Synthesis of phenylacetaldehyde amidines and their intramolecular cyclization

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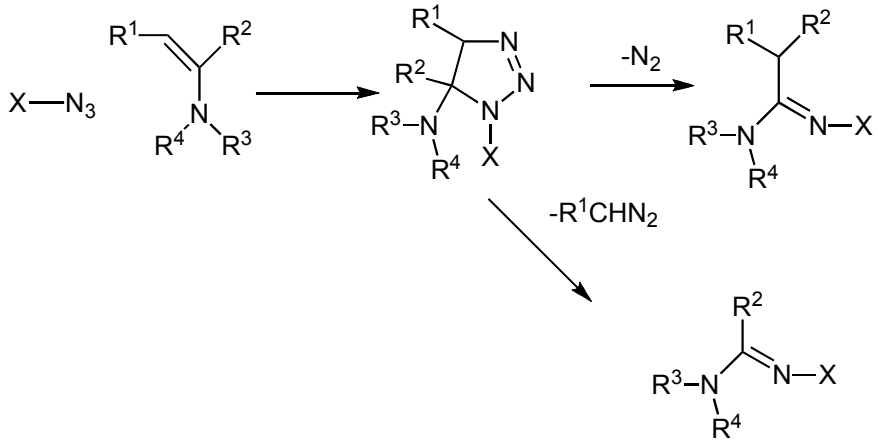
Abstract

The one-pot reaction of phenylacetaldehyde with a primary amine followed by tosyl azide yields the corresponding benzamidine **1** along with the N^1-monosubstituted-N^2-tosylformamidine **2**. The participation of α-amino acid esters as reactants permitted the base-promoted intramolecular condensations of benzamidines **1d**, **1e**, **1f** and **1i** to give the corresponding 1,2-dihydropyrol-3-ones **6a-6d**, respectively. The combination of phenylacetaldehyde, a pair of heterocyclic secondary amines, and 4-nitrophenyl azide in turn led to the two dihydrotriazole derivatives, **4b** and **4c**. Loss of nitrogen from **4** in refluxing toluene afforded trisubstituted benzamidines **5b** and **5c**, that also undergo base-promoted intramolecular condensation, forming 1,2-dihydropyrrol-3-ones **7a** and **7b** in turn.

Keywords: Amidines, intramolecular cyclization, pyrrol-3-ones, multicomponent reactions

Introduction

Amidines are versatile starting materials in several synthetic schemes. Our group recently developed a simple and useful route to optically pure α-amino acid amidines[1] through a heterocyclic transformation. The cycloaddition of tosyl azide or aryl azides with enamines gives rise to 4,5-dihydrotriazole intermediates which convert into the expected branched amidines by nitrogen loss and substituent migration from the 5- to the 4 position. However, a different evolution for the 4,5-dihydrotriazole intermediates is also possible, indeed the corresponding linear amidines were obtained by alkyl diazomethane loss as represented in Scheme 1.

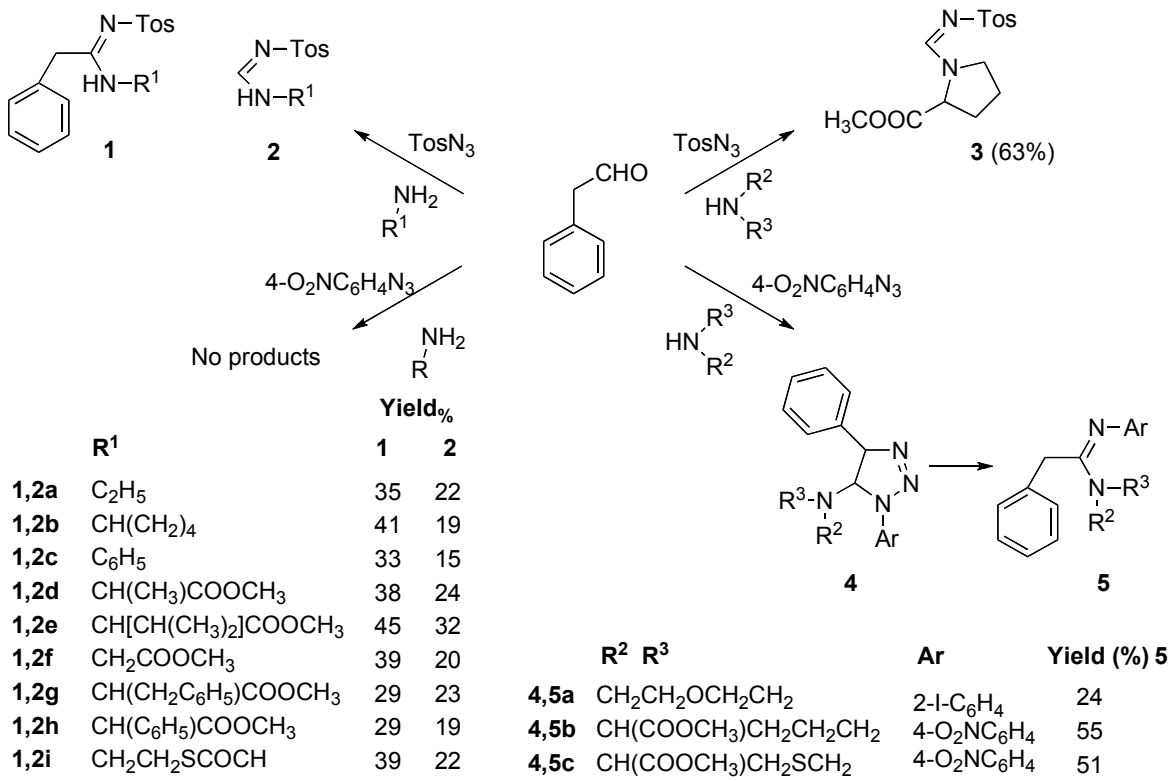


Scheme 1

Such a versatile multicomponent reaction has been extensively investigated by our group,[2] but several aspects still remains unknown. For example, it is known that the nature of the starting carbonylic reactant appears to govern the outcome of the reaction.[3] Aiming to thoroughly investigate the behaviour of phenylacetaldehyde as the carbonylic reactant, as well as to obtain material for new heterocyclic syntheses, several primary or secondary amines and tosyl- or 4-nitrophenyl azide were reacted with phenylacetaldehyde according to Scheme 2.

Results and Discussion

The reaction of phenylacetaldehyde with tosyl azide and primary amines produced both *N*-tosyl-2-benzylamidines **1a-i,** with N_2 loss, and *N*-tosyl-formamidines **2a-i** with benzyldiazomethane loss. In all cases the 2-benzyl-amidine derivatives **1** were the main reaction products. It is already known that the reaction between phenylacetaldehyde and a secondary amine in presence of tosyl azide provides only formamidine.[2a] We verified the reaction trend by using proline methyl ester as the amine and the formamidine **3**, bearing the proline moiety, was obtained as the only product.

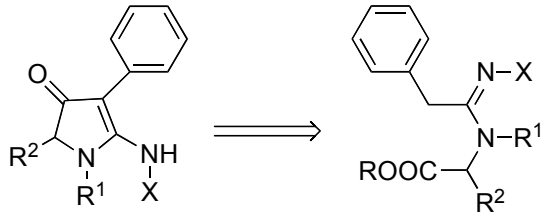


	R[1]	Yield% 1	2
1,2a	C_2H_5	35	22
1,2b	$CH(CH_2)_4$	41	19
1,2c	C_6H_5	33	15
1,2d	$CH(CH_3)COOCH_3$	38	24
1,2e	$CH[CH(CH_3)_2]COOCH_3$	45	32
1,2f	CH_2COOCH_3	39	20
1,2g	$CH(CH_2C_6H_5)COOCH_3$	29	23
1,2h	$CH(C_6H_5)COOCH_3$	29	19
1,2i	CH_2CH_2SCOCH	39	22

	R[2] R[3]	Ar	Yield (%) 5
4,5a	$CH_2CH_2OCH_2CH_2$	2-I-C_6H_4	24
4,5b	$CH(COOCH_3)CH_2CH_2CH_2$	4-$O_2NC_6H_4$	55
4,5c	$CH(COOCH_3)CH_2SCH_2$	4-$O_2NC_6H_4$	51

Scheme 2

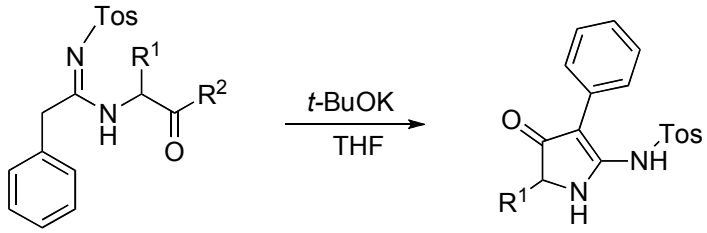
The same conditions were chosen for the reaction with 4-nitrophenylazide, but an equimolar amount of phenylacetaldehyde, a suitable secondary amine and 4-nitrophenylazide yielded the stable triazoline **4** which, through prolonged heating, was transformed into the *N*-aryl-2-benzylamidine derivatives **5** as the main products. No reaction occurred when phenylacetaldehyde was reacted with primary amines and 4-nitrophenylazide and the same behaviour was observed starting from α-amino acid esters. As demonstrated below, this multicomponent reaction proved to be an efficient way to achieve useful intermediates for synthetic transformations. As the structures of the *N*-tosyl-benzylamidines **1d-i,** obtained from linear α-amino acid esters, and of the aryl-benzylamidines **5b-c**, obtained from cyclic α-amino acid esters, are quite similar, we proposed to take advantage of the α-amidine methylene group, as well as of the presence of the ester moiety. By carrying out the reaction under basic conditions, an intramolecular condensation providing an heterocyclic ring could be expected between the nucleophilic methylene group[4] and the ester function (Scheme 3).



Scheme 3

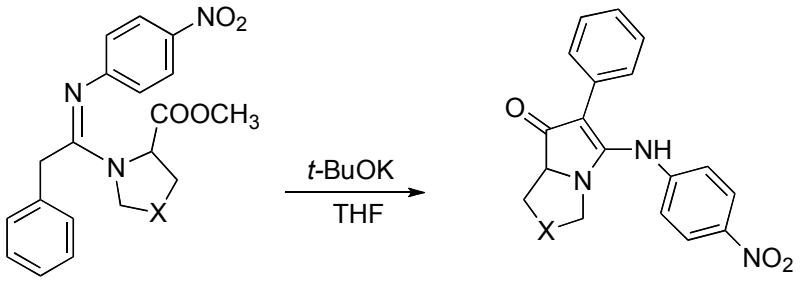
The prolonged heating of N-tosyl-benzylamidines **1a-d** in a 1M solution of *t*-BuOK in THF supplied in good yield the 1*H*-2-methyl-4-phenyl-5-(4-methylbenzensulfonamide)-1,2-dihydropyrrol-3-one **6a** as a single product. The structure of **6a** was supported by analytical and spectroscopic data. Besides the expected signals for the aromatic protons, the ^{1}H NMR spectrum showed at 4.10 ppm a quartet associated with a proton coupled with a methyl group, confirmed by the ^{13}C signal at 57.1 ppm associated with CH-2. On the other hand the ^{13}C NMR spectrum showed three quaternary carbons at 104.8, 166.1 and 180.4 ppm associated with C-4, C-5 and C-3, respectively. The analysis of the spectroscopic data infers the existence of the 3-oxo pyrrole tautomers, as recently reported by Friedrichsen *et al*.[5] for similar structures. Likewise, amidines **1e,f,i** heated in the same reaction conditions supplied the corresponding 1*H*-2-alkyl-4-phenyl-5-(4-methylbenzensulfonamide)-1,2-dihydropyrrol-3-ones **6b-d** (Scheme 4).

The *N*-aryl-benzylamidines **5b,c** also yielded the analogous bicyclic pyrrol-3-ones **7a,b** in basic medium**.** Unfortunately the basic reaction conditions gave rise to the loss of optical activity, explained by the enolization of the intermediate products.



	R^1	R^2
1d	CH_3	OCH_3
1e	$CH(CH_3)_2$	OCH_3
1f	H	OCH_3
1i	CH_2CH_2S	

	R^1	Yield (%)
6a	CH_3	49
6b	$CH(CH_3)_2$	58
6c	H	82
6d	CH_2CH_2SH	36



5b,c **7a,b**

	R^1	Yield (%)
5b, 7a	CH_2	45
5c, 7b	S	39

Scheme 4

Conclusions

In conclusion, in this work the chemical behaviour of phenylacetaldehyde was thoroughly investigated in multicomponent reactions with primary or secondary amines and various azides. The benzylamidines obtained proved to be useful intermediates in heterocyclic synthesis through a straightforward intramolecular condensation. Indeed starting from amidines **1d-f,i** and **5b,c** a new pyrrol-3-ones series were synthesized.

Experimental Section

General Procedures. Mps were determined by a Büchi 510 (capillary) apparatus. IR spectra were measured with a JASCO IR Report 100 instrument (Nujol; cm^{-1}). NMR spectra were obtained with Bruker Advance 300 and Varian Gemini 200 spectrometers in $CDCl_3$ solution at 25 °C, unless otherwise stated. *J* values are given in Hz. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ ADVANTAGE AP electrospray/ion trap equipped instrument using a syringe pump device for the direct injection of sample solutions. 4-[3-(2-iodophenyl)-5-phenyl-4,5-dihydro-3*H*-1,2,3-triazol-4-yl]morpholine **4a**[2d] is a known compound.

General procedure for the reaction of phenylacetaldehyde with tosylazide and primary or secondary amines

The selected amine (10 mmol) was dissolved in 20 ml of CH_2Cl_2 and 7 g of 4Å molecular sieves were added to the solution. Phenylacetaldehyde (10 mmol) and, after 30 min., 10 mmol of tosyl azide were added to the reaction mixture. The solution was stirred at room temperature for 12 h until disappearance of the starting materials (TLC: ethyl acetate/cyclohexane 1:1). The resulting suspension was filtered and evaporated. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:1). When primary amines were used as reactants, two main fractions were collected containing 2-benzyl-*N*-alkyl-*N*'-tosyl-amidine **1** and *N*-alkyl-*N*'-tosyl -formamidine **2**, respectively. Starting from secondary amines, only formamidine **3** was obtained.

***N*-Ethyl-2-phenyl-N'-tosylacetimidamide (1a).** Yield 25%. Yellow oil. ^{1}H NMR (200 MHz) 0.99 (t, *J* 7.3Hz, 3H, CH_3), 2.39 (s, 3H, CH_3Ph), 3.20-3.33 (m, 2H, CH_2), 4.32 (s, 2H, CH_2Ph), 5.25 (s, 1H, NH), 7.09-7.87 (m, 9H, ArH) ppm. ^{13}C NMR (50 MHz) 13.7 (CH_3), 21.6 (CH_3), 37.2 (CH_2), 39.9 (CH_2), 126.5 (CH), 128.3 (CH), 129.4 (CH), 129.6 (CH), 130.3 (CH), 133.4 (C), 141.1 (C), 142.3 (C), 166.7 (C) ppm. ESI-MS: *m/z* 339 [M+Na]. $C_{17}H_{20}N_2O_2S$ (316.36): calcd. C 64.54, H 6.36, N 8.85% found C 64.32, H 6.54, N 8.69%

***N*-Ethyl-*N*'tosyl-formimidamide (2a).** Yield 20%. Mp 100-101°C (white crystals from CH_2Cl_2 and *i*-Pr_2O). ^{1}H NMR (200 MHz) 1.15-1.25 (m, 3H, CH_3), 2.40 (s, 3H, CH_3Ph), 3.29-3.43 (m, 2H, CH_2), 6.80 (sb, 1H, NH), 7.28 e 7.56 (2d, 2+2H, 4ArH), 8.21 (d, *J*=4.80Hz, 1H, CH) ppm. ^{13}C NMR (50 MHz) 13.9 (CH_3), 21.6 (CH_3), 36.9 (CH_2), 126.6 (CH), 129.8 (CH), 139.6 (C),

142.0 (C), 157.9 (CH) ppm. ESI-MS: *m/z* 249 [M+Na], 225 [M-H]. $C_{10}H_{14}N_2O_2S$ (226.24): calcd. C 53.09, H 6.24, N 12.38% found C 52.93, H 6.50, N 12.21%

***N*-Cyclopentyl-2-phenyl-*N*'-tosylacetimidamide (1b).** Yield 35%. Mp 77-78 °C. (white crystal from Et_2O). ^{1}H NMR (200 MHz) 1.12-1.96 (m, 8H, $4CH_2$), 2.41 (s, 3H, CH_3Ph), 4.09-4.19 (m, 1H, CH), 4.24 (s, 2H, CH_2Ph), 5.15 (bs, 1H, NH), 7.15-7.18 (m 9H, ArH) ppm. ^{13}C NMR (50 MHz) 21.8 (CH_3), 23.9 (CH_2), 32.8 (CH_2), 34.1 (CH_2), 40.0 (CH_2), 53.8 (CH), 126.7 (CH), 128.4 (CH), 129.5 (CH), 129.7 (CH), 130.3 (CH), 133.7 (C),141.4 (C), 142.4 (C), 166.2 (C) ppm. ESI-MS: *m/z* 379 [M+Na], 355 [M-H]. $C_{20}H_{24}N_2O_2S$ (356.427): calcd. C 67.40, H 6.79, N 7.86% found C 67.28, H 6.82, N 7.71%

***N*-Cyclopentyl-*N*'formimidamide (2b).** Yield 18%. Mp 116.117 °C (white crystals from Et_2O). ^{1}H NMR (200 MHz) 1.25-2.02 (m, 8H, $4CH_2$), 2.39 (s, 3H, CH_3Ph), 4.16-4.29 (m, 1H, CH), 6.47 (bs, 1H, NH), 7.22-7.81 (m, 4H, ArH), 8.24 (d *J*=5.0Hz, 1H, CH) ppm. ^{13}C NMR (50MHz) 21.6 (CH_3), 23.6 (CH_2), 23.8 (CH_2), 32.7 (CH_2), 33.7 (CH_2), 53.6 (CH), 126.5 (CH), 129.5 (CH), 139.8 (C), 142.6 (C), 157.6 (CH) ppm. ESI-MS: *m/z* 289 [M+Na], 265 [M-H]. $C_{13}H_{18}N_2O_2S$ (266.301): calcd. C 58.63, H 6.81, N 10.52% found C 58.50, H 6.99, N 10.39%

***N*-2-Diphenyl-*N*'-tosylacetimidamide (1c).** Yield 24%. Mp 161-162 °C (white crystal from CH_2Cl_2 and *i*-Pr_2O). ^{1}H NMR (200 MHz) 2.32 (s, 3H, CH_3Ph), 4.26 (s, 2H, CH_2Ph), 7.08-7.61 (m, 10H, ArH), 10.46 (s, 1H, NH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 40.5 (CH_2), 40.7 (CH_2), 121.7 (CH), 126.6 (CH), 127.3 (CH), 128.6 (CH), 129.0 (CH), 129.5 (CH), 129.8 (CH), 130.4 (CH), 133.2 (C), 134.7 (CH), 136.9 (CH), 140.7 (CH), 163.7 (CH), 166.4 (C) ppm. ESI-MS: *m/z* 387.4[M+Na], 363.6[M-H]. $C_{21}H_{20}N_2O_2S$ (364.46): calcd. C 69.20, H 5.53, 7.69% found C 69.12, H 5.77, N 7.48%

***N*-Phenyl-*N*'tosyl-formimidamide (2c).** Yield 12%. Mp 197 °C (white crystal from CH_2Cl_2 and *i*Pr_2O). ^{1}H NMR (200 MHz) 2.41 (s, 3H, CH_3Ph), 7.12-7.82 (m, 10H, ArH + NH), 8.71 (d *J*=5.9Hz, 1H, CH) ppm. ^{13}C NMR (50 MHz) 21.6 (CH_3), 118.6 (CH), 121.4 (CH), 126.9 (CH), 130.2 (CH), 138.8 (C), 139.8 (C), 143.0 (C), 155.2 (CH) ppm. ESI-MS: *m/z* 273 [M-H]. $C_{14}H_{14}N_2O_2S$ (274.08): calcd. C, 61.29; H, 5.14; N, 10.21% found C, 61.43; H, 5.21; N, 10.21%

Methyl 2-(2-phenyl-*N*'-tosylacetimidamido)propanoate (1d). Yield 28%. Mp 95 °C (white crystal from Et_2O). $[\alpha]_D$= -6.3. ^{1}H NMR (300 MHz) 1.29 (d *J*=7.3Hz, 3H, CH_3), 2.41 (s, 3H, CH_3Ph), 3.63 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2Ph), 4.48-4.55 (m, 1H, CH), 5.87-5.90 (bd, 1H, NH), 7.21-7.84 (m, 9H, ArH) ppm. ^{13}C NMR (75 MHz) 17.5 (CH_3), 21.7 (CH_3), 39.8 (CH_2), 50.30 (CH_3), 52.76 (CH), 126.6 (CH), 128.4 (CH), 129.4 (CH), 129.6 (CH), 130.2 (CH), 133.0 (C), 140.8 (C), 142.5 (C), 165.9 (C), 172.5 (C) ppm. ESI-MS: *m/z* 373.3[M-H]. $C_{19}H_{22}N_2O_4S$ (374.45): calcd. C 60.94, H 5.92, N 7.48% found C 60.81, H 6.08, N 7.22%

Methyl 2-(*N*'-tosylformimidamido)propanoate (2d). Yield 20%. Mp75°C (white crystals from CH_2Cl_2 and *i*-Pr_2O). $[\alpha]_D$=+9.25. ^{1}H NMR (300 MHz) 1.44 (d *J*=7.3Hz, 3H, CH_3), 2.39 (s,3H, CH_3Ph), 3.63 (3H, s, CH_3), 4.61-4.68 (m, 1H, CH), 6.43-6.60 (bs, 1H, NH), 7.24 (d *J*=8.4Hz, 2H, ArH), 7.74 (d *J*=8.4, 2H, ArH), 8.27 (d *J*=4.7, 1H, CH) ppm. ^{13}C NMR (75 MHz). 17.7 (CH_3), 21.6 (CH_3), 50.2 (CH_3), 52.9 (CH), 126.7 (CH), 129.5 (CH), 139.1 (C), 142.9 (C), 156.9

(CH), 172.3 (C) ppm. ESI-MS: *m/z* 307 [M+Na], 283 [M-H]. $C_{12}H_{16}N_2O_4S$ (248.33): calcd. C 50.69, H 5.67, N 9.85% found C 50.84, H 5.60, N 9.68%

Methyl 3-methyl-2-(2-phenyl-*N*'-tosylacetamidamido)butanoate (1e). Yield 40%. Mp 115 °C (yellow crystals from CH_2Cl_2 and *i*-Pr_2O). $[\alpha]_D$=-2.8. ^{1}H NMR (300 MHz) 0.65 (d *J*=6.9Hz, 3H, CH_3), 0.74 (d *J*=6.9Hz, 3H, CH_3), 2.00-2.21 (m, 1H, CH), 2.41 (s, 3H, CH_3Ph), 3.61 (s, 3H, CH_3), 4.32 (AB system *J*=17.6 Hz, 2H, CH_2Ph), 4.42-4.52 (m, 1H, CH), 5.66 (bd, 1H, NH), 7.25-7.84 (m, 9H, ArH) ppm. ^{13}C NMR (75 MHz) 17.9 (CH_3), 18.9 (CH_3), 21.7 (CH), 30.9 (CH_3), 39.9 (CH_2), 52.4 (CH), 126.5 (CH), 128.5 (CH), 129.4 (CH), 129.7 (CH), 130.3 (CH), 133.0 (C), 140.7 (C), 142.5 (C), 166.6 (C), 171.3 (C) ppm. ESI-MS: *m/s* 425 [M+Na], 401[M-H]. $C_{21}H_{26}N_2O_4S$ (402.51): calcd. C 62.66, H 6.51, N 6.96% found C 62.51, H 6.58, N 6.66%

Methyl 3-methyl-2-(2-phenyl-*N*'-tosylformimidamido)butanoate (2e). Yield 30%. Mp 95 °C (withe crystals from CH_2Cl_2 and *i*-Pr_2O). $[\alpha]_D$=-1.4. ^{1}H NMR (300 MHz) 0.88-1.04(m, 6H, 2CH_3), 2.17-2.29 (m, 1H, CH), 2.39 (s, 3H, CH_3Ph), 3.71 (s, 3H, CH_3), 4.67-4.70 (m, 1H, CH), 6.35 (bs, 1H, NH), 7.48 (d, *J*=8.0Hz, 2H, ArH), 7.73 (d *J*=8.0Hz, 2H, ArH), 8.33 (d *J*=2.8Hz, 1H, CH) ppm. ^{13}C NMR (75 MHz) 18.0 (CH_3), 18.9 (CH_3), 21.7 (CH), 31.2 (CH_3), 52.6 (CH_3), 59.3 (CH), 126.7 (CH), 129.5 (CH), 139.1 (C), 142.9 (C), 157.9 (CH), 171.4 (C) ppm. ESI-MS: *m/s* 335 [M+Na], 311 [M-H]. $C_{14}H_{20}N_2O_4S$ (312.38) calcd. C 53.83, H 6.45, N 8.97% found C 53.70, H 6.64, N 8.72%

Methyl 2-(2-phenyl-*N*'-tosylacetimidamido)acetate (1f). Yield 28%. Yellow oil. ^{1}H NMR (200 MHz) 2.42 (s, 3H, CH_3Ph), 3.63 (s, 3H, CH_3), 3.98 (AB system, *J*=21.6Hz, 2H, CH_2), 4.32 (s, 2H, CH_2Ph), 5.85 (bs, 1H, NH), 7.22-7.90 (m, 9H, ArH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 39.7 (CH_2), 43.5 (CH_2), 52.7 (CH_3), 126.7 (CH), 128.4 (CH), 129.4 (CH), 129.7 (CH), 130.3 (CH), 132.9 (C), 140.6 (C), 142.6 (C), 166.7 (C), 169.3 (C) ppm. ESI-MS: *m/z* 359 [M-H]. $C_{18}H_{20}N_2O_4S$ (360.43): calcd. C 59.98, H 5.59, N 7.77% found C 59.79, H 5.67, N 7.61%

Methyl 2-(*N*'-tosylformimidamido)acetate (2f). Yield 22%. Mp 85 °C (Yellow crystals from CH_2Cl_2 and *i*-Pr_2O). ^{1}H NMR (200 MHz) 2.40 (s, 3H, CH_3Ph), 3.76 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 6.44 (bs, 1H, NH), 7.25 and 7.75 (2d *J*=8.7Hz, 2+2H, ArH), 8.33(d, *J*=4.8Hz,1H, CH) ppm. ^{13}C NMR (75 MHz) 21.6 (CH_3), 43.2 (CH_2), 52.9 (CH_3), 126.9 (CH), 129.6 (CH), 138.9 (C), 143.1 (C), 157.3 (CH), 169.2 (C) ppm. ESI-MS: *m/z* 293 [M+Na]. $C_{11}H_{14}N_2O_4S$ (270.3): calcd C 48.88, H 5.22; N 10.36% found C 48.81, H 5.37, N 10.21%

Methyl 3-phenyl-2-(2-phenyl-*N*'-tosylacetimido)propanoate (1g). Yield 27%. Mp 138 °C (whitish crystals from Et_2O). $[\alpha]_D$=+42.4 ^{1}H NMR (200 MHz) 2.43 (s, 3H, CH_3Ph), 2.97 (ABX system *J*= 5.5, 5.9 and 13.9Hz, 2H, CH_2Ph), 3.61 (s, 3H, CH_3), 4.34 (AB system *J*=17.59Hz, 2H, CH_2), 4.72 (dd *J*=5.5 and 5.9Hz, 1H, CH), 5.68 (bs, 1H, NH), 6.72-7.85 (m, 14H, ArH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 36.8 (CH_2), 39.8 (CH_2), 52.6 (CH_3), 55.2 (CH), 126.6 (CH), 127.4 (CH), 128.4 (CH), 128.9 (CH), 129.1 (CH), 129.4 (CH), 129.6 (CH), 130.2 (CH), 132.7 (C), 135.1 (C), 140.8 (C), 142.5 (C), 165.9 (C), 171.0 (C) ppm. ESI-MS: *m/z* 473 [M+Na], 449 [M-H]. $C_{22}H_{26}N_2O_4S$ (450.55): calcd. C 66.64, H 5.82, N 6.22% found C 66.58, H 5.98, N 6.07%

Methyl 3-phenyl-2-(*N*'-tosylformimidamido)propanoate (2g). Yield 25%. Mp 110 °C (white crystals from CH_2Cl_2 and Et_2O). $[\alpha]_D$=+155.1. ^{1}H NMR (200 MHz) 2.41 (s, 3H, CH_3), 3.19 (ABX system *J*= 5.1, 5.5 and 14.3Hz, 2H, CH_2Ph), 3.73 (s, 3H, CH_3), 4.93 (dd, *J*=5.1 and 5.5Hz, 1H, CH), 6.22 (bs, 1H, NH), 6.92-7.82 (m, 9H, ArH), 8.26 (d *J*=3.6Hz, 1H, CH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 37.0 (CH_2), 52.8 (CH_3), 55.2 (CH), 126.8 (CH), 127.5 (CH), 128.8 (CH), 129.4 (CH), 129.6 (CH), 135.1 (C), 139.1 (C), 143.0 (C), 156.8 (CH), 170.9 (C) ppm. ESI-MS: *m/s* 383 [M+Na], 359 [M-H]. $C_{18}H_{20}N_2O_4S$ (360.43): calcd. C 59.98, H 5.59, H 7.77% found C 59.74, H 5.66, N 7.54%

Methyl 2-phenyl-2-(2-phenyl-*N*'-tosylacetimidamido)acetate (1h). Yield 20%. Mp 60 °C (yellow crystals from Et_2O). $[\alpha]_D$=-57.3. ^{1}H NMR (200 MHz) 2.41 (s, 3H, CH_3Ph), 3.58 (s, 2H, CH_2), 4.31 (AB system *J*=17.6 Hz, 2H, CH_2), 5.40 (d, *J* 6.3 Hz, 1H, CH), 6.33 (bd *J*=6.3, 1H, CH), 7.05-7.63 (m, 14H, ArH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 39.8 (CH_2), 53.1 (CH_3), 58.5 (CH), 126.5 (CH), 127.4 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 129.2 129.7 (CH), 130.2 (CH), 133.0 (C), 135.5 (C), 140.6 (C), 142.4 (C), 165.5 (C), 170.5 (C) ppm. ESI-MS: *m/z* 459[M+Na], 435[M-H]. $C_{24}H_{24}N_2O_4S$ (436.52): calcd. C 66.03, H 5.54, N 6.42% found C 65.98, H 5.66, N 6.32%

Methyl 2-phenyl-2-(*N*'-tosylformimidate)acetate (2h). Yield 18%. Mp 104 °C (whitish crystals from CH_2Cl_2 and *i*-Pr_2O). $[\alpha]_D$=-86.92. ^{1}H NMR (200 MHz) 2.34 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 5.62 (d *J*=7.0 Hz, 1H, CH), 6.91 (bs, 1H, NH), 7.15-7.82 (m, 9H, ArH), 8.29 (d *J*=4.7 Hz, 1H, CH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 53.3 (CH_3), 58.3 (CH); 126.6 (CH), 127.7 (CH), 129.1 (CH), 129.4 (CH), 135.1 (C), 139.1 (C), 140.8 (C), 156.6 (CH), 170.4 (C) ppm.
ESI-MS: *m/z* 345 [M-H]. $C_{17}H_{18}N_2O_4S$ (346.40): calcd. C 58.94, H 5.24, N 8.09% found C 58.77, H 5.46, N 7.98%

***N*-(2-Oxo-tetrahydrothiophen-3-yl)-2-phenyl-*N*'-tosylacetimidamide (1i).** Yield 35%. Mp 135 °C (light pink crystals from CH_2Cl_2 and *i*Pr_2O). ^{1}H NMR (200 MHz) 1.65-1.87 (m, 1H, CH), 3.41 (s, 3H, CH_3Ph), 2.82-2.94 (m, 1H, CH), 3.11-3.48 (m, 2H, CH_2), 4.26 (AB system *J*=17.6Hz, 2H, CH_2Ph), 4.36-4.52 (m, 1H, CHN), 5.74 (bs, 1H, NH), 7.12-7.82 (m, 9H, ArH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 27.7 (CH_2), 31.1 (CH_2), 39.6 (CH_2), 61.1 (CH), 126.7 (CH), 128.5 (CH), 129.6 (CH), 129.7 (CH), 130.2 (CH), 132.6 (C), 140.3 (C), 142.8 (C), 167.3 (C), 203.9 (C) ppm. ESI-MS: *m/z* 388 [M-H]. $C_{19}H_{20}N_2O_3S_2$ (388.5): calcd. C 58.74, H 5.19, N 7.21% found C 58.80, H 5.14, N 7.50%

***N*-(2-Oxo-tetrahydrothiophen-3-yl)-*N*'-tosylformimidamide (2i).** Yield 15%. Mp 143 °C (white crystals from CH_2Cl_2 and *i*-Pr_2O). ^{1}H NMR (200 MHz) 1.92-2.08 (m, 1H, CH), 2.39 (s, 3H, CH_3Ph), 2.86-3.17 (m, 1H, CH), 3.21-3.41 (m, 2H, CH_2), 4.41-4.66 (m, 1H, CHN), 6.85 (bs, 1H, NH), 7.04-7.74 (m, 4H, ArH), 8.35 (d, *J*=4.7 Hz, 1H, CH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 27.8 (CH_2), 31.1 (CH_2), 60.9 (CH), 126.8 (CH), 129.7 (CH), 138.6 (C), 134.3 (C), 158.1 (CH), 208.9 (C) ppm. ESI-MS: *m/z* 299 [M+H]. $C_{12}H_{14}N_2O_3S_2$ (298.38): calcd. C 48.30, H 4.73, N 9.39% found C 48.19, H 4.89, N 9.17%

Methyl 1-[(tosylimino)methyl]-pyrrolidine-2-carboxylate (3). Yield 62%. Mp 124-125 °C (white crystals from *i*-Pr_2O). ^{1}H NMR (200 MHz) 1.85-2.42 (m, 6H, 3CH_2), 3.52-3.62 (m, 3H,

CHPh), 3.78-3.82 (s, 3H, CH_3), 4.39-4.49 (m, 1H, CH), 7.31 e 7.78 (2d, *J*=8. Hz, 4H, ArH), 8.39 (s, 1H, CH) ppm.^{13}C NMR (75 MHz) (*E* and *Z* isomers) 21 (CH_3), 23.2 and 24.2 (CH_2), 29.8 and 29.9 (CH_2), 47.3 and 50.4 (CH_2), 52.5 and 53.6 (CH), 59.4 and 52.0 (CH_3), 126.6 and 126.8 (CH), 129.4 and 129.6 (CH), 139.5 and 139.6 (C), 142.6 and 142.7 (CH), 156.5 and 157.7 (C), 171.2 and 171.4 (C) ppm. $C_{14}H_{18}N_2O_4S$ (310.37): calcd. C 54.18, H 5.85, N 9.03% found C 54.37, H 5.88, N 8.88%

General procedure for the reaction of phenylacetaldehyde with 4-nitrophenyl azide and secondary amines

The selected amine (6 mmol) was dissolved in 20 mL of CH_2Cl_2 and 7 g of 4Å molecular sieves were added (if the amine used was a hydrochloride, 10 mmol of TEA were added). Then, to the mixture, phenylacetaldehyde (6 mmol) was added and, after 30 min, 4-nitrophenylazide (6 mmol). The mixture was stirred for 20 h until disappearance of the starting materials (TLC ethyl acetate/ cycloexane 1:1). The reaction mixture was filtered, washed with fresh water, dried with Na_2SO_4 and evaporated at reduced pressure. The residue was purified by chromatography over silica gel to supply triazoline **4**.

Methyl 1-[(4S,5R)3-(4-nitrophenyl)-5-phenyl-4,5-dihydro-3*H*-1,2,3,triazol-4-yl]pyrrolidine-2-carboxylate and methyl 1-[(4*R*,5*S*)3-(4-nitrophenyl)-5-phenyl-4,5-dihydro-3*H*-1,2,3,triazol-4-yl] pyrrolidine-2-carboxylate (4b). Yield 48%, Mp 135 °C (white crystals from *i*-Pr_2O). ^{1}H NMR 1.75-2.78 (m, 6H, 3CH_2), 3.57-3.69 (m, 1H, CH), 3.57 and 3.77 (2s, 3H, CH_3), 5.18 and 5.19 (2d *J*=3.1 and *J*=3.3 Hz, 1H, CHPh), 5.49 and 5.68 (2d *J*=3.3 and *J*=3.1 Hz, 1H, CHN), 7.00-8.34 (m, 9H, ArH) ppm. ^{13}C NMR 23.4 (CH_2), 30.2 (CH_2), 45.8 (CH_2), 52.4 (CH), 59.4 (CH_3), 76.0 (CH), 81.1 (CH), 115.5 (CH), 125.7 (CH), 126.8 (CH), 128.8 (CH), 129.6 (CH), 136.4 (C), 142.9 (C), 144.9 (C), 173.5 (C) ppm. $C_{20}H_{21}N_5O_4$ (395.41): calcd. C 60.75, H 5.35, N 17.71% found C 60.54, H 5.55, N 17.66%

Methyl 3-[(4S,5R)3-(4-nitrophenyl)5-phenyl-4,5-dihydro-3H-1,2,3-triazol-4-yl]-thiazolidine-4-carboxylate and methyl 3-[(4R,5S)3-(4-nitrophenyl)5-phenyl-4,5-dihydro-3H-1,2,3-triazol-4-yl]-thiazolidine-4-carboxylate (4c). Yield 47%. Mp 95 °C (white crystals from *i*-Pr_2O). ^{1}H NMR (200 MHz) 3.1-3.3 (m, 2H, CH_2), 3.49-3.77 (2s, 3H, CH_3), 3.82-3.91 (m, 2H, CH_2), 3.60-4.30 (m, 3H, CH_2 + CH), 5.00 and 5.08 (2d *J*=4 *J*=3.3Hz, 1H, CH), 6.00 (2d *J*=4 *J*=3.3Hz, 1H, CH), 7.01- 8.30 (m, 9H, ArH) ppm. ^{13}C NMR (50 MHz) 50.1 (CH_2), 52.8 (CH), 53.2 (CH_2), 64.7 (CH_3), 78.9 (CH), 83.8 (CH), 115.6 (CH), 125.3 (CH), 127.1 (CH), 128.2 (CH), 129.9 (CH), 136.5 (C), 144.8 (C), 157.1 (C), 171.7 (C) ppm. $C_{19}H_{19}N_5O_4S$ (413.45): calcd. C 55.19, H 4.63, N 16.94% found C 55.02, H 4.80, N 16.74%

General procedure for the transformations dihydrotriazole-amidines

Dihydrotriazole **4** (5 mmol) was suspended in toluene (10 mL) and heated at reflux for 8 h. At the end, the solution was evaporated under reduced pressure and the residue chromatographed with ethyl acetate-cyclohexane (1:4) yielding pure **5**.

Methyl 1-[1-(4-nitrophenylimino)-2-phenylethyl]pyrrolidine-2-carboxylate (5b). Yield 55%. Light yellow oil. $[\alpha]_D$=+20.85. ^{1}H NMR (200 MHz) 1.82-2.45 (m, 4H, 2CH_2), 3.35-3.55 (m, 2H, CH_2N), 3.55-3.82 (m, 2H, CH_2Ph), 3.70 (s, 3H, CH_3), 4.50-4.68 (m, 1H, CH), 6.75 (d, *J*= 8.5Hz, 2H, ArH), 7.15-7.39 (m, 5H, ArH), 8.04 (d, *J*=8.5, 2H, ArH) ppm. ^{13}C NMR (50 MHz) 25.2 (CH_2), 29.8 (CH_2), 35.6 (CH_2), 47.9 (CH_2), 52.4 (CH), 60.49 (CH_3), 122.8 (CH), 125.2 (CH), 127.2 (CH), 128.2 (CH), 129.3 (CH), 135.4 (C), 142.7 (C), 155.4 (C), 158.1 (C), 174.0 (C) ppm. ESI-MS: *m/z* 368 [M+H]. $C_{20}H_{21}N_3O_4$ (367.4): calcd. C 65.38, H 5.76, N 11.44% found C 65.24, H 5.88, N 11.26%

Methyl 3-[1-(4-nitrophenylimino)-2-phenylethyl]thiazolidine-4-carboxylate (5c). Yield 51%. Light yellow oil. ^{1}H NMR (300 MHz) 3.15-3.36 (m, 2H, CH_2), 3.60-3.91 (m, 2H, CH_2Ph), 3.77 (s, 3H, CH_3), 4.41-4.48 (m, 1H, CH), 4.44-4.62 (m, 1H, CH), 5.00-5.21 (m, 1H, CH), 6.78 (d, *J*=8.8, 2H, ArH), 7.17-7.37 (m, 5H, ArH), 8.06 (d, *J*=8.8, 2H, ArH) ppm.^{13}C NMR (75 MHz) 33.5 (CH_2), 35.7 (CH_2), 49.9 (CH_2), 52.8 (CH), 62.5 (CH_3), 122.3 (CH), 125.2 (CH), 127.4 (CH), 128.0 (CH), 129.4 (CH), 134.6 (C), 143.0 (C), 154.8 (C), 156.9 (C), 171.3 (C) ppm. ESI-MS: *m/z* 386 [M+H]. $C_{19}H_{19}N_3O_4S$ (385.44): calcd. C 59.21, H 5.97, N 10.90% found C 59.07, H 5.03, N 10.88%

General procedure for cyclization: Amidines **1d-f,i** and **5b,c** (1 mmol) were dissolved in 10 mL of anhydrous THF in N_2 atmosphere. To the solution was added 1 mL of *t*-BuOK 1M solution. The stirred mixture was refluxed for 2-10 h until disappearance of the starting material [TLC ethyl acetate-cyclohexane (7:3)]. The resulting solution was evaporated and the crude taken up with ethyl acetate and washed with aqueous acid. The neutral organic phase was dried on Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized with the indicated solvent or, if necessary, chromatographed over a silica gel column (eluent from ethyl acetate-cycloexane 7:3 to ethyl acetate).

4-Methyl-*N*-(5methyl-4-oxo-3-phenyl-4,5-dihydro-1*H*-pyrrol-2-yl)benzensolfonamide (6a). Yield 49%. Mp 90 °C (light yellow crystals from *i*-Pr_2O). ^{1}H NMR (200 MHz) 1.39 (d *J*=7.9, 3H, CH_3), 2.41 (s, 3H, CH_3Ph), 2.75-4.10 (bs, 2H, 2NH), 4.00-4.21 (m, 1H, CH), 7.16-7.83 (m, 9H, ArH) ppm. ^{13}C NMR (50 MHz) 17.6 (CH_3), 21.7 (CH_3), 57.1 (CH), 104.8 (C), 126.6 (CH), 127.2 (CH), 128.6 (CH), 128.9 (CH), 129.6 (CH), 129.9 (C), 139.0 (C), 143.5 (C), 166.1 (C), 180.4 (C) ppm. ESI-MS: *m/z* 343 [M+H]. $C_{18}H_{18}N_2O_3S$ (342.41): calcd. C 63.14, H 5.30, N 8.18% found C 62.98, H 5,45, N 8.06%

***N*-(5-Isopropyl-4-oxo-3-phenyl-4,5-dihydro-1*H*-pyrrol-2-yl)-4-methylbenzensulfonamide (6b).** Yield 58%. Glassy solid. ^{1}H NMR (200 MHz) 0.65 (d *J*=6.6Hz, 3H, CH_3), 1.02 (d *J*=7.0, 3H, CH_3), 2.03-2.36 (m, 1H, CH), 2.40 (s, 3H, CH_3Ph), 2.60-3.45 (bs, 2H, 2NH), 3.95-4.02 (m, 1H, CH), 7.21-7.89 (m, 9H, ArH) ppm . ^{13}C NMR (50 MHz) 14.7 (CH_3), 20.7 (CH_3), 29.9 (CH), 66.1 (CH), 106.8 (C), 126.7 (CH), 127.3 (CH), 128.7 (CH), 128.9 (CH), 129.7 (CH), 135.6 (C), 138.8 (C), 142.6 (C), 167.1 (C), 203.0 (C) ppm. ESI-MS: *m/z* 371 [M+Na], 369 [M-H]. $C_{20}H_{22}N_2O_3S$ (370.43): calcd. C 64.84, H 5.99, N 7.56% found C 64.75, H 6.08, N 7.34%

4-Methyl-*N*-(4-oxo-3-phenyl-4,5-dihydro-1*H*-pyrrol-2-yl)benzensulfonamide (6c). Yield 82%. Mp 85 °C (light yellow crystal from *i*-Pr_2O). ^{1}H NMR (300 MHz) 2.38 (s, 3H, CH3), 3.00-4.40 (bs, 2H, 2NH), 3.90-4.10 (m, 2H, CH2), 7.07-7.81 (m, 9H, ArH) ppm. ^{13}C NMR (75 MHz) 21.6 (CH_3), 50.5 (CH_2), 106.7 (C), 126.4 (CH), 127.0 (CH), 128.2 (CH), 128.8 (CH), 129.7 (CH), 130.1 (C), 139.5 (C), 143.2 (C), 168.8 (C), 174.3 (C) ppm. ESI-MS: *m/z* 327 [M-H]. $C_{17}H_{16}N_2O_3S$ (328.39): calcd. C 62.18, H 4.91, N 8.53% found C 62.05, H 5.11, N 8.39%

***N*-[5-(2-Mercaptoethyl)-4-oxo-3-phenyl-4,5-dihydro-1*H*-pyrrol-2-yl]-4-methylbenzen sulfonamide (6d).** Yield 36%. Mp 98-100 °C (light yellow crystal from *i*Pr_2O). ^{1}H NMR (200 MHz) 2.41 (s, 3H, CH_3Ph), 2.60-3.45 (bs, 2H, 2NH), 2.87-3.17 (m, 4H, 2CH_2), 4.28-4.39 (m, 1H, CH), 7.11-8.17 (m, 9H, ArH), 8.11-8.17 (bs, 1H, SH) ppm. ^{13}C NMR (50 MHz) 21.7 (CH_3), 31.6 (CH_2), 34.0 (CH_2), 60.9 (CH), 101.6 (C), 126.5 (CH), 127.8 (CH), 128.9 (CH), 129.6 (CH), 130.8 (CH), 134.3 (C), 134.1 (C), 139.3 (C), 167.3 (C), 170.0 (C) ppm. ESI-MS: *m/z* 389 [M+H]. $C_{19}H_{20}N_2O_3S_2$ (388.5): calcd. C 58.74, H 5.19, N 7.21% found C 58.60, H 5.33, N 7.15%

3-(4-Nitrophenylamino)-2-phenyl-5,6,7,7a-tetrahydropyrriolizin-1-one (7a). Yield 45%. Mp 235°C (light yellow crystals from *i*-Pr_2O). ^{1}H NMR (DMSO, 300 MHz) 1.75-1.81 (m, 1H, CH), 1.82-2.05 (m, 2H, CH_2), 2.12-2.36 (m, 1H, CH), 2.81-3.12 (m, 2H, CH_2), 4.08-4.22 (m, 1H, CHN), 7.02-8.18 (m, 9H, ArH), 10.18 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO, 75 MHz) 27.4 (CH_2), 27.5 (CH_2), 49.4 (CH_2), 70.5 (CH), 102.6 (C), 119.6 (CH), 125.9 (CH), 127.9 (CH), 128.7 (CH), 130.1 (CH), 133 (C), 141.9 (C), 147.4 (C), 169.4 (C), 197.1 (C) ppm. ESI-MS: *m/z* 335 [M+H]. $C_{19}H_{17}N_3O_3$ (335.36): calcd. C 68.05, H 5.11, N 12.53% found C 67.89, H 5.26, N 12.48%

4-(4-Nitrophenylkamino)-6-phenyl-1,7-dihydropyrrolo[1,2-*c*]thiazol-7(3*H*)-one (7b). yield 39%. Mp 110 °C (light yellow crystals from *i*-Pr_2O). ^{1}H NMR (DMSO, 200 MHz) 3.06-3.38 (m, 2H, CH_2), 3.88-4.61 (m, 3H, CH and CH_2), 6.94-8.05 (m, 9H, ArH), 10.34 (bs, 1H, NH) ppm. ^{13}C NMR (DMSO, 50 MHz) 32.2 (CH_2), 53.8 (CH_2), 70.5 (CH), 106.0 (C), 119.8 (CH), 125.7 (CH), 126.5 (CH), 128.0 (CH), 128.7 (CH), 132.0 (C), 142.1 (C), 147.0 (C), 168.6 (C), 196.9 (C) ppm. ESI-MS: *m/z* 354 [M+H]. $C_{18}H_{15}N_3O_3S$ (353.39): calcd. C 61.02, H 4.33, N 11.69% found C 60.88, H 4.33, N 11.69%

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