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RECYCLIZATION OF TOSYLAMINO DERIVATIVES OF 2-ARYL-5-BENZYLFURAN TO GIVE INDOLES THROUGH TWO ALTERNATIVE PATHWAYS

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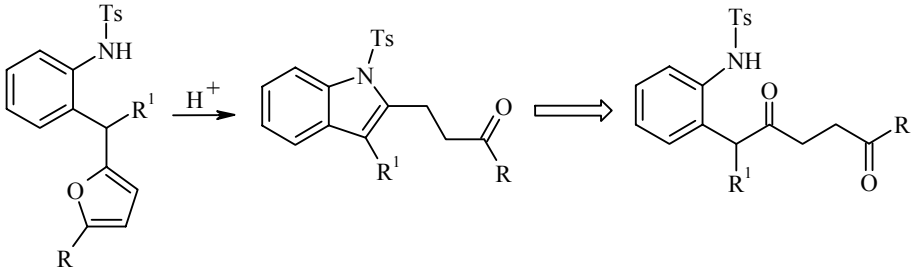
The recyclization of derivatives of 2-aryl-5-benzylfuran containing a tosylamine fragment to give indoles has been studied. If the tosylamino group is in the ortho position of the aryl substituent, the recyclization proceeds such that the furan ring may be seen as a formal equivalent of a 1,3-diketone. If, on the other hand, the tosylamino group is in the ortho positions of both the aryl and benzyl substituents, the recyclization proceeds through a pathway, in which the furan ring acts as the equivalent of a 1,4-dicarbonyl compound.

Keywords: 1,3-diketone, 1,4-diketone, indole, furan, recyclization.

The capacity of alkylfurans under acid catalysis conditions to undergo opening to give 1,4-dicarbonyl compounds is well known and commonly used in preparative chemistry [1-4]. Sometimes, the 1,4-diketones enter a further reaction and cannot be isolated from the reaction mixture. In this case, the furan may be seen as the equivalent of a 1,4-dicarbonyl compound. For many years, we have employed this property of furan compounds in the synthesis of benzo-fused heterocycles through the recyclization of *ortho*-substituted benzyl furans. In particular, we have reported that 2-(2-tosylaminobenzyl)furans under acid conditions are converted to indole derivatives [5-7].



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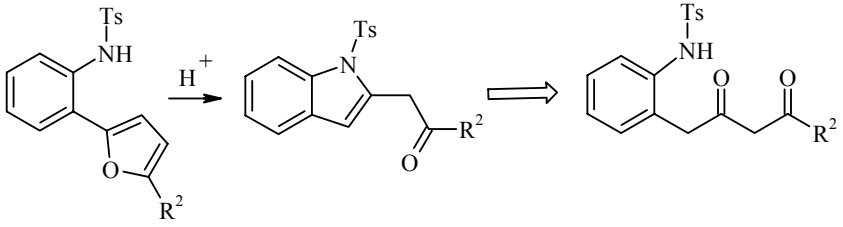
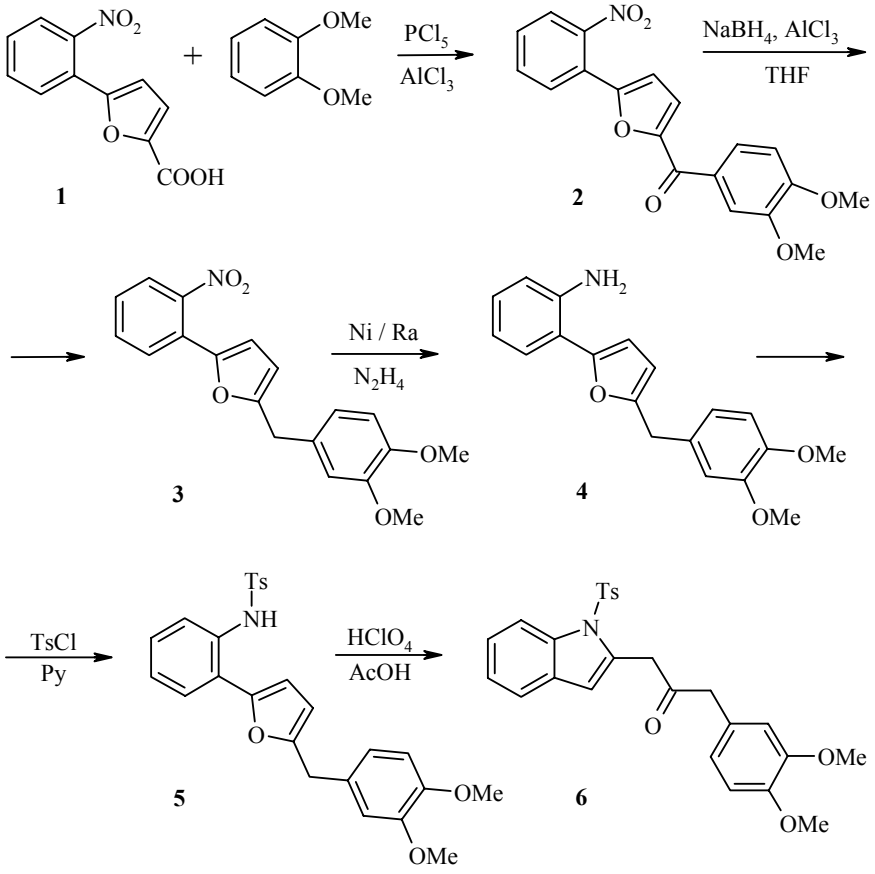
We have recently found that 2-alkyl-5-(2-tosylaminoaryl)furans under protolytic conditions also undergo recyclization and give indole derivatives [8]. However, in this case, furan, in contrast to 2-(2-tosylaminobenzyl)furans, may be seen as the formal equivalent of 1,3-dicarbonyl compounds. Such reactivity of furan compounds had never been reported prior to our work.



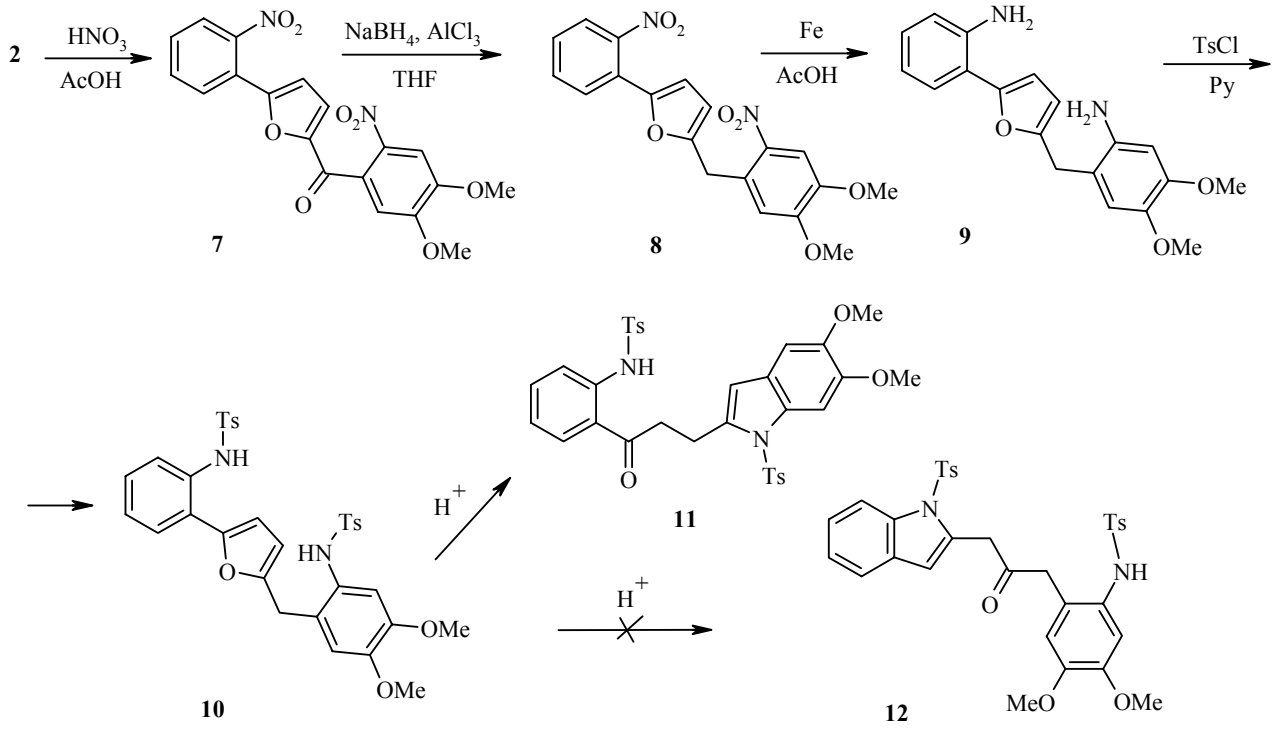
In the present work, we carried out a comparative analysis of the activity of furan in both types of recyclization mentioned above through the synthesis and investigation of the reactivity of furan compound, for which the two pathways were possible, at least in principle. 2-Aryl-5-benzylfurans are such compounds containing nucleophilic functions in the *ortho* positions of both aromatic rings.

We previously established that 2-aryl-5-(2-tosylaminobenzyl)furans under acid catalysis conditions are converted into indoles, while the furan in this case acts as a 1,4-diketone equivalent [6]. Before addressing the major aim of this work, we decided to show that recyclization into indoles for both 2-benzyl-5-(2-tosyl-aminoaryl)furans and 2-alkyl-5-(2-tosylaminoaryl)furans is possible through a pathway, in which the furan acts as crypto equivalent of a 1,3-diketone.



Ketone **2** was obtained as the result of the acylation of veratrole by the acid chloride of 5-(2-nitrophenyl)pyromucic acid **1**. Reduction of acid **1** by $NaBH_4$ in the presence of an equimolar amount of anhydrous $AlCl_3$ in dry tetrahydrofuran led to benzylfuran **3**. Reduction of the nitro group by hydrazine hydrate in the presence of Raney nickel and tosylation of amine **4** gave 2-benzyl-5-(2-tosylaminoaryl)furan **5**. Indeed, heating furan **5** in acetic acid in the presence of a significant amount of perchloric acid gave indole **6**.

The following sequence of transformations was carried out for the synthesis of a model compound containing toslyamine functions in the *ortho* positions of both aromatic rings. Nitration of ketone **2** by fuming nitric acid in acetic acid gave dinitro derivative **7**, whose reduction by $NaBH_4$ in the presence of an equimolar amount of anhydrous $AlCl_3$ gave furan derivative **8**. Further reduction of furan **8** by iron in acetic acid led to diamine **9**, whose tosylation gave the required 2-(2-tosylaminophenyl)-5-(2-tosylaminobenzyl)furan **10**.



Maintaining furan **10** in ethanolic hydrogen chloride at 50°C for 90 min gave indole **11** as the sole product. The furan ring in this case acts as the equivalent of a 1,4-diketone. The use of more vigorous reaction conditions, in particular, heating furan **10** in acetic acid at reflux in the presence of perchloric acid did not lead to reaction by an alternative pathway but rather gave considerable tar formation.

Thus, when the molecule has two suitable nucleophilic sites, the recyclization of the furan ring, in which the furan acts as the equivalent of a 1,4-dicarbonyl compound, is preferred over the recyclization, in which the furan acts as the formal equivalent of a 1,3-dicarbonyl compound.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on a Bruker DPX 300 spectrometer at 300 and 75 MHz, respectively, in DMSO-d_6 for **2, 7, 10, 11** and $CDCl_3$ for **5** and **6** with TMS as the internal standard. The electron impact mass spectra were taken on Finnigan MAT INCOS 50 mass spectrometer at 70 eV. The IR spectra were taken on an InfraLUM FT-02 spectrometer in KBr pellets. The monitoring of the reaction course

and purity of the products obtained was carried out by thin-layer chromatography on Silufol plates using 1:1:2 acetone–dichloromethane–hexane as the eluent. The plates were developed either by iodine or bromine vapor. Sorbpolimer KSK silica gel (5-40 μm) was used for column chromatography to isolate pure products.

3,4-Dimethoxyphenyl[5-(2-nitrophenyl)-2-furyl]methanone (2). A sample of PCl_5 (10.8 g, 52 mmol) was added to a suspension of compound **1** (10 g, 43 mmol) in benzene (80 ml) with water bath cooling and heated for 2 h at 50-55°C. The reaction mixture was then cooled to -2°C and anhydrous $AlCl_3$ (8 g, 60 mmol) was added in portions at temperatures not exceeding +5°C. Then, veratrole (5.5 ml, 43 mmol) was added dropwise and heated for 5 h at 55°C with monitoring by thin-layer chromatography. The reaction mixture was poured into 500 ml ice chips and acidified by adding concentrated hydrochloric acid (2-3 ml). The organic layer was separated. The solvent and unreacted veratrole were removed by steam distillation. The residue obtained was separated by column chromatography using 1:2 CH_2Cl_2–hexane as the eluent to give 9.3 g (61%) methanone **2** as light-yellow crystals, mp 118-119°C (CH_2Cl_2–hexane), R_f 0.65. IR spectrum, ν, cm^{-1}: 1627, 1595, 1535, 1510, 1459, 1420, 1373, 1306, 1275, 1236, 1138, 1024, 812, 760, 754, ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.84 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 7.08 (1H, d, *J* = 8.4, H Ar); 7.18 (1H, d, *J* = 3.9, H Fur); 7.46 (1H, d, *J* = 2.1, H Ar); 7.52 (1H, d, *J* = 3.9, H Fur); 7.63 (1H, dd, *J* = 2.1, *J* = 8.4, H Ar); 7.66-7.72 (1H, m, H Ar); 7.78-7.83 (1H, m, H Ar); 7.93-8.01 (2H, m, H Ar). Found, %: C 64.71; H 4.07; N 4.15. $C_{19}H_{15}NO_6$. Calculated, %: C 64.59; H 4.28; N 3.96.

2-(3,4-Dimethoxybenzyl)-5-(2-nitrophenyl)furan (3). Anhydrous $AlCl_3$ (6.85 g, 50 mmol) and $NaBH_4$ (1.9 g, 50 mmol) were added to a solution of compound **2** (10 g, 28 mmol) in dry THF (200 ml) with cooling to -10°C and heated at reflux for 2 h. The reaction mixture was poured into water (800 ml) and extracted with three ether portions (100 ml). The extract was dried over Na_2SO_4, filtered with activated charcoal, and evaporated to dryness to give 9 g (93%) compound **3** as a yellow oil, R_f 0.80. This product was used in the next step without further purification.

2-[5-(3,4-Dimethoxybenzyl)-2-furyl]aniline (4). Activated Raney nickel **(**2 g) was added to a solution of compound **3** (5 g, 14.7 mmol) in ethanol (40 ml). Then, hydrazine hydrate (7 ml) was added with ice bath cooling. The reaction mixture was heated at reflux for 30 min with monitoring by thin-layer chromatography. The reaction mixture was filtered to remove the nickel. The solvent was evaporated in vacuum produced by a water pump to give 4 g (87%) aniline **4** as a red oil, R_f 0.75. This product was used in the next step without additional purification.

2-[5-(3,4-Dimethoxybenzyl)-2-furyl]-1-(4-methylphenylsulfonylamino)benzene (5). Tosyl chloride (5 g, 26 mmol) was added to a solution of aniline **4** (4 g, 13 mmol) in pyridine (15 ml) with ice bath cooling and stirred for 12 h with monitoring by thin-layer chromatography. The reaction mixture was poured into 200 ml 6 M hydrochloric acid. The precipitate formed was filtered off. The product obtained was separated by column chromatography with 1:3 benzene–hexane as the eluent to give 3 g (61%) compound **5** as light-yellow crystals, mp 114-115°C (benzene–hexane), R_f 0.85. IR spectrum, ν, cm^{-1}: 3284, 1520, 1416, 1332, 1264, 1160, 1144, 1092, 1024, 904, 820, 756, 672. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (3H, s, CH_3); 3.84 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 3.95 (2H, m, CH_2); 6.05 (1H, d, *J* = 3.3, H Fur); 6.24 (1H, d, *J* = 3.3, H Fur); 6.81 (1H, br. s, H Ar); 6.85-6.89 (2H, m, H Ar); 6.98 (2H, d, *J* = 7.8, H Ts); 7.03-7.08 (1H, m, H Ar); 7.15-7.21 (1H, m, H Ar); 7.26-7.32 (3H, m, H Ar+Ts); 7.57-7.60 (1H, m, H Ar); 7.93 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.3, 34.2, 55.8, 55.9, 107.8, 108.6, 111.6, 111.8, 120.7, 122.3, 123.2, 125.1, 126.8 (2C), 127.0, 128.3, 129.2 (2C), 129.8, 132.6, 135.7, 143.3, 147.9, 149.0, 150.7, 155.0. Mass spectrum, *m/z* (I_{rel}, %): 463 $[M]^+$ (7), 308 (52), 191 (69), 151 (100), 91 (29). Found, %: C 67.45; H 5.51; N 2.97. $C_{26}H_{25}NO_5S$. Calculated, %: C 67.37; H 5.44; N 3.02.

1-(3,4-Dimethoxyphenyl)-3-[1-(4-methylphenylsulfonyl)-1H-indol-2-yl]acetone (6). 70% Perchloric acid (3 ml) was added to a solution of compound **5** (3 g, 6.5 mmol) in acetic acid (30 ml) and heated at reflux for 7 min with monitoring by thin-layer chromatography. The reaction mixture was poured into 300 ml water. The precipitate formed was filtered off and separated by column chromatography using1:3 benzene–hexane

as the eluent to give 2.3 g (61%) compound **6** as colorless crystals, mp 108-109°C (benzene–hexane), R_f 0.60. IR spectrum, ν, cm^{-1}: 1727, 1594, 1515, 1450, 1354, 1259, 1172, 1092, 1050, 1023, 752, 685. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3); 3.82 (3H, s, OCH_3); 3.83 (2H, s, CH_2); 3.86 (3H, s, OCH_3); 4.12 (2H, s, CH_2); 6.45 (1H, s, H Ind); 6.78-6.85 (3H, m, H Ar); 7.15-7.23 (4H, m, H Ar+Ts); 7.41-7.43 (1H, m, H Ar); 7.63 (2H, d, *J* = 8.4, H Ts); 7.91-7.94 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.4, 42.1, 49.1, 55.7, 55.8, 111.2, 112.4, 112.6, 114.2, 120.5, 121.7, 123.4, 124.3, 126.4, 126.5 (2C), 129.1, 129.7 (2C), 133.9, 135.7, 136.5, 144.8, 148.0, 148.9, 204.1. Mass spectrum, *m/z* (I_{rel}, %): 463 $[M]^+$ (37), 309 (10), 178 (12), 151 (100), 130 (25), 91 (24). Found, %: C 67.29; H 5.56; N 3.08. $C_{26}H_{25}NO_5S$. Calculated, %: C 67.37; H 5.44; N 3.02.

(**4,5-Dimethoxy-2-nitrophenyl)-[5-(2-nitrophenyl)-2-furyl]methanone (7).** Fuming nitric acid (4.2 ml, 98 mmol) was cautiously added dropwise to a solution of compound **2** (5 g, 14 mmol) in 10 ml acetic acid cooled on an ice bath. The reaction mixture was maintained for 20 min at 0°C and for 20 min at room temperature with monitoring by thin-layer chromatography. The mixture was poured into ice chips (200 ml). The precipitate was filtered off, washed with aqueous sodium bicarbonate, and recrystallized from acetone–ethanol to give 4.2 g (77%) compound **7** as yellow crystals, mp 188-189°C, R_f 0.50. IR spectrum, ν, cm^{-1}: 1668, 1576, 1524, 1508, 1460, 1356, 1336, 1280, 1264, 1068, 812, 788. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.94 (3H, s, OCH_3); 3.96 (3H, s, OCH_3); 7.20 (1H, d, *J* = 3.9, H Fur); 7.25 (1H, s, H Ar); 7.44 (1H, d, *J* = 3.9, H Fur); 7.65-7.71 (1H, m, H Ar); 7.76-7.82 (1H, m, H Ar); 7.78 (1H, s, H Ar); 7.90-7.94 (2H, m, H Ar). Found, %: C 57.43; H 3.62; N 7.06. $C_{19}H_{14}N_2O_8$. Calculated; %: C 57.29; H 3.54; N 7.03.

2-(4,5-Dimethoxy-2-nitrobenzyl)-5-(2-nitrophenyl)furan (8) was obtained analogously to the synthesis of furan **3** in 85% yield (8 g) as a yellow oil, R_f 0.75. This product was used in the next step without further purification.

2-[5-(2-Aminophenyl)-2-furylmethyl]-4,5-dimethoxyaniline (9). A mixture of furan **8** (5 g, 12.5 mmol), 30 g iron powder, 40 ml acetic acid, 100 ml water, and 30 ml ethyl acetate was heated at reflux for 90 min with monitoring by thin-layer chromatography. The reaction mixture was carefully neutralized by adding sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with three 70 ml portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered with activated charcoal. The solvent was removed in vacuum produced by a water pump to give 3 g (70%) aniline **9** as a red oil, R_f 0.65. This product was used in the next step without further purification.

4,5-Dimethoxy-1-(4-methylphenylsulfonylamino)-2-{5-[2-(4-methylphenylsulfonylamino)phenyl]-2-furylmethyl}benzene (10). Tosyl chloride (5.4 g, 28 mmol) was added to a solution of compound **9** (3 g, 9.2 mmol) in pyridine (10 ml) with ice bath cooling and stirred for 12 h with monitoring by thin-layer chromatography. The reaction mixture was poured into 100 ml 6 M hydrochloric acid and the precipitate formed was filtered off. The product was separated by column chromatography using 1:4 benzene–hexane as the eluent to give 2.5 g (43%) compound **10** as light-yellow crystals, mp 113-114°C (CH_2Cl_2–hexane), R_f 0.70. IR spectrum, ν, cm^{-1}: 3263, 1599, 1519, 1415, 1334, 1227, 1163, 1096, 674. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, CH_3); 2.34 (3H, s, CH_3); 3.41 (3H, s, OCH_3); 3.66 (3H, s, OCH_3); 3.93 (2H, s, CH_3); 6.03 (1H, d, *J* = 3.3, H Fur); 6.19 (1H, s, H Ar); 6.77 (1H, s, H Ar); 6.82-6.85 (1H, m, H Ar); 6.88 (1H, d, *J* = 3.3, H Fur); 7.10-7.16 (1H, m, H Ar); 7.24-7.37 (5H, m, H Ar+Ts); 7.53-7.62 (5H, m, H Ar+Ts); 9.41 (1H, s, NH); 9.53 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.0 (2C), 29.0, 55.1, 55.5, 108.7, 111.0, 111.3, 112.8, 126.5, 126.6, 126.7 (2C), 127.1 (2C), 127.3, 127.4 (2C), 127.9, 128.1, 129.6 (4C), 131.5, 137.0, 137.9, 143.0, 143.1, 146.9, 147.6, 148.7, 153.8. Mass spectrum, *m/z* (I_{rel}, %): 477 $[M+H–Ts]^+$ (14), 323 (23), 190 (32), 120 (41), 91 (100). Found, %: C 62.48; H 5.17; N 4.45. $C_{33}H_{32}N_2O_7S_2$. Calculated, %: C 62.64; H 5.10; N 4.43.

2-{3-[5,6-Dimethoxy-1-(4-methylphenylsulfonyl)-1H-indol-2-yl]propanoyl}-1-(4-methylphenyl-sulfonylamino)benzene (11). Ethanolic HCl (20 ml) prepared by dissolving gaseous HCl (100 g) in ethanol (200 g) was added to a solution of compound **10** (3 g, 4.7 mmol) in ethanol (20 ml) and the reaction mixture was maintained for 90 min at 50°C with monitoring by thin-layer chromatography. The reaction

mixture was poured into 200 ml water. The precipitate formed was filtered off, washed with saturated aqueous sodium bicarbonate, and recrystallized from ethanol to give 2.1 g (70%) compound **11** as light-yellow crystals, mp 185-186°C (CH_2Cl_2–hexane), R_f 0.60. IR spectrum, ν, cm^{-1}: 1654, 1491, 1327, 1196, 1156, 1092, 663. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 2.30 (3H, s, CH_3); 3.22-3.31 (2H, m, CH_2); 3.43-3.52 (2H, m, CH_2); 3.73 (3H, s, OCH_3); 3.84 (3H, s, OCH_3); 6.51 (1H, s, H Ind); 7.00 (1H, s, H Ar); 7.17-7.41 (6H, m, H Ar+Ts); 7.52-7.70 (6H, m, H Ar+Ts); 8.03-8.06 (1H, m, H Ar); 11.22 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 20.9, 21.1 (2C), 23.2, 55.6, 55.8, 98.6, 102.5, 109.9, 119.6, 122.4, 123.8, 124.4, 126.2 (2C), 127.0 (2C), 129.9 (2C), 130.2 (2C), 130.3, 131.7, 134.6 (2C), 135.7, 138.0, 138.8, 144.1, 145.3, 146.9, 147.1, 203.5. Mass spectrum, *m/z* (I_{rel}, %): 478 $[M–Ts]^+$ (4), 322 (16), 274 (17), 190 (22), 120 (74), 91 (100). Found, %: C 62.75; H 5.21; N 4.37. $C_{33}H_{32}N_2O_7S_2$. Calculated, % : C 62.64; H 5.10; N 4.43.

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