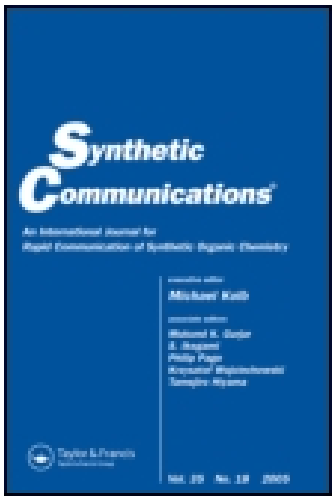

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# On the 3-Aminophenothiazine Synthesis

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## ABSTRACT

Investigation of the key step of 3-aminophenothiazine (**5**) synthesis, that is thiation of *N*-(4-phenylaminophenyl)-phthalimid (**3**) was carried out. The best results were achieved using microwave irradiation, when 55% of the pure thiation product 3-phalimidophenothiazine (**4**) were isolated in 10–20 min reaction time.

*Key Words:* Aminophenothiazine; Microwave irradiation.

Phenothiazines are well known as intermediates for pharmaceuticals, they are active as insecticides as well as antioxidants. These compounds are usually prepared by thiation of diphenylamines with octasulfur.[1]

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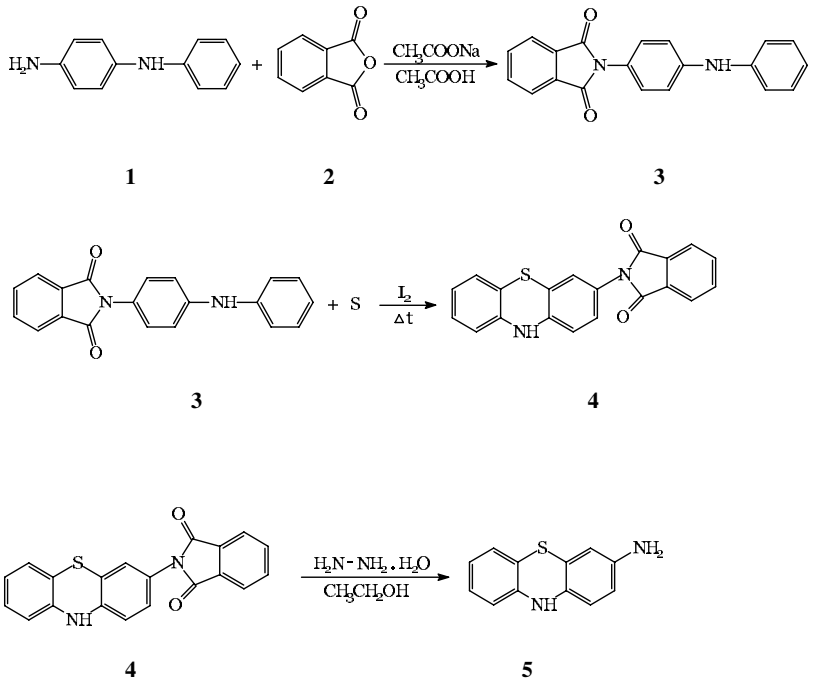
## RESULTS AND DISCUSSION

The reaction course of 3-aminophenothiazine (**5**) is depicted in Sch. 1. Synthesis of 3-aminophenothiazine (**5**) started with the protection of the primary amino group of 4-aminodiphenylamine (**1**). Heating the reaction mixture containing 4-aminodiphenylamine (**1**), phthaloic anhydride (**2**), and sodium acetate in acetic acid to reflux for 2 h resulted in 92% yield of *N*-(4-phenylaminophenyl)-phthalimid (**3**) (Lit.[2] 99%).

To prepare 3-phalimidophenothiazine (**4**), we first tried to repeat the procedure desribed in literature.[2] *N*-(4-Phenylaminophenyl)-phthalimid (**3**), octasulfur and diiodine were dissolved in 1,2-dichlorobenzene and refluxed (180°C) for 2 h. After cooling to room temperature, black solid material was filtered off and crystallized from acetone/water (7:2) mixture. 3-Phthalimidophenothiazine (**4**) was obtained in 10% yield (Table 1, Entry 1) (Lit.[2] 30.8%).

In continuation, we tried to change the solvent. Decahydronaphthalene (Decalin®) was used instead of 1,2-dichlorobenzene. Reaction




**1** **2** **3**

**3** **4**

**4** **5**

*Scheme 1.*

***Table 1.*** Results of thiation of *N*-(4-phenylaminophenyl)-phthalimid (**3**) by different methods.

| Entry | Reaction conditions | Conversion of **3** (%) |
|---|---|---|
| **1** | 1,2-Dichloromethane, thermal heating, 180°C, 2 h | 10[a] |
| **2** | Decalin®, thermal heating, 190°C, 4 h | 15 |
| **3** | Decalin®, ultrasonic irradiation, 95°C, 1 h | 0 |
| **4** | Nitrobenzene, thermal heating, 211°C, 2h | 0[b] |
| **5** | Solvent-free, microwave irradiation, 420 W, $T_{final} = 236°C$, 10 min | 100 (55[c]) |
| **6** | Solvent-free, microwave irradiation, 240 W, $T_{final} = 228°C$, 20 min | 100 (55[c]) |
| **7** | Decalin®, microwave irradiation, 360 W, $T_{final} = 180°C$, 30 min | 50 |
| **8** | Solvent-free, thermal heating, 200°C, 3 h | 100 (50[c]) |

[a]Yield isolated by crystallization from acetone/water (7:2) mixture.
[b]Yield detected by TLC.
[c]Yields isolated by chromatography.

mixture was heated to reflux (190°C) for 4 h. Conversion of *N*-(4-phenylaminophenyl)-phthalimid (**3**) was after 4 h 15% only (Table 1, Entry 2), what is probably due to the poor solubility of the reactants in the solvent.

To improve the solubilty of the reactants in Decaline®, the reaction was performed under ultrasonic irradiation. An immersed horn reactor (20 kHz, 300 W) was used as a source of ultrasonic irradiation. The temperature of reaction mixture attained after 1 h of irradiation 95°C and just starting material *N*-(4-phenylaminophenyl)-phthalimid (**3**) was detected in the reaction mixture by TLC (Table 1, Entry 3).

When nitrobenzene was used as a solvent and the reaction of *N*-(4-phenylaminophenyl)-phthalimid (**3**) with octasulfur under diiodine catalysis was performed at the temperature of its boiling point (211°) for 2 h, no product was detected (Table 1, Entry 4) in the reaction mixture (TLC). Black tarry material was isolated, what is probably result of strong oxidizing ability of the solvent.

Thiation of diphenylamine with octasulfur catalyzed by diiodine was described[1], working under solvent-free conditions under microwave irradiation. The yield of phenothiazine was 87% after 2 min of reaction. We decided therefore to apply microwave irradiation to our reaction mixture. The mixture of *N*-(4-phenylaminophenyl)-phthalimid (**3**),

octasulfur and diiodine was exposed to microwave irrradiation. Final temperature attained in the reaction mixture was 228 and 236°C, respectively. Conversion of *N*-(4-phenylaminophenyl)-phthalimid (**3**) was 100% after 10–20 min of irradiation (Table 1, Entries 5, 6). Yield of 3-phthalimidophenothiazine (**4**) was 55% after column chromatography. In the case when this reaction was performed under microwave irradiation with Decaline® as a solvent, temperature of the reaction mixture was after 30 min irradiation 180°C and the conversion of *N*-(4-phenylaminophenyl)-phthalimid (**3**) was acccording to $^1$H NMR spectra 50%.

To achieve 100% conversion of *N*-(4-phenylaminophenyl)-phthalimid (**3**) in solvent-free thiation reaction without microwave irradiation, it was necessary to heat the reaction mixture in oil bath under magnetic stirring for 3 h. Yield of 3-phthalimidophenothiazine (**4**) was 50% (Entry 8).

An attempt has been made on thiathion of *N*-phenylphenylene diamine (**1**) with unprotected primary amino group. The reaction resulted in formation of unidentified products of oxidation and polymerization reactions.

Deprotection of the amino group was performed with hydrazine hydrate solution in ethanol. Crude product was purified by column chromatography and the yield of chromatographed product was 48% (lit.[2] 42% after crystallization from toluene). Purification of the crude product by crystallization from toluene resulted in thick oil material.

## EXPERIMENTAL

$^1$H NMR spectra were measured on Varian Gemini 2000 instrument, working frequency 300 MHz and 75 MHz, respectively, with DMSO as the solvent and tetramethylsilane as an internal standard. Melting points were determined on a Kofler apparatus and are not corrected. All microwave experiments were carried out in the SYNTHEWAVE 402, PROLABO reactor.

### Protection of Primary Amino Group

*N*-phenylphenylene diamine **1** (36.8 g, 0.2 mol), phthaloic anhydride **2** (29.6 g, 0.2 mol), anhydrous sodium acetate (26.2 g, 0.32 mol) were refluxed in acetic acid (360 mL) for 2 h. Reaction mixture was then cooled down to the room temperature and the yellow solid precipitated.

The product *N*-(4-phenylaminophenyl)-phthalimid (**3**) was filtered off with suction and washed with water and acetone.

***N*-(4-Phenylaminophenyl)-phthalimid (3).** Yield 92%; m.p. 277–279°C (lit.[2] 273–274°C); $\delta_H$ (300 MHz, DMSO): 6.88 (t, J 7.2 Hz, 1H), 7.13–7.17 (m, 4H), 7.25–7.30 (m, 4H), 7.88–7.97 (m, 4H), 8.40 (s, NH).

## Thiation of *N*-(4-Phenylaminophenyl)-phthalimide

*N*-(4-Phenylaminophenyl)-phthalimid **3** (15 g, 48 mmol), octasulfur (7.5 g, 235 mmol), diiodine (0.75 g, 3 mmol) were ground together in a mortar and the mixture was then microwave irradiated. The final temperature was 228–236°C. 100% conversion of *N*-(4-phenylaminophenyl)-phthalimid (**3**) was achieved after 10–20 min of irradiation. Reaction mixture was cooled down to room temperature and then dissolved in DMSO (300 mL) in boiling water bath. DMSO solution was after cooling poured in water (800 mL). Yellow solid, which precipitated from water, was collected by filtration with suction, washed with ether and dried under reduced pressure.

**3-Phthalimidophenothiazine (4).** Yield 55%; m.p. 258°C (lit.[2] 255–257°C); $\delta_H$ (300 MHz, DMSO): 6.70–6.82 (m, 2H), 6.95 (dd, J 7.5 Hz, 1.2 Hz, 1H), 6.99–7.06 (m, 4H), 7.87–7.96 (m, 4H), 8.83 (s, NH).

## Deprotection of Primary Aminogroup

3-Phthalimidophenothiazine **4** (10 g, 29 mmol), hydrazine hydrate 98–100% solution (2.76 mL, 55.3 mmol) were suspended in ethanol (100 mL) under magnetical stirring and heating to 60–70°C for 2.5 h. After the reaction, precipitated phthaloyl hydrazide was filtered off. Ethanol from fitrate was evaporated under reduced pressure and the solid portion was dissolved in diethyl ether. Undissolved particles were filtered off and ether was evaporated from the filtrate. Crude product was purified by column chromatography on $Al_2O_3$ and 1:1 mixture of toluene/ethyl acetate with 5% of triethylamine was used as the eluent.

**3-Aminophenothiazine (5).** Yield 48%; m.p. 140–142°C (lit.[2] 139–141°C); $\delta_H$ (300 MHz, DMSO): 4.78 (s, $NH_2$), 6.28–6.35 (m, 2H), 6.60 (dd, J 8.0 Hz, 1.2 Hz, 1H), 6.70–6.75 (m, 2H), 6.92–7.02 (m, 2H), 8.14 (s, NH); $\delta_C$ (75 MHz, DMSO): 111.59, 113.15, 113.81, 115.07, 116.73, 119.55, 120.44, 126.13, 127.15, 131.64, 137.40, 143.69.

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