New Azomethine Derivatives of 3-substituted-4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles as Potential Anti-inflammatory Agents

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A microwave-assisted syntheses of some Schiff-base via condensation of 3-substituted-4H-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles with aromatic aldehydes without solvent is described.

Keywords: Schiff base, 1,2,4-triazole, microwave assisted synthesis

Schiff base (azomethine) derived from 4*H*-4-amino-1,2,4-triazoles attracted growing interest due to analgesic[1], anticancer[1], anti-inflammatory[1], anticonvulsant[1,2], antifungal[2] and antimicrobial [1,3,4] properties. Also, Schiff bases containing triazoles are interesting bridging ligands in the coordination chemistry of metal ions [5-8]. On the other hand, non-steroidal anti-inflamatory drugs containing acetate moiety are used in the treatment of pain and inflamation [9].

There is also a posibility, recently mentioned in literature, to attach triazoles and their derivatives to mono-saccharides, in order to obtain new physiologically active compounds[10-12].

For this reason, our concerns are directed towards obtaining new Schiff bases derived from 3-substituted-4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles (**2**), compounds with potential biological activity and an increased capacity of complexing metal cations.

For the synthesis of Schiff bases derived from 3-substituted-4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles, are essentially two possible routes (scheme 1):

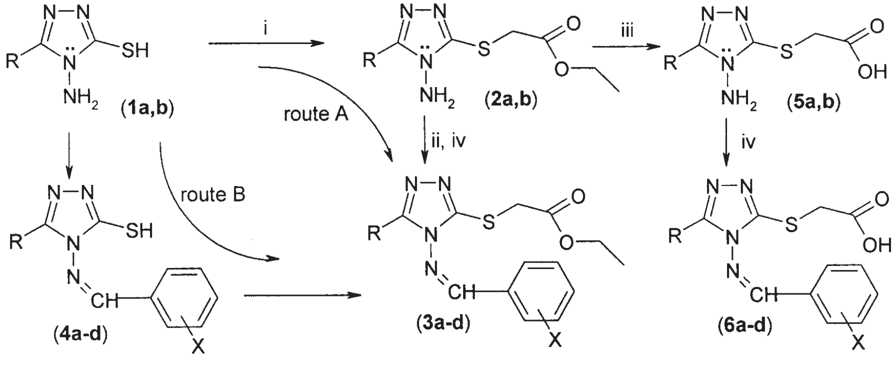
A. The alkylation of 3-substituted-4*H*-4-amino-5-mercapto-1,2,4-triazoles (**1**) to 3-substituted-4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazole (**2**) followed by their conversion into Schiff bases (**3**).

B. Obtaining Schiff bases (**4**) from 3-substituted-4*H*-4-amino-5-mercapto-1,2,4-triazoles (**1**), followed by ethyl chloroacetate alkylation, leading to new alkylated Schiff bases (**3**).

First time, we chose route A.

Synthesis of azomethine compound is usually carried out in organic medium, acid or base catalyzed, by refluxing the carbonyl and the amino compounds in the desired molar ratio[13], and for the synthesis of Schiff bases derived from 3-substituted-4*H*-4-amino-5-mercapto-1,2,4-triazoles (**1**), literature data indicate their reaction with carbonyl compounds in various conditions: ethanol in the presence of acetic acid [14], in presence of an excess amount of concd. sulphuric acid [15], in presence of diluted HCl (at *p*H=5-6) [16], or in presence of piperidine [17].

After several attempts using above-mentioned reaction conditions, the complete conversion of raw materials into Schiff bases failed, we resorted to using microwave-assisted synthesis method, more often indicated in literature [18,19].



R=C_6H_5- (**1a-4a**), $C_6H_5CH_2$- (**1b-4b,3b-d, 4b-d**) X=4-Br (**3a,3c**), 4-O_2N(**3b**), 2-HO (**3d**)

i= a) NaOH / C_2H_5OH; distilled to dryness; b) $ClCH_2COOC_2H_5$ / C_2H_5OH / reflux;

ii= X-C_6H_4-CHO, M.W. iii= 1)NaOH 1N reflux; 2) dil. HCl iv= X-C_6H_4-CHO / EtOH / catalyst

Scheme 1. The synthesis of the azomethines (**3a-b**) derived from 3-substituted-4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles

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Experimental Part

Matherials and methods

The reagents were commercial products and used without further purification. 4*H*-4-amino-5-mercapto-3-phenyl-1,2,4-triazole (**1a,** R=C_6H_5-) and 4-*H*-4-amino-3-phenyl-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazole (**2a**, R=C_6H_5-) were prepared according to the literature [20,21] and 4*H*-4-amino-3-benzyl-5-mercapto-1,2,4-triazole (**1b,** R=C_6H_5-CH_2-) and 4*H*-4-amino-3-benzyl-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazole (**2b,** R=C_6H_5-CH_2-) were obtained by our own method [22].

The microwave-assisted synthesis of azomethines was carried out in a 1100 W Emerson domestic owen. Melting points were determined on a Böetius PHMK (Veb Analytik Dresden) instrument, and thin-layer chromatography was carried out on silica gel-coated plates 60 F_{254} Merck using benzene:methanol 7:3 as eluant. IR spectra were recorded in KBr pellet on a Jasco FT/IR-410 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance III 400 spectrometer in DMSO-d_6, using TMS as reference; chemical shifts being reported in ppm and the coupling constants in Hz. UV-VIS spectra were recorded on a Jasco UV-VIS V-530 spectrophotometer.

Microwave-assisted synthesis of azomethine from 3-substituted-4-H-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles

0,9 mmol of ethoxycarbonyl-methylsulfanyl triazoles (**2a-b**) are mixed with 0,9 mmol of corresponding benzaldehyde in a 5 mL glass flask which was placed inside a Teflon sealed container. The mixture was subjected to microwave on 800W for an optimized time. The crude products were dissolved in the minimum amount of absolute EtOH and allowed to crystallize over night at room temperature. Products (**3a-d**) were separated by filtration and recrystallised from absolute ethanol.

4H-4-(4-Nitro-benzylidene-amino)-5-benzyl-3-ethoxycarbonyl-methylsulfanyl-1,2,4-triazole (**3b**)

Yellowish powder (40% yield), m.p.=144-147 °C,

IR(KBr): 3456, 2984, 2923, 2360, 1738, 1525, 1525, 1442, 1347, 1175, 1027, 851, 731, 688, 491cm^{-1}

UV-VIS(methanol) λ[nm](εx10^{-4}) : 286.3; (1.54832)

^{1}**H-NMR**δ_H (DMSO-d_6, 400MHz): 9.00 (s, 1H, -CH=N-); 8.39 (d, 2H, J=8.6Hz, 3“-H, 5“-H); 8.12 (d, 2H, J=8.6Hz, 2“-H, 6“-H); 7.29-7.18 (m, 5H, 2‘-H, 3‘-H, 4‘-H, 5‘-H, 6‘-H); 4.34 (s, 2H, Ph-$C\underline{H}_2$-); 4.09-4.05 (m, 4H, -O-$C\underline{H}_2$-, -S-$C\underline{H}_2$-); 1.14 (t, 3H, J=7.1Hz, -$C\underline{H}_3$)

^{13}**C-NMR** δ_C (DMSO- d_6, 100MHz): 168.0 (C=O); 161.5 (-$\underline{C}H$=N-); 151.8 (3-C); 149.6 (4“-C); 146.3 (5-C); 137.4 (1“-C); 135.4 (1‘-C); 129.8 (2“-C, 6“-C); 128.6 (2‘-C, 6‘-C); 128.5 (3‘-C, 5‘-C); 126.8 (4‘-C); 124.2 (3“-C, 5“-C); 61.2 (-O-$\underline{C}H_2$-); 34.5 (-S-$\underline{C}H_2$-); 30.8 (Ph-$\underline{C}H_2$-); 13.8 (-$\underline{C}H_3$)

4H-4-(4-Bromo-benzylidene-amino)-5-benzyl-3-ethoxycarbonyl-methylsulfanyl-1,2,4-triazole (**3c**)

White powder (48% yield), m.p.=104-106 °C,

IR(KBr): 2982, 2934, 1742, 1614, 1592, 1442, 1305, 1173, 1009, 818, 727, 574, 499 cm^{-1}

UV-VIS(methanol)λ[nm](εx10^{-4}): 392.6; (0.01567); 276,7; (2.22067)

^{1}**H-NMR**δ_H (DMSO-d_6, 400MHz): 8.82 (s, 1H, -$C\underline{H}$=N-); 7.80 (d, 2H, J=9.0 Hz, 3“-H, 5“-H); 7.78 (d, 2H, J= 9.0Hz, 2“-H, 6“-H); 7.28-7.24 (m, 2H, 3‘-H, 5‘-H); 7.21-7.17 (m, 3H, 2‘-H, 4‘-H, 6‘-H); 4.65 (q, 2H, J= 7.1Hz, -O-CH_2-CH_3); 4.28 (s, 2H, Ph-$C\underline{H}_2$-); 4.05 (s, 2H, -S-$C\underline{H}_2$-); 1.14 (t, 3H, J=7.1Hz, -O-CH_2-$C\underline{H}_3$)

^{13}**C-NMR** δ_C (DMSO- d_6, 100MHz): 168.0 (C=O); 163.8 (-$\underline{C}H$=N-); 151.6 (3-C); 145.8 (5-C); 135.5 (1‘-C); 132.3 (2“-C, 6“-C); 130.8 (1“-C); 130.5 (3“-C, 5“-C); 128.6 (2‘-C, 6‘-C); 128.4 (3‘-C, 5‘-C); 126.72 (4‘-C); 126.70 (4“-C); 61.1 (-O-$\underline{C}H_2$-); 34.4 (-S-$\underline{C}H_2$-); 30.7 (Ph-$\underline{C}H_2$-); 13.8 (-$\underline{C}H_3$)

Results and discussion

In our preliminary attempts to obtain the azomethinic compounds **3a-d**, **6a-d** derived from 3-substituted-4*H*-4-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles (**2a-b**) or 3-substituted-4*H*-4-amino-5-carboxymethylsulfanyl-1,2,4-triazoles (**5a-b**) and substituted benzaldehydes (4-bromobenzaldehyde, 4-nitro-benzaldehyde, 2-hydroxy-benzaldehyde) following the literature data, as a reaction medium we use absolute ethanol in the absence or presence of acid catalysts (5% acetic acid, <1% concd. HCl, <1% concd. H_2SO_4 or 10% concd. H_2SO_4) or base (piperidine) for 3-18 h reflux, respectively azeotropic distillation method of water formed in the reaction medium in the presence of p-toluene sulphonic acid. In our attempts, performed in the absence of catalysts, starting materials did not react, and in the case of catalyzed reactions, complex mixtures containing starting materials and one up to three products were obtained.

With our knowledge, azomethines **3a-d** derived from 4*H*-4-amino-3-substituted-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles are not mentioned in the literature. For this reason their structures were careffuly confirmed by IR, UV-VIS and NMR spectroscopy (^{1}H-NMR, ^{13}C-NMR, COSY-2D, DEPT-135, HMQC and HMBC).

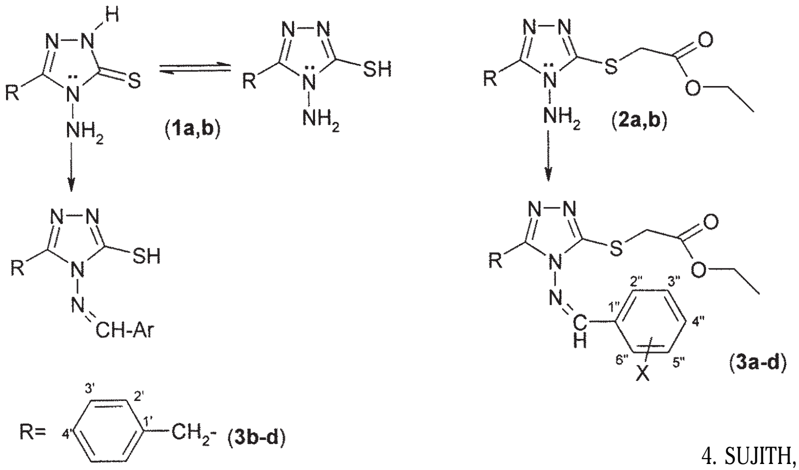
Analyzing the IR spectra, charactersitic vibrations of functional groups are present: esteric $\nu_{C=O}$ (1737 - 1742 cm^{-1}), methylen (ν^{as}_{CH2}=2982-2986 cm^{-1}, ν^{s}_{CH2}=2923-2934 cm^{-1}).

As a result of electronic transitions, in UV-VIS spectra, the compounds exhibit light absorption near 393nm and at 277 (respectively 286) nm.

By analysing the NMR and IR spectroscopic results, the condensation reaction between 4*H*-4-amino-3-benzyle-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazole (**2b,** R=C_6H_5-CH_2-) with 2-hydroxybenzaldehyde lead to a mixture (product **3d** could not be separated), and the condensation between 4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-3-phenyl-1,2,4-triazole(**2a**,R=C_6H_5-) and 4-bromo-benzaldehyde did not occured (product **3a** was not obtained).

At the same time, analyzing 2D NMR ^{1}H-^{13}C HMBC spectra of (**3b**), long-distance coupling ^{3}J of phenylic carbons 2”-C and 6”-C with azomethinic proton (-N=$C\underline{H}$-), $^3J_{2'',6''\text{-C, -N=CH-}}$ is observed.It should be also noted that a long-distance coupling ^{2}J of the carbon atom 1”-C with azomethinic proton –N=$C\underline{H}$-, $^2J_{1''\text{-C, -N=CH-}}$ occurs. These long-distance couplings confirm the structure of the synthesized compound and allow a correct assign of chemical shifts from ^{1}H-NMR and ^{13}C-NMR spectra.

The difficulty of obtaining azomethine derivatives of 3-substituted-4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles (**2a, b**) comparing with the facile route of obtaining them from 3-substituted-4*H*-4-amino-5-mercapto-1,2,4-triazoles (**1a, b**) [23] finds a possible explanation in tautomeric forms involved in the condensation reaction with benzaldehyde. It is known that the condensation reaction of carbonyl compounds with amines is accomplished by the nucleophilic attack of amines to the carbonyl group, followed by the elimination of a water molecule; the reaction occurs more readily with the increase of the amine nucleophilicity (scheme 2).



Scheme 2. Tautomeric forms for (**1a,b**) triazoles and the condensation reactions with benzaldehydes for (**1a,b**) and (**2a, b**)

The decreased reactivity of the S-alkylated compounds **2a, b** can be explained by the fact that the electrone lone pair of nitrogen from position 4 is involved in the triazolic aromatic system, which makes the exocyclic amino group from triazoles to be an aromatic amine, slightly basic and a weak nucleophile.

Regarding the **1a, b** triazoles which prefer thionic tautomeric form [24], the aromatic conjugation cannot be maintained with the lone pair of the nitrogen atom from position 4, and as a result, the exocyclic amino group is a "hydrazinic" one, with an increased density of electrons, an increased nucleophilicity, and hence an increased reactivity.

Also, the presence of benzenic nucleus in **2a** compound (R = C_6H_5-) with the inductive effect -I, entails an additional decrease in electron density at exocyclic amino group, which may explain its lack of reactivity in reactions with benzaldehydes, in contrast to compound **2b** (R = C_6H_5-CH_2-), where inductive effect of the phenyl group is diminished.

Conclusion

The condensation of 4*H*-4-amino-3-substituted-5-ethoxycarbonyl-methylsulfanyl-1,2,4-triazoles (**2a,b**) with substituted benzaldehydes under microwave irradiation lead with medium yields to corresponding Schiff bases, unlike the methods of condensation in organic solvent in the presence of acid or alkaline catalysts, which lead to mixtures.

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