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Acetylation and trifluoroacetylation reactions of tetrahydropyrrolo[3,2-*c*]pyridines

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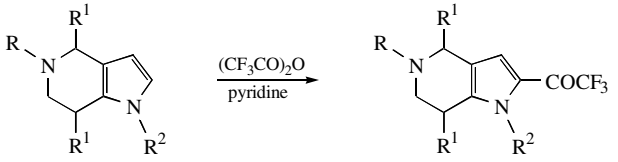
4-Methyl-substituted tetrahydropyrrolo[3,2-*c*]pyridines reacted with acetic anhydride to produce substituted 3-vinylpyrroles in low to moderate yields.

Tetrahydropyrrolo[3,2-*c*]pyridines (THPPs) are easy available building blocks for the construction of heterocyclic systems;[1] at the same time, many of THPPs exhibited biological activity.[2,3] Recently, we have reported tandem piperidine ring cleavage in tetrahydropyrrolo[3,2-*c*]pyridines under the action of dimethyl acetylene dicarboxylate (DMAD) resulting in the formation of α- and β-vinylpyrroles in moderate to good yields.[4] We report here on the unusual cleavage of THPPs **1–6** under the action of acetic anhydride.

To synthesise functionalised THPPs interesting from the biological viewpoint,[5] we have carried out the acetylation and trifluoroacetylation of derivatives **1–6** according to the protocols reported for pyrroles.[6,7] The trifluoroacetylation reaction† proceeds smoothly giving expected 2-trifluorosubstituted THPPs **7–12** in 60–70% yields (Scheme 1).



1–6 **7–12** (60–70%)

1,**2**,**7**,**8** R^1 = H, R = Et **3**,**4**,**9**,**10** R^1 = H, R = Bn **5**,**6**,**11**,**12** R^1 = R = Me

1,**3**,**5**,**7**,**9**,**11** R^2 = H **2**,**4**,**6**,**8**,**10**,**12** R^2 = vinyl

Scheme 1

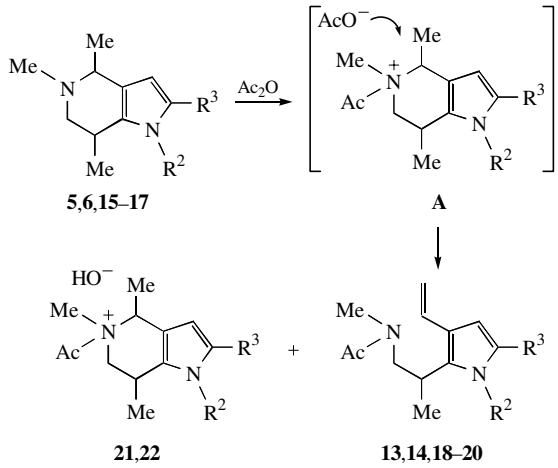
Surprisingly, we failed to isolate the expected 2-acetyl derivatives in the case of acetylation. No trace of the target product has been detected in the reaction mixtures. Under the reaction conditions used,‡ compounds **1–4** afforded multicomponent inseparable mixtures of tar products, while derivatives **5** and **6** provided 3-vinylpyrroles **13** (16%) and **14**. Although NMR and GC–MS analysis of the reaction mixture showed at least 80% divinyl THPP derivative **14**, we failed to isolate it because of its instability under the isolation conditions.

The cleavage most likely starts with the formation of quaternary ammonium salt **A** followed by an attack of the acetoxy anion on the 4-Me group (Hofmann-like cleavage) to afford 3-vinylpyrroles. The lower basicity of the trifluoroacetoxy anion explains the absence of cleavage in the trifluoroacetylation (Scheme 2).

Taking into account the limited availability of 3-vinylpyrroles and their possible use as building blocks for the synthesis of more elaborated substrates,[8] we studied the acetylation of α-substituted THPP derivatives **15–17**. α-Formylvinylpyrrole **18**‡ was isolated in 25% yield, while the cleavage of **16** and **17** proceeds with difficulties and corresponding vinylpyrroles **19** and **20** were obtained in 15 and 10% yields, respectively. The oxime group of **17** was dehydrated to provide nitrile under the action of acetic anhydride. The main products isolated in this case were quaternary ammonium bases **21**§ and **22** (48 and 42%, respectively, as amorphous solids), which were most likely formed during column chromatography of the reaction mixture from intermediate salts **A**. Compounds **21** and **22** were formed as mixtures of two isomers with approximate ratio of 1:1.5.

Target 2-acetyl THPP **23** can be obtained under Vilsmeier–Haack acetylation conditions by treating THPP **5** with dimethylacetamide (DMAA) and phosphorous oxychloride (Scheme 3).

Finally, we studied the acetylation and trifluoroacetylation of THPP derivatives and found that the corresponding α-trifluoroacetyl derivatives can be obtained in high yields by the subsequent action of trifluoroacetic anhydride and DMAA–$POCl_3$.



5,**6**,**15–17** **A**

21,**22** **13**,**14**,**18–20**

13 $R^2 = R^3$ = H **14** R^2 = vinyl, R^3 = H **15**,**18** R^2 = H, R^3 = CHO

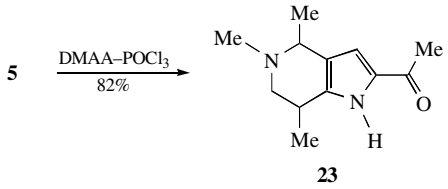
16,**19**,**21** R^2 = H, $R^3 = COCF_3$ **17** R^2 = vinyl, R^3 = CH=NOH

20,**22** R^2 = vinyl, R^3 = CN

Scheme 2

† *General conditions for the trifluoroacetylation reaction by the example of* **3**. Compound **3** (0.6 g, 2.8 mmol) was dissolved in a mixture of 25 ml of freshly distilled CH_2Cl_2 and freshly distilled pyridine (1.5 g, 19 mmol) at room temperature. Trifluoroacetic anhydride (2.1 ml, 12 mmol) was added dropwise, and the reaction mixture was refluxed for 3 h. The reaction mixture was quenched with a 10% aqueous NaOH solution and extracted with CH_2Cl_2 (3×50 ml). The extract, after drying over magnesium sulfate, was evaporated, the residue was dissolved in an ethyl acetate–hexane (1:1) mixture and percolated through a short column with aluminium oxide to provide **7**, 0.54 g (63%) as yellow crystals: mp 134–136 °C (ethyl acetate–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.5 (br. s, 1H, NH), 7.4–7.2 (m, 5H, CH_{arom}), 6.9 (m, 1H, H-3), 3.71 (s, 2H, CH_2-benzyl), 3.48 (s, 2H, CH_2-4), 2.8 (s, 4H, CH_2-6 and CH_2-7). MS, *m*/*z* (%): 308 (M^+, 64), 307 (M – H, 30), 239 (6), 217 (16), 189 (100), 120 (63), 91 (82). Found (%): C, 62.12; H, 5.12; N, 9.43. Calc. for $C_{16}H_{15}F_3N_2O$ (%): C, 62.33; H, 4.87; N, 9.09.

‡ *General conditions by the example of* **15**. Compound **15** (0.3 g, 1.6 mmol) in 6 ml of freshly distilled acetic anhydride was heated at 70 °C for 1 h. The excess of acetic anhydride was removed under reduced pressure, and the residue was purified by column chromatography (aluminium oxide, ethyl acetate) to afford 93 mg (25%) of *N*-[2-(5-formyl-3-vinyl-1*H*-pyrrol-2-yl)propyl]-*N*-methylacetamide **18** as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (br. s, 1H, NH), 9.45 (s, 1H, CHO), 7.05 (d, 1H, H-4, *J* 2.1 Hz), 6.57 (dd, 1H, α-CH-vinyl, *J* 17.7 and 11.3 Hz), 5.48 (dd, 1H, H_{trans}-vinyl, *J* 17.7 and 1.5 Hz), 5.08 (dd, 1H, H_{cis}-vinyl, *J* 11.3 and 1.5 Hz), 3.70 (m, 2H, N–CH_2), 3.30 (m, 1H, C*H*Me), 2.75 (s, 3H, N–Me), 2.02 (s, 3H, Me-acetyl), 1.28 (d, 3H, CH*Me*, *J* 6.8 Hz). MS, *m*/*z* (%): 234 (M^+, 8), 161 (18), 148 (12), 94 (85), 79 (100). Found (%): C, 66.32; H, 7.52; N, 11.86. Calc. for $C_{13}H_{18}N_2O_2$ (%): C, 66.66; H, 7.69; N, 11.97.



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Scheme 3

Under the action of acetic anhydride, 4-methyl-substituted THPP derivatives underwent Hofmann-like cleavage of the tetrahydropyridine ring to provide 3-vinylpyrroles in low to moderate yields.

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§ *5-Acetyl-4,5,7-trimethyl-2-trifluoroacetyl-4,5,6,7-tetrahydro-1*H*-pyrrolo-[3,2-*c*]pyridin-5-ium hydroxide* **21**: IR (KBr, ν/cm^{-1}): 1220, 1350, 1660, 1740, 3300, 3500. MS, *m*/*z* (%): 302 (M – H_2O, 33), 277 (5), 260 (5), 229 (41), 216 (11), 86 (50), 44 (100).

^{1}H NMR (400 MHz, $CDCl_3$) δ: (major isomer with pseudo-equatorial 7-Me group) 10.6 (br. s, 1H, NH), 7.18 (q, 1H, H-3, *J* 1.5 Hz), 4.96 (q, 1H, H-4, *J* 6.4 Hz), 4.04 (dd, 1H, H-6a, *J* 13.7, 9.2 Hz), 3.32 (dd, 1H, H-6e, *J* 13.7, 7.0 Hz), 3.7–3.45 (m, 1H, H-7), 2.95 (s, 3H, N–Me), 2.02 (s, 3H, Me-acetyl), 1.54 (d, 3H, Me-4, *J* 6.4 Hz), 1.34 (d, 3H, Me-7, *J* 7.0 Hz); (minor isomer with pseudo-axial 7-Me group) 10.6 (br. s, 1H, NH), 7.18 (q, 1H, H-3, *J* 1.5 Hz), 4.91 (q, 1H, H-4, *J* 6.4 Hz), 3.89 (dd, 1H, H-6a, *J* 13.7, 7.6 Hz), 3.7–3.45 (m, 1H, H-7 and H-6e), 2.98 (s, 3H, N–Me), 2.06 (s, 3H, Me-acetyl), 1.55 (d, 3H, Me-4, *J* 6.4 Hz), 1.33 (d, 3H, Me-7, *J* 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) major isomer, δ: 171.5, 168.8, 144.7, 129.9, 123.9, 120.4, 117.1, 62.3, 52.3, 36.7, 30.7, 24.0, 21.5, 17.5; minor isomer, δ: 171.9, 168.8, 145.2, 129.8, 124.0, 119.8, 117.1, 61.7, 53.2, 37.5, 30.1, 23.3, 21.6, 17.4. Found (%): C, 52.42; H, 5.92; N, 8.80. Calc. for $C_{14}H_{19}F_3N_2O_3$ (%): C, 52.50; H, 5.98; N, 8.75.

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