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NOVEL APPLICATIONS OF THE "*t*-AMINO EFFECT" IN HETEROCYCLIC CHEMISTRY. SYNTHESIS OF A PYRROLO[1,2-*a*]QUINAZOLINE AND 5*H*-PYRROLO[1,2-*a*][3,1]BENZOTHIAZINES

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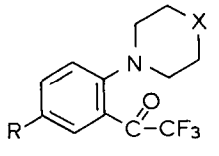
Abstract. *1-(1-Pyrrolidinyl)benzenes substituted with an imino- or an* in situ *generated thiocarbonyl group in the 2-position rearrange upon heating to quinazoline and benzothiazine derivatives, respectively.*

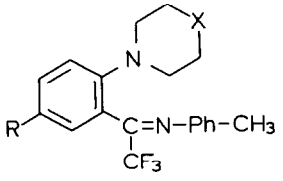
In the course of our investigations of the "*t*-amino effect"[1] in heterocyclic chemistry we have reported previously the formation of *N*-heterocycles by ring closure reactions of substituted 2-*vinyl*-*N*,*N*-dialkylanilines. We found that the type of reaction products varies with the structure of the vinyl moiety.[2,3] Ring closure of the carbonyl analogue *viz.* 2-(trifluoroacetyl)-*N*,*N*-dialkylanilines (e.g. 1) afforded 5*H*-pyrrolo- and 1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazines.[4] In the present paper we wish to present the preliminary results of our studies on the reactivity of *N*,*N*-dialkylanilines having other 2π-substituents at the 2-position *viz.* an *imino*- or a *thiocarbonyl* group.

A number of years ago Yagupol'skii et al.[5] reported the synthesis of *N*-(2,2,2-trifluoro-1-phenylethylidene)benzenamine [PhC(CF_3)=N-Ph] by reaction of 2,2,2-trifluoro-1-phenylethanone [PhC(O)CF_3] with *N*-(triphenylphosphoranylidene)benzenamine (Ph_3P=N-Ph). We found that reaction of the ketone 1a[4] with 4-methyl-*N*-(triphenylphosphoranylidene)benzenamine (Ph_3P=N-Ph-CH_3)[6] in refluxing toluene for 7 days afforded the 4-methyl-*N*-[2,2,2-trifluoro-1-[5-methyl-2-(1-pyrrolidinyl)]-



1

a. R = CH_3, X = -
b. R = OCH_3, X = CH_2



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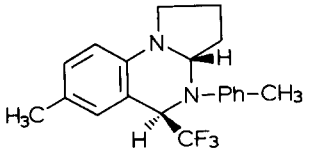
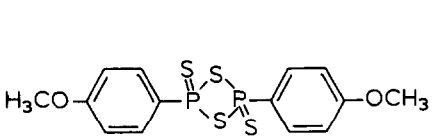


3

phenylethylidene]benzenamine (2a) in a yield of only 25%. However, reaction of 1a with the anion of 1,1,1-trimethyl-*N*-(4-methylphenyl)silanamine [H_3C-Ph-NH-Si$(CH_3)_3$][7] in tetrahydrofuran for 1 h at -70 °C and subsequently for 20 h at room temperature yielded after column chromatography (silica gel, chloroform) one isomer of 2a[8] as a yellow solid in a yield of 74% [mp 89-89.5 °C (subl. 80 °C/1 mm Hg); *m/e* 346.163 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.15-6.8 (m, 4 H, Ar H), 6.6-6.35 (m, 3 H, Ar H), 3.25-2.9 (m, 2 H, NCH_2), 2.65-2.3 (m, 2 H, NCH_2), 2.30 and 2.22 (s, 3 H, CH_3), 2.0-1.5 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 156.5 (q, J = 33.0 Hz, C=N), 120.2 (q, J = 279.8 Hz, CF_3)]. Ketone 1b[4] reacted in a similar way to give 2b in a yield of 69% [mp 57 °C (methanol)]. To the best of our knowledge this type of imine formation (an example of the Peterson reaction[9]) has hitherto only been reported once in literature by Wannagat *c.s.*[10] for the preparation of *N*-trimethylsilylimines.

Heating of 2a in 1-butanol at 118 °C for 5 days gave, after chromatography [silica gel, chloroform/petroleum ether (bp 60-80 °C)], besides starting material (14%) one isomer of the 1,2,3,3a,4,5-hexahydro-7-methyl-4-(4-methylphenyl)-5-trifluoromethylpyrrolo[1,2-*a*]quinazoline (3) as a white crystalline compound in a yield of 66% [mp 127-128 °C (diisopropyl ether); *m/e* 346.165 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.15-6.8 (m, 6 H, Ar H), 6.51 (d, 1 H, J = 8.8 Hz, H-9), 5.0-4.7 (m, 1 H, NCHN), 4.47 (q, 1 H, J = 8.5 Hz, $CHCF_3$), 3.45-3.2 (m, 2 H, NCH_2), 2.27 (s, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 125.5 (q, J = 283.9 Hz, CF_3), 71.1 (d, C-3a), 64.2 (q, J = 28.4 Hz, C-5), 46.1 (t, C-1)]. The trans stereochemistry of 3 was determined by using ^{1}H NOE difference spectroscopy. The piperidine analogue 2b did not react in a similar way either in refluxing 1-butanol or in acetonitrile in the presence of zinc chloride at 81 °C.

A few years ago Lawesson *c.s.*[11] published a very efficient method for the synthesis of thiocarbonyl compounds using the so-called Lawesson reagent 4. Reaction of 1a with 0.6 mol. equiv. of 4 in toluene at 110 °C for 3.5 h afforded a complete conversion of the starting material 1a. After column chromatography [silica gel, chloroform/petroleum ether (bp 60-80 °C)] not the expected thione 6a was isolated but one isomer of the 5-(trifluoromethyl)-1,2,3,3a-tetrahydro-7-methyl-5*H*-pyrrolo-[1,2-*a*][3,1]benzothiazine (7a) as a white solid in a yield of 77% [mp 58 °C (subl. 100 °C/0.08 mm Hg); *m/e* 273.080 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.2-7.0 (m, 2 H, Ar H), 6.70 (d, 1 H, J = 8.8 Hz, H-9), 4.9-4.7 (m, 1 H, NCHS), 4.33 (q, 1 H, J = 9.5 Hz, $HCCF_3$), 3.85-3.55 (m, 1 H, NC*H*H), 3.45-3.1 (m, 1 H, NCH*H*), 2.6-1.8 (m, 4 H, CH_2), 2.27 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 142.1 (s, C-9a), 126.1 (q, J = 280.0 Hz, CF_3), 56.8 (d, C-3a), 44.7 (q, J = 29.6 Hz, C-5), 32.5 (t, C-3)]. Reaction of the compounds 5a,[12] 5b,[13] and 5c[13] with 4 in refluxing toluene for 2.5 h, 5 h, and 75 h, respectively, gave, after column chromatography, the corresponding 5*H*-pyrrolo[1,2-*a*][3,1]benzothiazines 7b [mp 73-73.5 °C (methanol)], 7c (oil) and 7d[15] [mp 115.5-117 °C (methanol)] in yields of 33%, 49%, and 42%, respectively. Since in compounds 7 the NOE enhancement factor between the protons H-3a and H-5 is 1.00 we concluded that these protons are in the trans position. We found that 7a could also be obtained starting from the benzoxazine 8 by reaction with 4 in refluxing



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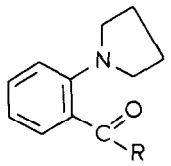
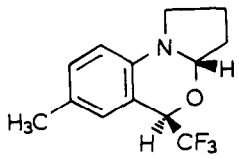


5

a. R = H
b. R = CH_3
c. R = C_6H_5



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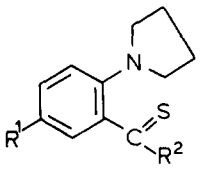

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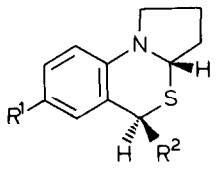
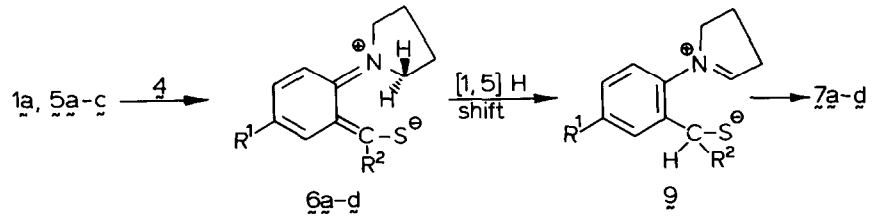


7

a. R^1 = CH_3; R^2 = CF_3
b. R^1 = H ; R^2 = H
c. R^1 = H ; R^2 = CH_3
d. R^1 = H ; R^2 = C_6H_5

toluene for 40 h in a yield of 36%.

The formation of 7a-d from 1a, 5a-c can be explained by three consecutive reactions as depicted in the Scheme. The first step comprises the *in situ* formation of the thiocarbonyl compounds 6a-d. These compounds undergo further reaction by a thermal suprafacial [1,5] hydrogen shift producing the zwitterion 9. Finally, intramolecular addition of the sulphur nucleophile to the iminium double bond gives rise to compounds 7a-d. The two last steps - which also accounts for the analogous formation of 3 - are similar to those described for the formation of the benzoxazines (e,g. 8).[4] In the formation of the benzoxazines a strongly elec-



6a-d 9

Scheme

tron-withdrawing CF_3-group adjacent to the carbonyl moiety is necessary for the stabilization of the negative charge at oxygen in the intermediate dipole in order to allow the hydrogen shift to take place.[4] However, because of the better stabilization of the negative charge in the intermediate zwitterion 9 by sulphur compared with oxygen, an additional electron-withdrawing substituent is not required for the hydrogen transfer in compounds 6b-d.

The formation of 7a starting from the benzoxazine 8 may be rationalized assuming that under the reaction conditions there is an equilibrium between 8 and 1a from which the latter reacts with 4 to afford 6a that ultimately cyclizes to 7a as depicted in the Scheme.

In the present study we have demonstrated that 1-(1-pyrrolidinyl)benzenes with at the 2-position an imino or a thiocarbonyl substituent are interesting precursors for the synthesis of the heterocyclic compounds 3 and 7. The 1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzothiazine structure is a novel heterocyclic system. Finally, the reactions described comprise a further extension of the scope of the "*t*-amino effect" in heterocyclic chemistry with imino-[16] and thiocarbonyl substituents.

The reaction of the thiocarbonyl compounds represents the first example in our work where the intramolecular [1,5] hydrogen shift does not require a strongly electron-withdrawing group for the stabilization of the negative charge in the dipolar intermediate.

References and notes

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