** and **2** have been illustrated towards three kinds of substrates: nitro-aromatic aldehydes, maleimide derivatives, and acetylenic Michael acceptors. The main results can be summarized as follows.

(i) Condensation of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one with aromatic aldehydes takes place readily in acidic medium. Elimination products of aldol adduct were obtained stereoselectively.
(ii) Stereoselective Michael addition of 11*H*-isoindolo[2,1-*a*]quinazoline-5-one to ethylenic or acetylenic α,β-unsaturated amides, esters, and ketones takes place under either base- or acid-catalyzed conditions.
(iii) New stable α-substituted isoindoles were obtained from the Michael adducts.

These results pave the way to further studies of chemical reactivity, biological activity, and optical properties (in particular for fully conjugated chromophores **5c**, **14a**, **14b**). With the aim of preparing symmetrically bridged bisisoindoles from **1** and **2**, generalization of these results to dielectrophiles is the next challenge.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-200, Bruker-250 or Varian-400 instruments in specified deuterated solvents. NMR chemical shifts δ are in parts per million, with positive values to high frequency relative to the tetramethylsilane reference; coupling constants *J* are in hertz. IR spectra were recorded on a Pye Unicam SP3-300 spectrometer in $CHCl_3$ solution or in KBr pellets. IR absorptions frequencies ν are given in cm^{-1}. UV spectra were recorded on a Specord UV–vis instrument. UV–vis absorption wave lengths are given in nanometer. The mass spectra were recorded on a Nermag R10 spectrometer. The melting temperatures were determined on a Boetius instrument Monitoring of the reaction and checking of the purity of the obtained substances were achieved with the help of thin-layer cromatography (Silufol UV-254).

*3.1.1. 11H-Isoindolo[2,1-a]quinazoline-5-one (**1**).* It was obtained following the described procedure.[11,30] Mp=320–323 °C. IR (KBr), ν: 1645 (C=O), 1600 (C···N). ^{1}H NMR (100 MHz, DMSO-d_6), δ: 5.46 (2H,s, N–CH_2), 7.42–8.22 (8H, m, aromatic C*H*). Elemental analysis ($C_{15}H_{10}N_2O$), found: % N 11.79 (calcd: % N 11.96).

*3.1.2. 11-Hydroxy(4-nitrophenyl)methyl-5,11-dihydroisoindolo[2,1-a]-quinazolin-5-one (**4a**).* In a round-bottom flask equipped with a backflow condenser, 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** (2.5 g, 0.0107 mol.), *p*-nitrobenzaldehyde **3a** (1.62 g, 0.0107 mol.) and a catalytic amount of sodium acetate were dissolved in ice acetic acid (15 mL). The mixture was heated for 2 h at 90 °C. The mixture slowly turned to light yellow. The precipitate was filtered out, washed with small quantities of acetic acid and diethylether, and then dried in the air. Product **4a** was obtained as a white fine-grained substance (3.0 g, 73%).

Mp>300C. IR (KBr), ν: 3300–3000 (O–H), 1645 (C=O), 1600 (C···N), 1535 (NO_2 as.), 1350 (NO_2, s). ^{1}H NMR (DMSO-d_6), δ: 5.82 (1H, s, O*H*), 6.10 (1H, dd, $^3J_{HcOH}$=5.9 Hz, *Hc*), 6.31 (1H, d, $^3J_{HcHd}$=2.9 Hz, *Hd*), 6.35 (1H,d, $^3J_{H1H2}$=6.8 Hz, *H*1), 7.40 (1H, dd, $^3J_{H3H2}$=7.8 Hz, $^3J_{H3H4}$=7.8 Hz, *H*3), 7.52 (1H, dd, $^3J_{H7H8}$=7.8 Hz, $^3J_{H8H9}$=6.8 Hz, *H*8), 7.56 (1H, dd, $^3J_{H9H8}$=6.8 Hz, $^3J_{H9H10}$=7.8 Hz, *H*9), 7.85 (2H, d, $^3J_{H\text{-}o,H\text{-}m}$=8.8 Hz, *H*2′, *H*6′), 7.88 (1H, dd, $^3J_{H2H3}$=7.8 Hz, $^3J_{H1H2}$=6.8 Hz, *H*2), 7.99 (1H, d, $^3J_{H9H10}$=7.8 Hz, *H*10), 8.13 (1H, d, $^3J_{H7H8}$=7.8 Hz, *H*7), 8.20 (1H, d, $^3J_{H4H3}$=7.8 Hz, *H*4), 8.29 (2H, d, $^3J_{H\text{-}o,H\text{-}m}$=8.8 Hz, *H*3′, *H*5′). Elemental analysis ($C_{22}H_{15}N_3O_4$), found: % N 9.91 (calcd: % N 10.9).

*3.1.3. 11-Hydroxy(2-nitrophenyl)methyl-5,11-dihydroisoindolo[2,1-a]-quinazolin-5-one (**4b**).* In a round-bottom flask (50 ml) equipped with a backflow condenser, 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** (3.2 g, 0.0134 mol.), *o*-nitrobenzaldehyde **3b** (2.02 g, 0.0134 mol.) and a catalytic amount of sodium acetate were dissolved in ice acetic acid (15 mL). The mixture was heated at 90 °C for 2 h. The mixture slowly turned to light yellow. The precipitate was filtered out, washed with small quantities of acetic acid and diethylether, and then dried in the air. Product **4b** was obtained as a white fine-grained substance (3.9 g, 76%).

Mp=290–293 °C. IR (KBr), ν: 3500–3300 (O–H), 3300–3000 (O–H), 1650 (C=O), 1600 (C···N), 1530 (NO_2 as.), 1345 (NO_2 s.). ^{1}H NMR (DMSO-d_6), δ: 6.02–6.18 (3H, m, *Hc*,*Hd*,*H*1), 6.32 (1H, br s, O*H*), 7.33 (1H, dd, $^3J_{H3H4}$=7.8, Hz, $^3J_{H3H2}$=6.8 Hz, *H*3), 7.42–7.58 (3H, m, *H*2, *H*8, *H*9), 7.64–7.75 (2H, m, *H*4′,*H*6′), 7.88 (1H, dd, $^3J_{H5'H4'}$=7.8 Hz, $^3J_{H5'H6'}$=6.8 Hz, *H*5′), 7.99 (1H, d, $^3J_{H9H10}$=7.8 Hz, *H*10), 8.03 (1H, d, $^3J_{H7H8}$=7.8 Hz, *H*7), 8.20 (1H, d, $^3J_{H4H3}$=7.8 Hz, *H*4), 8.25 (1H, d, $^3J_{H3',H4'}$=7.8 Hz, *H*3′). Elemental analysis ($C_{22}H_{15}N_3O_4$), found: %N 11.34 (calcd: % N 10.9).

*3.1.4. 11-[(E)-1-(4-Dimethylaminophenyl)methylidene]-5,11-dihydroisoindolo[2,1-a]quinazolin-5-one (**5c**).* In a round-bottom flask (50 ml) equipped with a backflow condenser, 11*H*-isoindolo[2,1-*a*] quinazoline-5-one **1** (3.3 g, 0.014 mol) and *p*-*N*,*N*-dimethylaminobenzaldehyde (2.08 g, 0.014 mol) were dissolved in acetic anhydride (10 mL). This mixture is heated at reflux for 6 h. The reacting mixture became insensibly deep red. The sediment was filtered and washed out with small amounts of acetic acid, and then dried in the Fisher's pistol. The product was separated from the mixture by column chromatography on silica gel. The elution was carried out with a mixture of MeOH and $CHCl_3$ in a 1:16 ratio. The product **5c** was obtained as a white fine-grained substance (3.12 g, 58%).

Mp=255–258 °C. ^{1}H NMR ($CDCl_3$), δ: 3.09 (6H, s, $N(CH_3)_2$), 6.81 (2H, d, $^3J_{Ho-Hm}$=8.8 Hz, *H*3′, *H*5′), 7.39–7.52 (5H, m, *H*8, *H*9, *H*3, *H*2′, *H*6′), 7.65 (1H, s, *Holefin*), 7.73 (1H, dd, $^3J_{H1-H2}$=8.0 Hz, $^3J_{H2-H3}$=7.2 Hz, *H*2), 7.82 (1H, d, $^3J_{H9-H10}$=7,6 Hz, *H*10), 8.10 (1H, d, $^3J_{H7-H8}$=8.8 Hz, *H*7), 8,22 (1H, d, $^3J_{H4-H3}$=7.6 Hz, *H*4), 8,47 (1H, d, $^3J_{H1-H2}$=8.0 Hz, *H*1). Elemental analysis ($C_{24}H_{19}N_3O$), found: % N 9.48 (calcd: % N 10.96).

*3.1.5. 1-(4-Methylphenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-pyrrolidin-2,5-dione (**7a**) under acidic conditions.* In a round-bottom flask (50 ml) equipped with a backflow condenser, 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** (5.1 g, 0.022 mol) and *p*-*N*-methylphenylmaleimide (4.08 g, 0.022 mol) and catalytic amount of sodium acetate were dissolved in ice acetic acid (30 mL). The mixture was heated at reflux for 2 h, while it became insensibly light yellow. The precipitate was filtered and washed out with small amounts of acetic acid, then with diethylether, and then dried in the air. Product **7a** was obtained as a white fine-grained substance (7.8 g, 85%).

Mp=275–277 °C. IR (KBr), ν: 1765 and 1690 (C(O)NC(O)), 1660 (C=O), 1595 (C=N). ^{1}H NMR (DMSO-d_6), δ: 1.76 (1H, d, $^2J_{HaHb}$=18.1 Hz, *H*b), 2.40 (3H, s, CH_3), 2.68 (1H, dd, $^3J_{HaHc}$=9.3 Hz,

Ha), 4.77 (1H, m, $^3J_{HbHc}$=4.4 Hz, *Hc*), 6.12 (1H, d, $^3J_{HcHd}$=2.9 Hz, *Hd*), 7.10 (2H, d, $^3J_{H-oH-m}$=7.8 Hz, *Ho-tolyl*), 7.29 (2H, d, *Hm-tolyl*), 7.45 (1H, d, $^3J_{H1H2}$=7.8 Hz, *H1*), 7.56 (1H, t, $^3J_{H2H3}$=7.8 Hz, *H3*), 7.66–7.83 (3H, m, *H7*, *H8*, *H9*), 7.86 (1H, t, *H2*), 8.17 (1H, t, $^3J_{H9H10}$=7.8 Hz, *H10*), 8.26 (1H, d, $^3J_{H3H4}$=7.8 Hz, *H4*). Elemental analysis ($C_{26}H_{19}N_3O_3$), found: % N 9.78 (calcd: % N 9.97).

Similar procedures were used for the synthesis of the following products **7b**–**j**.

*3.1.6. 1-Benzyl-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-pyrrolidin-2,5-dione (**7b**).* Yield 75%. Mp=245–247 °C. IR (KBr), *ν*: 1770 and 1690 (C(O)NC(O)), 1665 (C=O), 1600 (C=N). ^{1}H NMR ($CDCl_3$, CD_3CN), *δ*: 1.43 (1H, dd, $^2J_{HaHb}$=18.4 Hz, $^3J_{HbHc}$=4.9 Hz, *Hb*), 2.26 (1H, dd, $^3J_{HaHc}$=9.3 Hz, *Ha*), 4.07 (1H, m, *Hc*), 4.57 (1H, d, $^2J_{HeHf}$=14 Hz, *CHeHf*), 4.69 (1H, d, *CHeHf*), 6.05 (1H, d, $^3J_{HcHd}$=3.8 Hz, *Hd*), 6.68 (1H, d, $^3J_{H10H9}$=7.7 Hz, *H10*), 7.10 (1H, dd, $^3J_{H2H3}$=7.7 Hz, $^3J_{H3H4}$=7.6 Hz, *H3*), 7.27–7.37 (5H, m, *Ph*), 7.40–7.50 (3H, m, *Harom*), 7.75 (1H, dd, $^3J_{H1H2}$=6.4 Hz, $^3J_{H3H2}$=7.7 Hz, *H2*), 8.10 (1H, d, $^3J_{H7H8}$=7.7 Hz, *H7*), 8.32 (1H, d, $^3J_{H3H4}$=7.6 Hz, *H4*). ^{13}C NMR ($CDCl_3$, CD_3CN), *δ*: 28.0 (CH_2C=O), 41.5 (*CH*C=O), 42.9 (NCH_2), 61.7 (*CH*N), 114.2, 122.6, 124.8, 126.3, 128.4, 128.8 (two signals), 129.4 (two signals), 129.7, 130.5, 133.6, 134.3 (*HCarom*), 116.6 (two signals), 135.2, 137.5, 138.9, 142.4 (*Carom*); 174.6, 175.8, 178.0 (*C*=O). Elemental analysis ($C_{26}H_{19}N_3O_3$), found: % N 10.14 (calcd: % N 9.97).

*3.1.7. 1-(4-Methoxyaphenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]-quinazolin-11-yl)-pyrrolidin-2,5-dione (**7c**).* Yield 82%. Mp>300 °C. ^{1}H NMR (DMSO-d_6), *δ*: 1.72 (1H, d, $^2J_{HaHb}$=18.0 Hz, *Hb*), 2.64 (1H, $^3J_{HaHc}$=8.8 Hz, *Ha*), 3.82 (3H, s, OCH_3), 4.77 (1H, m, *Hc*), 6.11 (1H, d, $^3J_{HcHd}$=2.9 Hz, *Hd*), 6.99 (2H, d, $^3J_{H-oH-m}$=7.8 Hz, *H3′*, *H5′*), 7.13 (2H, d, *H2′*, *H6′*), 7.44 (1H, d, $^3J_{H1H2}$=7.8 Hz, *H1*), 7.55 (1H, dd, $^3J_{H7H8}$=6.8 Hz, $^3J_{H8H9}$=7.8 Hz, *H8*), 7.67–7.80 (3H, m, *H3*, *H9*, *H10*), 7.85 (1H, dd, $^3J_{H1H2}$=7.8 Hz, $^3J_{H2H3}$=7.8 Hz, *H2*), 8.16 (1H, d, $^3J_{H7H8}$=6.8 Hz, *H7*), 8.26 (1H, d, $^3J_{H3H4}$=8.8 Hz, *H4*). Elemental analysis ($C_{26}H_{19}N_3O_4$), found: % N 10.1 (calcd: % N 9.6).

*3.1.8. 1-(4-Hexylphenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-pyrrolidin-2,5-dione (**7d**).* Yield 89%. Mp=283–284 °C. ^{1}H NMR (DMSO-d_6), *δ*: 0.93 (3H, s), 1.77–1.35 (9H, m, CH_2), 2.61 (1H, dd), 3.98 (2H, dd), 4.80 (1H, dd), 6.13 (1H, d, $^3J_{HH}$=5.6 Hz), 6.96 (2H, d, $^3J_{HH}$=8.8 Hz), 7.12 (2H, d, $^3J_{HH}$=8.8 Hz), 7.45 (1H, d, ^3J=6.8 Hz), 7.54 (1H, dd, $^3J_{HH}$=7.6 Hz, $^3J_{HH}$=6.8 Hz), 7.86–7.69 (4H, m), 8.17 (1H, d, $^3J_{HH}$=7.2 Hz), 8.27 (1H, d, $^3J_{HH}$=8.0 Hz). Elemental analysis ($C_{31}H_{29}N_3O_3$), found: % N 8.61 (calcd: % N 8.55).

*3.1.9. 1-Methyl-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-1-phenyl-pyrrolidin-2,5-dione (**7e**).* Yield 81%. Mp=265–266 °C. ^{1}H NMR (DMSO-d_6), *δ*: 1.50 (1H, d, $^2J_{HH}$=13.6 Hz), 2.50 (1H), 2.94 (3H, s), 4.66 (1H, s), 6.07 (1H, d, $^3J_{HH}$=3.6 Hz), 7.30 (1H, d, $^3J_{HH}$=4.4 Hz), 7.53 (1H, dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=7.1 Hz), 7.67 (2H, m), 7.75 (1H, d, $^3J_{HH}$=8.0 Hz), 7.83 (1H, dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=8.0 Hz), 8.15 (1H, d, $^3J_{HH}$=6.0 Hz), 8.25 (1H, d, $^3J_{HH}$=8.0 Hz). Elemental analysis ($C_{18}H_{15}N_3O_3$), found: % N 12.81 (calcd: % N 12.70).

*3.1.10. 1-(2,5-Dimethylphenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-pyrrolidin-2,5-dione (**7f**).* Yield 79%. Mp=278–279 °C. ^{1}H NMR (DMSO-d_6), *δ*: 1.85 (1H, d), 2.08 (3H, s), 2.34 (3H, s), 4.84 (1H, d), 6.13 (1H, d, $^3J_{HH}$=13.2 Hz), 7.14–7.19 (2H, m), 7.50–7.85 (8H, m), 8.09–8.28 (2H, m), 8.64 (1H, dd). Elemental analysis ($C_{26}H_{21}N_3O_3$), found: % N 9.71 (calcd: % N 9.65).

*3.1.11. 3-(5-Oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-1-phenyl-pyrrolidin-2,5-dione (**7g**).* Yield 74%. Mp >300 °C. ^{1}H NMR (DMSO-d_6), *δ*: 1.78 (1H, d, $^2J_{HH}$=18 Hz), 2.67 (1H, dd), 4.82 (1H, s), 6.14 (1H, s), 7.25 (2H, d, $^3J_{HH}$=7.2 Hz), 7.43–7.57 (5H, m.), 7.72–7.87 (4H, m.), 8.17 (1H, d, $^3J_{HH}$=7.6 Hz), 8.28 (1H, d, $^3J_{HH}$=7.6 Hz). Elemental analysis ($C_{19}H_{17}N_3O_3$), found: % N 10.28 (calcd: % N 10.31).

*3.1.12. 1-(2-Bromophenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]-quinazolin-11-yl)-pyrrolidin-2,5-dione (**7h**).* Yield 83%. Mp >300 °C. ^{1}H NMR (DMSO-d_6), *δ*: 1.80 (1H, s), 2.59 (1H, dd), 5.00 (1H, s), 6.21 (1H, d, $^3J_{HH}$=4 Hz), 7.43–7.85 (10H, m.), 8.15 (1H, d, $^3J_{HH}$=8.4 Hz), 8.27 (1H, d, $^3J_{HH}$=8 Hz). Elemental analysis ($C_{25}H_{16}N_3O_3Br$), found: %N 8.69 (calcd: % 8.64), found: % Br 16.41 (calcd: % Br 16.45).

*3.1.13. 1-(4-Nitrophenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-pyrrolidin-2,5-dione (**7i**).* Yield 85%. Mp >300 °C. ^{1}H NMR (DMSO-d_6), *δ*: 1.75 (1H, s), 2.74 (1H, dd), 4.85 (1H, dd), 6.14 (1H, d), 7.49 (1H, d, $^3J_{HH}$=7.2 Hz), 7.55 (1H, dd, $^3J_{HH}$=8.0, 6.8 Hz), 7.61 (2H, d, $^3J_{HH}$=9.2 Hz), 7.70–7.79 (3H, m.), 7.85 (1H, dd, $^3J_{HH}$=8.0 , 6.8 Hz), 8.17 (1H, d, $^3J_{HH}$=7.6 Hz), 8.27 (1H, d, $^3J_{HH}$=8.0 Hz), 8.36 (2H, d, $^3J_{HH}$=8.8 Hz). Elemental analysis ($C_{18}H_{16}N_4O_5$), found: % N 12.46 (calcd: % N 12.38).

*3.1.14. 3-Methyl-4-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-1-phenyl-pyrrolidin-2,5-dione (**7j**, major isomer).* In a round-bottom flask (50 ml) equipped with a backflow condenser, 11*H*-isoindolo[2,1-*a*]quinazoline-5-one **1** (2.5 g, 0.011 mol), *N*-phenylcitraconylimide (2.0 g, 0.011 mol) and a catalytic amount of sodium acetate were disolved in ice acetic acid (15 mL). The mixture was heated at reflux for 2 h, while it became insensibly light yellow. The precipitate was filtered and washed out with a small quantity of acetic acid, then with diethylether, and then dried in the air. Product **7j** was obtained as a white fine-grained substance (3.6 g, 80%). Mp=300–303 °C. IR (KBr), *ν*: 1775 and 1700 (C(O)NC(O)), 1670 (C=O), 1600 (C=N). ^{1}H NMR (DMSO-d_6), *δ*: 0.94 (3H, d, $^3J_{HbCH3}$=6.8 Hz, CH_3), 1.93 (1H, m, *Hb*), 4.60 (1H, dd, $^3J_{HbHc}$=4.9 Hz, *Hc*), 6.21 (1H, d, $^3J_{HcHd}$=2.9 Hz, *Hd*), 7.27 (2H, d, $^3J_{H-oH-m}$=7.8 Hz, *H2′*, *H6′*), 7.40–7.59 (5H, m, *H3′*, *H4′ H5′*, *H1*, *H3*), 7.68–7.82 (3H, m, *H8*, *H9*, *H10*), 7.86 (1H, dd, $^3J_{H1H2}$=7.8 Hz, $^3J_{H2H3}$=7.8 Hz, *H2*), 8.17 (1H, d, $^3J_{H7,H8}$=7.8 Hz, *H7*), 8.28 (1H, d, $^3J_{H3H4}$=7.8 Hz, *H4*). Elemental analysis ($C_{26}H_{19}N_3O_3$), found: % N 8.94 (calcd: % N 9.97).

*3.1.15. 3-Methyl-4-(5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-11-yl)-1-phenyl-pyrrolidin-2,5-dione (**7j** minor isomer).* The mother liquors of previous synthesis experiment were diluted by 10 mL of water. The formed precipitate was filtered and washed out with small amounts of acetic acid, then with diethylether, and then dried in the air. The product **7j** was obtained as a white fine-grained substance (0.5 g, 11%). Mp=274–276 °C. ^{1}H NMR (DMSO-d_6), *δ*: 1.04 (3H, d, $^3J_{HbCH3}$= 6.8 Hz, CH_3), 2.65 (1H, m, *Hb*), 3.90 (1H, d, $^3J_{HbHc}$=5.9 Hz, *Hc*), 6.09 (1H, s, *Hd*), 7.24 (2H, d, $^3J_{H-oH-m}$=7.8 Hz, *H2′*, *H6′*), 7.32–7.96 (9H, m, *Harom*), 8.11 (1H, d, $^3J_{H7H8}$=7.8 Hz, *H7*), 8.24 (1H, d, $^3J_{H3H4}$=7.8 Hz, *H4*). Elemental analysis ($C_{26}H_{19}N_3O_3$), found: % N 9.04 (calcd: % N 9.97).

Compounds **7a**–**c** and **7j** were also synthesized by the method using basic conditions (Scheme 5). All physical and spectral data for compounds obtained by the two different methods were identical. For example:

*3.1.16. 1-(4-Methylphenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-a]-quinazolin-11-yl)-pyrrolidin-2,5-dione (**7a**) under basic conditions.* 11*H*-Isoindolo[2,1-*a*]quinazoline-5-one **1** (3.3 g, 14 mmol), *N*-(4-methylphenyl)maleimide (2.64 g, 14 mmol) and *t*-BuONa (0.1 g, 1.04 mmol) were mixed in dry pyridine (20 mL). The mixture was stirred during 30 days at ambient temperature. The dark final mixture was filtered to give 4.3 g of a colorless fine-crystalline substance **7a**. Spectroscopical data were identical to those of **7a** obtained from **1** using acidic conditions (see above).

3.1.17. 6-Methyl-11-[1-(4-methylphenyl)-2,5-dioxotetrahydro-1H-3-pyrrolyl]-5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-6-ium 4-methyl-

*1-benzenesulfonate (**8a**).* In a round-bottom flask (50 mL) were placed 4.0 g of 1-(4-methylphenyl)-3-(5-oxo-5,11-dihydroisoindolo[2,1-*a*]quinazoline-11-yl)-pyrrolidin-2,5-dione **7a** (0.00949 mol) and 5.3 g of methyl tosylate (0.0285 mol). The mixture was thoroughly shuffled and heated at 125–130 °C over 6 h. The reacting mixture was fusing and darkening, while the mass did not solidify. The mixture was finally quenched and rubbed over with diethylether until a spongiform mass was formed. Product **8a** was obtained as a white fine-grained substance (4.7 g, 82%). Mp=220–223 °C. IR (KBr), *ν*: 1770 and 1695 (C(O)NC(O)), 1740–1580 (C=O and C=N). ^{1}H NMR (DMSO-d_6), *δ*: 1.77 (1H, d, $^2J_{HaHb}$=17.6 Hz, *Ha*), 2.34 (3H, s, *C*–CH_3), 2.40 (3H, s, *C*–CH_3), 2.67 (1H, dd, $^3J_{HbHc}$=8.8 Hz, *Hb*), 4.53 (3H, s, *N*–CH_3), 4.78 (1H, m, $^3J_{HaHc}$=3.9 Hz, *Hc*), 6.12 (1H, sh.s, *Hd*), 7.00–8.00 (14H, m, *Harom*), 8.18 (1H, d, $^3J_{H9H10}$=6.8 Hz, *H*10), 8.27 (1H, d, $^3J_{H3H4}$=7.8 Hz, *H*4). Elemental analysis ($C_{34}H_{29}N_3O_6S$), found: % N 7.02 (calcd: % N 6.91).

*3.1.18. 11-(1-Benzyl-2,5-dioxotetrahydro-1H-3-pyrrolyl)-6-methyl-5-oxo-5,11-dihydroisoindolo[2,1-a]quinazolin-6-ium 4-methyl-1-benzenesulfonate (**8b**).* In a ground-bottom flask (50 mL) were placed 3.0 g (0.00712 mol) of 1-benzyl-3-(5-oxo-5,11-dihydroisoindolo[2,1-*a*]quinazoline-11-yl)-pyrrolidin-2,5-dione **7b** and 4.0 g (0.0214 mol) of methyl tosylate. The mixture was thoroughly shuffled and heated at 125–130 °C over 3 h. The reacting mixture was fusing and solidified, and was quenched and rubbed over with diethylether. Product **8b** was obtained as a white fine-grained substance (3.2 g, 74%). Mp=238–240 °C. IR (KBr), *ν*: 1765 and 1700 (C(O)NC(O)), 1680 (C=O), 1600 (C=N). ^{1}H NMR (DMSO-d_6), *δ*: 2.28 (3H, s, *C*–CH_3), 3,30 (1H, dd, $^2J_{HaHb}$=19.1 Hz, $^3J_{HaHc}$=9.6 Hz, *Ha*), 3.46 (1H, dd, $^3J_{HbHc}$=4.4 Hz, *Hb*), 4.18 (3H, s, *N*–CH_3), 4.10–4.20 (2H, m, CH_2Ph), 4.56 (1H, m, *Hc*), 6.56 (1H, d, $^3J_{HdHc}$=1.7 Hz, *Hd*), 6.40–6.85 (15H, m, *Harom*), 8.48 (1H, d, $^3J_{H7H8}$=7.9 Hz, *H*7), 8.63 (1H, d, $^3J_{H3H4}$=7.8 Hz, *H*4). ^{13}C NMR (DMSO-d_6), *δ*: 20.7 (*C*–CH_3), 30.9 (CH_2–*C*=*O*), 32.5 (*CH*–*C*=*O*), 41.1 (*N*–CH_3), 41.7 (*N*–CH_2), 64.4 (*N*–*CH*); 117.0, 127.3, 134.9, 135.5, 137.5, 142.5, 157.7, 158.6 (*Carom*); 118.5, 123.6, 125.4 (2), 126.8 (2), 127.9 (2), 128.2 (2), 137.3, 135.9, 131.1, 129.6, 128.8, 128.5, 127.1(*HCarom*); 174.7 (*C*=O), 174.9 (*C*=O), 175.1 (*C*=O). MS (FAB, DMSO): 436 ([M–TsO]$^+$, 100%), 248 ([M–TsO–{CHC(O)}$_2$NCH$_2$Ph]$^+$, 25%). Elemental analysis ($C_{34}H_{29}N_3O_6S$), found: % N 7.12 (calcd: % N 6.91).

*3.1.19. 3-(6-Methyl-5-oxo-5,6-dihydroisoindolo[2,1-a]quinazoline-11-yl)-1-(4-methylphenyl)-2,5-pyrrolidinedione (**9a**).* In a flask (50 ml), 4.0 g (0.00658 mol) of 6-methyl-11-[1-(4-methylphenyl)-2,5-dioxotetrahydro-1*H*-3-pyrrolyl]-5-oxo-5,11-dihydroisoindolo[2,1-*a*]quinazoline-6-ium tosylate **8a** was dissolved in hot water (20 mL). The solution was added under vigorous stirring to a concentrated aqueous solution (20 mL) of potassium carbonate (1.5 g, 0.011 mol). The resulting red precipitate was extracted with chloroform, and the organic layer was separated and evaporated to dryness. The residue was recrystallizated from dry chloroform to give **9a** as a white fine-grained substance (2.3 g, 79%). Mp=182–183 °C.

MS (DCI, NH_3) *m*/*z*: 469 ([M+2NH_3]$^+$, 12%), 452 ([M+NH_3]$^+$, 46.5%), 436 (MH$^+$, 100%), 249 ([MH–{CHC(O)}$_2$NC$_6$H$_4$CH$_3$]$^+$, 8%). ^{1}H NMR (DMSO-d_6),: 2.37 (3H, s, *C*–CH_3), 3.01 (1H, dd, $^2J_{HaHb}$=17.2 Hz, $^3J_{HaHc}$=6.1 Hz, *Ha*), 3.29 (1H, dd, $^3J_{HbHc}$=9.3 Hz, *Hb*), 4.24 (3H, s, NCH_3), 5.30 (1H, dd, *Hc*), 6.86 (1H, dd, $^3J_{H3H4}$=8.8 Hz, $^3J_{H3H2}$=6.4 Hz, *H*3), 7.10 (1H, dd, $^3J_{H2H1}$=9.1 Hz, *H*2), 7.28 (2H, d, $^3J_{H-oH-m}$=7.8 Hz, *Ho-tolyl*), 7.36 (2H, d, *Hm-tolyl*), 7.66 (1H, d, *H*1), 7.77–7.90 (3H, m, *H*7, *H*8, *H*9), 8.10 (1H, d, $^3J_{H9H10}$=8.7 Hz, *H*10), 8.31 (1H, d, *H*4). Elemental analysis ($C_{27}H_{21}N_3O_3$), found: % N 9.48 (calcd: % N 9.65).

*3.1.20. 3-Methyl-4-(6-methyl-5-oxo-5,6-dihydroisoindolo[2,1-a]quinazolin-11-yl)-1-phenyl-2,5-pyrrolidine (**9j**).* In a flask (50 mL), 6-methyl-11-[3-methyl-2,5-dioxo-1-phenyltetrahydro-1*H*-3-pyrrolyl]-5-oxo-5,11-dihydroisoindolo[2,1-*a*]quinazoline-6-ium 4-methyl-1-benzenesulfonate **8j** (2.0 g, 0.00329 mol) was dissolved in hot water (15 mL). The solution was added to a concentrated aqueous solution (10 mL) of ammonia under vigorous stirring. The resulting red precipitate was filtered and washed with small amounts of ethanol to give **9j** as a white fine-grained substance (1.96 g, 98%). Mp=193–195 °C. ^{1}H NMR ($CDCl_3$), *δ*: 1.52 (3H, d, $^3J_{HbCH3}$=7.8 Hz, C–CH_3), 3.33 (1H, m, *Hb*), 4.20 (3H, s, NCH_3), 4.46 (1H, d, $^3J_{HbHc}$=6.8 Hz, *Hc*), 6.87 (1H, dd, $^3J_{H3H4}$=7.8 Hz, $^3J_{H3H2}$=8.8 Hz, *H*3), 7.10 (1H, dd, $^3J_{H2H3}$=8.8 Hz, $^3J_{H2H1}$=7.8 Hz, *H*2), 7.24 (1H, d, $^3J_{H1H2}$=7.8 Hz, *H*1), 7.38–7.45 (2H, m, *H*9, *H*7), 7.49–7.59 (5H, m, C_6H_5), 7.76 (1H, dd, $^3J_{H7H8}$=7.8 Hz, $^3J_{H8H9}$=7.8 Hz, *H*8), 7.91 (1H, d, $^3J_{H9H10}$=8.8 Hz, *H*10), 8.42 (1H, d, $^3J_{H3H4}$=7.8 Hz, *H*4). Elemental analysis ($C_{27}H_{21}N_3O_3$), found: % N 9.71 (calcd: % N 9.65).

*3.1.21. (E)-2-(6-Methyl-5-oxo-5,6-dihydroisoindolo[2,1-a]quinazolin-11-yl)-2-butendioate (**12**).* Dimethyl acetylenedicarboxylate **11** (0.359 mL, 2.9 mmol) was added dropwise to a suspension of 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazoline-5-one **2** (0.725 g, 2.9 mmol) in EtOH (20 mL). The dark red reaction mixture was then refluxed for 10 min, and the formed solid was filtered out to give the *E* isomer of isoindole **12** as red crystals (0.71 g, 62%). Mp=192–194 °C. IR (KBr), *ν*: 1715 (C=O, CO_2Me), 1660 (C=O, C(O)N), 1250 (C–O, as), 1160 (C–O, s). UV–vis (EtOH, *c*=1.5 10−5 M), *λ* (log *ϵ*): 230.5 (4.63), 252.0 (4.58), 297.5 (3.98), 404.5 (3.74), 507.5 (3.77). MS (DCI, NH_3) *m*/*z* (%): 408 (0.803, [MNH$_4$]$^+$), 396 (0.665), 395 (3.034), 394 (5.629), 393 (26.081), 392 (28.410), 391 (100, MH$^+$), 390 (14.050), 389 (1.064), 335 (0.815), 334 (0.541), 333 (1.338), 332 (0.949), 331 (1.906), 330 (1.550), 272 (0.973), 249 (1.373), 110 (0.655). ^{1}H NMR (400 MHz, $CDCl_3$), *δ*: 3.43 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 4.12 (3H, s, NCH_3), 6.93 (1H, dd, $^3J_{H8H7}$=8.95 Hz, $^3J_{H8H9}$=6.39 Hz, *H*8), 7.09 (1H, dd, $^3J_{H9H10}$=8.81 Hz, *H*9), 7.09 (1H, s), 7.17 (1H, d, *H*10), 7.47 (1H, dd, $^3J_{H3H4}$=7.92 Hz, $^3J_{H3H2}$=8.03 Hz, *H*3), 7.68 (1H, dd, $^3J_{H1H2}$=8.19 Hz, *H*2), 7.87 (1H, d, *H*1), 7.93 (1H, d, *H*7), 8.47 (1H, d, $^4J_{H4H2}$=1.55 Hz, *H*4). ^{13}C NMR ($CDCl_3$), *δ*: 32.12 (NCH_3), 52.15, 53.04 (OCH_3), 97.70, 100.88, 109.56, 118.14, 127.71, 135.03 (Carom+Colefin); 117.70, 118.33, 120.78, 121.28, 124.73, 125.49, 125.99, 129.60, 133.96 (HCarom+HColefin); 137.43 (N–*C*=N), 158.14 (*C*(O)N), 165.83, 166.86 (*C*O$_2$Me). Elemental analysis ($C_{22}H_{18}N_2O_5$), found: % N 7.33 (calcd: % N 7.18).

*3.1.22. Methyl-3-(6-methyl-5-oxo-5,6-dihydroisoindolo[2,1-a]quinazolin-11-yl)-acrylate (**14a**).* Methyl propiolate **13a** (0.34 mL, 0.34 g, 4.03 mmol) was added at room temperature to a solution of 6-methylisoindolo[2,1-*a*]]quinazoline-5-one **2** (1.00 g, 4.03 mmol.) in methanol (5 mL). After stirring for 30 min, a red-orange precipitate was filtered and dried under vacuum. Isoindole **14a** was obtained as a reddish solid (1.28 g, 96%). After heating in methanol, recrystallization afforded pure (thermodynamic) *E*-isomer (85%).

IR (mixture of isomers, $CHCl_3$), 3621 (sharp), 3462 (br) (H_2O), 3018, 2976 (sp^2-C–H), 2926, 2896 (sp^3-C–H), 1711 (OC=O), 1669, 1602 (C···N), 1546, 1486, 1446, 1389 (C=C), 1223, 1046. MS (DCI/NH_3): 433 (100%, [MH]$^+$). UV–vis ($CHCl_3$, *c*=1.5 10−5 M), *λ* (absorbance): 299.0 (0.27), 309.8 (0.27), 372.6 (0.12), 562.4 (0.22). ^{1}H NMR (*E* isomer, 250 MHz, $CDCl_3$), *δ*: 3.83 (3H, s, OCH_3), 4.08 (3H, s, NCH_3), 6.27 (1H, d, $^3J_{HH}$=15.4 Hz; MeO_2C–C*H*), 7.02 (1H, dd, $^3J_{HH}$=7.7 Hz, $^4J_{HH}$=1.6 Hz), 7.24 (1H, pseudo t, $^3J_{HH}$=8.9 Hz), 7.55 (1H, pseudo t, $^3J_{HH}$=7.6 Hz), 7.79–7.85 (2H, m), 7.95 (1H, d, $^3J_{HH}$=8.8 Hz), 8.10 (1H, d, $^3J_{HH}$=8.5 Hz), 8.21 (1H, d, $^3J_{HH}$=15.4 Hz; MeO_2CC=C*H*), 8.47 (1H, dd, $^3J_{HH}$=7.8, 1.1 Hz). Few ^{1}H NMR data for the *Z* isomer could be deduced from selective irradiations in the spectrum of the mixture *δ*: 3.63 (3H, s, OCH_3), 4.11 (3H, s, NCH_3), 5.97 (1H, d, $^3J_{HH}$=11.5 Hz; MeO_2C–C*H*), 7.32 (1H, d, $^3J_{HH}$=11 Hz; MeO_2CC=C*H*), other signals overlap with those of the *E* isomer. ^{13}C NMR (62.9 MHz, $CDCl_3$), *δ*: 32.0 (NCH_3), 51.4 (OCH_3), 109.3 (*C*H), 110.4, 111.3, 118.6, 118.9 (*C*H), 119.7 (*C*H), 120.9 (*C*H), 121.8 (*C*H), 126.3 (*C*H), 126.7 (*C*H), 127.9, 128.7, 129.4 (*C*H), 133.6 (*C*H), 134.2 (*C*H), 136.5, 157.9 (NC=O), 168.6 (OC=O) (*C*H assignments on the basis of relative intensities). Elemental analysis for **14a**·2H_2O ($C_{20}H_{20}N_2O_3$), found: % C 68.6, % H 4.1, % N 8.06 (calcd: % C 68.2, % H 5.7, % N 7.95).

*3.1.23. 1,4-Diphenyl-2-(6-methyl-5-oxo-5,6-dihydroisoindolo[2,1-a] quinazolin-11-yl)-but-2-en-1,4-dione (**14b**).* A solution of dibenzoylacetylene **13b** (0.94 g, 4.03 mmol) in methanol (4 mL) was added at room temperature to a solution of 6-methylisoindolo[2,1-*a*]]quinazoline-5-one **2** (1.00 g, 4.03 mmol) in methanol (5 mL). A dark-blue precipitate formed immediately and was filtered out after 30 min, washed with methanol and dried under vacuum. Isoindole **14b** was obtained as a purple solid consisting in a mixture of *Z* and *E* isomers (1.81 g, 93%).

IR ($CHCl_3$), *ν*: 3621 (sharp), 3463 (br) (H_2O), 3018, 2976 (sp^2-C–H), 2926, 2896 (sp^3-C–H), 1661 (br, C=O), 1620, 1602 (C···N), 1500, 14,861, 460, 1448, 1390 (C=C), 1238, 1046. MS (DCI/NH_3): 483 (100%, $[MH]^+$). UV–vis ($CHCl_3$, *c*=6.2 10−5 M), *λ* (absorbance): 404.4 (0.30), 549.8 (0.55). ^1H NMR (250 MHz, $CDCl_3$), *δ*: 1.62 (broad, H_2O), 4.10 (pseudo s, 3H, NCH_3), 6.95–7.01 (1H, pseudo dt), 7.07–7.11 (1H, pseudo dt), 7.25 (1H, pseudo s), 7.28–7.32 (2H, pseudo d), 7.36–7.39 (2H, pseudo d), 7.41–7.50 (4H, pseudo dd), 7.67–7.71 (1H, pseudo dt), 7.78–7.86 (4H, pseudo t), 7.92–7.96 (1H, pseudo d), 8.36–8.40 (1H, pseudo dd), 8.44–8.47 (1H, d) (19 differentiated sp^2-C*H* signals were found, as expected for one of the isomers). ^{13}C NMR (62.9 MHz, $CDCl_3$), *δ* (major signals): 32.3 (NCH_3), 119.2, 119.9, 121.5, 121.6, 122.4, 127.0, 128.0, 129.5, 132.8, 133.1, 134.0 (11 *C*H signals of similar intensities, as expected for one of the isomers), 128.4, 128.5, 128.7, 128.8 (4 (*CH*)$_2$ signals of similar intensities, as expected for one of the isomers), 159.5 (NC=O), 188.1 (PhC=O), 196.3 (*PhC*=O). Other minor signals (in particular at: 32.2, 111.5, 112.0, 132.0, 136.3, 136.9 and 145.5 ppm) were observed (but it could not be determined whether they correspond to quaternary carbons of the major isomer or to *C*H carbons of the minor one). Elemental analysis for **14b**·0.6H_2O ($C_{32}H_{23}\cdot 2N_2O_{3.6}$), found: %C 80.3, % H 4.11, % N 5.86 (calcd: % C 80.5, % H 4.87, % N 5.87).

3.2. Crystallographic and structural parameters for 10 (Fig. 1)

X-ray crystallographic structure determination. Data were collected on a Stoe Imaging Plate Diffraction System (IPDS), equiped with an Oxford Cryosystems Cryostream Cooler Device, and using graphite-monochromated Mo K*α* radiation. The final unit cell parameters were obtained by means of a least-squares refinement of a set of well-measured reflections, and crystal decay was monitored during data collection; no significant fluctuations in intensity were observed The structures were solved by Direct Methods using the program SIR92,[31] and refined by least-squares procedures on F^2 with SHELXL-97.[32] All hydrogen atoms were located on a difference Fourier map, but introduced and refined by using a riding model. All non-hydrogen atoms were anisotropically refined.

Crystal data and structure refinement.

Empirical formula	$C_{16}H_{12}N_2O_3$
Formula weight	280.28
Temperature	180(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, *P b c a*
Unit cell dimensions	*a*=12.829(3) Å, *b*=7.5405(15) Å, *c*=27.710(6) Å
Volume	2680.6(9) Å^3
Z, calculated density	8, 1.389 mg m^{-3}
Absorption coefficient	0.098 mm^{-1}
F(000)	1168
Theta range for data collection	(2.16–23.26) ø
Index ranges	$-30\le l\le 30$, $-14\le h\le 14$, $-8\le k\le 8$
Reflections collected/unique	18,173/18,173/1,925 [*R*(int)=0.0539]
Completeness to 2*θ*=46.52	99.9%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1925/0/196
Goodness-of-fit on F^2	1.032
Final *R* indices [$I>2\sigma(I)$]	R_1=0.0426, wR_2=0.1065
R indices (all data)	R_1=0.0662, wR_2=0.1202
Extinction coefficient	0.0024(12)
Largest diff. peak and hole	(0.146 and −0.124) e A^{-3}

Acknowledgements

R.C., S.K. and C.L. thank the Centre National de la Recherche Scientifique (CNRS) for providing working expedients and the Research Associate fellowship of S.K. The authors also thank the Paul Sabatier University for the support of the Kiev-Toulouse collaboration, and CALMIP (Calcul intensif en Midi-Pyrénées, Toulouse, France) for computing facilities.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.08.013.

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14. For **7f** bearing a very bulky *o*-xylyl *N*-substituent, the $^3J_{HcHd}$ coupling constant is much higher (13.2 Hz) in comparison to **7a**–**e**, **7g**–**i**. It is however difficult to determine whether this extreme value is due to a change in stereochemistry or to a change in conformation (especially in the angle between the planes of the isoindole and pyrrolidin-2,5-dione rings).
15. It remains however possible that both diastereomers of **7j** may possess the same *cis* configuration with respect to the pyrrolidin-1,5-dione ring, as suggested by the similarity of the weak $^3J_{HbHc}$ coupling constants of 4.9 Hz and 5.9 Hz in the major and minor stereoisomers, respectively. In the non-substituted series **7a**–**i**, the $^3J_{HbHc}$ values for the *cis* vicinal protons are indeed generally close to 5 Hz, while the $^3J_{HaHc}$ values for the trans vicinal protons are close to 9 Hz.
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21. Another monocarbonyl acetylene substrate, *p*-NO_2-C_6H_4–C(O)–C≡C–$SiMe_3$ (**13c**), was tested. Since trimethylsilylpropynal is known to undergo nucleophilic attack at the carbonyl center exclusively, the case of **13c** in the presence of the soft isoindole **2** deserved examination. To solution of **2** (1.00 g, 4.03 mmol) in methanol (5 mL), a solution of **13c** (1.00 g, 4.03 mmol) in methanol (4 mL) was thus added at room temperature. A violet-blue precipitate formed immediately, which was filtered out, washed with methanol, and dried under vacuum. The purple product (1.75 g, 86%) was submitted to MS analysis, showing that it corresponds to the stoichiometric addition **2**+**13c** ($C_{28}H_{25}N_4O_4Si$=495). The exact structure of the product could not be determined, but the absence of carbonyl absorption in the IR spectrum shows that

the C=O group has indeed been attacked. Crude spectroscopic data are listed below. MS (DCI/NH_3): 496 (100%, $[MH]^+$), 514 (12%, $[MNH_4]^+$). IR ($CHCl_3$): 3621 (sharp), 3463 (br), 3022 (br), 1521 (br), 1479, 1425, 1215, 1207 (br). UV–vis ($CHCl_3$, c=3.5 10^{-2} M), λ (absorbance): 371.4 (0.65), 565.3 (1.06). ^{1}H NMR (250 MHz, $CDCl_3$), δ (the broadness of the signals are possibly due to intermolecular $\pi-\pi$ associations): 0.16 (9H, br; Si(CH_3)$_3$), 3.46 (3H, br, NCH_3), 4.15–4.25 (0.8H, br), 5.59 (1H, br), 7.96–8.33 (16H, br m; sp^2-*CH*). ^{13}C NMR (62.9 MHz, $CDCl_3$), δ: 0.9 (Si(CH_3)$_3$), 33.0 (NCH_3), 70.0, 91.0, 928, 93.4 (*CH*), 120.9, 122.5, 123.9 (*p*-nitrophenyl *m*- or *o*-(*C*H)$_2$), 126.1 (*p*-nitrophenyl *o*- or *m*-(*C*H)$_2$), 126.9 (*C*H), 127.3 (*C*H), 127.8 (*C*H), 128.5 (*C*H), 129.2 (*C*H), 130.0 (*C*H), 132.4 (*C*H), 134.5 (*C*H), 137.6, 143.0, 147.6, 148.0, 158.0, 162.6 (tentative assignment is based on the shift range and relative intensity, but weak signals can correspond to either quaternary carbons of the main product or to *C*H signals of a minor component).

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