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NOVEL APPLICATIONS OF THE "*t*-AMINO EFFECT" IN HETEROCYCLIC CHEMISTRY; SYNTHESIS OF 5*H*-PYRROLO- AND 1*H*,6*H*-PYRIDO[1,2-*a*][3,1]BENZOXAZINES

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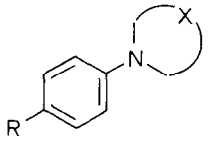
Abstract. *Trifluoroacetylated* N,N-*dialkylanilines react in refluxing 1-butanol to benzoxazine derivatives via an intramolecular [1,5] hydrogen shift and subsequent cyclization of the dipolar intermediate*

Hitherto 1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine and 2,3,4,4a-tetrahydro-1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazine were unknown classes of heterocycles However, Kienzle[1] very recently published the preparation of these types of compounds by oxidation of the appropriate benzyl alcohols with MnO_2. This publication prompts us to report the preliminary results of an alternative approach to these types of heterocycles.

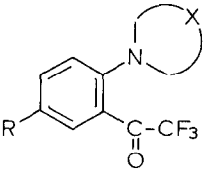
In the course of our investigations of the "*t*-amino effect"[2] in heterocyclic chemistry we have reported previously the formation of *N*-heterocycles by ring closure reactions of substituted 2-*vinyl*-*N*,*N*-dialkylanilines[3]. We have subsequently investigated the reactivity of 2-*acyl*-*N*,*N*-dialkylanilines (e.g. 2).

In a previous paper we have described the reaction of pyrrolidine and piperidine enamines with trifluoroacetic anhydride. The trifluoroacetylated enamines were found to undergo thermal isomerization to 1,3-oxazines[4] Reaction of the 1-(4-methyl-, and 4-methoxyphenyl)pyrrolidines[5] (1a) and (1b) with trifluoroacetic anhydride in tetrahydrofuran at room temperature for 2 days or for 18 h at 40 °C gave in yields of more than 90% the 2,2,2-trifluoro-1-[5-methyl- and 5-methoxy-2-(1-pyrrolidinyl)phenyl]ethanones (2a) and (2b), respectively[6] The corresponding piperidine analogues 1c-d yielded, after aqueous work up, mixtures of the



1

a R = CH_3, X = $(CH_2)_2$
b R = OCH_3, X = $(CH_2)_2$



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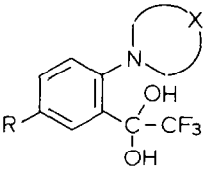
c R = CH_3, X = $(CH_2)_3$
d R = OCH_3, X = $(CH_2)_3$

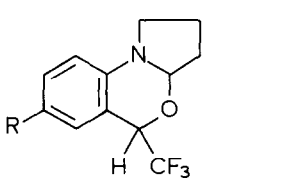


3

e R = CH_3, X = HC=CH

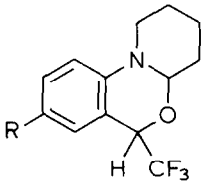
trifluoroacetylated compounds 2c-d and of the corresponding hydrates[7] 3c-d. The latter were isolated as pure crystalline materials[9] after trituration of the crude reaction mixture with diisopropyl ether in yields of 38% [mp 78-85 °C (dec)] and 35% [mp 105-112 °C (dec)], respectively. 2,5-Dihydro-1-(4-methylphenyl)-1*H*-pyrrole (1e) reacted with trifluoroacetic anhydride in a similar way to give 2e in high yield. Trichloroacetylation of 1a with trichloroacetic anhydride could not be achieved neither in refluxing tetrahydrofuran nor in refluxing 1,2-dichloroethane.

Heating of 2a in 1-butanol at 118 °C for 45 h gave a quantitative conversion into 5-(trifluoromethyl)-1,2,3,3a-tetrahydro-7-methyl-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazine (4a). This compound was isolated after column chromatography [alumina (III-IV), chloroform/petroleum ether (bp 60-80 °C)] as an oil in a yield of 91%. The ^{1}H NMR spectrum showed the presence of two isomers in a ratio of about 4.5:1. Upon addition of a few drops of methanol the major isomer crystallized [mp 60-60.5 °C (methanol); *m/e* 257.102 (M^+); ^{1}H NMR ($CDCl_3$) δ 5.25-5.05 (m, 1 H, NCHO), 4.95 (q, *J* = 8.3 Hz, 1 H, $HCCF_3$), 3.8-3.1 (m, 4 H, NCH_2), 2.28 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 84.7 (d, NCHO), 72.1 (dq, *J* = 30 Hz, $HCCF_3$), 50.8 (t, NCH_2), 22.6 (q, CH_3)]. The minor isomer showed in the ^{1}H NMR spectrum the characteristic $HCCF_3$-absorption at δ 5.20 (q, *J* = 6.3 Hz) and the NCHO-signal at δ 4.8-4.65 (m). Heating of the pure major isomer in 1-butanol for 3 days gave according to the ^{1}H NMR spectrum the thermodynamic isomer mixture with a ratio of the isomers of about 4.5:1.



4

a R = CH_3 b R = OCH_3



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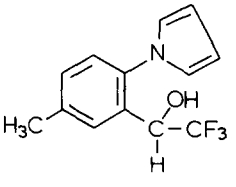


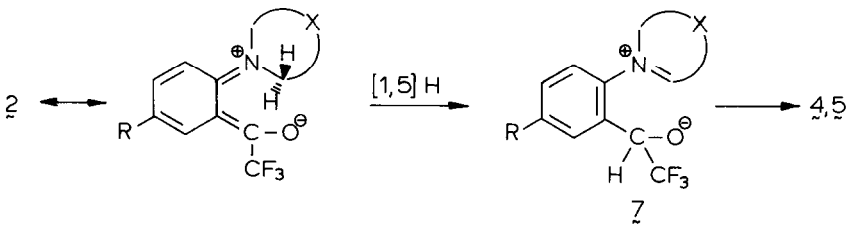
6

Heating of the hydrate 3c or a mixture of 2c and 3c in 1-butanol for 90 h gave after chromatography a 1:1 isomer mixture of 6-(trifluoromethyl)-2,3,4,4a-tetrahydro-8-methyl-1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazine (5a) as an oil in a yield of 95% from which one isomer crystallized spontaneously [mp 66.5-68 °C (methanol); ^{1}H NMR ($CDCl_3$) δ 5.03 (q, *J* = 8.1 Hz, 1 H, $HCCF_3$), 4.6-4.4 (m, 1 H, NCHO); ^{13}C NMR ($CDCl_3$) δ 82.0 (d, NCHO), 71.8 (dq, *J* = 30 Hz, $HCCF_3$)]. The other isomer showed characteristic absorptions in the ^{1}H NMR spectrum at δ 5.28 (q, *J* = 6.3 Hz, 1 H, $HCCF_3$) and 4.4-4.2 (m, 1 H, NCHO) and in the ^{13}C NMR spectrum at δ 84.0 (d, NCHO) and 74.0 (dq, *J* = 30 Hz, $HCCF_3$). The methoxy analogues 2b and 3d reacted similarly. After heating in 1-butanol at 118 °C for only 20 h isomer mixtures of 4b (2.5:1) and 5b (2:1) were obtained as oils in yields of 77 and 90%, respectively.

Starting from 2e the ring closure could not be accomplished in refluxing 1-butanol. Instead 2,2,2-trifluoro-1-[5-methyl-2-(1*H*-pyrrol-1-yl)phenyl]ethanol (6)

was isolated as an oil from the reaction mixture in a yield of 60% [IR (NaCl) 3450 cm^{-1} (OH); *m/e* 255.087 (M^+); ^1H NMR ($CDCl_3$) δ 6.73 and 6.28 (t, *J* = 2 Hz, 2 H, pyrrole H's), 4.79 (br q, *J* = 6.6 Hz, 1 H, *HC*(OH)CF_3), 2.75 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 124.3 (q, *J* = 283 Hz, CF_3), 66.9 (dq, *J* = 33 Hz, *HC*(OH)CF_3)].

The formation of 4 and 5 can be explained by two consecutive reactions as depicted in the Scheme. The first step comprises a thermal suprafacial [1,5] hydrogen shift producing the zwitterion 7. Subsequently, intramolecular addition of the negative charged oxygen atom to the iminium double bond gives rise to compounds 4 and 5. We have obtained strong evidence that the hydrogen shift indeed is a concerted process, because when the reaction of 2a was performed in 1-deuterio-1-butanol no incorporation of deuterium was detected at C-3a and C-5 of 4a. Besides, no loss of deuterium was observed starting from 2a in which the hydrogens of the carbon atoms adjacent to nitrogen were replaced by deuterium. It is likely that in the cases of the hydrates 3c-d under the conditions used firstly dehydration takes place to 2c-d.



Scheme

In order to allow the hydrogen shift to take place the strongly electron-withdrawing CF_3-group adjacent to the carbonyl moiety seems to be crucial, because starting from methyl 2-(1-pyrrolidinyl)benzoate and 1-[2-(1-pyrrolidinyl)phenyl]-ethanone the ring closure could not be achieved. The effect of the substituent R in compound 2 on the rate of reaction ($k_{OCH_3} > k_{CH_3}$) can be explained in terms of a more effective stabilization of the positive charge at the nitrogen atom in the zwitterion 7 by the methoxy group.

The formation of 6 comprises aromatization to a pyrrole by deprotonation of the intermediate 7 which is obviously faster than the cyclization reaction.

This synthesis of benzoxazines (4 and 5) is a further example of the potential use of the "*t*-amino effect" of 2-substituted *N*,*N*-dialkylanilines in heterocyclic chemistry.

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References and Notes

1. F. Kienzle, Tetrahedron Lett. 24, 2213 (1983).
2. O. Meth-Cohn and H. Suschitzky, Adv. Heterocyclic Chem. 14, 211 (1972).
3. W. Verboom, D. N. Reinhoudt, R. Visser and S. Harkema, J. Org. Chem. submitted for publication.
4. W. Verboom, D. N. Reinhoudt, S. Harkema and G. J. van Hummel, J. Org. Chem. 47, 3339 (1982).
5. Compounds 1 were prepared by dialkylation of the corresponding anilines with 1,4-dibromobutane, 1,5-dibromopentane and *cis*-1,4-dichlorobutene, respectively, in refluxing toluene in the presence of ethyldiisopropylamine.
6. For other examples of the facile trifluoroacetylation of activated aromatic compounds see: W. Verboom, G. W. Visser and D. N. Reinhoudt, Tetrahedron 38, 1831 (1982), and references cited therein.
7. Stewart et al.[8] have recently published several other examples of the formation of hydrates of trifluoromethyl phenyl ketones.
8. R. S. McDonald, K.-C. Teo and R. Stewart, J. Chem. Soc., Perkin Trans. 2 1983, 297, and references cited therein.
9. Satisfactory elemental analyses were obtained for all new crystalline compounds (C,H,N $\pm$ 0.3%).

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