SYNTHESIS AND IR, NMR CARACTERISATION OF NEW *P*-(N,N-DIPHENYLAMINO) CHALCONES

Sîrbu Dumitru, Marin Ion*

Institute of Chemistry of the ASM, 3 Academiei str., Chisinau, MD-2028, Republic of Moldova
E-mail: marininbox@yahoo.com; tel.: + 373 22 729761.

Abstract: This article reports on the high yield synthesis and novel chalcones with isothiocyanate and imidazol groups. The synthesis was started from N,N-diphenilamine and finished with 4-(N,N-diphenylamino)-4'-(2-thioxo-imidazolidin-4-one)-chalcone, where the cheap and accessible reagents were used.

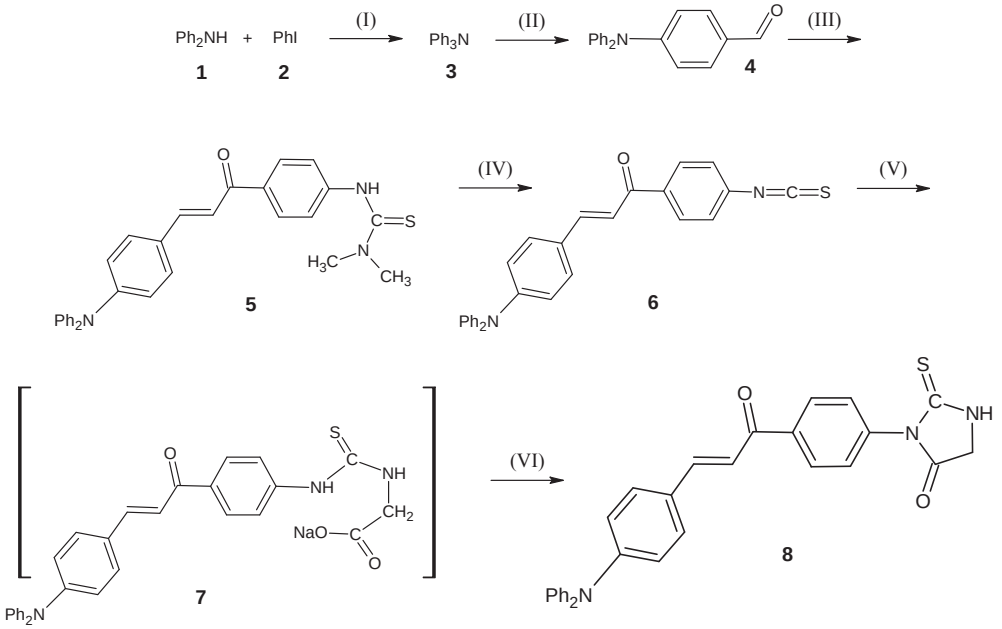
Keywords : chalcone, isothiocyanat, imidazole, NMR, IR.

Introduction

Since its discovery, chalcones became of interest due to its biological activities such as antibacterial, antifungal, antimalarial and anticancerous properties[1]. The possibility to use chalcones in application domains of luminophore pigments [2], developing of lasers, photographic techniques, photocopying, data storage elements, in dye-sensitized solar cells [3] gave an impulse for the intensification of luminescent chalcones investigation [4].

Results and discussion

In order to obtain 4-(N,N-diphenylamino)benzaldehyde, (4, Scheme 1), two reactions were carried out. Initially, diphenylamine (1) was condensed with iodobenzene (2) to obtain triphenylamine (3). The reaction is catalyzed by activated copper in nitrobenzene [5]. For the introduction of the carbonyl group in the *para* position of the phenyl ring the Vilsmeier reaction was used [6]. The presence of formyl group in the final product (4) was demonstrated by IR spectroscopy (ν (C=O) = 1685 cm^{-1}.



Scheme 1: **Synthetic Route of the 4-(N,N-diphenylamino)-4'-(2-thioxo-imidazolidin-4-one)-chalcone**
(I) Cu/K_2CO_3, $PhNO_2$, reflux (II) $POCl_3$, DMF, 95-100 ºC, 20 h (III) 4-N,N-dimethylthioureidoacetophenone, NaOH, EtOH/DMF, 25 ºC, 5 h (IV) acetic anhydride, dioxane/H_2O, reflux, 2 h (V) glycine, Na_2CO_3, reflux, 2 h (VI) $CHCl_3$, reflux, 1 h.

The synthesis of 4-(N,N-diphenylamino)-4'-(N,N-dimethylthioureido)-chalcone (5) was carried using the alkaline catalysis (Scheme 1). The acetophenone carboanion attack the positively charged carbon of the carbonyl group. As a result, aldol condensation occurs and aldol products are obtained. Thus, by removal of hydroxyl group and formation of the double bond (crotonic condensation), the final compound is obtained (5). To inhibit secondary reactions, alkaline catalysis was carried out at temperatures not more 25 °C.

To confirm the proposed structure of product (5) the 1H-NMR spectrum of this substance was measured. The main information was provided by doublet with chemical shift 7.78 ppm and integral 1 which indicates the presence of the double bond C=C. Also, the peaks for protons of the following groups were found:

- 4'-(N,N-dimethylthioureido) – 3.37 ppm (s, 6H, CH_3) and 9.81 ppm (s, 1H, NH);
- parasubstituted phenyl ring from acetophenone group – 8.01 ppm (d, 2H, 2',6'-C_{ph});
- parasubstituted phenyl ring from 4-(N,N-diphenylamino) group – 7.48 ppm (d, 2H, 2,6-C_{ph});
- Other proton peaks were found as multiplets in the region 7.00 ÷ 7.41 ppm.

Reaction yield is relatively high (70%) compared with those described in the literature for analogue compounds [7].

In order to obtain the isothiocyanato product (6) the elimination of dimethylamine from dimethylthioureidochalconic compound (5) was performed. This was achieved by boiling the latter one in benzene in the presence of acetic anhydride. As a result, the compound (5) was completely consumed and the final product was easily separated.

To confirm the proposed structure of product (6) ^{1}H-NMR, Cosy45–NMR and IR spectroscopy methods were used. The main changing in ^{1}H-NMR spectrum (fig. 1) for compound (6) versus the analog spectrum of the initial compound (5) is the disappearance of the proton peaks for CH_3 and NH groups from 4'-(N,N-dimethylthioureido) fragment. Proton spectrum has provided information about the presence of the following fragments:

- double bond C=C – 7.77 ppm (d, 1H, 2-C);
- parasubstituted phenyl ring from acetophenone group – 8.00 ppm (d, 2H, 2',6'-C_{ph});
- parasubstituted phenyl ring from 4-(N,N-diphenylamino) group – 7.02 ppm (d, 2H, 3,5-C_{ph}), 7.48 ppm (d, 2H, 2,6-C_{ph});
- other proton peaks are overlapped and were assigned to multiplets in the regions – 7.10 ÷ 7.16 ppm (m, 2H, 2*4''-C_{dpha} + 4H, 2*2'',6''-C_{dpha}) and 7.29 ÷ 7.33 (m, 2H, 3',5'-C_{ph} + 4H, 2*3'',5''-C_{dpha} + 1H, 3-C).

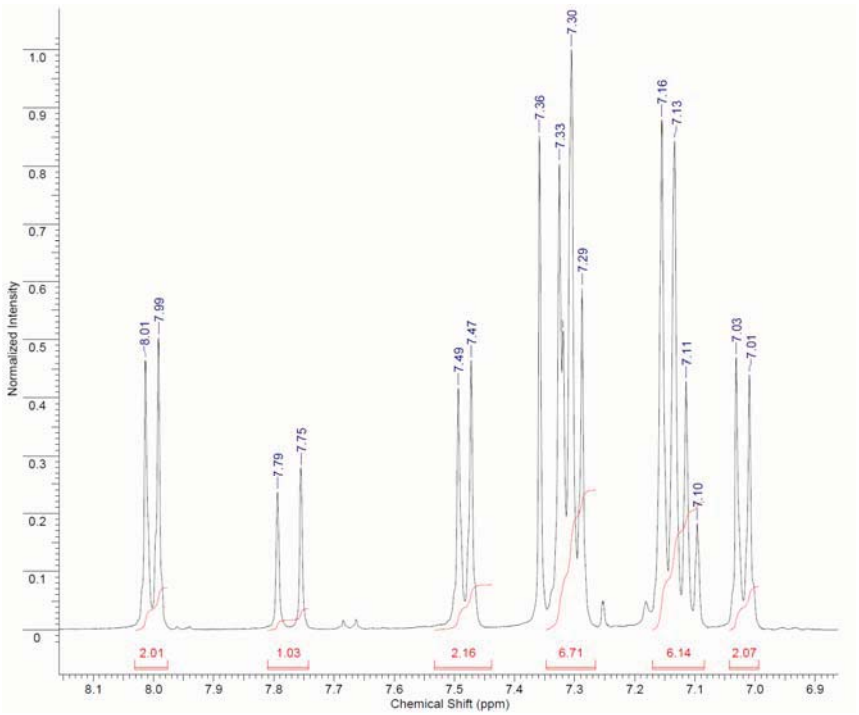


Fig. 1. ^{1}H-NMR spectrum of 4-(N,N-diphenylamino)-4'-isothiocyanato-chalcone

For correct assignment of other proton peaks in the NMR spectrum, Cosy45-NMR spectroscopy was used (fig. 2), that provided information about all protons of compound (6):

- double bond C=C – 7.33 : 7.77 ppm (1H, 3-C : 1H, 2-C);
- parasubstituted phenyl ring from acetophenone group – 7.30 : 8.00 ppm (3',5'-C_{ph} : 2',6'-C_{ph});
- monosubstituted phenyl ring from 4-(N,N-diphenylamino) group – 7.09 : 7.30 ppm (4''-C_{dpha} : 3'',5''-C_{dpha}) and 7.13 : 7.30 ppm (2'',6''-C_{dpha} : 3'',5''-C_{dpha});
- parasubstituted phenyl ring from 4-(N,N-diphenylamino) group – 7.01 : 7.48 (3,5-C_{ph} : 2,6-C_{ph}).

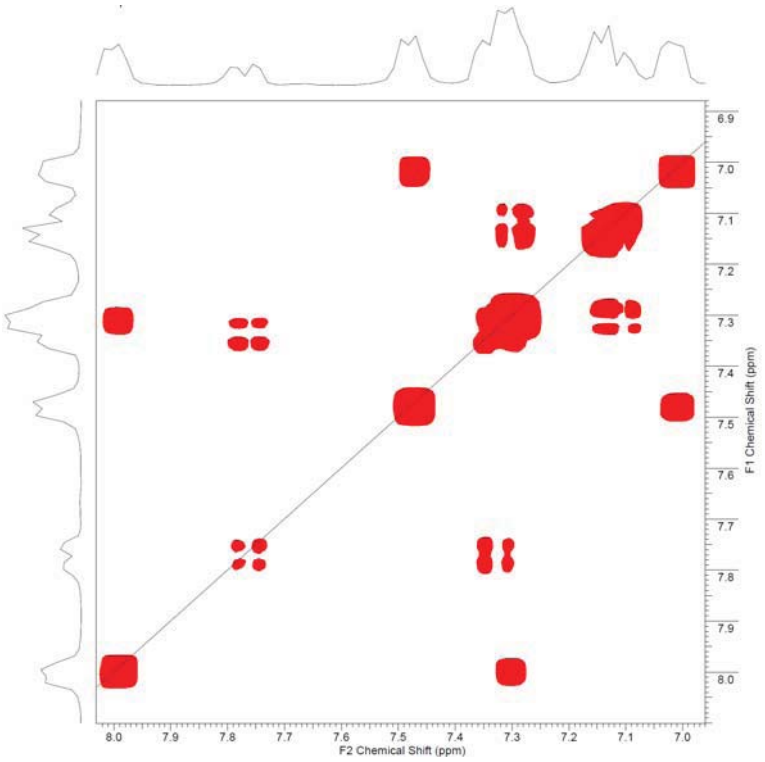


Figure 1: Cosy45-NMR spectra of 4-(N,N-diphenylamino)-4'-isothiocyanato-chalcone

IR spectroscopy was used to demonstrate the presence of functional groups in the studied compound. For product (6) ketone and isothiocyanato groups were studied. Their presence was indicated by intense peaks at following wavelength:

- ν (CO) = 1650 cm^{-1}, medium – ketone group;
- ν (CN) = 2115 cm^{-1}, strong – isothiocyanato group.

^{1}H-NMR, Cosy45-NMR and IR spectroscopic data unequivocally demonstrate the proposed structure of compound (6).

The synthesis of the 4-(N,N-diphenylamino)-4'-(2-thioxo-imidazolidin-4-one)-chalcone (8) was performed by addition of glycine to 4-(N,N-diphenylamino)-4'- isothiocyanato chalcone (6) and subsequent cyclization of the intermediate compound (7). Sodium glycinate is more active in addition reactions as compared to its acid form, therefore glycinic acid was neutralized with sodium carbonate. The addition of sodium glycinate to compound (6) leads to obtaining of sodium chalcone-4-(N,N-diphenylamino)-4'-((carbamothioyl)aminoacetate) (7). The neutralization and subsequent heating in chloroform of the intermediate compound (7) lead to the final product (8).

To confirm the proposed structure of product (8) ^{1}H-NMR and IR spectra were measured. Proton spectrum has provided information about the presence of the following fragments:

- 2-thioxo-imidazolidin-4-one substituted on 3-C – 4.38 (s, 2H, CH_2) and 9.25 (s, 1H, NH);
- parasubstituted phenyl ring from acetophenone group – 8.21 ppm (d, 2H, 2',6'-C_{ph});
- monosubstituted phenyl ring from 4-(N,N-diphenylamino) group – 7.00 ppm (d, 2H, 3,5-C_{ph}) and 7.54 ppm (d, 2H, 2,6-C_{ph});
- parasubstituted phenyl ring from 4-(N,N-diphenylamino) group – 7.75 ppm (m, 4H, 3'',5''-C_{dpha}).
- other protons peaks are overlapped and were assigned to multiplets in the regions – 7.14 – 7.17 ppm (m, 1H, 2-C + 2H, 2*4''-C_{dpha} + 4H, 2*2'',6''-C_{dpha}), 7.36 – 7.40 ppm ((m, 2H, 3',5'-C_{ph} + 1H, 3-C).

Using IR spectroscopy the presence of the following functional groups was demonstrated:

- ν (CO) = 1654 cm^{-1} – ketone group from acetophenone;
- ν (CO) = 1761 cm^{-1} – ketone group from glycine;
- ν (NH) = 3229 cm^{-1} – secondary amine group.

Experimental section

NMR spectra were performed in $CDCl_3$ on BRUKER AVANCE-III 400 MHz spectrometer. NMR methods utilized in this research are: ^{1}H-NMR, ^{13}C-NMR, Cosy45-NMR.

IR spectra were measured at the Spectrum 100 FT-IR Spectrometer Perkin Elmer.

Synthesis of 4-(N,N-diphenylamino)-4'-(N,N-dimethylthioureido)-chalcone (5).

An amount of 5 ml of dried DMF was added to the mixture of 0.40 g (1.45 mmol) 4-((N,N-diphenyl)amino) benzaldehyde and 0.35 g (1.57 mmol) (1:1 equivalent) of 4-N,N-dimethylthioureidoacetophenone. Complete dissolution of initial compounds was observed after addition of solution formed by adding 0.5 g NaOH in 6.5 ml of absolute ethanol. The reaction was performed at 25 ºC under stirring for 5 h. The end of reaction was determined from TLC (Thin Layer Chromatography) analysis by consuming of 4-((N,N-diphenyl)amino)benzaldehyde. The reaction mixture was neutralized with aqueous solution of HCl (4 %) and the precipitate was formed, which was washed with distilled water. The crude product was purified on silica gel column (hexane/benzene, 1/3) to afford the target compound (5) (0.56 g, 70 % yield). ^{1}H-RMN ($CDCl_3$), δ (ppm): 3.37 (s, 6H, CH_3), 7.00 ÷ 7.41 (m, 2H, 3,5-C_{ph} + 2H, 2*4''-C_{dpha} + 4H, 2*2'',5''-C_{dpha}, 2H, 3',5'-C_{ph} + 4H, 2*3'',5''-C_{dpha} + 1H, 3-C), 7.48 (d, 2H, 2,6-C_{ph}), 7.78 (d, 1H, 2-C), 8.01 (d, 2H, 2',6'-C_{ph}) 9.81 (s, 1H, NH).

Synthesis of 4-(N,N-diphenylamino)-4'-isothiocyanato-chalcone (6).

An amount of 0.22 g (2.15 mmol) of acetic anhydride in 4 ml of benzene was added to 1.0 g (2.1 mmol) of 4-diphenylamino-4'-(N,N-dimethylthioureido)-chalcone. The mixture was refluxed for 2 h, the formed precipitate was filtrated, the solvent from filtrate was removed by low pressure distillation. The crude product was purified on silica gel column (hexane/benzene, 1/3) to afford the target compound (6) (0.9 g, 80 % yield). ^{1}H-RMN ($CDCl_3$), δ (ppm): 7.02 (d, 2H, 3,5-C_{ph}), 7.10 ÷ 7.16 (m, 2H, 2*4''-C_{dpha} + 4H, 2*2'',6''-C_{dpha}), 7.29 ÷ 7.33 (m, 2H, 3',5'-C_{ph} + 4H, 2*3'',5''-C_{dpha} + 1H, 3-C), 7.48 (d, 2H, 2,6-C_{ph}), 7.77 (d, 1H, 2-C), 8.00 (d, 2H, 2',6'-C_{ph}). COSY 45 - RMN ($CDCl_3$), δ (ppm): 7.01 : 7.48 (3,5-C_{ph} : 2,6-C_{ph}), 7.09 : 7.30 (4''-C_{dpha} : 3'',5''-C_{dpha}), 7.13 : 7.30 (2'',6''-C_{dpha} : 3'',5''-C_{dpha}), 7.33 : 7.77 (1H, 3C : 1H, 2C), 7.30 : 8.00 (3',5'-C_{ph} : 2',6'-C_{ph}). IR ν (cm^{-1}): 620 w, 643 w, 667 m, 684 m, 694 s, 703 s, 745 m, 756 s, 772 m, 798 m, 810 s, 835 w, 856 vw, 864 vw, 890 w, 929 m, 952 w, 976 m, 1003 m, 1014 m, 1030 s, 1051 w, 1073 m, 1109 w, 1155 m, 1172 s, 1187 s, 1212 s, 1261 m, 1288 m, 1304 s 1314 s, 1337 vs, 1432 m, 1450 m, 1488 vs, 1507 s, 1553 s, 1568 vs, 1576 vs, 1593 s, 1650 m, 1688 w, 1740 vw, 2115 s, 2189 m, 2287 vw, 2510 w, 2600 w, 2743 vw, 2850 w, 2919 w, 3033 w, 3060 w, 3294 vw.

Synthesis of 4-(N,N-diphenylamino)-4'-(2-thioxo-imidazolidin-4-one)-chalcone (8).

The mixture of 0.30 g (0.004 mol) glycine and 0.21 g (0.002 mol) of Na_2CO_3 was dissolved in minimal quantity of water, this solution of sodium glycinate was added drop wise to dioxane solution of 0.86 g (0.002 mol) *4-(N,N-diphenylamino)-4'-isothiocyanato-chalcone*. After refluxing for 2 h, the solution was cooled at room temperature and neutralized with HCl solution ($HCl_{conc.}/H_2O$ = 1/2). The intermediary noncyclic compound was extracted with $CHCl_3$. After refluxing for 1 h, the solvent was removed by low pressure distillation. The crude product was purified on silica gel column (ethyl acetate/benzene, 1/2) to afford the target compound (8) (0.39 g, 40% yield). ^{1}H-RMN ($CDCl_3$), δ (ppm): 4.38 (s, 2H, CH_2), 7.00 (d, 2H, 3,5-C_{ph}), 7.14-7.17 (m, 1H, 2C + 2H, 2*4''-C_{dpha} + 4H, 2*2'',6''-C_{dpha}), 7.36-7.40 (m, 2H, 3',5'-C_{ph} +1H, 3-C), 7.54 (d, 2H, 2,6-C_{ph}), 7.75 (m, 4H, 2*3'',5''-C_{dpha}), 8.21 (d, 2H, 2',6'-C_{ph}), 9.25 (s, 1H, NH). IR, ν (cm^{-1}): 665 w, 696 s, 754 m, 817 m, 897 vw, 959 w, 981 m, 1017 m, 1031 m, 1076 w, 1173 vs, 1187 s, 1215 s, 1269 vs, 1295 s, 1315 s, 1327 s, 1396 m, 1425 m, 1452 m, 1489 vs, 1504 vs, 1580 s, 1603 m, 1654 m, 1761 m, 2599 vw, 2852 w, 2922 w, 3034 w, 3060 w, 3229 w (band).

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