NOVEL APPROACH TO 1H-BENZO[f]PYRROLO[1,2-a]INDOLE-5,10-DIONES

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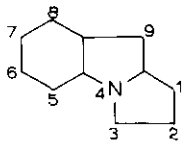
Abstract - The Friedel-Crafts reaction product of 1,4-dimethoxynaphthalene (3) and (S)-1-(trifluoroacetyl)-2-pyrrolidinecarbonyl chloride (4) could be converted in two steps into the benzo[f]pyrrolo[1,2-a]indole 10 following two different pathways. Compound 10 could easily be dehydrated using acid to 11. Upon reduction of 10 to the corresponding hydroquinone 12, spontaneous dehydration occurred.

The pyrrolo[1,2-a]indoles 1 represent an important class of heterotricyclic compounds in particular because a 2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indole-5,8-dione forms the basic skeleton of the antitumour antibiotic mitomycins.[1,2] In spite of the relative high toxicity, mitomycin C (2) is currently employed clinically and consequently several groups are involved in synthetic studies on mitomycins with the aim to prepare less toxic analogues.[3-5] One of the key problems in the synthesis of such compounds is the construction of the pyrrolo[1,2-a]indole skeleton.[6]



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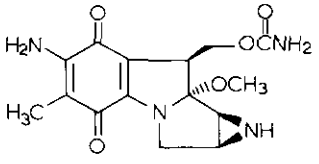

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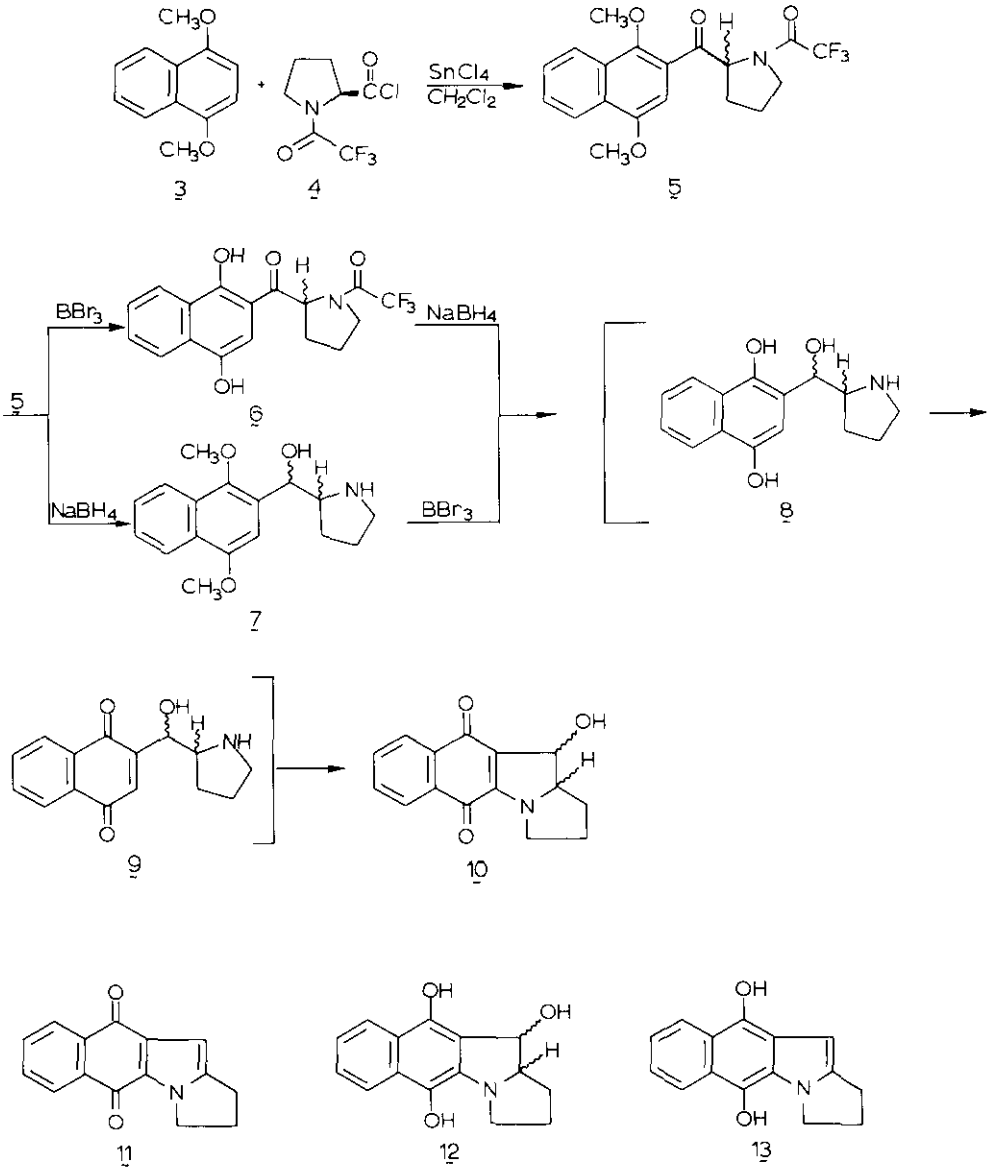
An approach that has hardly been investigated involves the formation of the N-4 - C-4a bond in the last step. Only intramolecular nucleophilic aromatic substitution reactions in the presence of copper(I) bromide involving a pyrrolidinylidene moie-

ty,[7,8] or variations of the Nenitzescu reaction have been reported.[9]

Recently, we have described novel routes to both dihydro-[10] and tetrahydro-1H-pyrrolo[1,2-a]indoles[11] which are based on C-9 - C-9a bond formation in the key step by a modified Madelung reaction or a 1,5-electrocyclization, respectively. In the present paper we wish to report our preliminary results on the synthesis of 1H-benzo[f]pyrrolo[1,2-a]indole-5,10-diones via a Friedel-Crafts acylation[12] of 1,4-dimethoxynaphthalene (3) and subsequent formation of the N-4 - C-4a bond.

Recently, the Friedel-Crafts acylations of benzene, anisole, and veratrole by chiral N-(trifluoroacetyl)- α -amino acid chlorides have been described.[13] We found that reaction of 1,4-dimethoxynaphthalene[14](3) with (S)-1-(trifluoroacetyl)-2-pyrrolidinecarbonyl chloride[15](4) in dichloromethane using tin(IV) chloride as a Lewis acid for 12 h gave the racemic ketone 5 [mp 105-106.5°C (MeOH)][16] in a yield of 65%. Evidently, under these reaction conditions the enolization of the ketone function is particularly favoured.[17] The Friedel-Crafts reaction product 5 could be easily converted into 2,3,11,11a-tetrahydro-11-hydroxy-1H-benzo[f]pyrrolo-[1,2-a]indole-5,10-dione (10) following two different pathways. In the first route, 5 was demethylated in 2 h at room temperature with boron tribromide in dichloromethane leading to the stable hydroquinone 6 [mp 209.5-211°C (MeOH)][18] which was isolated in a yield of 95%. On treatment of 6 with excess of sodium borohydride in ethanol for 12 h at room temperature both the carbonyl group was reduced and the amino group deprotected. After evaporation of the solvent, the residue was taken up in a mixture of water and chloroform and stirred vigorously for 0.5 h. The colour of the mixture turned red and after workup, the crude residue was purified by chromatography [neutral alumina (II-III), ethyl acetate] to afford 10 as a mixture of stereoisomers in a yield of 80%.[19] Separation of the diastereomers was possible using silica gel (ethyl acetate), however, under the influence of this column material 10 partly dehydrated with formation of the known 2,3-dihydro-1H-benzo[f]pyrrolo[1,2-a]indole-5,10-dione (11)[20] (mp 180-182.5°C, ref. 20 mp 181-184°C). This result provided additional proof for the structure of 8.



In the second route the Friedel-Crafts reaction product 5 was treated with excess of sodium borohydride in ethanol for 12 h at room temperature leading to the amino alcohol 7[21] as a mixture of stereoisomers in a quantitative yield. Demethylation of 7 using boron tribromide in dichloromethane for 2 h afforded after neutral workup 10 as a mixture of stereoisomers in a yield of 75%. We assume that during the aqueous workup the intermediate hydroquinone 8 is oxidized to the corres-

ponding quinone 9, which undergoes an intramolecular Michael reaction with the amino moiety, with ultimate formation of 10. A somewhat related reaction, starting from 6-hydroxydopamine, which leads to an indoline, has been reported by Senoh and Witkop.[22]

Benzo[f]pyrrolo[1,2-a]indole 10 is rather unstable, because at room temperature it slowly dehydrates to produce 11 ($t_{0.5}$ about 7 weeks). The dehydration reaction was accelerated considerably (reaction time about 15 sec) upon the addition of a few drops of trifluoroacetic acid to a solution of 10 in acetone. Spontaneous conversion to 11 within a few sec took also place upon treatment of a solution of 10 in acetone with a to pH 7 adjusted solution of sodium dithionite in water. Under these conditions 10 is transformed to its hydroquinone 12, which instantaneously dehydrates to 13, followed by oxidation to the quinone 11. The difference in rate of dehydration between 10 and 12 may especially be attributed to the assistance of the nitrogen lone pair in hydroquinone 12. This is not possible in the quinone 8 in which the nitrogen lone pair constitutes part of a vinylogous amide system.

This phenomenon resembles the bioreductive activation of mitomycin C which after reduction and the consequent elimination of methanol acts as a highly reactive alkylating agent.[1,2]

In summary we can conclude that this sequence represents a short and attractive method for the construction of 1H-benzo[f]pyrrolo[1,2-a]indole-5,10-diones. Further work on the synthesis of other substituted 1H-benzo[f]pyrrolo[1,2-a]-indole-5,10-diones and the related pyrrolo[1,2-a]indoles is in progress.

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12. Previously, Friedel-Crafts methodology has been used to construct one of the 5-membered rings of pyrrolo[1,2-a]indoles via bond formation between C-8 - C-9 and/or C-9 - C-9a. See: (a) M.E.K. Cartoon and G.W.H. Cheeseman, J. Organometal. Chem., 1981, 212, 1 and references cited therein, and 1982, 234, 123. (b) S. Rault, M. Cugnon de Sévricourt, A.M. Godard and M. Robba, Tetrahedron Lett., 1985, 26, 2305.

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16. Satisfactory elemental analyses (± 0.4%) were obtained for all compounds, unless otherwise stated. Data of compound 5: ^{1}H NMR ($CDCl_3$): δ 8.35-8.0 and 7.7-7.55 (m, 2H, ArH), 7.07 (s, 1H, H-3), 6.0-5.9 (m, 1H, CHC=O), 4.06 and 4.00 (s, 3H, OCH_3), 4.0-3.65 (m, 2H, $H_2CNC=O$), 2.3-1.8 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): δ 197.3 (C=O), 179.0 (NC=O), 66.3 (CHC=O), 55.7 (OCH_3). MS m/z: M^+, 381.117 (381.119 for $C_{19}H_{18}F_3NO_4$).

17. Nordlander et al.[13a] reported that reaction of (S)-1-(trifluoroacetyl)-2-pyrrolidinecarbonyl chloride (4) with 1,2-dimethoxybenzene also gave a racemic mixture, while reaction of 4 with benzene yielded an almost pure enantiomer.

18. ^{1}H NMR ($CDCl_3$): δ 12.90 (s, 1H, OH-1), 8.1-7.9 and 7.65-7.35 (m, 2H, ArH), 6.80 (s, 1H, H-3), 6.17 (s, 1H, OH), 5.55-5.4 (m, 1H, HCC=O), 3.95-3.8 (m, 2H, NCH_2), 2.35-2.0 (m, 4H, CH_2). ^{13}C NMR (DMSO-d_6): δ 199.8 (C=O), 178.5 (NC=O), 48.2 (CHC=O), 47.0 (NCH_2). MS m/z: M^+, 353.087 (353.088 for $C_{17}H_{14}F_3NO_4$).

19. Due to the instability of 10 no satisfactory elemental analysis could be obtained. Data of the mixture of isomers: ^{1}H NMR ($CDCl_3$): δ 8.15-7.95 and 7.7-7.6 (m, 2H, ArH), 4.4-4.1 (m, 1H, NCH), 3.8-3.55 (m, 2H, NCH_2), 2.2-1.75 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): δ 181.2, 180.7, 180.6 (C=O), 70.5, 68.7 (NCH), 48.1, 47.2 (NCH_2). MS m/z: M^+, 255.087 (255.090 for $C_{15}H_{13}NO_3$).

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21. Data of the mixture of isomers: ^{1}H NMR ($CDCl_3$): δ 8.3-7.95 and 7.7-7.4 (m, 2H, ArH), 7.06 and 6.90 (s, 1H, H-3), 5.25 and 4.90 (d, J = 8.0 and 6.4 Hz, respectively, 1H, CHOH), 4.00 and 3.91 (s, 3H, OCH_3), 3.8-3.4 (m, 1H, NCH), 3.2-2.8 (m, 3H, NH and NCH_2), 1.8-1.6 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): δ 152.2 and 152.0 (C-5, C-10), 69.4 and 68.4 (CHOH), 64.8 and 63.1 (NCH), 55.7 (OCH_3) 46.4 and 46.1 (NCH_2). MS m/z: M^+, 287.150 (287.152 for $C_{17}H_{21}NO_3$).

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