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SYNTHESIS AND CHARACTERIZATION OF NEW α-AMINOKETONE THIOSEMICARBAZONES

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● Resumen

Fueron sintetizadas nuevas tiosemicarbazonas (4a-c) a partir de α-aminocetonas mediante la reacción de condensación con tiosemicarbazida. Las estructuras fueron confirmadas por análisis elemental, espectroscopia IR, RMN^{1}H, RMN^{13}C y espectrometría de masas. Las geometrías fueron determinadas utilizando el nivel de cálculo HF/6-31G (d,p).

Palabras clave: tiosemicarbazonas, α-aminocetonas, síntesis, estructura.

● Abstract

Novel thiosemicarbazones (4a-c) have been synthesized by condensation reaction of 2-(4-arylamino)-1,2-diphenyl-1-ethanones (3a-c) with thiosemicarbazide. Their structures were confirmed by elemental analysis, IR, ^{1}HNMR, ^{13}CNMR and MS spectra. The geometries were determined at the Hartree-Fock level of theory employing 6-31G(d,p) basis set.

Keywords: thiosemicarbazone, α-aminoketone, synthesis, structure.

● Introduction

Thiosemicarbazones are a class of compounds obtained by condensing thiosemicarbazide with suitable aldehydes or ketones and are well known to possess antitumor, antiviral, antibacterial, antimalarial, and other activities /1/. Thiosemicarbazones can be used for making electrodes due to formation of easy complexes with some metals and in recent years, aryl and heteroaryl semicarbazones and thiosemicarbazones have emerged as structurally novel anticonvulsants /2/.

The thiosemicarbazone moiety acts as a chelating agent for metal ions /3/ and some complexes show abilities to mimic the action of some enzyme /4/. In view of these facts, the aim of the present work is to obtain thiosemicarbazone derived from 2-(4-arylamino)-1, 2-diphenyl-1-ethanones as possible antitiberculosis, antimicrobial, anti-inflammatory, antiviral, anticonvulsant, antihypertensive, local anesthetic, anticancer, hypoglycemic and cytotoxic agents.

Experimental

General Procedures. The melting points reported are uncorrected. Elemental analyses were carried out on a Therno Finnigan EA1112 Series Flash Elemental Analyser with AS 2000 Liquid and Solid Autosampler. The IR spectra were measured as potassium bromide pellets using a Midac M2000 Series FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Brucker DPX 250 MHz spectrometer. The chemical shift (δ) is reported in ppm using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as internal standard in absence of D_2O. The Mass spectra were measured with a Micro Mass spectrometer (EI and CI). 2-(4-arylamino)-1, 2-diphenyl-1-ethanones (3a-c) were obtained as previously reported /5/.

General method for the synthesis of 2-(4-arylamino)-1,2-diphenyl-1-ethanone thiosemicarbazones (4a-c)

In a 250 mL round bottom flask appropriate 2-(4-arylamino)-1, 2-diphenyl-1-ethanones 3a-c (5 mmol) and thiosemicarbazide (5 mmoL) were taken. To reaction content 1 mL of pure chorhidric acid was added and dissolved. The mixture was refluxed for 6 hour and then cooled, filtered, washed and recrystallized from absolute ethanol.

2-(4-methylanilino)-1, 2-diphenyl-1-ethanone thiosemicarbazone (4a)

Yield 84%; mp 286-287 °C; yellow powder; IR (KBr): cm^{-1} 3423, 3377, 3224, 3168, 3066, 2920, 1663, 1608, 1560, 1534, 1500, 1440, 1413; 1245, 1169, 1063, 918, 867; ^{1}H-NMR (250 MHz,DMSO-d_6): δ (ppm) 12.5 (1H, s, HN–CS), 8.1(1H, s, H_2N–CS), 7.7 (1H, s, H_2N–CS), 7.5 - 6.7(14H, m, Ar-H), 6 (1H, s, CH aliph.), 3.5(1H, s, HN–Ar) 2.3 (3H, s, CH_3); ^{13}C-NMR (250 MHz, DMSO-d_6): δ (ppm) 20 (-CH_3), 60 (C_3), 125.7 (C_5), 127.1 (C_6), 127.3(C_7) 128.0 (C_9), 128.8 (C_{10}), 130.0 (C_{11}), 131.5 (C_{13}), 133.0 (C_{14}), 136.0 (C_{15}), 139.0 (C_4), 145.7 (C_8), 147.5 (C_2), 148.75 (C_{12}), 198.68(C_1); MS(*m/z,%*): 374.20 (M^+,4), 299.15 (6), 196.15 (100), 106.05 (25), 91.05 (19), 77.05 (24); Anal.Calcd. for $C_{22}H_{22}N_4S$: C, 70.56; H, 5.92; N, 14.96; S, 8.56%. Found: C, 70.63; H, 5.87; N, 14.95; S, 8.54%.

2-(4-chloroanilino)-1, 2-diphenyl-1-ethanone thiosemicarbazone (4b)

Yield (74%); mp 296-287 °C; yellow powder; IR (KBr): cm^{-1} 3490 3385, 3125, 3060, 2916, 1666, 1583, 1500, 1448, 1239, 1156, 1083, 968, 822; ^{1}H-NMR (250, MHz,DMSO-d_6): δ (ppm) 7.9 (1H, s, HN–CS); 7.5-6.8 (15H, m, Ar-H, CH aliph.); 6.5 (1H, s broad, H_2N–CS); 6.2 (1H, s broad, H_2N–CS); ^{13}C-NMR (250MHz, DMSO-d_6): δ (ppm); 63.62 (C_3), 117.46 (C_{13}), 122.62 (C_{15}), 130.49 (C_5, C_{10}), 131.07 (C_7), 131.13 (C_6), 131.38 (C_{11}), 131.53 (C_{14}), 136.36 (C_9), 137.55 (C_4), 140.48 (C_8), 148.65(C_2, C_{12}) 199.86 (C_1); MS(CI-*m/z*):397.1023(7.3), 396.0989(22.0), 395.1052(22.7), 394.1010 (M^+,100); MS(*m/z*): 323.2(0.2), 321.2 (2), 257.17(1), 255.75(1), 218.15(32) 216.15 (100), 138.00(26), 111.05(25), 77.05 (29); Anal.Calcd. for $C_{21}H_{19}ClN_4S$: C, 63.87; H, 4.85; Cl, 8.98; N, 14.19; S, 8.12 %. Found: C,63.87; H,4.81; Cl, 8.99; N, 14.19; S, 8.11%

2-(anilino)-1, 2-diphenyl-1-ethanone thiosemicarbazone (4c)

Yield (88%); mp 186-187 °C; yellow powder; IR (KBr): 3412,3368, 3333, 3219, 3166, 3060, 1692, 1614, 1543-1350 (s,sh), 1166, 1114, 1070, 912, 815cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 12.9 (1H, s, HN–CS); 8.1 (1H, d, H_2N–CS); 7.9 -7.2 (15H, m, Ar-H), 6.9(1H, s, CH aliph.); 6.7 (1H, d, H_2N–CS); 3.2 (1H, s, Ar-NH-); MS(*m/z*): 360.14 (M+, 100), 361.14 $(M+1)^+$, 255.55 (26), 191.9 (10), 159.8 (24) 129.9 (6) ; Anal.Calcd. for $C_{21}H_{20}N_4S$: C, 69.97 ;H, 5.59; N,15.54; S, 8.89 %. Found: C, 69.99 ; H, 5.54; N, 15.53; S, 8.87 %

Computational details

The geometries of 4(a-c) were determined at the Hartree-Fock (HF) level of theory emlpoying 6-31G(d,p) basis set on a Dual Core/2,8 GHz personal Computer using the Gaussian 03W program package, version 6,0 /6/ and GaussView molecular visualization program /7/.

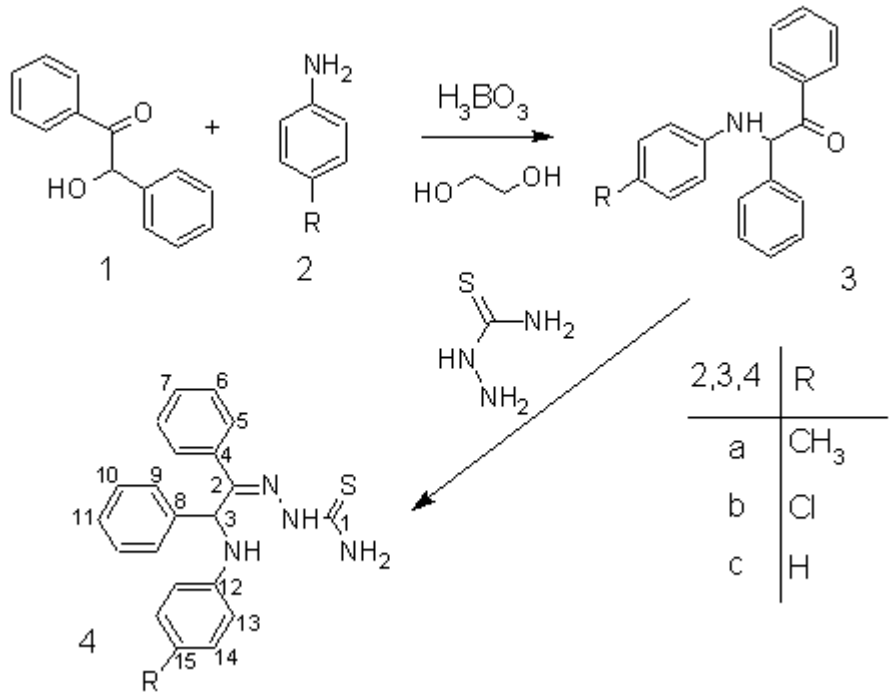
Results and discussion

The thiosemicarbazone 4(a-c) have been synthesized in good yield by condensation of thiosemicarbazide with appropriate 2-(4-arylamino)-1, 2-diphenyl-1-ethanones 3(a-c) (1:1 molar ratio) in absolute ethanol in the presence of pure hydrochlorhidric acid /8/. (Scheme 1).

The structures of the synthesized compounds 4 a-c were established on the basis of IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

In the IR spectrum of 4a the bands in the region 3 423 - 3 224 cm^{-1} are due to the stretching frequences $\nu^a_{NH_2}$ and $\nu^s_{NH_2}$ while ν_{NH} is present at 3 168 cm^{-1}. The typical bands of the aliphatic CH appear in the frequency range 3 000-2 920 cm^{-1}. The strong band observed at 1 663 cm^{-1} is due $\nu_{C=N}$ stretch. The $\nu_{C=C}$ of the phenyl group are observed in the 1 608 – 1 413 cm^{-1} range. The compounds 4a-c may exist in thione - thiol tautomerization, however, due to

absence of the ν_{SH} stretch in the region 2 600-2 500 cm^{-1} indicate that all the compounds retain their thionic form. Another $\nu_{C=S}$ band is observed in the spectrum of the thiosemicarbazone 4a at 867 cm^{-1}. The bands observed at 1 245 cm^{-1} and 1 109 cm^{-1} in the spectrum of 4a are attributed to aromatic and aliphatic C-N stretching vibrations and the band at 918 cm^{-1} can be attributed to N-N stretching vibration.



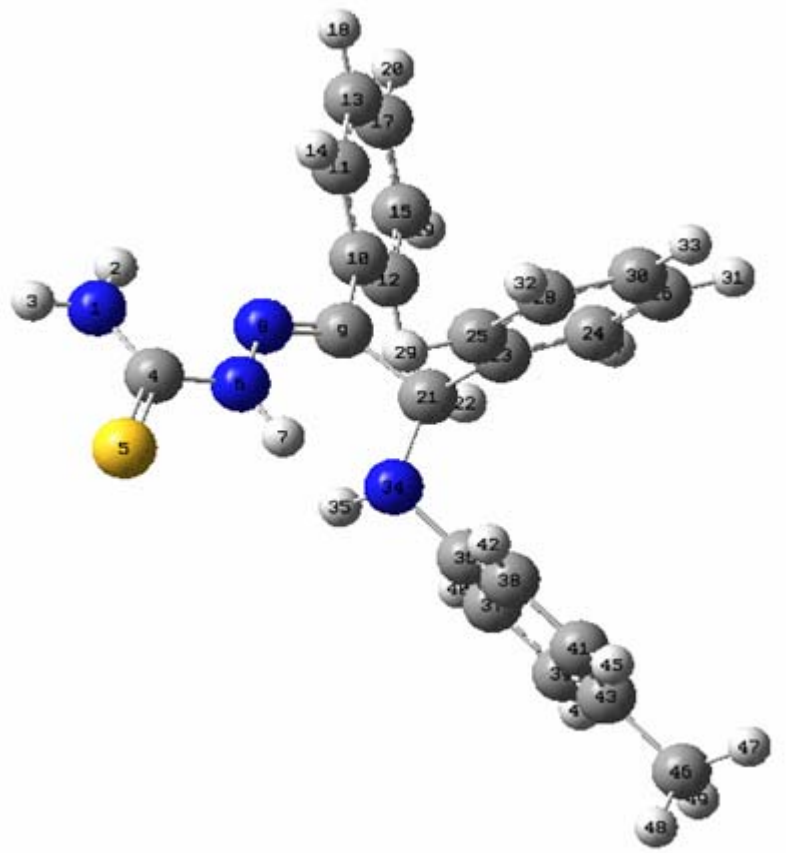
Scheme 1. Synthesis route for 2-(4-arylamino)-1, 2-diphenyl-1-ethanone thiosemicarbazones.

There is no IR band at 2 600-2 500 cm^{-1} in the spectrum of 4a in agreement with the thionic form of ligand. This is supported by the ^{1}H-NMR spectrum which does not show any peak at 4 ppm attributable to the S-H proton, but it shows at room temperature a singlet at 12,5 ppm relative to the NH next to C=S, very deshielded as expected.

It is interesting to notice the presence of two broad singlets for the two NH_2 protons of 4a, respectively at 8,1 and 7,7 ppm: it means that the free rotation around the C-N bonds is blocked because of its partial double bond character /9/. The hydrogens of the phenyl group are observed in the δ = 7,5 - 6,7 ppm range. At 6.0 ppm is observed the resonance frecuency of the aliphatic CH proton, at 3.5 is observed the aminic NH proton. The singlet appeared at 2.3 δ is due to CH_3.

The ^{13}C-NMR spectrum of compound 4a showed fourteen non equivalent carbon signals. However the compound is having sixteen types of non equivalent carbon atoms, the lack of two signals may be due to overlapping of two carbon signals, which may have identical chemical shifts. The signal observed at 20.7 is due to -CH_3 and the signal at 60.2 δ is due to C_3. The aromatic carbons appeared at 125.8, 127.2, 127.3, 128.1, 128.8, 130.1, 131.5, 133.0, 136.2, 139.4, 147.5 and 148.8 δ. The most downfield signals at 147.5 and 148.8 can be too attributed to C=N and C=S, respectively. The mass spectrum of 4a showed molecular ion peak at m/z 374.20 along with other fragments peaks. It exactly matches with the molecular weight of compound 4a and thus confirming the structure of 4a. Similarly all other compounds gave satisfactory spectral analysis.

The structure of 2-(4-methylanilino)-1, 2-diphenyl-1-ethanone thiosemicarbazone, 4a, calculated by ab initio HF level with the 6-31G (d,p) basis set is showed in scheme 2.



Scheme 2. The theoretical geometric structure of 2-(4-methylanilino)-1, 2-diphenyl-1-ethanone thiosemicarbazone, 4a, calculated by ab initio HF level with the 6-31G (d,p) basis set.

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