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Synthesis of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazol Schiff Base Derivatives as Intermediates for Polycondensed Heterocyclic Compounds

V.N. Bercean and V. Badea

POLITEHNICA University of Timişoara, 300006 – Timisoara, 6 Carol Telbisz, Romania
e-mail: valentin.badea@chim.upt.ro

Abstract: Schiff base derivatives of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) and the substituted benzaldehydes were condensed under acid catalysis with azeotropic removal of the water formed in the reaction. The obtained compounds were characterized by melting point, TLC, IR and UV-VIS spectroscopy.

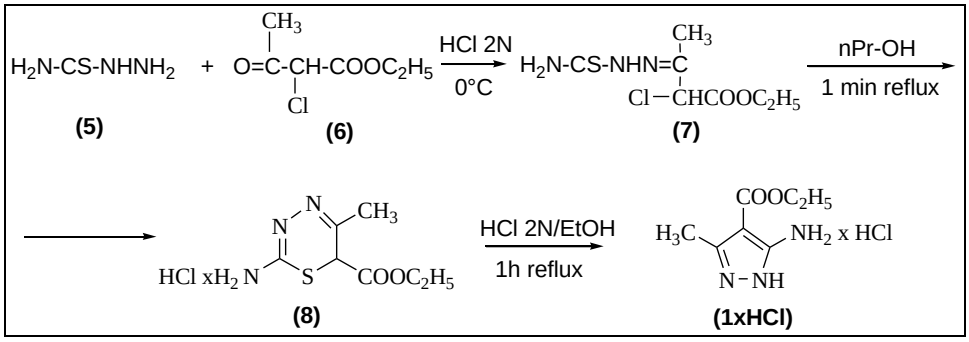
Keywords: Schiff base, 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole, azeotropic distillation.

1. Introduction

Amino-pyrazoles (1) and the Schiff bases derived therefrom, (2) are used in the synthesis of poly heterocyclic compounds, such as: pyrazolo [3,4-b] quinolines and pyrazolo [3,4-b] pyridine [1] pyrazolyl-triazole anti-microbial activity [2], pyrazolopyrimidines as purine analogs [3], 1-(5-pyrazolyl) benzimidazole [4]. It was demonstrated that the Schiff bases derived from amino pyrazoles exhibit activity against tuberculosis [5].

In order to obtain 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) in the literature, from our knowledge, only one method have been described. This method involves the following synthesis steps [6]:

- condensation of the thiosemicarbazide (5) with α-chloroacethylacetate (6) in the presence of 2N HCl at 0° C, when the thiosemicarbazone of the α-chloroacethylacetate (7) is obtained;
- insertion of the compound (7) into propyl alcohol, preheated to 70° C, followed by the heating of the solution at reflux, rapidly cooling to 50° C, filtration and precipitation with ether, when 2-amino-5-methyl-6-ethoxycarbonyl-1,3,4-dioxide (8) is obtained with the yield of 74%.
- heating compound (8) with an alcoholic 2N HCl for 1 hour at reflux, when the hydrochloride of the 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1xHCl) is formed with a yield of 80%.



Scheme 1: Synthesis of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1xHCl)

The synthesis of azomethine compounds (Schiff bases) could be realized in organic medium by using acidic or basic catalyst, followed by refluxing the carbonyl compound and amine, with or without azeotropic removal of water [7.8], in the presence of acetic acid and ethanol at reflux [9], by using an excess of concentrated sulfuric acid [10] in the presence of dilute hydrochloric acid [11] in the presence of piperidine [12], or under the influence of microwaves [13,14].

The aim of this work was the synthesis and preliminary characterization of Schiff bases (2) derived from 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1), as intermediates for the synthesis of polycondensed heterocyclic compounds from the imidazolo[1,2-b] pyrazole (3) and pyrazolo [3,2-b] pyrimidine (4) class.

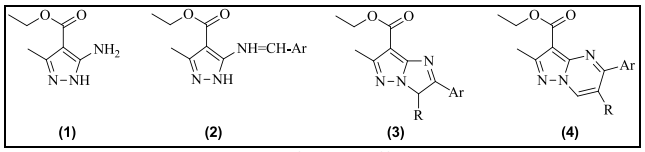


Figure 1. Chemical structure of the Schiff bases and polycondensed heterocyclic compounds.

2. Experimental

All the raw materials used were purchased from Merck, Sigma-Aldrich, Maybridge, Chimopar and used as received.

The melting points were determined by using a Boethius PHMK (Veb Analytik Dresden) device.

The thin-layer chromatography was performed on silica gel 60F254 plates Merck, using as the mobile phase benzene: ethyl acetate = 1: 1 (vol) or benzene: methanol = 7: 3 (v).

Infrared Spectra (IR) were recorded as KBr disks on a Jasco FT/IR-410 spectrometer and UV-VIS spectra in methanolic solution on a Jasco V-530 UV-VIS spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker Avance 500 MHz using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are reported in ppm units and the coupling constants are given in Hz.

Synthesis of Schiff's bases by the condensation of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) with substituted benzaldehydes

In a 250 mL flask equipped with an azeotropic distillation device for phase separation (0.05 mol) 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole, optionally substituted benzaldehyde (Scheme 3) 0.05 mol, 100 mL 0.25 benzene and p-toluenesulfonic acid were added. The mixture was refluxed (bath temperature 100-120°C) until no more water could be collected in the separating device (2-5 hours). After cooling, the benzene solution was washed successively with 50 mL water, 10 mL and 50 mL of 5% aqueous Na_2CO_3 solution and then dried on anhydrous Na_2SO_4. After decanting the solvent and distilling to dryness under reduced pressure, the crude product was recrystallized from a suitable solvent.

3. Results and Discussion

Synthesis of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1xHCl)

First the thiosemicarbazone (7) was synthesised as previously described [6] and the yield of the reaction was about 86-88%. The value of the melting point was in the range of 82-84°C (identical to the previously reported value).

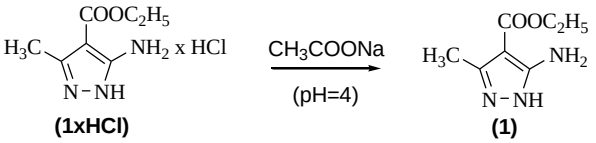
The thiadiazine (8) was obtained with a yield of 40% (to 74%) and the melting point 115-119°C (lit. 90°C) and the amino-pyrazole (1xHCl) with a yield of 25% (vs 80%) and m.p 153-157°C lower than the 187-189°C. Thin layer chromatography indicated the presence of three impurities in addition to the main product. These results indicate that the transformation of hydrochloride (1xHCl) to the free base (1) by treatment with sodium acetate at heating in aqueous medium was required.

Synthesis of the 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) as free base

The crude product (1xHCl) previously synthesized (10 g, from 18 g thiosemicarbazide) was dissolved at 80°C in a solution of 10 g of sodium acetate in 100 ml of water and filtered hot.

The filtrate was cooled to room temperature and vigorous stirring was seeded with product crystals. After 24 hours, the product was separated by filtration and washed with water. After drying at room temperature 8.2 g were obtained (yield: 90%) (50% yield related to the thiosemicarbazide) and m.p. 45-49°C; (lit [6] 69°C); On the thin layer chromatography plates (eluent, methanol: benzene = 7: 3, developing by iodine vapour) one main spot and traces of impurities were observed.

To confirm the free base formation, the reconversion into the corresponding hydrochloride was necessary.



Scheme 2. Synthesis of the 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) as free base

Preparation 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1xHCl)

The free base was dissolved at about 40°C in 10 ml of concentrated HCl. After cooling to 20°C for 24 hours, the product was filtered, washed with diethyl ether and dried. 9 g of white crystals with mp = 182-185 low pink ° C; (lit [6] = 187-189 ° C) were obtained.

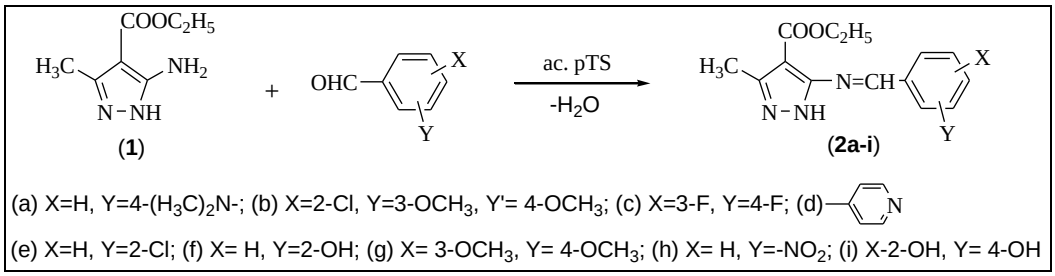
^{1}H-NMR (500 MHz): 9.52(NH), 4.28(q, 2H, *J*=7.1Hz), 2.45 (s, 3H), 1.32(t, 3H, *J*=7.1Hz)

^{13}C-NMR (125 MHz): 162.5(C=O), 151.2(C-NH_2), 147.2, 94.7(C-$COOC_2H_5$), 59.6(OCH_2CH_3), 13.9(OCH_2CH_3), 11.6(CH_3)

Synthesis of Schiff's bases by the condensation of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) with substituted benzaldehydes by using acids as catalyst and azeotropic distillation of water

The synthesis of the Schiff's bases by the condensation of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) with substituted benzaldehydes by using acids as catalyst and azeotropic distillation of water were perfomed as descriebed in the experimental section, based on Scheme 3.

The reaction products were purified by using different solvents and all details for each compound are given below.



Scheme 3. The chemical synthesis of Schiff's bases by the condensation of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) substituted benzaldehydes.

1H-4-ethoxycarbonyl-3-methyl-5- (4-N, N-dimethylamino) benzylideneamino-pyrazole (2a)

The crude product obtained is a semi-solid; on the thin layer chromatography plate four blue spotlights were observed. The hot drying of the plate revealed the presensce of other blue spots. Unfortunately the purification from various solvents did not succeed.

1H-4-ethoxycarbonyl-3-methyl-5- (2-chloro-3,4-dimethoxy) benzylideneamino-pyrazole (2b)

The crude product was purified by slurring in 75 ml ethanol under boiling; after cooling was the product was filtered, dried at 60 ° C and yellow needles were obtained 6 g (η = 56%) with m.p. = 242º-248º C. The purity of the product was confirmed by the presence of one singe spot on the TLC.

IR (cm^{-1}): ν_{NH}= 3198 (m),ν_{CarH}=3097(s), ν^{as}_{CH3}= 2980(s); 2940(s), ν^{as}_{CH2}= 2911(s), $\nu_{C=O}$= 1740(m), $\nu_{CH=N}$= 1673(i), νsk ar= 1593 (m); 1567(i); 1530(m); 1495(i), $\nu_{COCester}$=1285(i); $\gamma_{sk\ ar}$= 801(s)

UV-VIS λ_{max} [nm](ε x 10^{-4})=365,8(1,8951)

1H-4-ethoxycarbonyl-3-methyl-5- (3,4-difluoro) benzylideneamino-pyrazole (2c)

The product (3.3g η = 22%) in the form of cream-colored precipitate m.p. = 209º-213ºC (at 165ºC-172ºC turns needles)

IR (cm^{-1}): ν_{NH}=3193(s); ν_{CarH}=3006(s); ν^{as}_{CH3}=2989(s), 2931(s); ν^{as}_{CH2}=2908(s); $\nu_{C=O}$=1707(m); $\nu_{CH=N}$=1623(m); νsk ar=1560(m), 1516(i); $\nu_{COCester}$=1282(i); γsk ar=820(s), 758(m).

UV-VIS λ_{max} [nm](ε x 10^{-4})= 351,4 (1,2972).

1H-4-ethoxycarbonyl-3-methyl-5- (4-pyridyl) - metilenamino-pyrazole (2d)

The crude product (5.2 g) was suspended for one hour at 40°C in 25 ml ethyl acetate and separated by filtration. After drying, 3.4g (η = 13%) of yellow crystals m.p. 252-258°C were obtained. TLC indicated the presence of a single spot and a trace in the start line.

IR (cm^{-1}): ν_{NH}=3215(s); ν_{CarH}=3072(s), 3045(s); νas_{CH3}=2985(s), 2940(s); $\nu_{C=O}$=1709(s); $\nu_{CH=N}$=1638(m); ν_{skar}=1609(m0, 1553(i), 1504(i); $\nu_{COCester}$=1268(i) $\gamma_{sk\ ar}$=815(m), 758(s)

UV-VIS λ_{max} [nm](ε x 10^{-4})= 362,8 (0,9811).

1H-4-ethoxycarbonyl-3-methyl-5- (2-chloro) benzylideneamino-pyrazole (2e)

The crude product was suspended under reflux in 75 ml methanol. After cooling and filtration a white powder (η = 68%) with mp = 125-128 ° C and one chromatographic spot on TLC was obtained.

IR (cm^{-1}): ν_{NH}=3423(s); ν_{CarH}=3066(s); ν^{as}_{CH3}=2979(s), 2931(s); νas_{CH2}=2905(s); $\nu_{C=O}$=1699(i); $\nu_{CH=N}$=1685(i); $\nu_{sk\ ar}$=1564(i), 1540(i), 1499(m); $\gamma_{sk\ ar}$=875(s), 747(m)

UV-VIS λ_{max} [nm](ε x 10^{-4})= 392,8 (0,476).

1H-4-ethoxycarbonyl-3-methyl-5- (2-hydroxy) benzylideneamino-pyrazole (2f)

The crude product was suspended under reflux in a mixture of 150 mL hexane + 50 mL EtOAc + 20 mL MeOH and filtered hot. Obtained as a yellow solid (η = 42%), m.p. 140-142ºC and a single chromatographic spot.

IR (cm^{-1}): ν_{NH}=3202(m); ν_{CarH}=3075(s); ν^{as}_{CH3}=2994(s), 2938(s); ν^{as}_{CH2}=2908(s); $\nu_{C=O}$=1683(i); νsk ar=1605(i), 1569(m), 1510(i); γsk ar=754(i), 850(s)

UV-VIS λ_{max} [nm](ε x 10^{-4})= 344(0,7973).

1H-4-ethoxycarbonyl-3-methyl-5- (2,4-dimethoxy) benzylidene amino pyrazole (2g)

The crude product was suspended under reflux in 50 mL hexane + 5 mL EtOAc + 5 mL MeOH, and after cooling, filtered off, washed with AcOEt and dried to ≈60ºC; to obtain a yellow solid (η = 39%) with mp = 197-201 ° C and a single chromatographic spot.

IR (cm^{-1}): ν_{NH}=3384; ν_{CarH}=3067(s); νas_{CH3}=2979(s), 2959(s); ν^{as}_{CH2}=2908(s); $\nu_{C=O}$=1688(m); νsk ar=1608(i), 1546(s), 1503(s); γsk ar=885(s), 830(s), 847(s)

UV-VIS λ_{max} [nm](ε x 10^{-4})= 364,1(1,2116).

1H-4-ethoxycarbonyl-3-methyl-5- (2-nitro) benzylideneamino-pyrazole (2h)

24,4g of compound were obtained (0,0807mol) as yellow precipitate (η = 54%) with mp = 156-159 ° C and a single spot on TLC plate.

IR (cm^{-1}): ν_{NH}=3368(s); ν_{CarH}=3104(s), 3071(s), 3033(s); νas_{CH3}=2982(s), 2935(s); ν^{as}_{CH2}=2904(s); $\nu_{C=O}$=1701(i); ν_{NO2}as= 1532(i); νsk ar=1551(m), 1505(m); γsk ar=885(s), 733(m)

UV-VIS λ_{max} [nm](ε x 10^{-4})= 390,6 (0,7)

1H-4-ethoxycarbonyl-3-methyl-5-(2,4-dihydroxy)benzilidenamino-pyrazol (2i)

The crude product was obtained as red precipitate (η=98%), m.p.>210°C and a single spot on TLC plate.

IR (cm^{-1}): ν_{OHasoc}=3467(s), 3353(s); ν_{NH}=3245(s); ν_{CarH}=3101(s); ν^{as}_{CH3}=2983(s); ν^{as}_{CH2}=2906(s); $\nu_{C=O}$=1679(m); $\nu_{CH=N}$=1665(m); νsk ar=1598(i), 1536(m); γsk ar= 814(s)

UV-VIS λ_{max} [nm](ε x 10^{-4})= 349,2 (0,8464)

4. Conclusions

The 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1x HCl) hydrochloride was synthesized as previously described [6]. A decrease of the yield value was observed when the synthesis was scaled-up.

The hydrochloride (1xHCl) compound was purified by transformation to the free base (1) and back into the hydrochloride and the chemical structure was confirmed by ^{1}H-NMR and ^{13}C-NMR analysis.

Synthesis of Schiff bases by the condensation of 1H-3-methyl-4-ethoxycarbonyl-5-amino-pyrazole (1) and the substituted benzaldehydes was carried out under acid catalysis with azeotropic removal of the water formed in the reaction. The yields of the synthesis were between 13 and 98% and the purity of the compounds was acceptable. Synthesis of the compound 2a, when 4-N,N-dimethylamino-benzaldehyde was used did not occur, probably due to the oxidation reactions.

The reaction products have been characterized by melting point, thin-layer chromatography, IR and UV-VIS spectroscopy.

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