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Synthesis of *N*-benzylated indole-, indazole- and benzotriazole-4,7-diones

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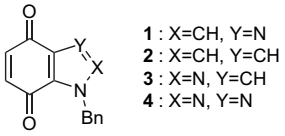
Abstract—The benzylation of 4,7-dimethoxy-1*H*-indole (**5**) followed by an oxidative demethylation led to 1-benzyl-1*H*-indole-4,7-dione (**2**) with a 73% overall yield. From the commercially available 7-nitro-1*H*-indazole (**7**), a three-step pathway was developed to access 1-benzyl-1*H*-indazole-4,7-dione (**3**). Two of these steps were investigated in order to improve the process. The direct synthesis of 1-benzyl-1*H*-benzotriazole-4,7-dione (**4**), through a 1,3-dipolar cycloaddition between benzyl azide and *para*-benzoquinone (**13**), was also studied. The simplicity of the methodologies described offers wide perspectives in obtaining 1-alkylated indole-, indazole- and benzotriazole-4,7-diones.

1. Introduction

As part of a programme directed to the search of new antiparasitic compounds[1–3] we previously described[2,4] a synthesis of 1-benzyl-1*H*-benzimidazole-4,7-dione (**1**) (Fig. 1).



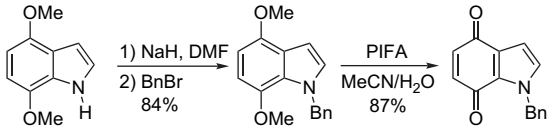
1 : X=CH, Y=N
2 : X=CH, Y=CH
3 : X=N, Y=CH
4 : X=N, Y=N

Figure 1. *N*-Benzylated benzimidazole-, indole-, indazole- and benzotriazole-4,7-diones.

In order to measure the influence of the number and the position of intracyclic nitrogen atoms on the biological activity, we planned to develop short routes to indole (**2**), indazole (**3**) and benzotriazole (**4**) analogues of **1**.

2. Results and discussion

The starting material used in the synthesis of 1-benzyl-1*H*-indole-4,7-dione (**2**) was the readily available 4,7-dimethoxy-1*H*-indole (**5**),[5–7] which was easily benzylated to afford **6** (Scheme 1).



5 **6** **2**

Scheme 1.

Trials to oxidize **6** into **2** with CAN failed, while the use of phenyliodine(III) bis(trifluoroacetate) (PIFA)[8,9] led to the quinone in good yield.

The most useful method to obtain indazole-4,7-dione skeleton is the reaction between diazomethane or its derivatives and a 1,4-benzoquinone substituted at C-2 or/and C-3 position(s).[10–13] As we needed a C-5 and C-6 unsubstituted quinone (**3**), we developed a new strategy, which is summarized in Scheme 2.

Our first attempt of benzylation[14] of the commercially available 7-nitro-1*H*-indazole (**7**) gave a mixture of isomers **8** and **9**, with a very important selectivity in favour of compound **9** (Table 1, entry 1). We then investigated different alkylating conditions for improving the ratio of isomer **8**. The reaction temperature seemed to have poor effect (entry 2) while the substitution of THF by DMF as solvent led to an important increase in the proportion of **8** (entry 3). By contrast neither the changes of the time of formation of the anion (entries 4 and 5) nor the amount of the base (entry 6) provided enhancement of the ratio. At last, the use of KOH[15] (entry 7) instead of NaH led to the more interesting result, with a smooth selectivity in favour of the isomer **8** and a quantitative overall yield.

Keywords: N-Benzylation; Oxidative demethylation; Catalytic hydrogenation; 1,3-Dipolar cycloaddition.
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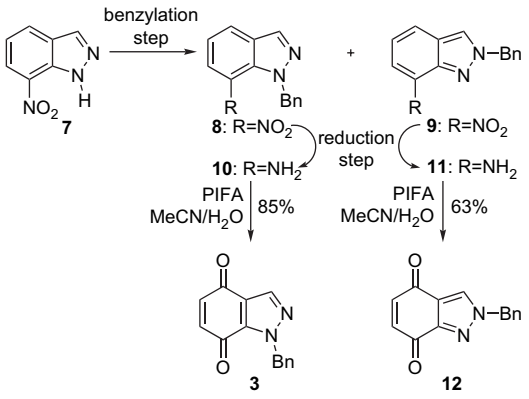


Scheme 2.

Table 1. Benzylation of 7-nitro-1*H*-indazole (**7**)

Entry	Base (equiv)	Solvent	Time[a] (min)	Temp (°C)	Ratio **8/9**	Overall yield
1	NaH (1,2)	THF	20	20	2/98[b]	85
2	NaH (1,2)	THF	20	0	6/94	71
3	NaH (1,2)	DMF	20	20	40/60	98
4	NaH (1,2)	DMF	2	20	39/61	85
5	NaH (1,2)	DMF	60	20	39/61	67
6	NaH (2)	DMF	60	20	43/57	100
7	KOH (1,2)	DMF	60	20	52/48	99

[a] Before addition of BnBr.
[b] A similar ratio was previously reported[16] using KOH/Me_2SO_4 in water.

After separation of compounds **8** and **9** by column chromatography, we studied the reduction of the nitro group of **8**. The use of tin/hydrochloric acid[17,18] (Table 2, entry 1) gave surprisingly a poor yield of amino derivative **10** with an important formation of a by-product. The mass spectra of this one indicated a probable chlorination of the benzenic ring, as previously reported.[17] In the presence of *N,N*-dimethylhydrazine and ferric chloride[19] (entry 2), the yield of **10** was appreciably increased, but the best result was obtained from catalytic hydrogenation in acidic medium[20] (entry 3). The same method was used to obtain compound **11** from isomer **9** (yield: 63%).

Table 2. Reduction of 1-benzyl-7-nitro-1*H*-indazole (**8**)

Entry	Reactants	Time (h)	Temp (°C)	Yield of **10** (%)
1	Sn, HCl	1.5	100	14
2	Me_2NNH_2, $FeCl_3\cdot 6H_2O$, MeOH	18	65	60
3	H_2, Pd/C, EtOAc, AcOH	24	20	82

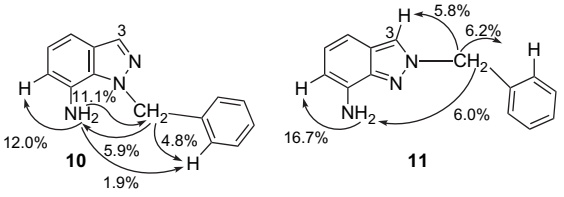
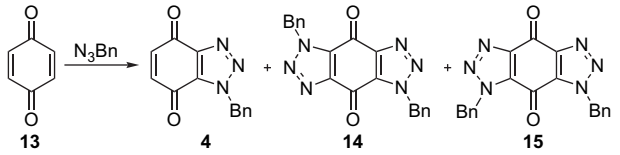


Figure 2. Correlations observed from NOE experiments carried out on compounds **10** and **11**.

Because of the failures noticed in the presence of Frémy's salt,[21] oxidations of amino derivatives **10** and **11** were finally achieved using PIFA.[8]

Structural assignments of regioisomers were based on the structural determination of amino derivatives **10** and **11**, which was established from NOE experiments (Fig. 2). No correlation was observed for H-3 in the case of compound **10**, while a significant one was evidenced for compound **11**.

Benzotriazole-4,7-dione (**4**) was obtained from a direct pathway using a 1,3-dipolar cycloaddition[22] of benzyl azide[23] on *para*-benzoquinone (**13**)[24,25] (Scheme 3).



Scheme 3.

The first reaction, carried out at 40 °C, gave a mixture of **4** and undesirable tricyclic derivative **14** (Table 3, entry 1). In order to reduce the formation of di-addition compound, we explored different reaction conditions. A lower temperature led to better result, but a much longer time of reaction was required to obtain acceptable yield of **4** (entry 2). The substitution of ethyl acetate by acetonitrile as solvent had no significant effect (entry 3) while reducing the amount of benzyl azide (entry 4) gave the best result. In the presence of 2 equiv of benzyl azide in refluxed ethyl acetate (entry 5), a mixture of regioisomers **14** and **15** was obtained. In all the above experiments, formation of numerous side products was encountered. Structural assignments of **14** and **15** were based on their ^{13}C NMR spectrum. In the case of compound **14**, only one signal was observed in the range of carbonyl chemical shifts, while two distinct singlets were present for **15**.

Table 3. Reaction of benzyl azide with *para*-benzoquinone (**13**)

Entry	Equiv of N_3Bn	Solvent	Time (days)	Temp (°C)	Recovered **13** (%)	Yield of **4** (%)	Yield of **14** and **15** (%)	Ratio **14/15**
1	1	AcOEt	6	40	21	19[a]	5	100/0
2	1	AcOEt	21	20	20	26[a]	Traces	—
3	1	MeCN	21	20	15	25[a]	Traces	—
4	0.75	AcOEt	21	20	28	32[b]	Traces	—
5	2	AcOEt	2	80	0	0	32	78/22

[a] Calculated as conversion rate of **13**.
[b] Calculated from benzyl azide.

3. Conclusion

We developed useful and short accesses to C-5 and C-6 unsubstituted 1-benzylated indole-, indazole- and benzotriazole-4,7-diones. The evaluation of antiparasitic potential of all compounds synthesized is actually underway. The versatility of the methodologies described in this paper will be built on in a future structure–biological activity study.

4. Experimental

4.1. General procedures

Melting points were measured with a Büchi apparatus (capillary tube). The ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Bruker AM 300 spectrophotometer. The chemical shifts are reported in parts per million (δ) using tetramethylsilane (TMS) as an internal reference. J values are given in hertz. The infrared spectra were recorded with a Perkin–Elmer 1310 spectrometer. Mass spectra (EI) were recorded with a GC–MS Nermag R10-10 spectrometer. Elemental analyses were performed at the Centre de Microanalyse du CNRS at Solaize (France). Column chromatography was carried out with Matrex (60 Å, 35–70 μm) acidic silica gel. 7-Nitroindazole and 1,4-benzoquinone were obtained from Sigma (L'Isle d'Abeau, France). 4,7-Dimethoxy-1*H*-indole **5**[5,6] and benzyl azide[23] were prepared according to the procedures described in the literature.

4.2. Indole derivatives

4.2.1. 1-Benzyl-4,7-dimethoxy-1*H*-indole (6). A solution of 4,7-dimethoxy-1*H*-indole **5** (0.22 g, 1.24 mmol) in dry DMF (20 mL) was added dropwise at 20 °C, over 15 min, to a suspension of NaH (60% in mineral oil, 0.134 g, 3.72 mmol) in the same solvent (5 mL). The reaction mixture was stirred for 15 min and benzyl bromide (0.16 mL, 1.24 mmol) was rapidly added. After stirring for 12 h, DMF was removed under vacuum. The residue was then dissolved in CH_2Cl_2 (50 mL). The solution was washed with a saturated K_2CO_3 solution (4×10 mL), dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography (CH_2Cl_2/petroleum ether, 4/1); yield 0.28 g (84%). Light white crystals; R_f=0.76 (CH_2Cl_2/petroleum ether, 4/1); mp 62 °C; IR (KBr) 1525, 1453, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25–7.07 (5H, m, H Ph), 6.95 (1H, d, J=3.0 Hz, H-2), 6.59 (1H, d, J=3.0 Hz, H-3), 6.50 (1H, d, J=8.1 Hz, H-5 or H-6), 6.36 (1H, d, J=8.1 Hz, H-5 or H-6), 5.61 (2H, s, CH_2), 3.91 (3H, OCH_3), 3.77 (3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 147.6, 142.5 (2C), 139.6 (2C), 128.5 (2C), 128.0, 127.1, 126.6 (2C), 102.6, 99.4, 98.4, 55.9, 55.6, 52.2. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.32; H, 6.37; N, 5.25. HRMS calcd for $C_{17}H_{18}NO_2$: 268.1338 [M+H]$^+$, found: 268.1338.

4.2.2. 1-Benzyl-1*H*-indole-4,7-dione (2). A solution of phenyliodine(III) bis(trifluoroacetate) (PIFA) (0.257 g, 0.6 mmol) in 7.5 mL of acetonitrile and 7.5 mL of water was added dropwise at 0 °C, over 15 min, to a solution of 1-benzyl-4,7-dimethoxy-1*H*-indole (**6**) (40 mg, 0.15 mmol) in the same mixture of solvents (15 mL). At the end of the addition, stirring was maintained for 15 min at 20 °C. The reaction mixture was extracted with 3×25 mL of CH_2Cl_2, washed with 3×25 mL of water, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography (CH_2Cl_2/petroleum ether, 4/1); yield 31 mg (87%). Orange crystals; R_f=0.55 (CH_2Cl_2); mp 135 °C; IR (KBr) 1650, 1496, 1405 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28–7.16 (5H, m, H Ph), 6.84 (1H, d, J=2.8 Hz, H-2), 6.55 (1H, d, J=2.8 Hz, H-3), 6.51 (1H, d, J=10.3 Hz, H-5 or H-6), 6.46 (1H, d, J=10.3 Hz, H-5 or H-6), 5.49 (2H, s, CH_2); ^{13}C NMR ($CDCl_3$) δ 183.7, 178.4, 137.7, 137.4, 136.5, 130.0, 129.3 (3C), 128.7 (2C), 128.0, 127.4, 108.1, 52.4. Anal. Calcd for $C_{15}H_{11}NO_2\cdot 0.15H_2O$: C, 75.08; H, 4.75; N, 5.84. Found: C, 75.53; H, 5.22; N, 5.47. HRMS calcd for $C_{15}H_{12}NO_2$: 238.0868 [M+H]$^+$, found: 238.0869.

4.3. Indazole derivatives

4.3.1. 1-Benzyl-7-nitro-1*H*-indazole (8) and 2-benzyl-7-nitro-1*H*-indazole (9). To a solution of 7-nitroindazole (**7**) (0.3 g, 1.84 mmol) in dry DMF (3 mL) was added at 20 °C NaH (60% in mineral oil, 89 mg, 2.21 mmol). After stirring for 10 min, benzyl bromide (264 μL, 2.21 mmol) was rapidly added and stirring maintained for 2 h. The solution was then poured into ice-water (60 mL) and diluted HCl was added to adjust the pH to about 6. This solution was extracted with AcOEt (2×60 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography (AcOEt/petroleum ether, 1/4) leading to **8** (yield 185 mg, 39%) and **9** (yield 275 mg, 59%). Compound **8**: orange powder; R_f=0.67 (AcOEt/petroleum ether, 1/2); mp 65 °C; IR (KBr) 1620, 1538, 1338 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.58 (1H, s, H-3), 8.32 (1H, dd, J=1.1, 8.0 Hz, H-6), 8.15 (1H, dd, J=0.9, 7.7 Hz, H-4), 7.37 (1H, dd, J=7.7, 8.0 Hz, H-5), 7.31–7.19 (3H, m, H Ph), 6.93 (2H, dd, J=2.1, 8.1 Hz, H Ph), 5.84 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 137.2, 135.5, 134.9, 129.8, 129.1, 128.9 (2C), 128.6, 127.5, 126.5 (2C), 124.9, 120.6, 55.7. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59; O, 12.63. Found: C, 66.10; H, 4.23; N, 16.42; O, 12.60. Compound **9**: yellow solid; R_f=0.33 (AcOEt/petroleum ether, 1/2); mp 123 °C; IR (KBr) 1511, 1332, 1295 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.92 (1H, s, H-3), 8.34 (1H, dd, J=0.8, 8.5 Hz, H-6), 8.31 (1H, d, J=8.5 Hz, H-4), 7.45–7.32 (5H, m, H Ph), 7.28 (1H, dd, J=8.3, 8.7 Hz, H-5), 5.83 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6)[26] δ 139.8, 136.6, 136.2, 130.2, 128.7 (2C), 128.1, 128.0 (2C), 127.4, 125.3, 124.9, 119.9, 56.7. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59; O, 12.63. Found: C, 66.32; H, 4.42; N, 16.53; O, 12.78.

4.3.2. 7-Amino-1-benzyl-1*H*-indazole (10). A solution of nitro compound **8** (1.75 g, 6.92 mmol) in AcOEt (35 mL) and acetic acid (12.5 mL) was added to a suspension of prereduced 10% Pd/C (0.58 g, 33% w/w) in AcOEt (15 mL). The mixture was then stirred under dihydrogen pressure (4 bar) for 6 h, filtered through Celite, neutralized with diluted cooled NH_4OH and extracted with AcOEt (2×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was then purified by column

chromatography (AcOEt/petroleum ether, 1/3) with silica gel previously neutralized with NEt_3; yield 1.270 g (82%). Light pink solid; R_f=0.47 (AcOEt/petroleum ether, 1/2); mp 131 °C; IR (KBr) 3329, 1585, 727 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.01 (1H, s, H-3), 7.33–7.20 (3H, m, H Ph), 7.18–7.11 (2H, m, H Ph), 7.06 (1H, dd, J=1.0, 8.0 Hz, H-4), 6.90 (1H, dd, J=7.3, 8.0 Hz, H-5), 6.63 (1H, dd, J=1.0, 7.3 Hz, H-6), 5.86 (2H, s, CH_2), 5.17 (2H, br s, NH_2); ^{13}C NMR (DMSO-d_6) δ 140.0, 134.3, 134.2, 132.1, 129.2, 128.0, 127.9, 127.8, 127.7, 127.1, 122.7, 112.0, 110.4, 54.9. Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.40; H, 5.97; N, 19.04.

4.3.3. 7-Amino-2-benzyl-2*H*-indazole (11). Compound **11** was prepared as above from **9** (1.44 g, 5.69 mmol); yield 0.849 g (67%). Red oil; R_f=0.17 (AcOEt/petroleum ether, 1/2); IR (KBr) 3435, 1627, 742 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.31 (1H, s, H-3), 7.45–7.24 (5H, m, H Ph), 6.88 (1H, dd, J=0.9, 8.1 Hz, H-4), 6.80 (1H, dd, J=7.0, 8.1 Hz, H-5), 6.30 (1H, dd, J=0.9, 7.0 Hz, H-6), 5.64 (2H, s, CH_2), 5,29 (2H, br s, NH_2); ^{13}C NMR (DMSO-d_6) δ 141.5, 136.5, 135.7, 129.1, 128.1 (2C), 127.4, 127.0 (2C), 122.6, 122.2, 108.3, 104.7, 56.2; HRMS calcd for $C_{14}H_{14}N_3$: 224.1188 $[M+H]^+$, found: 224.1191.

4.3.4. 1-Benzyl-1*H*-indazole-4,7-dione (3). A solution of aminoindazole **10** (40 mg, 0.179 mmol) in acetonitrile (1.5 mL) and water (0.5 mL) was added dropwise at 0 °C to PIFA (193 mg, 0.45 mmol) in the same mixture of solvents (2 mL). The solution was stirred for 30 min at 20 °C. Then, water (50 mL) and AcOEt (50 mL) were added. The organic layer was washed with brine to adjust the pH to about 7, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography (AcOEt/petroleum ether, 1/5); yield 40 mg (85%). Red solid; R_f=0.64 (AcOEt/petroleum ether, 1/2); mp 111 °C; IR (KBr) 1677, 1526, 712 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.31 (1H, s, H-3), 7.45–7.35 (5H, m, H Ph), 6.90 (1H, d, J=10.4 Hz, H-5 or H-6), 6.84 (1H, d, J=10.4 Hz, H-5 or H-6), 5.76 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 181.5, 177.6, 138.4, 137.2, 136.4, 135.8, 135.7, 128.6 (2C), 128.0, 127.7 (2C), 121.1, 54.0. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76; O, 13.43. Found: C, 70.16; H, 4.23; N, 11.61; O, 13.28.

4.3.5. 2-Benzyl-2*H*-indazole-4,7-dione (12). Compound **12** was prepared as above from **11** (0.551 g, 2.47 mmol); yield 0.370 g (63%). Red solid; R_f=0.31 (AcOEt/petroleum ether, 1/2); mp 125 °C; IR (KBr) 1677, 1541, 1225, 733 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.85 (1H, s, H-3), 7.44–7.28 (5H, m, H Ph), 6.81 (1H, d, J=10.4 Hz, H-5 or H-6), 6.74 (1H, d, J=10.4 Hz, H-5 or H-6), 5.45 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 181.4, 180.6, 147.0, 139.9, 138.8, 134.2, 131.2, 130.0, 129.8, 129.7, 129.0, 128.9, 121.6, 58.0; HRMS calcd for $C_{14}H_{11}N_2O_2$: 239.0821 $[M+H]^+$, found: 239.0817.

4.4. Benzotriazole derivatives

4.4.1. 1-Benzyl-1*H*-benzotriazole-4,7-dione (4). A mixture of 1,4-benzoquinone (**13**) (1.0 g, 9.26 mmol) and benzyl azide (0.924 g, 6.94 mmol), in ethyl acetate (73 mL) was stirred at room temperature for 21 days. Then, the mixture was filtered and the filtrate evaporated under vacuum. The residue was purified by column chromatography (dichloromethane/petroleum ether, 2/1) leading to recovered **13** (0.217 g) and **4**; yield 0.540 g (32% calculated from benzyl azide). Light brown solid; R_f=0.34 (dichloromethane); mp 110 °C; IR (KBr) 1680, 1497, 1032 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.54–7.43 (2H, m, H Ph), 7.42–7.31 (3H, m, H Ph), 6.86 (1H, d, J=10.5 Hz, H-5 or H-6), 6.79 (1H, d, J=10.5 Hz, H-5 or H-6), 5.90 (2H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 178.5, 176.8, 143.9, 138.3, 136.5, 133.6, 131.6, 129.1, 129.0 (2C), 128.6 (2C), 53.6; HRMS calcd for $C_{13}H_{10}N_3O_2$: 240.0773 $[M+H]^+$, found: 240.0780.

4.4.2. 1,5-Dibenzyl-1*H*,5*H*-benzo[1,2-*d*;4,5-*d*′]bistriazole-4,8-dione (14) and 1,7-dibenzyl-1*H*,7*H*-benzo[1,2-*d*;4,5-*d*′]bistriazole-4,8-dione (15). A mixture of 1,4-benzoquinone (**13**) (0.5 g, 4.63 mmol) and benzyl azide (1.23 g, 9.26 mmol) in ethyl acetate (73 mL) was refluxed for 54 h. Then, the mixture was filtered and pure bistriazole **14** was obtained (0.303 g). The filtrate was evaporated under vacuum and the residue purified by column chromatography (dichloromethane) to afford 0.242 g of an equimolar mixture (established from the deconvolution of the methylene signals of ^1H NMR spectrum) of the two isomers **14** and **15**; overall yield: 32%, **14/15**: 78/22. Compound **14**: beige solid; R_f=0.39 (dichloromethane); mp 260 °C (degradation); IR (KBr) 1699, 1520, 1496, 1476, 1376, 950 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.50–7.35 (10H, m, H Ph), 6.05 (4H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 168.2 (2C), 135.1 (2C), 134.5 (4C), 128.7 (4C), 128.4 (2C), 128.0 (4C), 52.8 (2C). Anal. Calcd for $C_{20}H_{14}N_6O_2\cdot 0.1H_2O$: C, 64.55; H, 3.84; N, 22.58; O, 9.03. Found: C, 64.37; H, 3.76; N, 22.61; O, 9.23. Compound **15**: R_f=0.39 (dichloromethane); ^1H NMR (DMSO-d_6) δ 7.50–7.35 (10H, m, H Ph), 6.03 (4H, s, CH_2); ^{13}C NMR (DMSO-d_6) δ 170.7, 165.7, 145.8 (2C), 134.9 (2C), 134.4 (2C), 128.8 (4C), 128.6 (2C), 128.0 (4C), 52.8 (2C).

References and notes

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