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Dedicated to Professor Ionel Haiduc
on the occasion of his 65th birthday

THE SYNTHESIS OF NEW PHENOTHIAZINE COMPOUNDS BY THE THIATION OF DIPHENYLAMINO DERIVATIVES

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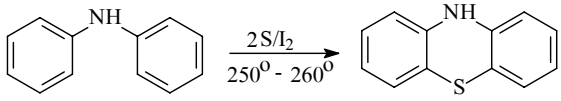
ABSTRACT. The thiation of 1, 3, 5 –*tris*-phenylamino-benzene was studied under various reaction conditions, such as conventional heating and microwaves activation. New 2, 4-diphenylamino-phenothiazine and 6-phenylamino-1,4-benzothiazino[3,2-b]-phenothiazine were thus obtained. Structural assignments were performed using high resolution NMR – spectroscopy.

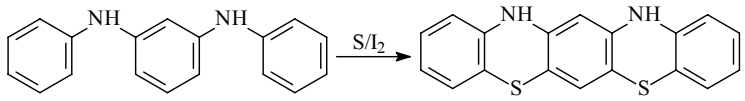
INTRODUCTION

The first phenothiazine synthesis, reported by Bernthsen more than one century ago [1], was performed by melting the diphenylamine with sulphur at high temperature as shown in scheme 1. Since, many improvements of this method were proposed, due to practical reasons. The use of catalysts such as iodine or $AlCl_3$ [2, 3], inert gas atmosphere [4] and a proper solvent [5, 7] were very effective improvements leading to higher yields and purity of the product.



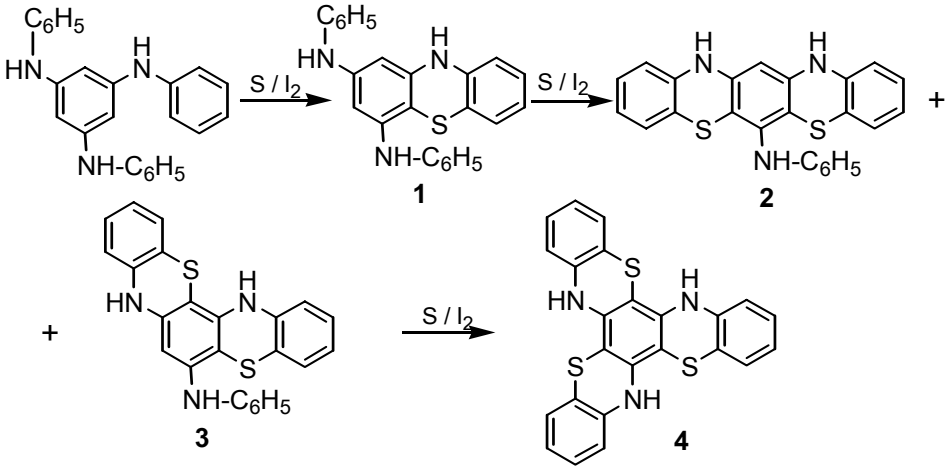
Scheme 1

The thiation of 1,3–diphenylaminobenzene [8] with sulphur in the presence of iodine lead to 1,4–benzothiazino[3,2-b]–phenothiazine [9] as shown in scheme 2:



Scheme 2

We studied the thiation of 1,3,5-*tris*-phenylamino-benzene, a reaction which may lead to various phenothiazine derivatives as shown in scheme 3, by a mono, double or triple thiation of the central benzene nucleus of this substrate.



Scheme 3

RESULTS AND DISCUSSIONS

1,3,5-*tris*-phenylaminobenzene, prepared by the condensation of fluoroglucine with aniline using a previously described method [8], was subjected to the thiation reaction under the following conditions:

a) A mixture of 1,3,5-*tris*-phenylaminobenzene and sulphur in 1:6 molar ratio and 1% iodine was heated at 250 – 260^{o}C for 30 minutes.
b) A mixture of 1,3,5-*tris*-phenylaminobenzene and sulphur in 1:6 molar ratio and 1% iodine were heated in 1,2,4-trichloro benzene solvent for 15 minutes.
c) The mixture of 1,3,5-*tris*-phenylaminobenzene, sulphur and 1% iodine were subjected to microwave activation (in a modified domestic microwave owen) under “dry medium” conditions. The reaction was performed with and without dry support. The tested supports were aluminum oxide and acid bentonite (in this later experiment no iodine catalyst was requested).

The main reaction product in all these conditions was 2,4–diphenylamino phenothiazine **1**, as shown in scheme 3.

Structural assignments for compound **1** were performed using the 400MHz ^{1}H-NMR and ^{13}C-NMR spectra together with the 2D correlation spectra: COSY 45

and HETCOR (HMQC and HMBC). Figure 1 shows the 2D homocorrelation COSY 45 spectrum used for the assignement of the spin-spin couplings between aromatic protons of compound **1**.

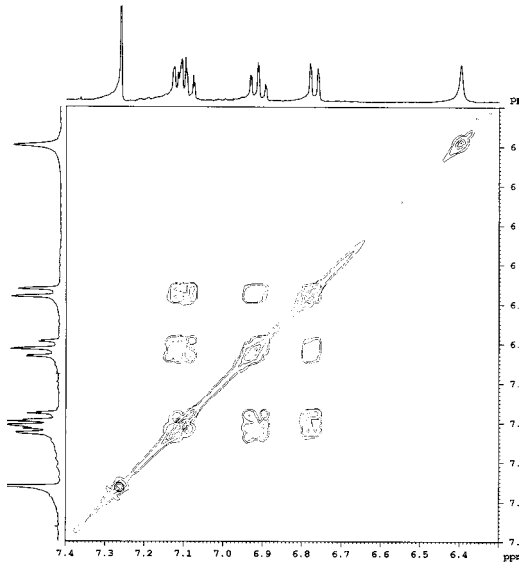


Fig. 1. 400MHz COSY 45 spectrum of compound **1** in $CHCl_3$-d_1

The thiation of 1,3,5-*tris*-phenylaminobenzene with a large excess of sulphur in 1,2,4-trichlorobenzene solvent, under prolonged reaction time, lead to a low yield of 6–phenylamino-1,4–benzothiazino[3,2-b]–phenothiazine **2** (scheme 3).

Structural assignments of this compound were performed using high resolution ^{1}H-NMR spectrum. The linear annelation by this double thiation, similar to the thiation which generated the 1,4–benzothiazino[3,2-b]-phenothiazine, suppressed the possibility of the third thiation of the central benzene nucleus.

Theoretical calculations of the rotational energy for the conformers of 2,4– diphenylamino-phenothiazine involved in the thiation reaction, showed a 10 kcal/mol rotational barrier for the rotation of the substituent at C^4 (conformer involved in the angular annelation) and only 2 kcal/mol rotational barrier for the rotation of substituent at C^2 (conformer involved in the linear annelation), may be due to the sterical hindrance of the sulphur atom of the phenothiazine heterocycle upon the neighboring substituent situated at C^4.

CONCLUSIONS

The thiation of 1,3,5-*tris*-phenylaminobenzene with sulphur in the presence of iodine as catalyst generated 2,4-diphenylamino-phenothiazine **1**, under classical thermal activation. Microwaves activation of this reaction in dry medium presents the same selectivity and it may be considered as a convenient alternative synthetic method for phenothiazine derivatives synthesis.

The thiation of the 2,4-diphenylamino–phenothiazine generated the 6–phenylamino-1,4–benzothiazino[3,2-b]-phenothiazine **2** in low yields under thermal conditions and a presumable steric control of the reaction.

EXPERIMENTAL

Modified domestic microwave owen
400 MHz Brucker NMR spectrometer.

2,4-Diphenilamino-phenothiazine 1

a) 1 mmol 1,3,5-*tris*-phenylaminobenzene, 6 mmols sulphur and one crystal of iodine were melted together in an open vessel; the temperature was maintained at 250 – 260^{o}C for 10 minutes and H_2S evolved. After cooling, the reaction mixture was extracted with acetone. After the solvent evaporation the raw product was recrystallised from xylene.

0,12 g (34 %) **1** with a green color and melting point 195-198^{o}C was obtained. ^{1}H-NMR: 6.4 ppm (s, 2H), 6,7 ppm (d, 4H), 6,9 ppm (t, 4H), 7,1ppm (m, 8H).

b) 1 mmol 1,3,5-*tris*-phenylaminobenzene, 6 mmols sulphur, one crystal of iodine and 4 ml 1,2,4 trichloro-benzene solvent were heated in a round bottom flask equipped with a reflux condenser. At 170^{o}C appeared with effervescence. After cooling the raw product was filtered and recrystallised from xylene. 0,18 g (52 %) **1** were obtained (m.p.=198^{o}C).

c) microwave activated syntheses

-0.17 g 1,3,5-*tris*-phenylaminobenzene, 0.1 g sulphur and 0.01 g iodine were solved in diethyl ether, then 1 g Al_2O_3 was added and the solvent was evaporated under stirring at reduced pressure. The mixture was introduced in a quartz open vessel and exposed to microwaves action for 30 seconds (at 500 W) or 20 seconds (at 750 W). After cooling, the product was extracted with acetone and after solvent evaporation it was recrystallised from xylene. Yields, 0,06g (35%) of **1**, m.p.=195^{o}C.

-0.17g 1,3,5-*tris*-phenylaminobenzene and 0.1 g sulphur were solved in diethyl ether, then 1 g acidic bentonite was added and the solvent evaporated under stirring. The product was obtained after 2 minutes irradiation at 500 W, 23 seconds at 750 W or 2 s at 900 W. (The reaction progress was monitored by thin layer chromatography). The product was extracted with acetone; the solvent was evaporated to dryness and then recrystallised from xylene. 0,05g (yield 26%) **1** were obtained (m. p.= 195^{o} C).

6–phenylamino-1,4–benzithiazino[3,2–b]–phenothiazine 2

0.19 g 2,4-diphenylamino-phenothiazine, 0.2g sulphur and 0.01 g iodine were heated in 4 ml 1,2,4–trichlorobenzene. At 175^{o}C the H_2S was evolved and this temperature was mantained for 30 minutes. After cooling, the dark colored precipitate was filtered and recrystallised from aniline. 0,02g (10% yield) product was obtained as a dark colored powder, which decomposes at temperature higher than 260^{o} C.

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