An unusual rearrangement of 1-(2-isothiocyanoaryl)-2-(2-furyl)ethane under Friedel-Crafts conditions

Alexander V. Butin,[a*] Fatima A. Tsiunchik,[a] Vladimir T. Abaev,[b] and Kristina V. Bosikova[b]

[a] *Research Institute of Heterocyclic Compounds Chemistry, Kuban State University of Technology, Moskovskaya st. 2, Krasnodar, 350072, Russian Federation*
[b] *North-Ossetian State University, Vatutina st. 46, Vladikavkaz, 362025, Russian Federation*
E-mail: alexander_butin@mail.ru

Dedicated to Prof. Alexander Pozharsky on the occasion of his 70th birthday

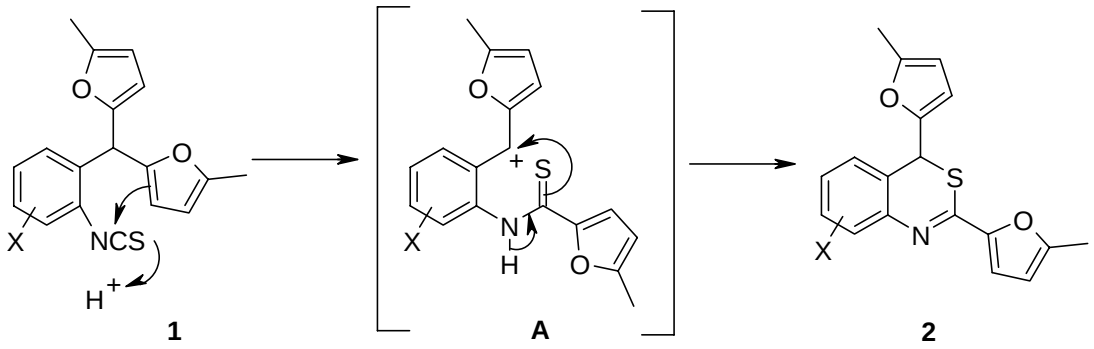
Abstract
Treatment of 1-(2-isothiocyanoaryl)-2-(2-furyl)ethane with anhydrous aluminum chloride under Friedel-Crafts conditions yielded a pyrrolo[1,2-*a*]quinoline derivative *via* electrophilic attack of the activated isothiocyano group onto the furan ring. The analogous diarylethane under these conditions underwent intramolecular cyclization leading to an eight-membered thioamide.

Keywords: Furan, isothiocyanate, rearrangement, pyrrolo[1,2-*a*]quinoline

Introduction

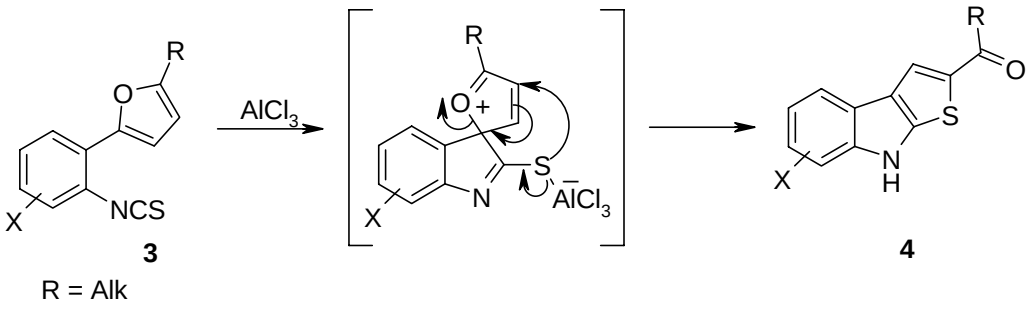
Interaction of arylisothiocyanates with aromatic hydrocarbons was studied for the first time by Gatterman as early as in 1892.[1] Now it is well known that under acid catalysis isothiocyanates react with aromatic and heteroaromatic compounds as C-electrophiles leading to thioamide derivatives.[2] If isothiocyanates are linked with the aromatic or heteroaromatic rings by some tether, intramolecular cyclizations proceed under treatment with Lewis acids or PPA.[3] However, direct thiocarbamoylation of furans with isothiocyanates under the Friedel-Crafts conditions has not been reported, a fact that can be attributed to the known sensitivity of furan compounds to acids. The known furan thioamides are usually synthesized by use of lithiated furan derivatives.[4]

The first example of intramolecular interaction of furan with an isothiocyano group in the presence of acid catalyst was reported by us in 1997. It was demonstrated that treatment of 2-[bis(2-furyl)methyl]aryl isothiocyanates **1** with perchloric acid in 1,4-dioxane led to formation of 2,4-difuryl-4*H*-3,1-benzothiazines **2** (Scheme 1).[5] Later we found that this transformation can be efficiently realized under catalysis with anhydrous $AlCl_3$ and showed that this process is also applicable for thiophene analogs[6] and triarylmethanes.[7]



Scheme 1

Obviously, one of the most important factors favoring furan ring migration is the intermediacy of the stable cation **A;** otherwise the reaction is impossible. It was of interest to study the intramolecular interaction of furan and isothiocyano group in substrates wherein the furan ring migration is impossible due to structural peculiarities of the molecule. In recent work, we showed that treatment of 2-alkyl-5-(2-isothiocyanoaryl)furans **3** with $AlCl_3$ is accompanied with furan ring opening followed by formation of thieno[2,3-*b*]indoles **4** (Scheme 2).[8]



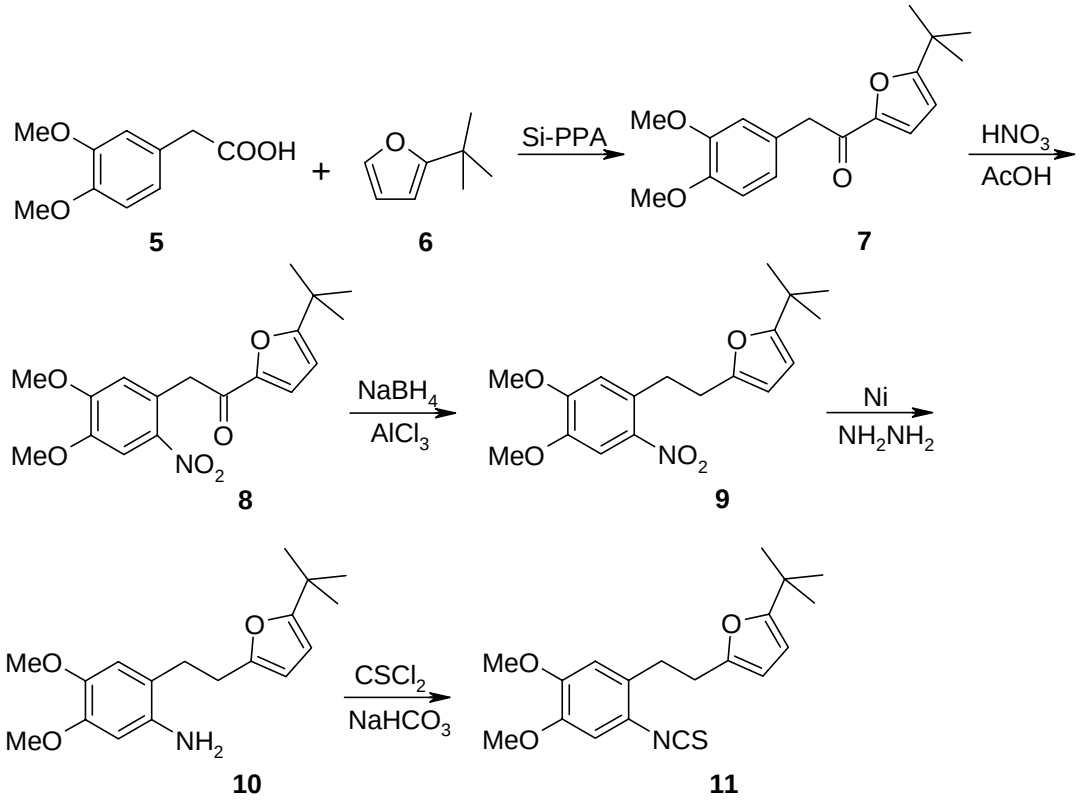
Scheme 2

As a continuation of these investigations, we studied $AlCl_3$-catalyzed transformation of 1-(2-isothiocyanoaryl)-2-(2-furyl)ethane. Similarly to the 2-alkyl-5-(2-isothiocyanoaryl)furans, the migration of the furan ring can not be realized for this compound.

Results and Discussion

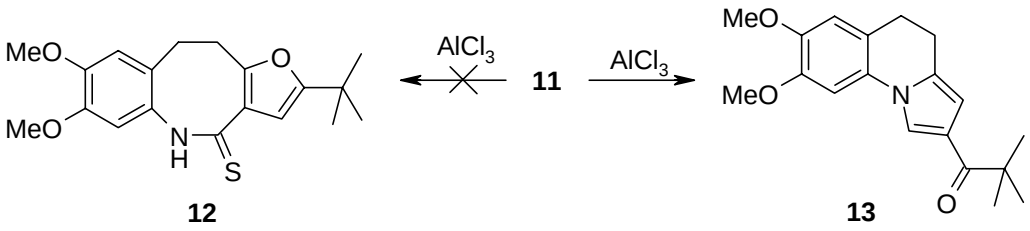
The synthesis of the starting isothiocyanate **11** is depicted in Scheme 3. Acylation of 2-*tert*-butylfuran **6** with homoveratric acid **5** in chloroform solution of trimethylsilyl ester of polyphosphoric acid[9] gave rise to ketone **7**. Its nitration with fuming HNO_3 in acetic acid furnished nitroketone **8**. Reduction of the compound **8** with $NaBH_4$ in the presence of equimolar

amount of anhydrous $AlCl_3$ led to diarylethane **9**. Nitro group of **9** was then reduced with NH_2NH_2 in the presence of Raney Ni to yielding amine **10**. Isothiocyanate **11** was obtained by the treatment of the compound **10** with $CSCl_2$ and an aqueous solution of $NaHCO_3$.



Scheme 3

Transformation of isothiocyanate **11** was performed at room temperature in 1,2-dichloroethane in the presence of an equimolar amount of anhydrous $AlCl_3$. It would be logical to suppose the formation of compound **12** is *via* intermolecular cyclization. However, similarly to the case of arylfurans, furan presented one more surprise to us. Pyrroloquinoline **13** (Scheme 4) was isolated as a single product. Its structure was confirmed unambiguously by spectroscopic methods and X-ray crystallography (Figure 1). The mechanism of this reaction is still unclear and calls for further study, which is under way.



Scheme 4

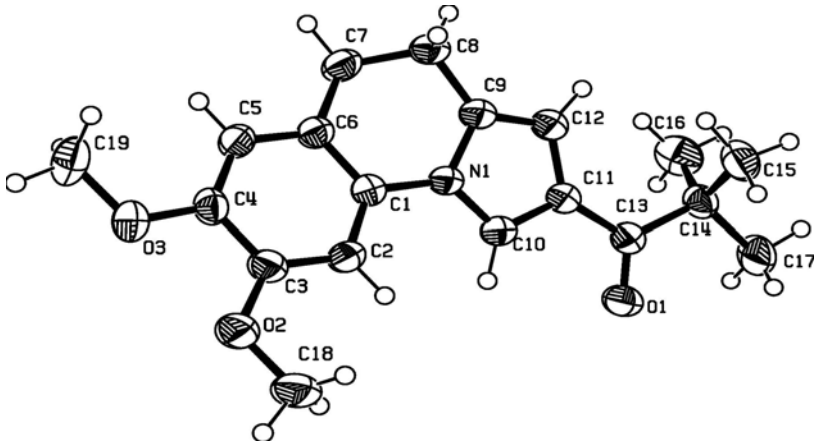
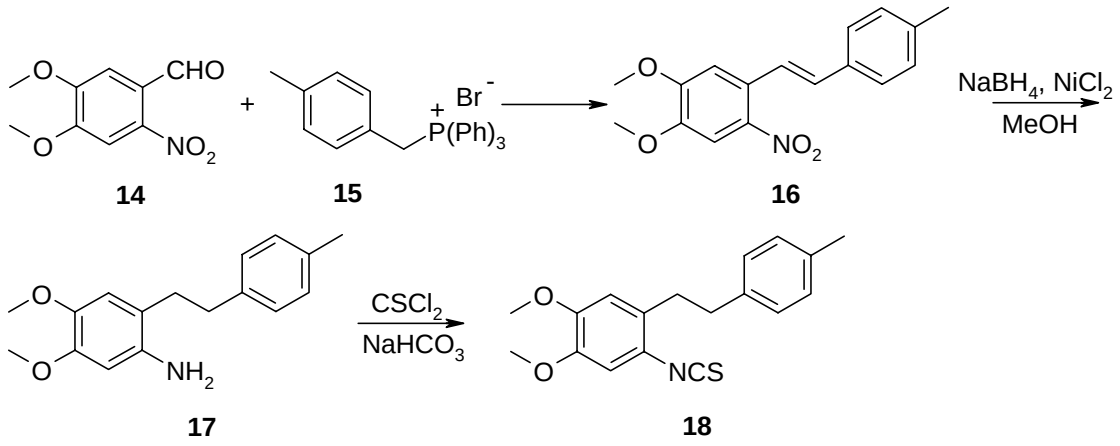


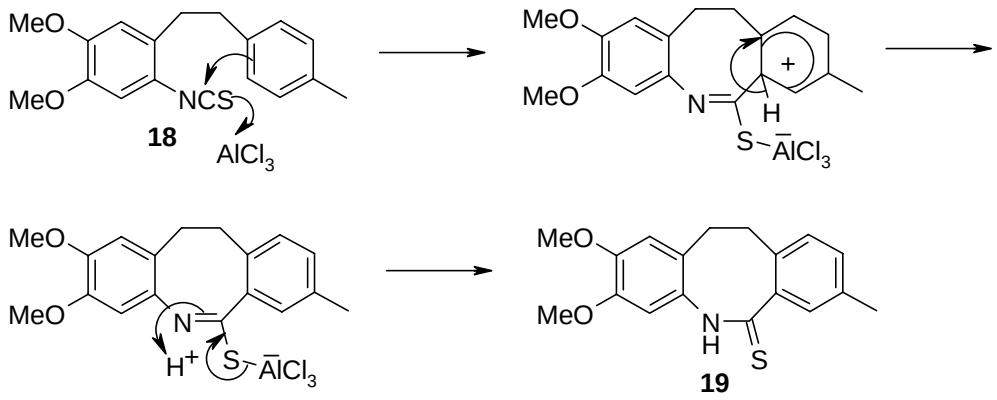
Figure 1. Crystal structure of **13**.

To compare the reactivity of the furan ring and benzene derivatives in this reaction we synthesized an analog of the isothiocyanate **11** containing a *p*-tolyl group instead of a furan ring. The synthesis of compound **18** is shown in Scheme 5. Reaction of 6-nitroveratraldehyde **14** and (*p*-methylbenzyl)triphenylphosphonium bromide **15** gave a mixture of *cis*- and *trans*-stilbenes which was reduced to amine **17** with sodium borohydride in the presence of anhydrous $NiCl_2$. The treatment of the amine **17** with thiophosgene and aqueous $NaHCO_3$ furnished isothiocyanate **18**.



Scheme 5

Under the treatment of the isothiocyanate **18** with a threefold excess of anhydrous $AlCl_3$ azocanethione **19** was isolated as the main product in 30% yield. In this case the reaction proceeded as expected *via* a common intramolecular cyclization leading to cyclic thioamide (Scheme 6).



Scheme 6

Conclusions

In conclusion, we have demonstrated that the chemical behaviors of the 1-(2-isothiocyanoaryl)-2-(2-furyl)ethane and the 1-(2-isothiocyanoaryl)-2-arylethane are quite different. The common intramolecular cyclization takes place in the case of 1-(2-isothiocyanoaryl)-2-arylethane in contrast to 1-(2-isothiocyanoaryl)-2-(2-furyl)ethane where an unusual rearrangement with formation of a dihydropyrrolo[1,2-*a*]quinoline derivative is observed. A study of the scope of the reaction is in progress.

Experimental Section

General Procedures. The microanalyses were carried out in the Laboratory of Physico-Chemical Methods of Research, Department of Chemistry, M.V. Lomonosov Moscow State University. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM 300 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard and coupling constants (*J*) are given in absolute values in *Hz* to the nearest 0.1 *Hz*. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV electron impact ionization at 200 °C. IR spectra were measured as KBr plates on InfraLUM FT-801 instruments. Column chromatography was performed using silica gel KSK (50-160 μm) manufactured by LTD Sorbpolymer.

Crystallographic data for the structure **13** in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 686650. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax; +44(0)-1223-336033 or E-mail: deposit@ccdc.cam.ac.uc]. Each request should be accompanied by the complete citation of this paper.

1-(5-*tert*-Butyl-2-furyl)-2-(3,4-dimethoxyphenyl)-1-ethanone (**7**)**.** Homoveratric acid **5** (4 g, 20 mmol) and *tert*-butylfuran **6** (2.73 g, 22 mmol) were added to a solution of silyl ester of polyphosphoric acid in $CHCl_3$ (50 mL). The mixture was stirred under refluxing for 40 min (TLC monitoring), then poured into 300 mL of water, stirred and extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure. The obtained oil was dissolved in hexane, solution was filtered through a pad of silica gel and left until crystallization of product. Yield 2.90 g (48%); colorless needles; mp 75-76 °C. IR (KBr): 1668, 1589, 1513, 1465, 1358, 1268, 1233, 1157, 1046, 1026, 955, 859, 810, 782, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H, *t*-Bu), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.01 (s, 2H, CH_2), 6.14 (d, *J* 3.5 Hz, 1H, H_{Fur}), 6.81 (d, *J* 8.6 Hz, 1H, H_{Ar}), 6.86 (s, 1H, H_{Ar}), 6.87 (d, *J* 8.6 Hz, 1H, H_{Ar}), 7.13 (d, *J* 3.5 Hz, 1H, H_{Fur}). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.61; H, 7.39.

1-(5-*tert*-Butyl-2-furyl)-2-(3,4-dimethoxy-2-nitrophenyl)-1-ethanone (**8**)**.** Fuming nitric acid (4.8 mL) was added dropwise to a solution of ketone **7** (7 g, 23 mmol) in AcOH (60 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 10 min and at room temperature for 20 min. Then it was poured into ice and the separated residue was filtered off and washed with a water solution of $NaHCO_3$ until pH 7 was reached. Recrystallization from hexane afforded compound **8**. Yield 6.50 g (81 %); pale yellow needles; mp 119-120 °C. IR (KBr): 1667, 1582, 1525, 1466, 1330, 1275, 1234, 1071, 1051, 1013, 953, 876, 795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9H, *t*-Bu), 3.97 (s, 6H, OCH_3), 4.54 (s, 2H, CH_2), 6.20 (d, *J* 3.5 Hz, 1H, H_{Fur}), 6.77 (s, 1H, H_{Ar}), 7.21 (d, *J* 3.5 Hz, 1H, H_{Fur}), 7.75 (s, 1H, H_{Ar}). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.35; H, 6.18; N, 4.09.

1-(5-*tert*-Butyl-2-furyl)-2-(3,4-dimethoxy-2-nitrophenyl)ethane (**9**)**.** To a cooled (0-5 °C) solution of ketone **8** (5.9 g, 17 mmol) in tetrahydrofuran (120 mL), anhydrous $AlCl_3$ (4.6 g, 34 mmol) and $NaBH_4$ (1.3 g, 34 mmol) were added portionwise under stirring. The resulting suspension was stirred at 0-5 °C for 20 min and then brought to reflux. After 2 h when the starting compound **8** vanished (TLC monitoring), the reaction mixture was cooled and poured into 500 mL of ice water. The product was extracted with EtOAc (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure. The obtained yellow oil **9** (3.85 g, 68%) was used in the next step without further purification.

1-(5-*tert*-Butyl-2-furyl)-2-(2-amino-3,4-dimethoxyphenyl)ethane (**10**)**.** To an ethanolic solution (20 mL) of compound **9** (1.87 g, 5.6 mmol) Raney nickel (1.5 g) and hydrazine hydrate (2 mL) were added and the reaction mixture was refluxed for 1-1.5 h. After completion of the reaction (TLC monitoring), the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The obtained yellow oil **10** (1.51 g, 89%) was used in the next step without further purification.

1-(5-*tert*-Butyl-2-furyl)-2-(2-isothiocyano-3,4-dimethoxyphenyl)ethane (**11**)**.** A solution of thiophosgene (0.5 mL, 6.5 mmol) in CH_2Cl_2 (10 mL) and $NaHCO_3$ (1.3 g, 15.5 mmol) in water (50 mL) were simultaneously added at room temperature to a stirred solution of compound **10** (1.5 g, 5 mmol) in CH_2Cl_2 (15 mL). When the reaction had finished (TLC monitoring), the

mixture was poured into water (150 mL) and stirred for 6 h. The organic layer was separated and water layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the dried extract was reduced to the half of its volume, and petroleum ether was added until the solution became cloudy. The solution was filtered through a pad of silica gel, evaporated to one third of its volume, and left to allow crystallization of the compound **11**. Yield 1.52 g (88 %); beige solid; mp 47-48 °C. IR (KBr): 2088, 1612, 1520, 1464, 1404, 1360, 1264, 1232, 1204, 1144, 1128, 1016, 856, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 9H, *t*-Bu), 2.87-2.91 (m, 2H, CH_2), 2.94-2.98 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.82 (d, *J* 3.0 Hz, 1H, H_{Fur}), 5.84 (d, *J* 3.0 Hz, 1H, H_{Fur}), 6.51 (s, 1H, H_{Ar}), 6.72 (s, 1H, H_{Ar}). Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05. Found: C, 65.93; H, 6.82; N, 4.01.

1-(2,3-Dimethoxy-5,6-dihydropyrrolo[1,2-*a*]quinolin-8-yl)-2,2-dimethyl-1-propanone (13). A mixture of the compound **11** (1.8 g, 5.2 mmol) and anhydrous $AlCl_3$ (0.69 g, 5.2 mmol) in dry 1,2-dichloroethane (20 mL) was stirred for 3.5-4 h at room temperature until the completion of the reaction (TLC monitoring). The reaction mixture was poured into water (400 mL) and extracted with CH_2Cl_2 (3 × 40 mL). Combined extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified on silica gel (50/60 μm) column with ethylacetate-hexan (1:3) as eluent. Yield 1.42 g (87 %); yellow cubes; mp 94-95 °C. IR (KBr): 1640, 1519, 1504, 1461, 1255, 1207, 1138, 1026, 907, 856, 796, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9H, *t*-Bu), 2.77-2.82 (m, 2H, CH_2), 2.85-2.90 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.45 (s, 1H, H_{Py}), 6.74 (s, 1H, H_{Ar}), 6.92 (s, 1H, H_{Ar}), 7.72 (s, 1H, H_{Py}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 31.4, 32.5, 55.7, 55.9, 108.9, 112.8, 128.3 (2C), 128.9, 130.3, 130.5, 131.9, 135.9, 141.1, 147.1, 148.3, 207.0. MS (EI, 70 eV): *m/z* (%) = 313 (18) [M^+], 257 (23), 256 (100), 240 (10), 43 (22). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 73.01; H, 7.29; N, 4.52.

(4-Methylbenzyl)triphenylphosphonium bromide (15). To a solution of 4-methylbenzyl bromide (28.1 g, 152 mmol) in toluene (75 mL) triphenylphosphine (40 g, 152 mmol) was added and the reaction mixture was stirred under reflux for 1 h. Resulted suspension was cooled, phosphonium salt was filtered off, washed successively with toluene, petroleum ether and dried. Colorless crystalline compound **15** (63.9 g, 94%) was used as such at the next step.

1-(3,4-Dimethoxy-2-nitrophenyl)-2-(4-methylphenyl)ethylene (16). To a stirred suspension of the 6-nitroveratraldehyde **14** (11 g, 52 mmol) and phosphonium salt **15** (22.4 g, 50 mmol) in methanol (150 mL) 4 N solution of sodium methoxide in methanol (15 mL, 60 mmol) was added dropwise under cooling with ice bath. The suspension was stirred for 1 h and left to stand overnight. The product was filtered off, washed with methanol and dried. Yield of orange crystals of a mixture of *cis*- and *trans*-isomers was 9.5 g. Another 4 g batch of the product was deposited from mother liquor after its reducing in volume and cooling. Total yield 13.5 g (90%). Stilbene **16** was used as such at the next step.

1-(2-Amino-3,4-dimethoxyphenyl)-2-(4-methylphenyl)ethane (17). Anhydrous nickel chloride (3.3 g) was added to a stirred suspension of compound **16** (7.4 g, 24.75 mmol) in methanol (50 mL) under cooling with water bath. Then $NaBH_4$ (2 g) was added portionwise. After completion

of the reaction (TLC monitoring), the mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (3 × 50 mL). Combined extracts were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the oily residue was dissolved in ethanol (30 mL). A solution of oxalic acid (2.3 g) in ethanol (10 mL) was added. Precipitated amine oxalate was filtered off after 1 h, washed with ethanol (20 mL), ether (10 mL) and treated with excess of aqueous sodium hydroxide. The product was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent evaporated under reduced pressure. The obtained beige solid **17** (5.57 g, 83%) was used in the next step without further purification.

1-(2-Isothiocyano-3,4-dimethoxyphenyl)-2-(4-methylphenyl)ethane (18). Compound **18** was obtained analogously to compound **11**. Yield 1.30 g (83 %); white solid; mp 72-73 °C. IR (KBr): 2120, 1608, 1468, 1456, 1440, 1404, 1356, 1300, 1260, 1228, 1208, 1144, 1128, 1012, 860, 844, 808, 796 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.80-2.92 (m, 4H, CH_2), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.51 (s, 1H, H_{Ar}), 6.70 (s, 1H, H_{Ar}), 7.08 (s, 4H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 34.4, 36.5, 56.0, 56.1, 109.3, 112.3, 121.7, 128.5 (2C), 129.1 (3C), 131.0, 135.6, 137.8, 147.6, 148.2. Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 69.13; H, 6.02; N, 4.41.

2,3-Dimethoxy-9-methyl-5,6,11,12-tetrahydrodibenzo[*b*,*f*]azocine-6-thione (19). A mixture of the compound **18** (0.7 g, 2.24 mmol) and anhydrous $AlCl_3$ (0.9 g, 6.7 mmol) in dry 1,2-dichloroethane (15 mL) was stirred at room temperature for 1 h until the completion of the reaction (TLC monitoring). The reaction mixture was poured into water (300 mL) and extracted with CH_2Cl_2 (3 × 40 mL). Combined extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified on silica gel (50/60 μm) column with hexane-acetone-benzene (3:1:1) as eluent. Yield 0.22 g (32 %); yellow plates; mp 112-114 °C. IR (KBr): 1516, 1452, 1248, 1228, 1168, 1112, 1036, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.22 (s, 3H, CH_3), 2.77-2.91 (m, 2H, CH_2), 3.33-3.41 (m, 2H, CH_2), 3.75 (s, 6H, OCH_3), 6.46 (s, 1H, H_{Ar}), 6.57 (s, 1H, H_{Ar}), 6.89 (d, *J* 7.8 Hz, 1H, H_{Ar}), 6.96 (dd, *J* 1.2 Hz, *J* 7.8 Hz, 1H, H_{Ar}), 7.19 (d, *J* 1.2 Hz, 1H, H_{Ar}), 10.04 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 26.3, 28.1 (3C), 43.6, 56.3, 56.4, 100.7, 107.0, 112.4, 119.7, 120.2, 123.1, 129.0, 129.6, 146.6, 148.6, 201.7. MS (EI, 70 eV): *m/z* (%) = 313 (57) [M^+], 298 (16), 280 (100), 264 (17), 249 (75), 234 (34), 222 (25), 147 (40), 134 (12), 103 (15), 77 (23). Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 68.69; H, 6.02; N, 4.54.

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