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# Synthesis of Substituted Salicylanilides under Microwave Irradiation

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**Summary.** Salicylanilides were prepared in 70–95% yields in 4–8 min from phenyl salicylate or phenyl 4-methoxysalicylate and substituted anilines under microwave irradiation under solvent free conditions.

**Keywords.** Salicylanilides; Microwave irradiation.

## Introduction

Salicylanilides have been of interest for synthetic organic chemists for long time due to their biological activity (antimicrobial and tuberculostatic activity) [1]. Anilides of salicylic acid based on phenylenediamine derivatives are known as nonvolatile antioxidants for plastics and rubber [2].

The classical synthesis of salicylanilides involves the interaction of chlorides or phenyl esters of substituted salicylic acids with amines in various solvents [3, 4] or under solvent-free conditions [5]. The main goal of this work was to improve the synthesis of salicylanilides from phenyl salicylates, which is the most frequently used method because it does not need protection and deprotection of the OH group.

## Results and Discussion

The beneficial effect of microwave irradiation on several organic reactions is well documented [6–11] and we decided therefore to explore if it could be applied for the synthesis of substituted salicylanilides. The method consists of a short exposure of a mixture of phenyl salicylates and anilines under microwave irradiation under solvent-free conditions. The temperature profile of this reaction was monitored by

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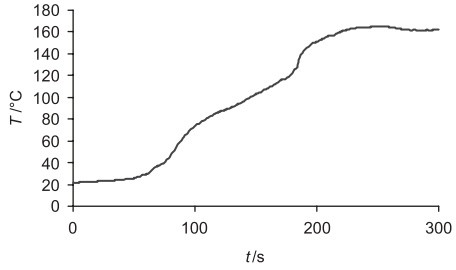
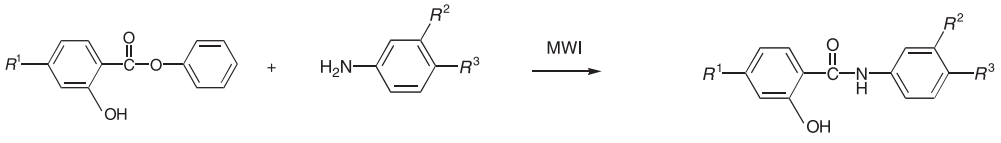



**Fig. 1.** Temperature profile of microwave assisted reaction of phenyl salicylate with 4-methyl-3-nitroaniline




| | $R^1$ |
|---|---|
| **1a** | H |
| **1b** | $OCH_3$ |

| | $R^2$ | $R^3$ |
|---|---|---|
| **2a** | H | H |
| **2b** | H | $CH_3$ |
| **2c** | H | $NO_2$ |
| **2d** | H | $NH_2$ |
| **2e** | H | NH*Ph* |
| **2f** | H | NH-*i*-hexyl |
| **2g** | $NO_2$ | $CH_3$ |

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **3a** | H | H | H |
| **3b** | H | H | $CH_3$ |
| **3c** | H | H | $NO_2$ |
| **3d** | H | H | $NH_2$ |
| **3e** | H | H | NH*Ph* |
| **3f** | H | H | NH-*i*-hexyl |
| **3g** | H | $NO_2$ | $CH_3$ |
| **3h** | $OCH_3$ | H | H |
| **3i** | $OCH_3$ | $NO_2$ | $CH_3$ |
| **3j** | $OCH_3$ | H | $NO_2$ |
| **3k** | $OCH_3$ | H | $NH_2$ |
| **3l** | $OCH_3$ | H | NH*Ph* |
| **3m** | $OCH_3$ | H | NH-*i*-hexyl |

**Scheme 1**

computer using Synthewave 402® (Fig. 1). The reaction route for the substituted salicyanilide derivatives is depicted in Scheme 1.

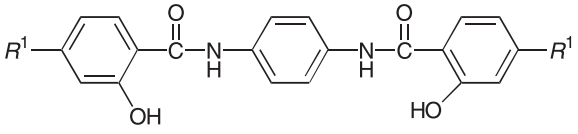
From the results in Table 1 follows that high yields (70–95%) of the products **3a**–**3m** were achieved after only 3–7 min of microwave irradiation. The versatility of this method was demonstrated by testing a wide range of different aromatic amines. This method can be also applied to 1,4-phenylenediamine ($R^2 = H$, $R^3 = NH_2$). In these cases the products of reactions on both amino groups were isolated in small amounts (**4a** 6%, **4b** 13%) (Fig. 2).

To examine if the reaction could be performed without microwave irradiation, an equimolar mixture of salicylanilide and 4-methyl-3-nitroaniline was immersed in a hot oil bath. When the temperature of the reaction mixture reached 162°C (the highest temperature in the microwave experiment) the mixture was kept at this temperature for 5 min. However, no product was observed (HPLC) (Entry 8). This could be explained by a specific microwave effect which is a consequence of the polar transition state interaction with the electric field [12].

**Table 1.** Microwave-assisted preparation of substituted salicylanilides

| Entry | Substrate | $T_{fin}$ [a] °C | Time min | Yield[b] % |
|---|---|---|---|---|
| 1 | **3a** | 171 | 4 | 95 |
| 2 | **3b** | 157 | 8 | 95 |
| 3 | **3c** | 205 | 4 | 96 |
| 4 | **3d** | 210 | 7 | 92 |
| 5 | **3e** | 186 | 5 | 93 |
| 6 | **3f** | 201 | 5 | 97 |
| 7 | **3g** | 162 | 5 | 98 |
| 8 | **3g** | 162 | 5 | 0[c] |
| 9 | **3h** | 192 | 7 | 94 |
| 10 | **3i** | 154 | 4 | 98 |
| 11 | **3j** | 210 | 4 | 99 |
| 12 | **3k** | 220 | 7 | 75 |
| 13 | **3l** | 205 | 7 | 70 |
| 14 | **3m** | 192 | 5 | 92 |

[a] $T_{fin}$ is temperature of the reaction mixture reached at the end of reaction; [b] yields refer to isolated products; [c] yield of the reaction performed under thermal heating without microwave irradiation




| | $R^1$ |
|---|---|
| **4a** | H |
| **4b** | $OCH_3$ |

**Fig. 2.** Formulae of by-products **4a** and **4b**

In conclusion, the advantages of the presented method are high yields, the solvent-free technique, easy work-up as well as purification, and short reaction time. This method can be applied also for the synthesis of 30–50 g samples of starting materials.

## Experimental

$^1$H NMR and $^{13}$C NMR spectra were measured on a Varian Gemini 2000 instrument at 300 MHz and 75 MHz. $CDCl_3$ and *DMSO* were used as solvents and tetramethylsilane as internal standard. Microanalyses were carried out on a Carlo Erba Strumenstacione Milano CHN analyser, model 1106. The results agreed with the calculated values. Melting points were determined on a *Kofler* apparatus and are not corrected. All microwave experiments were carried out in a SYNTHEWAVE 402®, PROLABO reactor. The temperature of the reaction mixture was monitored by an IR thermometer.

*General Procedure*

A mixture of phenyl salicylate (or phenyl 4-methoxysalicylate) (0.1 mol) and the amine (0.1 mol) was stirred under microwave irradiation in the microwave reactor (240 W input power) for 5 min. After cooling to room temperature, the reaction mixture was, treated with 50 $cm^3$ of $CH_2Cl_2$. The undissolved impurities were filtered off by suction, the solvent was evaporated, and formed phenol was distilled off under reduced pressure. The residue was recrystallized from *iso*-hexane/ethyl acetate (4/1) or purified by column chromatography on silica using $CHCl_3$/ethyl acetate (19/1) as eluent to give pure salicylanilides. The results are summarized in Table 1. Melting points and NMR data of products **3a** [5, 13], **3b** [5, 14], **3c** [15], **3d** [2], **3e** [2], **3h** [16, 17], and **3j** [16] were found to be identical with the data described in literature.

*2-Hydroxy-N-[4-[(1,3-dimethylbutyl)amino]phenyl]benzamide* (**3f**, $C_{19}H_{24}N_2O_2$)

White solid; m.p. 56–58°C; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 0.91$ (d, $J = 6.0$ Hz, $CH_3$), 0.93 (d, $J = 6.0$ Hz, $CH_3$), 1.18 (d, $J = 6.0$ Hz, $CH_3$), 1.27–1.34 (m, $C\underline{H}_A\underline{H}_B$), 1.42–1.53 (m, $CH_A\underline{H}_B$), 1.68–1.77 (m, $C\underline{H}(CH_3)_2$), 3.48–3.55 (m, $C\underline{H}NH$), 6.31 (d, $J = 9.0$ Hz, $2H_{arom}$), 6.87 (t, $J = 8.1$ Hz, $1H_{arom}$), 7.01 (d, $J = 9.0$ Hz, $1H_{arom}$), 7.31 (d, $J = 9$ Hz, $2H_{arom}$), 7.42 (t, $J = 8.1$ Hz, $1H_{arom}$), 7.52 (d, $J = 7.8$ Hz, $2H_{arom}$), 7.86 (bs, NH), 12.18 (s, OH) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta = 20.8$, 22.5, 22.9, 25.1, 46.6, 113.7, 114.7, 118.8, 118.8, 123.7, 125.4, 134.3, 161.8, 168.3 ppm.

*2-Hydroxy-N-(4-methyl-2-nitrophenyl)benzamide* (**3g**, $C_{14}H_{12}N_2O_4$)

Yellow solid; m.p. 190°C; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 2.43$ (s, $CH_3$), 6.96–7.06 (m, $2H_{arom}$), 7.46–7.56 (m, $3H_{arom}$), 8.10 (s, $1H_{arom}$), 8.73 (d, $J = 8.7$ Hz, $1H_{arom}$), 11.39 (s, NH), 11.83 (s, OH) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta = 20.6$, 114.5, 119.0, 119.5, 122.5, 125.8, 125.9, 131.8, 134.4, 135.3, 137.0, 162.3, 169.0 ppm.

*2-Hydroxy-4-methoxy-N-(4-methyl-2-nitrophenyl)benzamide* (**3i**, $C_{15}H_{14}N_2O_5$)

Yellow solid; m.p. 174–175°C; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 2.42$ (s, $CH_3$), 3.85 (s, $CH_3$), 6.50–6.56 (m, $2H_{arom}$), 7.51 (d, $J = 8.54$ Hz, $1H_{arom}$), 7.57 (d, $J = 8.85$ Hz, $1H_{arom}$), 8.07 (s, $1H_{arom}$), 8.70 (d, $J = 8.54$ Hz, $1H_{arom}$), 11.23 (s, NH), 12.17 (s, OH) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta = 20.6$, 55.6, 101.8, 107.5, 108.0, 122.4, 125.8, 127.4, 132.2, 133.9, 136.6, 137.0, 164.7, 165.3, 168.8 ppm.

*N-(4-Aminophenyl)-2-hydroxy-4-methoxybenzamide* (**3k**, $C_{14}H_{14}N_2O_3$)

Grey solid; m.p. 260–263°C; $^1$H NMR (*DMSO*, 300 MHz): $\delta = 3.78$ (s, $OCH_3$), 6.52–6.54 (m, $2H_{arom}$), 7.39 (d, $J = 8.4$ Hz, $2H_{arom}$), 7.80 (d, $J = 8.4$ Hz, $2H_{arom}$), 8.06 (d, $J = 8.7$ Hz, $1H_{arom}$), 10.46 (bs, NH), 12.39 (s, OH) ppm; $^{13}$C NMR (*DMSO*, 75 MHz): $\delta = 55.5$, 101.4, 106.3, 109.0, 122.2, 123.5, 127.7, 130.5, 137.7, 161.5, 163.84, 167.2 ppm.

*2-Hydroxy-4-methoxy-N-[4-(phenylamino)phenyl]benzamide* (**3l**, $C_{20}H_{18}N_2O_3$)

Grey solid; m.p. 164–165°C; $^1$H NMR (*DMSO*, 300 MHz): $\delta = 3.79$ (s, $CH_3$), 6.48 (s, $1H_{arom}$), 6.50 (d, $J = 9.0$ Hz, $1H_{arom}$), 6.71 (t, $J = 6.9$ Hz, $1H_{arom}$), 7.03–7.09 (m, $4H_{arom}$), 7.19–7.24 (m, $2H_{arom}$), 7.51 (d, $J = 9.0$ Hz, $2H_{arom}$), 7.98 (d, $J = 9.0$ Hz, $1H_{arom}$), 8.13 (s, NH), 10.11 (s, NH), 12.65 (s, OH) ppm; $^{13}$C NMR (*DMSO*, 75 MHz): $\delta = 55.2$, 101.2, 110.6, 112.9, 118.1, 118.3, 121.2, 129.6, 132.8, 134.6, 138.3, 141.5, 161.9, 162.5, 166.4 ppm.

*2-Hydroxy-4-methoxy-N-[4-[(1,3-dimethylbutyl)amino]phenyl]benzamide* (**3m**, $C_{15}H_{14}N_2O_5$)

Grey solid; m.p. 99–101°C; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 0.90$ (d, $J = 6.0$ Hz, $CH_3$), 0.93 (d, $J = 6.0$ Hz, $CH_3$), 1.15 (d, $J = 6.0$ Hz, $CH_3$), 1.27–1.34 (m, $C\underline{H}_A H_B$), 1.42–1.53 (m, $CH_A\underline{H}_B$) 1.72 (m, CH), 3.51 (m, CH), 3.81 ($OCH_3$), 6.44 (d, $J = 8.44$ Hz, $1H_{arom}$), 6.47 (s, $1H_{arom}$), 6.58 (d, $J = 8.7$ Hz, $2H_{arom}$), 7.26 (d, $J = 8.7$ Hz, $2H_{arom}$), 7.38 (d, $J = 8.44$ Hz, $1H_{arom}$), 7.66 (bs, NH), 12.61 (s, OH) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta = 20.9$, 22.5, 22.9, 25.1, 46.7, 47.0, 55.5, 101.7, 107.1, 107.5, 113.4, 123.8, 126.1, 126.6, 145.4, 164.1, 164.4, 168.3 ppm.

*N,N′-1,4-Phenylenebis(2-hydroxybenzamide)* (**4a**, $C_{15}H_{14}N_2O_5$)

Grey solid; m.p. 318°C; $^1$H NMR (*DMSO*, 300 MHz): $\delta = 6.94$–7.00 (m, $4H_{arom}$), 7.42 (d, $J = 8.4$ Hz, $2H_{arom}$), 7.71 (s, $J = 7.5$ Hz, $4H_{arom}$), 7.98 (d, $J = 7.5$ Hz, $2H_{arom}$), 10.41 (s, 2NH), 11.87 (s, 2OH) ppm; $^{13}$C NMR (*DMSO*, 75 MHz): $\delta = 117.2$, 117.3, 119.0, 121.3, 128.9, 133.6, 134.3, 158.6, 166.15 ppm.

*N,N′-1,4-Phenylenebis(2-hydroxy-4-methoxybenzamide)* (**4b**, $C_{22}H_{20}N_2O_6$)

Grey solid; m.p. 322–322°C; $^1$H NMR (*DMSO*, 300 MHz): $\delta = 3.78$ (s, $2OCH_3$), 6.51 (s, $2H_{arom}$), 6.56 (d, $J = 8.4$ Hz, $2H_{arom}$), 7.67 (s, $4H_{arom}$), 7.99 (d, $J = 8.4$ Hz, $2H_{arom}$), 10.24 (s, 2OH) ppm; $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta = 55.4$, 101.3, 106.3, 108.8, 121.5, 129.9, 134.2, 161.8, 163.8, 167.2 ppm.

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