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Formation of New 5,11b-Bridged Isoindolo[2,1-*b*]isoquinolinones Alkaloids through a Tandem Pummerer/π-Cationic Cyclization

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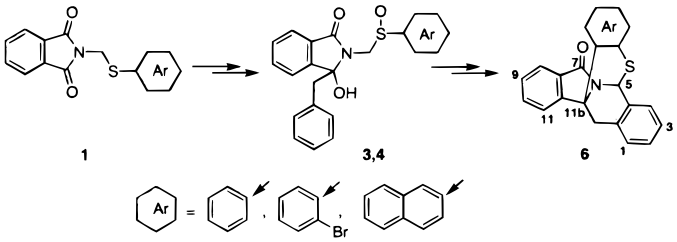
ABSTRACT



The tandem Pummerer/π-aromatic cyclization of α-acyliminium ion, leading efficiently in "one pot" to thioepoxyareno-bridged isoindoloisoquinolinone incorporating the arylthio group, has been demonstrated for the first time. During this sequence the angular hydroxylated isoindoloisoquinolinone, resulting from the Pummerer-type cyclization, was also obtained.

The Pummerer reaction initiated by several types of thionium ions has been proven to be a powerful synthetic tool for the preparation of α-substituted sulfides.[1]

When thionium ions are intramolecularly intercepted, this process becomes a versatile methodology to obtain polycyclic (or heterocyclic) systems such as **A**.[1,2] Structures such as **C**,[3] which include the heteronucleophile in the formed thiacycles, have been little explored.[4]

Tandem processes involving the Pummerer reaction and lactonization, Diels−Alder cycloaddition, 1,3-dipolar cycloaddition, *N*-acyliminium ion cyclization, or Mannich cyclization have been recently developed, by the Padwa group[5−13] and others,[14,15] for the construction of various complex polyheterocyclic ring systems. Prominent targets

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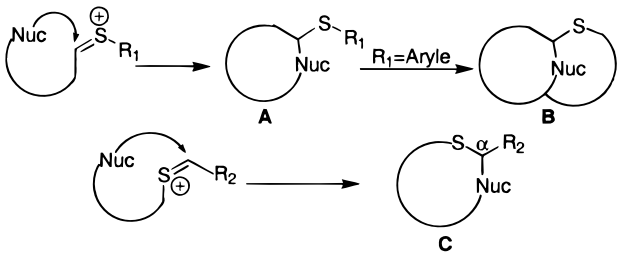
of these structures were exemplified by isodrimerin,[14] (±)-confertifolin,[15] sulfanyl-substituted naphthalenes,[6−8] taiwanin C,[7] justicidin E,[7] indeno[4,5-*b*]thiophenes,[8] furo[3,4-*b*]indoles,[9] thienopyridones,[10] and 3,4-benzoerythrinane alkaloid.[11] In all cases the thioalkyl (or aryl) group, which induced the sulfonium ion, was present in the final structure in an exocyclic position[7,10,11,14,15] or eliminated in an ultimate step.[6,8−10]

In view of our interest in the formation−cleavage of the thioether linkage in *N*,*S*-fused polyheterocyclic systems,[16] we describe herein an interesting short pathway, using a tandem Pummerer/*N*-acyliminium ion cyclization, to bridged isoindoloisoquinolinone alkaloids such as **B** (Scheme 1). In

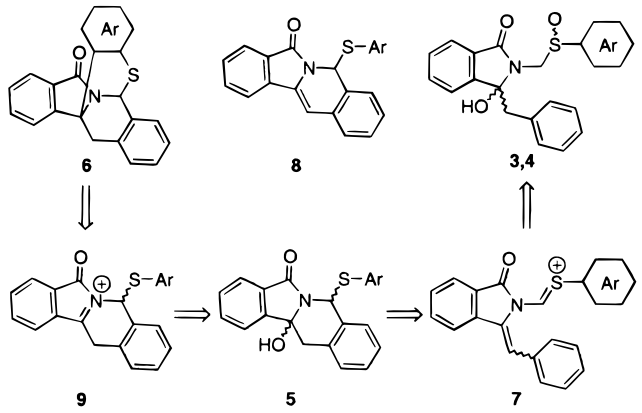
Scheme 1



this methodology, the phenylthio group as a sulfonium ion precursor, was incorporated in the thiazacyclic bridge.

As depicted in Scheme 2, our strategy envisioned the synthesis of intermediate thionium ion **7** in order to obtain

Scheme 2



Retrosynthetic sequence leading to bridged isoindoloisoquinolinone **6**.

the *N*-acyliminium ion precursor **5**. These latter compounds should be accessible from sulfide imide **1** (Scheme 3).

Indeed, taking into account that thionium-enamide ion **7**, derived from a Pummerer and dehydration reactions of sulfoxides **3** and **4**, could provide the 5-(phenylthio) lactam **8** via π-aromatic cyclization, its *N*-acyliminium ion **9** could

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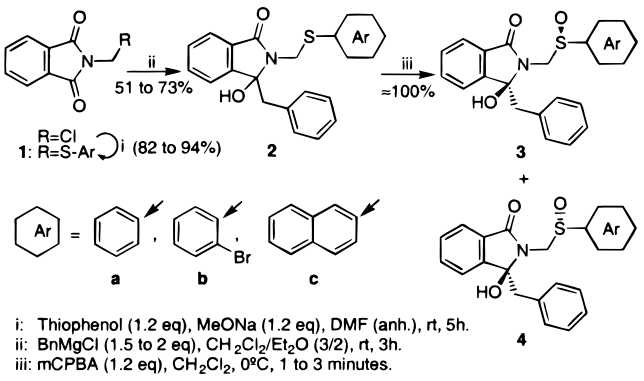
Scheme 3



lead, through an intramolecular α-amidoalkylation cyclization, to the highly condensed alkaloids derivatives **6**. Finally, subsequent hydration or hydration−deprotonation of, respectively, **8** or **9** should ultimately lead to the hydroxylated product **5**.

To establish the generality and versatility of the synthetic approach depicted in Scheme 2, the elaboration of different aromatic models, substituted by phenyl, bromophenyl, or naphthyl groups on the aromatic moiety, was explored.

The requisite sulfoxide **3**, **4** diastereomers were obtained in three steps successively by *S*-alkylation, Grignard carbophilic addition, and *S*-oxidation (Scheme 3). The alkylation reaction was carried out by condensation of *N*-chloromethylphthalimide with a slight excess of aryl mercaptan in an alkaline medium.[17] Treatment of the resulting *N*-alkylated phthalimides **1a**,**b**,**c** with benzylmagnesium chloride (1.5−2 equiv) at room temperature afforded the expected *ω*-benzyl-*ω*-carbinol lactams **2a**,**b**,**c** in 51%, 61%, and 73% yields, respectively.

To avoid the formation of sulfones during *m*-chloroperbenzoic acid (mCPBA) oxidation of sulfides **2**,[18] a short reaction time (1−3 min at 0 °C) was necessary. The ^{1}H, ^{13}C NMR, and GC-MS data for the crude sulfoxides showed a mixture of two diastereomers **3** and **4** in a variable ratio depending on the aryl group.[19,20]

Indeed, the methylene protons in N−CH_2−S and N−C(OH)−CH_2−Ar functionalities of the sulfoxides **3** and **4** appear as an AB system due to the diastereotopic effect with a coupling constant of J = 12.4−14.3 Hz for N−CH_2−S and J = 12.9−14.5 Hz for N−C(OH)−CH_2−Ar characteristic of *gem* protons (in the ^{1}H NMR spectra of sulfides **2**, the same facts were observed).[20] Furthermore, these protons were in general shifted to downfield compared to the parents sulfides **2**. This deshielding effect, notably in the functionality, was due to the proximity of the sulfoxide S→O group.

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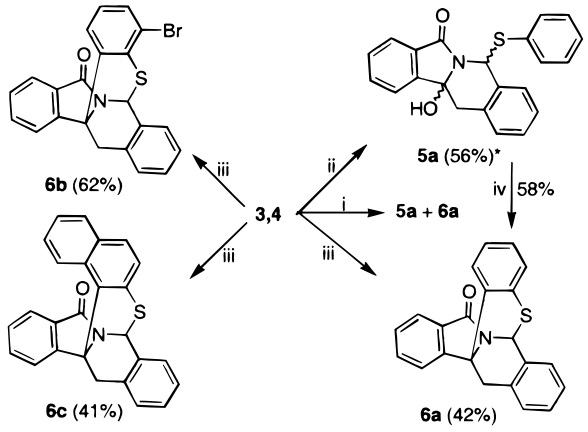
(18) Terauchi, H.; Tanitame, A.; Tada, K.; Nishikawa, Y. *Heterocycles* **1996**, *43*, 1719.

(19) ^{1}H NMR spectra of sulfoxides **3** and **4** have shown that sulfoxides **3a**/**4a** and **3b**/**4b** consist of 6.3:3.7 ratio while for **3c**/**4c**, it was of 5.9:4.1.

Another oxidation of **2a** derivative was performed at −20 °C; interestingly, the reaction occurred during 6 to 9 min, leading to **3a**/**4a** in a 7.5:2.5 ratio in favor of the major component obtained above. The diastereoselectivity observed during this process and the relative stereochemistry of these compounds **3a**/**4a**, which could not be separated chromatographically, are not yet elucidated.

In the first set of our Pummerer rearrangement experiments (Scheme 4), a mixture of sulfoxides **3a** and **4a** was subjected

Scheme 4



i: TFAA, CH_2Cl_2, rt, 12 h. ii: TFAA, pyridine, rt, 5 h. iii: TFAA, CH_2Cl_2, rt, 8 to 12 h then TFA, rt, 12 h. iv TFA neat, rt, 12 h.
* This product showd two diastereomers in 5.1:4.9 ratio and the relative % were determined by GC-MS

to trifluoroacetic anhydride (TFAA)[21] in CH_2Cl_2 at room temperature for 12 h. The ^{1}H NMR and GC-MS analysis of crude reaction products indicated the presence of three compounds **5a** + **6b** with **6b** as a major component (**5a** is a mixture of two diastereomers in 6.2:3.8 ratio).

The major product was isolated by FC, and its structure was established as **6a** by an array of mono- and bidimensional NMR experiments (homocorrelation ^{1}H−^{1}H and ^{13}C−^{13}C, heterocorrelation ^{1}H−^{13}C, DEPT). The structures of the inseparable diastereomers **5a** were deducted by their molecular ions at mass 359 and from the presence in their NMR spectrum of the altered alcohol proton after equilibration with deuterium oxide.

Interestingly, the thionium ion **7** as the Pummerer intermediate (Scheme 2)[22] is intercepted by a π-aromatic to give **5a** after an hydrolysis of **8** in equilibrium with **9** in an acidic medium. Diastereomers **5a**, in the presence of TFA,[23] are in facile equilibrium with ion **9** which was, in turn, capable of an intramolecular capture of a π-aromatic as an internal nucleophile.[17,24] Under this sequential set, the reaction produced polyheterocyclic system as **6a**.

Afterward we decided to study the effect of different reaction conditions on selectivity of the process. So, when we used more than 1 equiv of pyridine relative to the sulfoxides congeners **3** and **4** (i.e., TFAA, pyridine, rt, 5 h, Scheme 4),[25] the hydroxylated isoindoloisoquinolinone **5a** (56%) was isolated, as a mixture of two diastereomers in 5.1:4.9 ratio. The ^{1}H NMR spectrum of this mixture was identical to the one discussed above. This result indicated that the π-cyclization of *N*-acyliminium ion was interrupted due to the presence of pyridine as a TFA scavenger.

On the other hand, when the reaction was conducted under conditions **i** with addition of TFA, the reaction after 12 h at room temperature produced only the bridged tricycle **6a** (42% after recrystallization from ethanol).[26] In this case, the intermediate ω-carbinol lactam **5a** in acidic medium furnished, by intramolecular α-amidoalkylation cyclization, the expected product **6a**. This latter product was also obtained from isolated **5a** (i.e., TFA, rt, 12 h) in 58% yield.[27]

(20) General procedure for preparation of **3a**,**b**,**c** and **4a**,**b**,**c**: To a stirred solution of sulfides **2a**,**b**,**c** (1 mmol) in dry CH_2Cl_2 (10 mL) was added in one portion at 0 °C a solution of mCPBA (0.21 g, 1.2 mmol) in dry CH_2Cl_2 (5 mL). After 1−3 min of reaction, the mixture was alkalinized with a saturated solution of $NaHCO_3$ (15 mL). After a classical workup, the solid residue was recrystallized from ethanol to give quantitatively (1 mmol) the expected inseparable diastereosomers **3** and **4**. Selected data for major isomer of **3a**+**4a** (6.3:3.7): solid; EIMS *m*/*z* 377 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 3.22 (d, 1H, J = 13.7, CH_2Ar), 3.35 (d, 1H, J = 13.7, CH_2Ar), 4.14 (d, 1H, J = 12.4, NCH_2S), 5.00 (d, 1H, J = 12.4, NCH_2S), 5.75 (s, 1H, OH exchangeable with D_2O), 6.78−7.72 (m, 14H, arom H). Anal. Calcd For $C_{22}H_{19}NO_3S$ (377.46) (mixture): C, 70.00; H, 5.07; N, 3.71. Found: C, 69.89; H, 4.99; N, 3.69. Selected data for minor isomer of **3a**+**4a** (6.3:3.7): solid; EIMS *m*/*z* 377 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 3.22 (d, 1H, J = 14.3, CH_2Ar), 3.59 (d, 1H, J = 14.3, CH_2Ar), 4.76 (d, 1H, J = 13.7, NCH_2S), 5.23 (d, 1H, J = 13.7, NCH_2S), 6.40 (s, 1H, OH exchangeable with D_2O), 6.78−7.72 (m, 14H, H.-Aromatic). Selected data for major isomer of **3b**+**4b** (6.3: 3.7): solid; EIMS *m*/*z* 456 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 3.93 (d, 1H, J = 12.9, CH_2Ar), 4.02 (d, 1H, J = 12.4, NCH_2S), 4.11 (d, 1H, J = 12.4, NCH_2S), 4.79 (d, 1H, J = 12.9, CH_2Ar), 5.44 (s, 1H, OH exchangeable with D_2O), 6.93−7.74 (m, 13H, arom H). Anal. Calcd For $C_{22}H_{19}BrNO_3S$ (456.35) (mixture): C, 57.90; H, 3.98; N, 3.07. Found: C, 57.79; H, 3.77; N, 3.01. Selected data for minor isomer of **3b**+**4b** (6.3:3.7): solid; EIMS *m*/*z* 456 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 3.24 (d, 1H, J = 14.3, CH_2Ar), 3.62 (d, 1H, J = 14.3, CH_2Ar), 4.65 (d, 1H, J = 14.3, NCH_2S), 5.32 (d, 1H, J = 14.3, NCH_2S), 6.52 (s, 1H, OH exchangeable with D_2O), 6.93−7.74 (m, 13H, arom H). Selected data for major isomer of **3c**+**4c** (5.9:4.1): solid; EIMS *m*/*z* 427 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 4.24 (d, 1H, J = 14.0, CH_2Ar), 4.78 (d, 1H, J = 12.4, NCH_2S), 5.08 (d, 1H, J = 14.0, CH_2Ar), 5.35 (d, 1H, J = 12.4, NCH_2S), 6.27 (s, 1H, OH exchangeable with D_2O), 6.76−8.24 (m, 16H, arom H). Anal. Calcd For $C_{26}H_{21}NO_3S$ (427.52) (mixture): C, 73.04; H, 4.95; N, 3.27. Found: C, 73.00; H, 4.88; N, 3.12. Selected data for minor isomer of **3c**+**4c** (5.9:4.1): solid; EIMS *m*/*z* 427 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 3.23 (d, 1H, J = 14.0, CH_2Ar), 3.66 (d, 1H, J = 14.0, CH_2Ar), 4.71 (d, 1H, J = 14.5, NCH_2S), 5.45 (d, 1H, J = 14.5, NCH_2S), 5.80 (s, 1H, OH exchangeable with D_2O), 6.76−8.24 (m, 16H, arom H).

(21) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256.

(22) For further details on the Pummerer mechanism, see ref 1.

(23) TFA was liberated in the medium from TFAA during Pummerer rearrangement.

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(25) Procedure for preparation of 11b-hydroxy-11b,12-dihydro-5-(phenylthio)-5*H*-isoindolo[2,1-*b*]isoquinolin-7-one (**5a**): TFAA (8 mL, 57 mmol) and pyridine (3 mL, 37 mmol) were added neat to a mixture of **3a** and **4a** (377 mg, 1 mmol), and the mixture was stirred at room temperature for 5 h. Excess of TFAA and pyridine were removed under reduced pressure, and the brown residue was diluted with H_2O (15 mL) and neutralized with 5% aqueous Na_2CO_3. After classical workup, the oily residue was purified by flash chromatography on a silica gel column eluting with CH_2Cl_2 to provide 201 mg (56%) of **5a** as 5.9:4.9 mixture of two diastereomers. Selected data for major isomer of **5a**: oil; EIMS *m*/*z* 359 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 5.62 (s, 2H, CH_2Ar), 6.04 (s, 1H, NCH), 6.92 (s, 1H, OH exchangeable with D_2O), 7.14−8.23 (m, 13H, arom H). Anal. Calcd for $C_{22}H_{17}NO_2S$ (359.45) (mixture): C, 73.51; H, 4.76; N, 3.89. Found: C, 73.39; H, 4.66; N, 3.69. Selected data for minor isomer of **5a**: oil; EIMS *m*/*z* 359 (M^+); ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 4.31 (s, 1H, OH exchangeable with D_2O), 5.57 (s, 2H, CH_2Ar), 6.12 (s, 1H, NCH), 7.14−8.23 (m, 13H, arom H). Anal. Calcd for $C_{22}H_{17}NO_2S$ (359.45) (mixture): C, 73.51; H, 4.76; N, 3.89. Found: C, 73.39; H, 4.66; N, 3.69.

Finally as an extension of these studies, a mixture of sulfoxides **3b** and **4b** (or **3c** and **4c**) were prepared similarly as outlined in Scheme 3 to evaluate the effect of *o*-bromo phenylthio substitution and another electron-rich arylthio group in the cyclization step.

In a similar manner as above (i.e., TFAA, CH_2Cl_2, rt, 8 to 12 h then TFA, rt, 12 h, conditions iii in Scheme 4),[25] these sulfoxides afforded the bridged products **6b** or **6c** in 62% and 41% yields, respectively. Although the presence of the bromide atom seemed to facilitate the cyclization step, there was no discernible preference for the naphthyl group since more resignification was observed during the cyclization step into **6c** (41%).

In conclusion, we have shown that our tandem cyclization reaction involves an initial intramolecular arylation of thionium ion, followed by a π-aromatic cyclization of *N*-acyliminium ion. This process produces efficaciously 5,11b-bridged isoindoloisoquinolinone alkaloids **6**. However, in an interrupted π-aromatic intramolecular α-amidoalkylation cyclization, the *N*-acyliminium ion intermediate undergoes a hydrolysis leading to the expected difunctionalized isoindoloisoquinolinone alkaloid **5**.

Supporting Information Available: Physical data of all other products not described herein (**1** and **2**) and detailed descriptions of experimental procedures. This material is availabe available free of charge via the Internet at http://pubs.acs.org. The data may also be obtained at the following e-mail address: Adam@Daich@univ-lehavre.fr.

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(26) General procedure for preparation of **6a**,**b**,**c**: A solution containing a mixture of sulfoxides **3a**,**b**,**c** and **4a**,**b**,**c** (1 mmol) and TFAA (8 mL, 57 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature. After 8−12 h of reaction (the reaction was monitored by TLC using an silica gel column and CH_2Cl_2 as eluent), TFA (4 mL, 52 mmol) was added neat in one portion, and the mixture was allowed to react again at the same temperature for 12 h. Solvents were removed under reduced pressure, and the residue was diluted with CH_2Cl_2 (20 mL). After a classical workup, the residue was passed through a short silica gel column with CH_2Cl_2 as eluent, and the resulting solid was recrystallized from ethanol to give the expected product **6**. Selected data for 11b,12-dihydro-5,11b-thioepoxy[1′,2′]benzeno-5*H*-isoindolo[2,1-*b*]isoquinolin-7-one (**6a**): This product was obtained in 42% yield (m = 143 mg); mp 249 °C.; EIMS m/z 341 (M^+); IR (KBr): ν 3013 (CH), 2989 (CH), 1713 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 5.48 (s, 2H, CH_2Ar), 6.12 (d, 1H, J = 8.1 Hz, CH), 7.20−7.58 (m, 11H, benzene 8H + isoindole 3H), 8.78 (d, 1H, J = 7.5 Hz, isoindole H); ^{13}C NMR ($CDCl_3$, 50.13 MHz) δ 44.5 (CH_2), 119.6 (C), 122.5 (CH), 122.8 (CH_{Ar}), 128.0 (CH_{Ar}), 128.4 (C), 128.8 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 129.4 ($2CH_{Ar}$), 129.6 (CH_{Ar}), 130.9 (CH_{Ar}), 131.1 ($3CH_{Ar}$), 133.1 (C), 134.8 (C), 136.2 (C), 137.7 (C), 139.8 (C), 166.2 (C═O). Anal. Calcd For $C_{22}H_{15}NOS$ (341.43): C: 77.39; H, 4.43; N, 4.10. Found: C, 77.44; H, 4.49; N, 4.03. Selected data for 11b,12-dihydro-5,11b-(6′-bromothioepoxy[1′,2′]-benzeno)-5*H*-isoindolo[2,1-*b*]isoquinolin-7-one (**6b**): This product was obtained in 62% yield (m = 260 mg); mp 258 °C.; EIMS m/z 420 (M^+); IR (KBr): ν 3010 (CH), 2991 (CH), 1721 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 5.51 (s, 2H, CH_2Ar), 6.21 (d, 1H, J = 8.1 Hz, CH), 7.06−7.66 (m, 10H, benzene 7H + isoindole 3H), 8.78 (d, 1H, J = 7.5 Hz, isoindole H); ^{13}C NMR ($CDCl_3$, 50.13 MHz) δ 45.1 (CH_2), 118.7 (C), 122.6 (CH), 122.9 (CH_{Ar}), 125.6 (C), 128.3 ($2CH_{Ar}$), 128.4 (C), 129.1 (CH_{Ar}), 129.8 (CH_{Ar}), 130.2 (CH_{Ar}), 131.3 (CH_{Ar}), 131.4 ($3CH_{Ar}$), 133.2 (C), 133.3 (CH_{Ar}), 134.7 (C), 137.1 (C), 137.4 (C), 14.1 (C), 166.1 (C═O). Anal. Calcd for $C_{22}H_{14}BrNOS$ (420.32): C: 62.86; H, 3.36; N, 3.33. Found: C, 62.79; H, 3.33; N, 3.39. Selected data for 11b,12-dihydro-5,11b-thioepoxy[2′,1′]-naphthaleno-5*H*-isoindolo[2,1-*b*]isoquinolin-7-one (**6c**): This product was obtained in 41% yield (m = 160 mg); mp 238 °C; EIMS m/z 390 (M^+); IR (KBr): ν 3019 (CH), 2982 (CH), 1709 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz) δ 5.31 (s, 2H, CH_2Ar), 6.14 (d, 1H, J = 8.1 Hz, CH), 7.02−7.85 (m, 13H, naphthalene 6H + benzene 4H + isoindole 3H), 8.70 (d, 1H, J = 8.6 Hz, isoindole H); ^{13}C NMR ($CDCl_3$, 50.13 MHz) δ 39.6 (CH_2), 119.8 (C), 122.6 (CH), 122.8 (CH_{Ar}), 124.6 (CH_{Ar}), 126.7 (CH_{Ar}), 127.8 ($2CH_{Ar}$), 128.1 (CH_{Ar}), 128.4 (CH_{Ar}), 128.5 (C), 128.7 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 129.6 (CH_{Ar}), 131.1 ($3CH_{Ar}$), 131.5 (C), 133.3 (C), 133.7 (C), 134.7 (C), 135.0 (C), 136.7 (C), 137.8 (C), 166.5 (C═O). Anal. Calcd for $C_{26}H_{16}NOS$ (390.48): C, 79.77; H, 4.38; N, 3.58. Found: C, 79.83; H, 4.33; N, 3.51.

(27) We have used the same procedure, as reported in ref 22, with TFA instead TFAA and pyridine. The resulting solid was recrystallized from ethanol to give **6a** as yellow needles in 58% yield.