Synthesis of Unsymmetrical Aroyl Acyl Imides by Aminocarbonylation of Aryl Bromides

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Abstract: Aroyl imides were prepared by a palladium-catalyzed aminocarbonylation reaction of aryl bromides with carbon monoxide and primary amides in good yields (58−72%). The reactions were carried out under mild conditions (5 bar, 120 °C) using 1 mol % of a palladium phosphine complex. Several aryl bromides were reacted with formamide, acetamide, benzamide, and benzenesulfonamide, respectively. For activated aryl bromides, a phosphine-to-palladium ratio of 2:1 was sufficient, but less reactive aryl bromides required a ligand-to-palladium ratio of 6:1 in order to stabilize the catalyst and achieve full conversion. The imides were very sensitive to aqueous basic conditions and were easily converted to aroyl amides or benzoic acids.

The palladium-catalyzed carbonylation reactions of aryl halides in the presence of carbon monoxide constitute a versatile methodology for the selective and direct synthesis of benzoic acids and their derivatives.[1] Depending on the nucleophile used, acids, esters, amides, aldehydes, and ketones are easily prepared. A few reports in the literature indicated that the formation of imides by the carbonylation reaction should be possible. The formation to cyclic imides was investigated using either aryl halides bearing internal amide groups,[2] or by a 2-fold carbonylation of 1,2-diiodobenzene to phthalimides.[3] Fuchikami and Ojima[4] investigated the formation of dihydrouracil by the carbonylation of vinyl halides with ureas, and Yoneyama et al.[5] produced linear polyimide polymers from dihalobenzenes and bisamides. In addition, imides were reported as side products in the carbonylation reaction to primary amides.[6] However, the potential of the carbonylation reaction for the synthesis of imides has not been investigated so far.

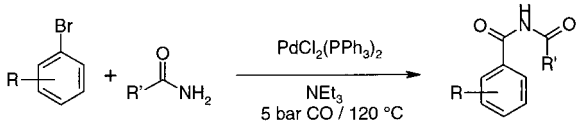
Table 1. Carbonylation Reaction of 1 with Formamides in the Presence of Different Bases[a]

entry	amide	base	workup	yield of **3**[b](%)	yield of **4**[b](%)
1	$HCONH_2$	NEt_3	acidic[c]	66	22
2	$HCONH_2$	NEt_3	basic	5	82
3	$HCONH_2$	DMAP	basic	−	71

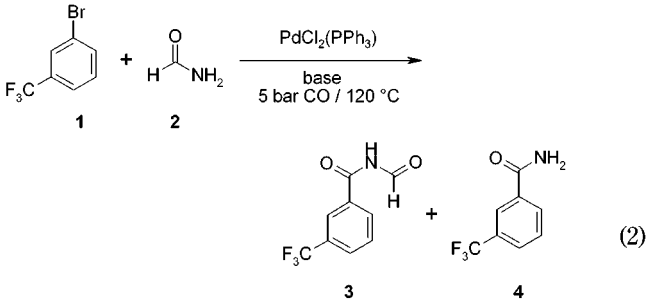
[a] Reaction conditions: **1** (35.6 mmol), formamide **2** (71 mmol), base (38 mmol), $PdCl_2(PPh_3)_2$ (0.36 mmol) in 25 mL of dioxane, in a 250 mL glass autoclave at 120 °C and 5 bar inital pressure for 18 h. [b] Isolated yield. [c] Reaction mixture was acidified prior to the distribution between organic solvent and water.

Classically, imides are prepared by the reaction of amides with acyl chlorides, anhydrides, and carboxylic esters or acids.[7] However, these methods are not as straightforward as they seem at the first glance, and several side reactions such as elimination to nitriles, formation of triacyl imides, or acyl group scrambling can occur. Best yields were reported for the acid-catalyzed reaction of anhydrides with amides. More sophisticated methods involve the treatment of amides with reagents such as dimethylacetals of amides,[8] *N*,*N*-bis(trimethylsilyl)formamide,[9] α,α,α-trichloromethylcarbonyl compounds,[10] diketene,[11] or vinyl esters,[12] respectively.

We investigated the carbonylation reaction in order to expand the scope for the synthesis of new substrate classes, and we recently described the synthesis of primary amides using formamide and a nucleophilic base such as DMAP.[13] The reaction involved the inital formation of a formimide that decomposed to the primary amide. By a careful investigation of this reaction and optimization of the reaction conditions and workup procedures, we have developed a practical method for the preparation of a wide variety of linear imides including sulfonimides in fair to good yields starting from stable and easy to handle aryl halides and primary amides (eq 1).



The outcome of the carbonylation reaction of aryl bromides with formamides depended strongly on the base and the workup procedure (eq 2, Table 1). With NEt_3 (triethylamine) as the base, formimide **3** was the main product, whereas with a nucleophilic base such as DMAP (entry 3), the primary amide **4** was isolated in high yields.



The change in the reaction course using DMAP instead of NEt_3 was also obvious from a distinctly different course

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(1) (a) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. In *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, 1997; p 250. (b) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal.* **1995**, *104*, 17. (c) Tsuji, J. In *Palladium Reagents and Catalysts*; John Wiley and Sons Ltd: Chichester, 1995; p 188. Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal.* **1995**, *104*, 17. (d) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. In *Carbonylation. Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991; p 146. (e) Heck, R. F. In *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985; p 352.

(2) (a) Mori, M.; Chiba, K.; Ohta, N.; Ban, Y. *Heterocycles* **1979**, *13*, 329. (b) Milstein D. US 5,034,534; 1991.

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(6) (a) Ueda, K.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 10722. (b) Morera, E.; Ortar, G. *Tetrahedron Lett.* **1998**, *39*, 2835.

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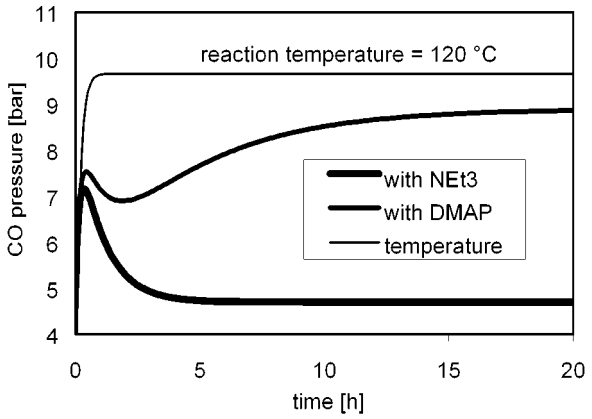


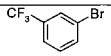
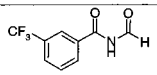
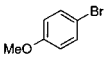
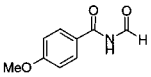
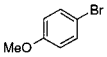
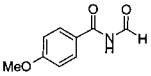
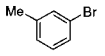
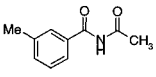
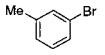
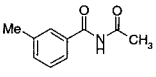
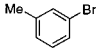
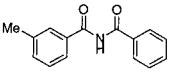
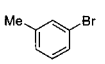
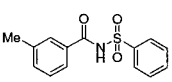
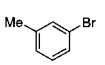
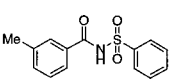
Figure 1. Schematic pressure curve of the reaction of **1** with formamide in dioxane with NEt_3 or DMAP as base in the presence of 1 mol % catalyst.

of the pressure curve as shown schematically (Figure 1). After the initial pressure increase due to the heating, the pressure decreased steadily with NEt_3 and became constant when 1 equiv of CO was consumed. With DMAP, the pressure decreased in the first few hours and thereafter increased again until it became constant after 20 h.

The imide **3** was very susceptible to hydrolysis under basic aqueous conditions (Table 1, entry 2), and it was necessary to neutralize the excess of base prior to the aqueous workup, to obtain high yields of the imide (entry 1). Under the proper conditions and with a suitable workup, the carbonylation reaction allowed the preparation of a variety of imides using different aryl bromides and amides as the starting materials (Table 2). With activated aryl bromides, a phosphine-to-palladium ratio of 2:1 was sufficient for complete conversion (entry 1), whereas with deactivated aryl bromides, it was necessary to increase the ratio to 6:1. Formamide, acetamide, and benzamide reacted readily under identical conditions (entries 1, 3, 5, and 6). With formamide, the primary amide was found as the side product due to hydrolysis (entry 1), whereas the acetimide was preferentially hydrolyzed to the acid (entry 3). In the case of benzenesulfonamide (entry 7 und 8), the reaction became sluggish after about 50% conversion (Figure 2). The sulfonimide might be sufficiently acidic to protonate NEt_3, and therefore after 50% conversion, no more triethylamine was available for an efficient regeneration of the catalyst. The problem was easily fixed by an additional equivalent of base.

The carbonylation reaction proceeds most likely according to the well-accepted mechanism with the amide as the nucleophile to yield the imide (Scheme 1).[14,15] Under the reaction conditions in the presence of a trialkylamine base, the imide is stable, but a nucleophilic base such as DMAP will catalyze the decomposition of the imide to the primary amide. By this process, CO is released, and a pressure increase occurs in the second part of the reaction (see Figure 1).[13]

Table 2. Aminocarbonylation of Aryl Bromides with Primary Amides to Unsymmetrical Imides[a]

Entry	Starting material	Amide	Pd/PPh_3 ratio	Product	Isolated Yield (%)	Conversion[b] (%)
1		$HCONH_2$	1:2		66[c]	100
2		$HCONH_2$	1:2		n.d.[d]	< 50
3		$HCONH_2$	1:6		58	100
4		CH_3CONH_2	1:4		n.d.[d]	< 30
5		CH_3CONH_2	1:6		67[e]	100
6		$PhCONH_2$	1:6		72	100
7		$PhSO_2NH_2$	1:6		69	ca. 70
8[f]		$PhSO_2NH_2$	1:6		n.d.[d]	100

[a] Reaction conditions and workup: see Experimental Section. [b] Conversion of the aryl halides estimated from the pressure curves. [c] In addition, 22% of the primary amide were isolated. [d] Not determined. [e] In addition, ca. 20% of the benzoic acid were detected. [f] With 2 equiv of NEt_3.

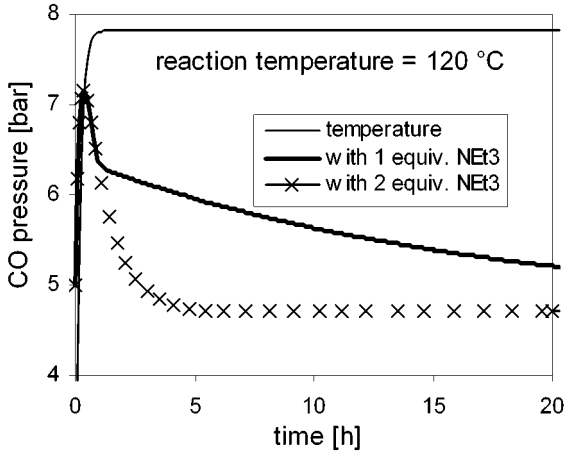


Figure 2. Schematic pressure curve of the reaction of 3-bromotoluene with benzenesulfonamide in dioxane with 1 or 2 equiv of NEt_3 (entries 7 and 8).

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(9) Kantlehner, W.; Fischer, P.; Kugel, W.; Moehring, E.; Bredereck, H. *Justus Liebigs Ann. Chem.* **1978**, 512.
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(11) Yamamoto, Y.; Onishi, S.; Azuma, Y. *Synthesis* **1981**, 122.
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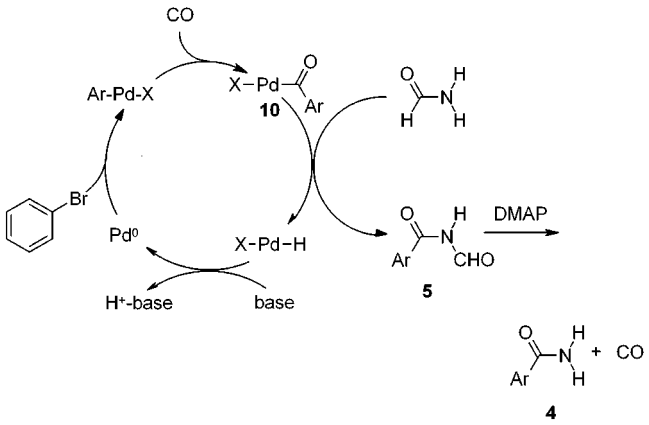
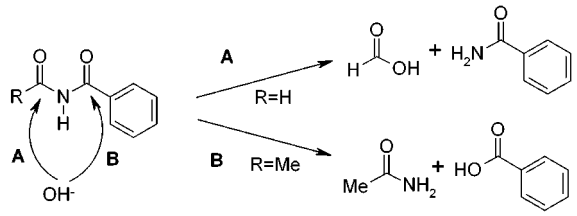
(14) (a) Heck, R. F. *Adv. Catal.* **1977**, *26*, 323. (b) Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115. (c) Yamamoto, A.; Ozawa, F.; Osakada, K.; Huang, L.; Son, T.; Kawasaki, N.; Doh, M. *Pure Appl. Chem.* **1991**, *63*, 687.
(15) Moser, W. R.; Wang, A. W.; Kjeldahl, N. K. *J. Am. Chem. Soc.* **1988**, *110*, 2816.

Scheme 1



Scheme 2



The imides were easily hydrolyzed under aqueous basic conditions which was already noticed for formimides by Ueda et al.[6a] Therefore, the excess base had to be neutralized prior to the workup, or alternatively, the workup had to be carried out under anhydrous conditions.

The course of the hydrolysis depends mainly on the R group of the amide and their influence on the electrophilicity of the carbonyl group (see Table 2). With formimides the more electrophilic formyl group was attacked by a nucleophile, and the primary benzoyl amide and formic acid were formed (Scheme 2), whereas acetylbenzimides were decomposed to the benzoic acids and acetamides.

The method described here is an interesting alternative to our previous protocol for the synthesis of primary benzamides using DMAP, especially since the yields of the primary amide was higher with NEt_3 followed by a basic workup than in the direct reaction with DMAP (Table 1, entries 2 and 3). Moreover, the reaction times were shorter, and it was easier to determine the end of the reaction.

Our protocol expands the scope of the aminocarbonylation of aryl halides to the synthesis of aroyl imides. Despite their low nucleophilicity, a broad range of primary amides and sulfonamides react readily to the corresponding imides. The reaction conditions are reasonably mild, and all starting materials are stable and easy to handle; therefore, the protocol is well suited for laboratory synthesis and has the potential for large scale production.

Experimental Section

General Considerations. For the carbonylation experiments, a 250 mL glass autoclave equipped with a magnet-driven hollow shaft stirrer was used. The reactions were carried out under nonisobaric conditions, and the progress of reaction was followed by measuring the pressure in the autoclave. CO gas (purity 99.97%) was purchased from Carbagas Chemical Co.

Commercially obtained materials were used as received without further purification. Aryl halides, ligands, reagents, and solvents were purchased from Fluka Chemical Co. with the exception 3-bromobenzotrifluoride (Novartis AG). Anhydrous dioxane (stored over molecular sieves) was used. $PdCl_2(PPh_3)_2$ was purchased from Avocado Chemical Co.

^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker dpx 300 spectrometer. Chemical shifts (δ) are given in ppm and refer to TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1710 spectrometer. Melting points were measured with a Büchi 520 apparatus and are uncorrected. The combustion analyses were carried out by Solvias AG, Switzerland.

***N*-Formyl-*m*-trifluoromethylbenzimide (Table 2, entry 1)**. The autoclave was charged with 3-bromobenzotrifluoride (8.01 g, 35.6 mmol), triethylamine (3.85 g, 38.0 mmol), formamide (3.20 g, 71.2 mmol), $PdCl_2(PPh_3)_2$ (243 mg, 0.35 mmol, 1 mol %), and 1,4-dioxane (25 mL). The autoclave was purged three times with nitrogen (6 bar) and charged with 5 bar CO, and the reaction mixture was heated to 120 °C. After 8 h and cooling to room temperature, acetic acid (5 mL) was added to the reaction mixture, and it was partitioned between dichloromethane and water. The aqueous layer was extracted two times with additional dichloromethane. The organic phases were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc/hexane 1:2 as eluent). The title compound (5.1 g, 23.5 mmol, 66%) was obtained as colorless crystals. $R_f = 0.42$ (EtOAc:hexane 1:2); mp: 130.0−130.5 °C; ^1H NMR (300.1 MHz, DMSO-d_6, 297 K) δ 11.96 (d, $J = 8.6$ Hz, 1H), 9.28 (d, $J = 8.4$ Hz, 1H), 8.34 (s, 1H), 8.30 (d, $J = 7.9$ Hz, 1H), 8.03 (dd, $J = 7.8$ Hz, 0.7 Hz, 1H), 7.79 (t, $J = 7.8$ Hz, 1H); $^{13}C\{^1H\}$ NMR (75.5 MHz, DMSO-d_6, 297 K) δ 167.2, 165.2, 133.6, 133.3, 130.8, 130.6 (q, J(C−F) = 4 Hz), 130.3 (q, J(C−F) = 32 Hz), 125.9 (q, J(C−F) = 4 Hz), 124.6 (q, J(C−F) = 272 Hz); IR (KBr, cm^{-1}) 3246, 1740, 1678, 1469; Anal. Calcd for $C_9H_6F_3NO_2$: C, 49.78; H, 2.79; N, 6.45; F, 26.25; O, 14.74. Found: C, 49.89; H, 2.83; N, 6.27; F, 26.08; O, 14.75.

In addition, 1.45 g (7.7 mmol, 22%) of 3-trifluoromethylbenzamide was obtained as yellow crystals. $R_f = 0.06$ (EtOAc:hexane 1:2);^1H NMR (300.1 MHz, DMSO-d_6, 297 K) δ 8.25 (s (br), 1H), 8.22−8.17 (m, 2H), 7.89 (dd, $J = 7.8$ Hz, 0.7 Hz, 1H), 7.71 (t, $J = 7.8$ Hz, 1H), 7.64 (s (br), 1H).

***N*-Formyl-*p*-methoxybenzimide (Table 2, entry 3)**. The reaction of 4-bromoanisole (6.86 g, 35.6 mmol) with formamide (3.21 g, 71.2 mmol) was effected using the procedure described above, but with additional triphenylphosphine (377 mg, 1.4 mmol). After a reaction time of 12 h, 10 M hydrochloric acid (0.5 mL) and methanol (170 mL) were added, the mixture was cooled to −78 °C, and the precipitate was filtered to afford 3.70 g (20.6 mmol, 58%) of the title compound as a colorless solid. mp: 203−205 °C; ^1H NMR (300.1 MHz, DMSO-d_6, 297 K) δ 11.42 (d, $J = 9.0$ Hz, 1H), 9.04 (d, $J = 9.0$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 3.65 (s, 3H); $^{13}C\{^1H\}$ NMR (75.5 MHz, DMSO-d_6, 297 K) δ 167.5, 165.4, 164.3, 131.5 (2C), 124.3, 114.8 (2C), 56.4; IR (KBr, cm^{-1}) 3261, 1725, 1675, 1465, 1375. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82; O, 26.79. Found: C, 60.09; H, 5.07; N, 7.83; O, 26.79.

***N*-Acetyl-*m*-toluimide (Table 2, entry 5)**. The reaction of 3-bromotoluene (6.15 g, 35.6 mmol) with acetamide (4.25 g, 71.2 mmol) was effected using the procedure described above, but with additional triphenylphosphine (377 mg, 1.4 mmol). After a reaction time of 20 h, acetic acid (5 mL) and dichloromethane (250 mL) were added to afford a orange solution. Diethyl ether (300 mL) was added, and the precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, EtOAc/hexane as eluent). Yellow crystals (4.97 g) were obtained containing ca. 90% (28.0 mmol, 67%) of the title compound. $R_f = 0.32$ (EtOAc:hexane 1:2); ^1H NMR (300.1 MHz, DMSO-d_6, 297 K) δ 10.73 (s (br), 1H), 7.53−7.48 (m, 2H), 7.24−7.15 (m, 2H), 2.16 (s 3H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (75.5 MHz, DMSO-d_6, 297 K) δ 172.9, 167.4, 138.7, 134.1, 134.0, 129.7, 129.2, 126.4, 26.4, 21.7; IR (KBr, cm^{-1}) 3304, 1713, 1682, 1672, 1458. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 67.78; H, 6.26; N, 7.90; O, 18.06. Found (after crystallization from hexane): C, 67.48; H, 6.24; N, 7.90; O, 17.95.

***N*-Benzoyl-*m*-toluimide (Table 2, entry 6)**. The reaction of 3-bromotoluene (6.15 g, 35.6 mmol) with benzamide (8.80 g, 71.2 mmol) was effected using the procedure described above, but with additional triphenylphosphine (377 mg, 1.4 mmol). After a reaction time of 15 h, acetic acid was added to the reaction mixture, and it was partitioned between dichloromethane and water. The aqueous layer was extracted two times with additional dichloromethane. The organic phases were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc/hexane as eluent). The title compound (6.10 g, 25.5 mmol, 72%) was obtained as colorless crystals. $R_f = 0.38$ (EtOAc:hexane 1:1); mp: 113−114.5 °C; ^{1}H NMR (300.1 MHz, DMSO-d_6, 297 K) δ 11.21 (s, 1H), 7.85−7.82 (m, 2H), 7.68−7.63 (m, 2H), 7.56−7.53 (m, 1H), 7.47−7.42 (m, 2H), 7.36−7.32 (m, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (75.5 MHz, DMSO-d_6, 297 K) δ 168.6, 168.5, 138.6, 134.8. 134.7, 134.1, 133.4, 129.9, 129.5 (2C), 129.3 (2C), 129.2, 126.7, 21.7; IR (KBr, cm^{-1}) 3246, 1697, 1505, 1472. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.08; H, 5.56; N, 5.69.

***N*-*m*-Toluylbenzenesulfonimide (Table 2, entry 7)**. The reaction of 4-bromotoluene (6.15 g, 35.6 mmol) with benzenesulfonamide (11.5 g, 71.2 mmol) was effected using the procedure described above, but with additional triphenylphosphine (377 mg, 1.4 mmol). After a reaction time of 15 h, acetic acid was added to the reaction mixture, and it was partitioned between dichloromethane and water. The aqueous layer was extracted two times with additional dichloromethane. The organic phases were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc/hexane as eluent). The title compound (6.77 g, 24.6 mmol, 66%) was obtained as colorless crystals. $R_f = 0.36$ (*tert*-butylmethyl ether/hexane/acetic acid 10:10:1); mp: 110 °C (decomp); ^{1}H NMR (300.1 MHz, DMSO-d_6, 297 K) δ 12.50 (s, (br), 1H), 8.06−8.03 (m, 2H), 7.74−7.61 (m, 5H), 7.42−7.33 (m, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (75.5 MHz, DMSO-d_6, 297 K) δ 166.4, 140.4, 138.9, 134.7, 134.5, 132.3, 130.0 (2C), 129.7, 129.4, 128.5 (2C), 126.4, 21.6; IR (KBr, cm^{-1}) 3188, 1707, 1686, 1671, 1446. Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09; S, 17.43. Found: C, 60.77; H, 4.67; N, 5.11; S, 17.19.

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