Organic Reaction in Water: A Highly Efficient and Environmentally Friendly Synthesis of Spiro Compounds Catalyzed by L-Proline

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We have developed a clean, simple and efficient method for the synthesis of spiro compounds by three-component reaction of isatins (= 1*H*-indole-2,3-diones) or acenaphthylene-1,2-dione, 1,3-diphenyl-1*H*-pyrazoles-5-amines, and tetronic acid (= furan-2,4-(3*H*,5*H*)-dione or 2-hydroxy-1,4-naphthoquinone in the presence of a catalytic amount of L-proline in aqueous media. The advantages of this procedure are mild reaction conditions, high yields of products, operational simplicity, and easy workup procedures employed.

Introduction. – Multicomponent reactions (MCRs), because of their efficiency, simple procedures, convergence, and facile execution, are among the best tools for the synthesis of organic compounds. Therefore, the design of novel MCRs for the synthesis of different groups of compounds, especially of those which are biologically active, have attracted great attention. Different research groups active in the areas such as drug discovery, material science, natural products, and organic synthesis have used this synthetic method [1–5]. Indole and dihydroindol are important moieties of a large number of natural products and medicinal agents [6], and several dihydroindoles, spiro-connected with heterocycles at C(3), have shown high biological activities [7–9]. The spiro-oxindole system is the core structure of many pharmacological agents and natural alkaloids [10–13]. For example, spirotryprostatins A and B, two natural alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as novel inhibitors of microtubule assembly. Other cytostatic alkaloids such as pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors [14] (*Fig.*).

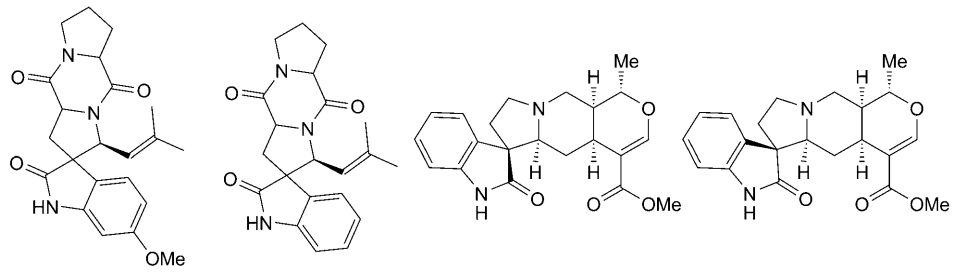


Figure. *Representatives of Spirooxindole-Containing Compounds*

As a consequence, several methods have been reported for the preparation of spiro-oxindole-containing heterocycles [15–17].

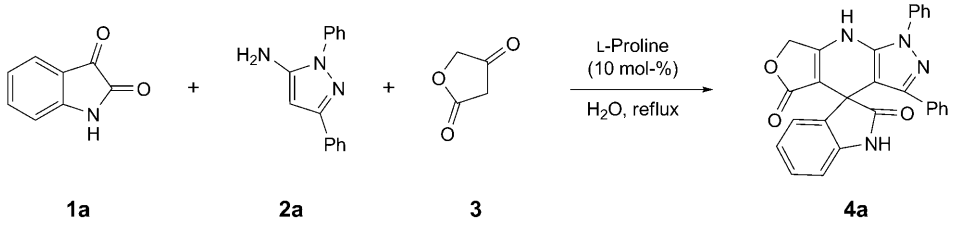
As small organic molecules like cinchona alkaloids, L-proline has been used as an inexpensive, nontoxic, readily available catalyst for various transformations under mild and convenient conditions, affording the corresponding products in excellent yields and with high selectivity [18]. On the other hand, recently, L-proline has been found to be very effective in enamine-based direct catalytic asymmetric aldol [19], *Mannich* [20], *Michael* [21], *Diels–Alder* [22], and *Knoevenagel* reactions [23]. More recently, L-proline and its derivatives have been used in MCRs.

Considering the reports mentioned above, development of new and simple MCRs for synthesis of spiro compounds catalyzed by L-proline emerged as an interesting field to study.

Results and Discussion. – We have recently reported several novel synthesis of spirooxindoles *via* isatin based MCRs [24–28]. Here, we report an environmentally benign three-component reaction for the synthesis of new spiro-oxindoles catalyzed by L-proline.

In a pilot experiment, a mixture of isatin (=1*H*-indole-2,3-dione; **1a**), 1,3-diphenyl-1*H*-pyrazol-5-amine **2a** and tetronic acid (=furan-2,4(3*H*,5*H*)-dione; **3**) in the presence of a catalytic amount of L-proline in refluxing H_2O was stirred for 6 h. After completion of the reaction (monitored by TLC), the crude product was separated from the mixture by filtration and washed with EtOH (5 ml) to afford product **4a** in 91% yield (*Scheme 1*).

Scheme 1



We examined this reaction in the absence and presence of several catalysts. The results are collected in *Table 1*. After screening a number of catalysts, it should be mentioned, that, when reactions were carried out in the absence of catalyst, the product was detected only in trace amounts (*Table 1*, *Entry 1*). The best result was obtained with 10 mol-% of L-proline as the catalyst in refluxing H_2O (*Entry 3*). Using lower amounts of catalyst resulted in lower yields, while higher amounts of catalyst did not affect the reaction times and yields (*Table 1*). To study the effect of temperature, we also performed three experiments at 70° and 80°, and under reflux conditions. It was observed that a lower reaction temperature led to a lower yield (*Table 1*).

To investigate the scope and limitations of this reaction, the procedure was extended to various isatins **1a**–**1e** and 1*H*-pyrazol-5-amines **2a**–**2d**. As compiled in *Table 2*, the reactions proceeded very efficiently, leading to the formation of the

Table 1. *Optimization of Reaction Conditions*

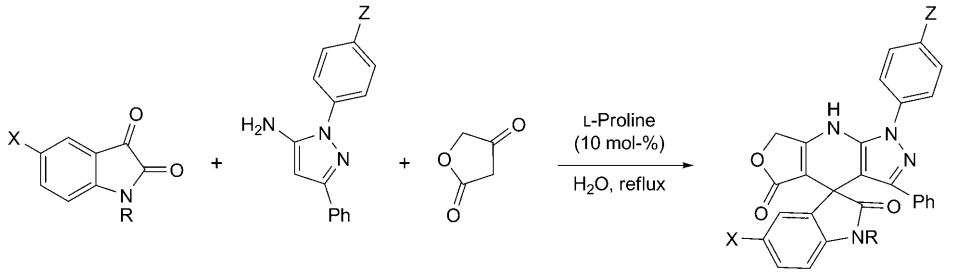
Entry	Catalyst [mol-%]	Conditions	Time [h]	Yield [%]
1	None	reflux	10	trace
2	L-Proline (5%)	reflux	6	76
3	L-Proline (10%)	reflux	6	91
4	L-Proline (15%)	reflux	6	92
5	L-Proline (10%)	70°	6	78
8	L-Proline (10%)	80°	6	84
9	$InCl_3$ (10%)	reflux	10	54
10	SSA (10%)[a])	reflux	10	47
11	HPAs (10%)[b])	reflux	10	68
12	AcOH (10%)	reflux	10	43
13	$ZnCl_2$(10%)	reflux	10	trace

[a]) SSA = Silica sulfuric acid. [b]) HPAs = Heteropoly acids.

corresponding highly functionalized spiro-oxindoles **4a**–**4k** in excellent yields (*Table 2*).

To further study the potential of this protocol for spiro-oxindole synthesis, we investigated the reaction of 2-hydroxy-1,11-naphthoquinone **5** and isatins **1** with 1*H*-pyrazol-5-amines **2**, and obtained 1,11-dihydro-spiro[benzo[*g*]pyrazolo[3,4-*b*]quinoline-4,3′-indole]-2′,5,10(1′*H*)-triones **6** in 73–82% yields under the same reaction conditions (*Table 3*).

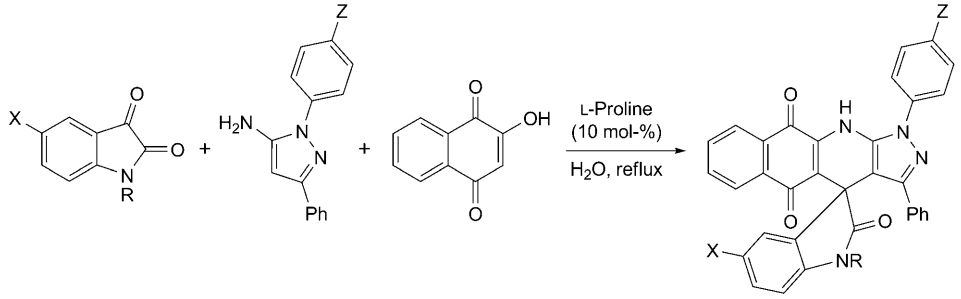
Table 2. *Synthesis of Spiro-oxindoles* **4**



1a – 1e **2a – 2d** **3** **4a – 4k**

Product	X	R	Z	Time [h]	Yield [%]
4a	H	H	H	6	90
4b	H	H	Br	6.5	88
4c	H	H	NO_2	7	91
4d	Br	Et	H	6	78
4e	Br	Et	Br	6.5	83
4f	Br	Et	NO_2	6.5	76
4g	NO_2	H	H	6	79
4h	NO_2	H	MeO	6	86
4i	NO_2	H	NO_2	6.5	77
4j	Me	H	H	6	82
4k	H	Bn	H	7.5	91

Table 3. *Synthesis of Spiro-oxindoles* **6**



1a – 1e **2a – 2d** **5** **6a – 6m**

Product	X	R	Z	Time [h]	Yield [%]
6a	H	H	H	6	93
6b	H	H	MeO	6.5	81
6c	H	H	Br	6	92
6d	H	H	NO_2	6	93
6e	Br	Et	H	6	90
6f	Br	Et	MeO	6.5	81
6g	Br	Et	Br	7.5	79
6h	Br	Et	NO_2	6.5	86
6i	NO_2	H	H	6	80
6j	NO_2	H	NO_2	6	82
6k	Me	H	H	7	90
6l	H	Bn	H	7.5	91
6m	H	Bn	Br	7	85

As expected, when isatin **1** was replaced by acenaphthylene-1,2-dione **7**, spiro compounds **8** were obtained in good yield under the same reaction conditions (*Table 4*).

The workup of these very clean reactions involves only a filtration and a simple washing step with EtOH. Using this simple purification protocol, the desired products are obtained in good purity. Compounds **4**, **6**, and **8** are stable solids structures which were established by IR, and ^{1}H- and ^{13}C-NMR spectroscopy, and elemental analysis. This method, based on a three-component L-proline-catalyzed reaction in H_2O, is the most simple and convenient procedure, and would be applicable to the synthesis of different types of spiro-oxindole-containing heterocycles.

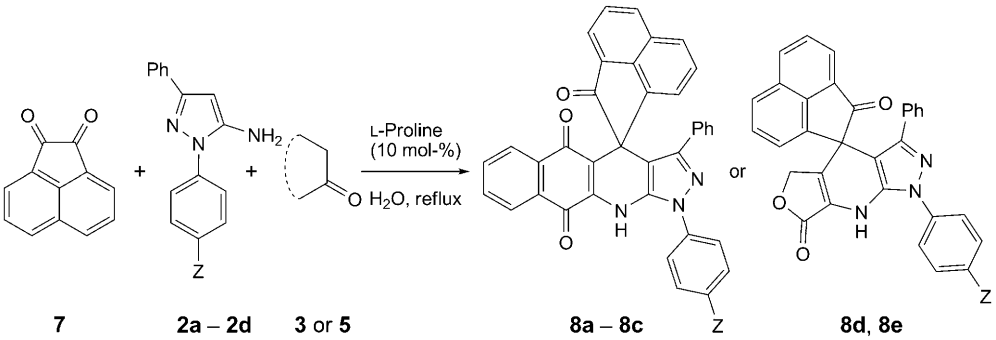
Although the mechanism of this reaction has not been established experimentally, the proposed mechanism is depicted in *Scheme 2*.

In brief, a convenient, clean, and environmentally friendly method was developed for the synthesis of spiro compounds in the presence of L-proline in aqueous media. The simple experimental procedure and purification, and good yields are the advantages of the present method.

Experimental Part

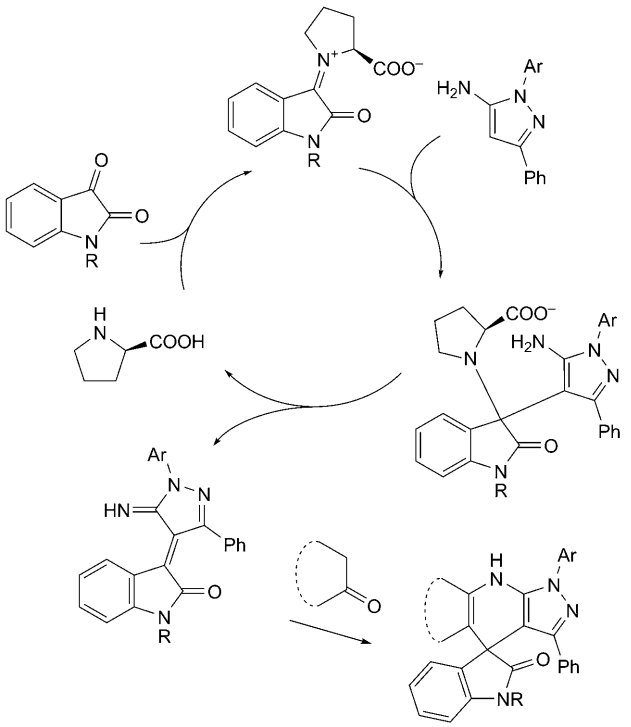
General. The chemicals used in this work were obtained from *Acros* and *Merck*, and were used without purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Bomem MB-Series*

Table 4. *Synthesis of Spiro Compounds* **8**



Product	Z	Time [h]	Yield [%]
8a	H	6	80
8b	MeO	7	76
8c	Br	7	77
8d	H	6.5	82
8e	NO_2	8	77

Scheme 2



FT-IR spectrophotometer. ^{1}H-NMR Spectra: *Bruker DRX-300 Avance* spectrometer at 300.13 MHz. MS: *Finnigan-MAT 8430* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses: *Heracus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Spiro Compounds: A mixture of isatins or acenaphthylene-1,2-dione (1 mmol), 1*H*-pyrazol-5-amines (1 mmol), tetronic acid or hydroxynaphthoquinone (1 mmol), and L-proline (0.1 mmol) in refluxing H_2O (5 ml) was stirred for 6–7 h. The progress of reaction was monitored by TLC. After completion of reaction, the mixture was filtered, and the precipitate was washed with H_2O and then EtOH (5 ml) to afford the pure products.

*1,8-Dihydro-1,3-diphenylspiro[furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-4,3′-indole]-2′,5(1′*H*,7*H*)-dione* (**4a**). Yellow powder. M.p. 258–261°. IR (KBr): 3383, 3205, 1721, 1669. ^{1}H-NMR ((D$_6$)DMSO): 4.98 (*s*, CH_2); 6.81–8.32 (*m*, 14 arom. H); 10.94 (*s*, NH); 11.07 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 46.9; 66.4; 96.1; 96.7; 100.3; 108.8; 120.3; 124.3; 126.3; 128.2; 128.4; 128.6; 130.1; 132.4; 135.4; 137.6; 139.5; 143.4; 149; 149.8; 160.6; 170.2; 177.4. Anal. calc. for $C_{27}H_{18}N_4O_3$: C 72.64, H 4.06, N 12.55; found: C 72.58, H 4.01, N 12.49.

*5′-Bromo-1′-ethyl-1,8-dihydro-1,3-diphenylspiro[furo[4,3-*b*]pyrazolo[4,3-*e*]pyridine-4,3′-indole]-2′,5(1′*H*,7*H*)-dione* (**4d**). Cream powder. M.p. >300°. IR (KBr): 3179, 1763, 1669. ^{1}H-NMR ((D$_6$)DMSO): 0.82 (*s*, Me); 3.32 (*s*, CH_2); 4.93 (*s*, CH_2); 6.75–7.66 (13 arom. H); 10.79 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 12.1; 34.7; 52.1; 66.1; 99.3; 100.3; 110.7; 114.6; 124.2; 127.8; 128.2; 128.5; 130.1; 131.8; 132.8; 137.4; 137.7; 139.6; 141.9; 149.7; 158.8; 159.1; 160.5; 170; 175.6. Anal. calc. for $C_{29}H_{21}BrN_4O_3$: C 62.94, H 3.82, N 10.12; found: C 62.86, H 3.88, N 10.04.

*1,8-Dihydro-1-(4-methoxyphenyl)-5′-nitro-3-phenylspiro[furo[4,3-*b*]pyrazolo[4,3-*e*]pyridine-4,3′-indole]-2′,5(1′*H*,7*H*)-dione* (**4h**). White powder. M.p. 275–277°. IR (KBr): 3305, 3067, 1738, 1705. ^{1}H-NMR ((D$_6$)DMSO): 3.86 (*s*, MeO); 4.98 (*s*, CH_2); 6.65–8.47 (*m*, 12 arom. H); 10.33 (*s*, NH); 10.94 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 47.5; 65.9; 99.1; 102.2; 109.8; 122.3; 124; 125.1; 125.6; 128.1; 128.3; 128.8; 129.1; 132.4; 135.7; 140; 142.1; 142.8; 146.2; 151.5; 159.3; 169.9; 177.9. Anal. calc. for $C_{28}H_{19}N_5O_6$: C 64.49, H 3.67, N 13.43; found: C 64.57, H 3.60, N 13.50.

*1′-Benzyl-1,8-dihydro-1,3-diphenylspiro[furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine-4,3′-indole]-2′,5(1′*H*,7*H*)-dione* (**4k**). Yellow powder. M.p. >300°. IR (KBr): 3426, 1755, 1694. ^{1}H-NMR ((D$_6$)DMSO): 4.19, 4.86 (*AB*, $J = 16$, CH_2); 6.49–8.48 (*m*, 23 arom. H); 11.08 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 43.8; 47.2; 66.1; 98.6; 102.3; 109.2; 123.2; 124.1; 125; 125.7; 127.3; 127.5; 128.1; 128.4; 128.8; 129.1; 132.1; 134.7; 136; 139.9; 142.5; 142.8; 146.3; 151.5; 159.8; 170.1; 176. Anal. calc. for $C_{34}H_{24}N_4O_3$: C 76.11, H 4.51, N 10.44; found: C 76.05, H 4.47, N 10.51.

*1,11-Dihydro-1,3-diphenylspiro[benzo[*g*]pyrazolo[3,4-*b*]quinoline-4,3′-indole]-2′,5,10(1′*H*)-trione* (**6a**). Red powder. M.p. 267–270°. IR (KBr): 3426, 3343, 1755, 1727, 1678. ^{1}H-NMR ((D$_6$)DMSO): 6.61–8.57 (*m*, 18 arom. H); 10.46 (*s*, NH); 11.47 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 51.4; 105.6; 109.9; 114.8; 120.9; 122.5; 123.3; 124; 125.9; 126.2; 127.5; 128; 128.6; 128.9; 129.5; 129.7; 131.8; 132.7; 133.2; 134.3; 134.7; 138.8; 143.9; 149.2; 152.4; 153.5; 176.3; 179.3; 181. Anal. calc. for $C_{33}H_{20}N_4O_3$: C 76.14, H 3.87, N 10.76; found: C 76.05, H 3.81, N 10.71.

*5′-Bromo-1-(4-bromophenyl)-1′-ethyl-1,11-dihydro-3-phenylspiro[benzo[*g*]pyrazolo[3,4-*b*]quinoline-4,3′-indole]-2′,5,10(1′*H*)-trione* (**6g**). Red powder. M.p. 268–271°. IR (KBr): 3255, 1722, 1705, 1677. ^{1}H-NMR ((D$_6$)DMSO): 0.83 (*s*, Me); 3.15 (*s*, CH_2); 6.63–8.05 (*m*, 16 arom. H); 9.98 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 11.8; 34.7; 50; 101;110.4; 114.6; 123.8; 124.1; 125; 126.5; 127.4; 128; 128.6; 128.9; 129; 129.3; 130.07; 131.4; 132.2; 132.6; 133.8; 135.6; 138.5; 139.5; 142.2; 146.1; 149.7; 152.1; 154.3; 176.3; 176.9; 181. Anal. calc. for $C_{35}H_{22}Br_2N_4O_3$: C 59.51, H 3.14, N 7.93; found: C 59.46, H 3.08, N 7.99.

*1,11-Dihydro-5′-methyl-1,3-diphenylspiro[benzo[*g*]pyrazolo[3,4-*b*]quinoline-4,3′-indole]-2′,5,10(1′*H*)-trione* (**6k**). Red powder. M.p. >300°. IR (KBr): 3194, 3056, 1716, 1678. ^{1}H-NMR ((D$_6$)DMSO): 2.17 (*s*, Me); 6.49–8.05 (*m*, 17 arom. H); 10.02 (*s*, NH); 10.07 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 50.6; 101.2; 111.4; 113.5; 123.8; 126.4; 127.3; 127.9; 128.2; 128.6; 129; 130; 130.3; 133.8; 135.7; 136.9; 138.5; 140.3; 141.7; 178.9; 181. Anal. calc. for $C_{34}H_{22}N_4O_3$: C 76.39, H 4.15, N 10.48; found: C 76.31, H 4.19, N 10.53.

*1′-Benzyl-1-(4-bromophenyl)-1,11-dihydro-3-phenylspiro[benzo[*g*]pyrazolo[3,4-*b*]quinoline-4,3′-indole]-2′,5,10(1′*H*)-trione* (**6m**). Red powder. M.p. >300°. IR (KBr): 3194, 1705, 1678, 1617. ^{1}H-NMR ((D$_6$)DMSO): 3.88, 4.77 (*AB*, $J = 16$, CH_2); 6.43–8.07 (*m*, 23 arom. H); 10.01 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 43.5; 47.6; 98.6; 101.5; 102.8; 109.2; 121.2; 122.1; 123; 125.1; 125.3; 125.8; 127.3; 127.6;

128;128.3; 128.5; 128.9; 129.1; 129.4; 129.7; 131; 131.3; 132.1; 133; 134.7; 136; 139.9; 142.3; 142.8; 146; 151.3; 159.8; 160.3; 176; 178.3; 179; 181. Anal. calc. for $C_{40}H_{26}N_4O_3$: C 78.67, H 4.29, N 9.17; found: C 78.60, H 4.24, N 9.10.

*1′,11′-Dihydro-1′,3′-diphenylspiro[2*H*-acenaphthylene-1,4′-benzo[*g*]pyrazolo[3,4-*b*]quinoline]-2,5′,10′-trione* (**8a**). Powder. M.p. 252–255°. IR (KBr): 3205, 1718, 1670, 1607. ^{1}H-NMR ((D$_6$)DMSO): 6.16–8.12 (*m*, 20 arom. H); 10.05 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 55; 103.4; 117.4; 123.7; 124.9; 126.3; 126.5; 127.1; 127.9; 128.1; 128.4; 128.6; 129.2; 130; 130.4; 131; 132; 133.9; 138.6; 140.6; 146.5; 149.8; 179.8; 181.3; 203.9. Anal. calc. for $C_{37}H_{21}N_3O_3$: C 79.99, H 3.81, N 7.56; found: C 79.91, H 3.88, N 7.62.

*5′,8′-Dihydro-1′-(4-nitrophenyl)-3′-phenylspiro[2*H*-acenaphthylene-1,4′-furo[3,4-*b*]pyrazolo[4,3-*e*]pyridine]-2,7′(1′*H*)-dione* (**8e**). Cream powder. M.p. 230–232°. IR (KBr): 3383, 1750, 1723. ^{1}H-NMR ((D$_6$)DMSO): 5.00 (*s*, CH$_2$); 6.31–8.20 (*m*, 15 arom. H); 10.84 (*s*, NH); 10.81 (*s*, NH). ^{13}C-NMR ((D$_6$)DMSO): 52; 66.3; 99.9; 103.7; 121.8; 122.3; 124; 125.2; 125.7; 127.3; 128; 128.2; 128.8; 129.4; 130; 131.6; 132; 132.7; 139.9; 141.4; 142.8; 143.7; 146.3; 151.5; 159.8; 170.4; 203.9. Anal. calc. for $C_{31}H_{18}N_4O_5$: C 70.72, H 3.45, N 10.64; found: C 70.67, H 3.39, N 10.57.

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