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Synthesis of Unsymmetrical Dipyrrolyl Sulfides

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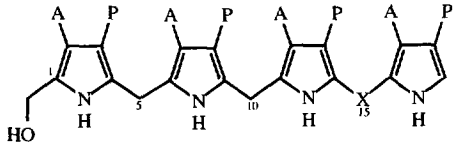
Abstract: The preparation of unsymmetrical dipyrrolyl sulfides bearing electron-withdrawing groups at the α-position is described. Copyright © 1996 Elsevier Science Ltd

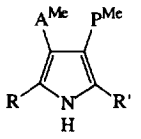
For some time, our laboratory has been studying the substrate specificity and mechanism of Uroporphyrinogen III synthase, the enzyme in the porphyrinoid pathway which cyclizes the linear tetrapyrrole 1-hydroxymethylbilane (HMB, **1**) to Uroporphyrinogen III, a key precursor for the biologically vital pigments, hemes, coenzyme F 430, vitamin B_{12} and chlorophyll.[1] In the course of our studies, we were interested in an analog of the natural substrate (**1**) bearing a sulfur bridge at the C-15 meso position (**2**). This should be obtained through preparation of an unsymmetrical dipyrrolyl sulfide bearing a formyl or carboxyester group at the α-carbon for further extension. A literature survey showed few examples of dipyrrolyl sulfides,[2] and only one was unsymmetrical.[3]



1 X=CH_2 (HMB)
2 X=S

A=CH_2CO_2H
P=$CH_2CH_2CO_2H$

We first turned our attention to the most logical approach: introduction of the thio group at the α-position of a β-substituted pyrrole (acetate and propionate methyl esters at both β-positions) followed by electrophilic substitution with another pyrrole to provide the unsymmetrical dipyrrolyl sulfide. With α-methylpyrrole, substitution was obtained in moderate to good yields by 3 different methods: (a) substitution of **3b** with sodium hydrosulfide[4] to afford, after work-up, the thiopyrrole **3c** (25%), (b) oxidation of thiolacetic acid by I_2/KI[5] in the presence of the α-free pyrrole **3a** to provide the acetylthiopyrrole **3d** (23%) and (c) by reaction of **3a** with thiourea in presence of an halogen[6] to give the S-(pyrrolyl)isothiuronium salt **3e** (73%). However, despite all our efforts, these procedures failed to provide any thiopyrrole when the starting material was substituted at the α-carbon with a formyl or ester group (**4a**, **4b**, **5a** and **5b** as appropriate) in place of methyl.



3 R=Me **a** R'=H **b** R'=I **c** R'=SH **d** R'=SAc **e** R=S(NH$_2$)$_2$ + I$^-$
4 R=CHO **a** R'=H **b** R'=I **c** R'=Cl
5 R'=CO_2CH_2Ph **a** R=H **b** R=I **c** R=Cl
6 R'=$CO_2{}^t$Bu **a** R=H **c** R=Cl
7 R=$CO_2{}^t$Bu **a** R'=H **c** R'=Cl

A^{Me}=CH_2CO_2Me, P^{Me}=$CH_2CH_2CO_2Me$

This result is not so surprising in view of the well-known substituent effects on electrophilic substitution of pyrrole.[2,7] In fact, electron-donating groups at the α-position, such as an alkyl group, enhance the reactivity of the other α-carbon, while electron-withdrawing groups, such as formyl or ester, show a deactivating effect. The presence of substituents at the β-carbons, which generally tend to decrease reactivity of neighboring positions, could also combine with and reinforce the previous effect, albeit slightly.

We next considered sulfur dichloride, which has given good results for the preparation of symmetrical dipyrrolyl sulfides,[8] but has not been mentioned in the preparation of unsymmetrical dipyrrolyl sulfides.

As expected, reaction of SCl_2 with α-free pyrroles afforded symmetrical dipyrrolylsulfides (table, entries 1, 3 and 5). If the pyrroles carry an ester group at the α-position (entries 3 and 5), good yields of the products are obtained with little formation of the chlorides (**5c** and **6c**) as by-products. In case of the α-formylpyrrole **4a** (entry 1), both sulfide **8** and disulfide **9** were isolated in moderate yields as well as the chloride **4c** as side-product. In the presence of two α-free pyrroles as substrates (entries 7 to 15), a mixture of compounds, symmetrical and unsymmetrical dipyrrolyl sulfides and α-chloropyrroles, was obtained, the main products being the symmetrical sulfides. The use of SCl_2 for the preparation of sulfenyl chlorides and their subsequent substitution with aromatic hydrocarbons is well documented[9] and a variety of conditions to improve the ratio of unsymmetrical/symmetrical sulfides was tried. First, it was observed that shielding the reaction from light lowered the formation of the chlorides, which are probably generated through disproportionation of the reagent and/or the sulfenyl chloride. In principle addition of one substrate to the reagent followed by addition of the second pyrrole (condition C) should provide a better ratio of unsymmetrical/symmetrical sulfides. However, such was not the case (entries 9 and 14). This could be explained by 2 combined factors: (i) the great reactivity of the sulfenyl chloride formed which competes with the reagent to attack the substrate; (ii) the greater deactivating effect on α-electrophilic substitution due to the formyl group possessing a greater electronegative effect than the ester group (entry 9).[7] However, other factors may well be involved, since in the inverse addition, *i.e.* **4a** followed by **5a** (not shown in the table), no unsymmetrical dipyrrolyl sulfide was detected.

Variations in the temperature, order of addition reagent/substrates and addition of catalyst (Lewis acids, inorganic supports) led to little improvement in the yields, although it was found best to carry out the reaction at room temperature with very little difference effected by the order of addition reagent/substrates. The presence of Friedel-Crafts catalysts often causes erratic results with aromatic hydrocarbons[9] and of the various catalysts tried, only tin(II) chloride showed a slightly better yield of unsymmetrical dipyrrolyl sulfide (entry 10). In recent years, solid supports (silica gel, clay, alumina) have shown interesting catalytic properties on a variety of reactions.[10] We observed no drastic effect in using neutral alumina especially for the preparation of symmetrical dipyrrolyl sulfides (entries 2, 4 and 6), however, the yields of unsymmetrical dipyrrolyl sulfides were increased

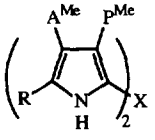
Table: Preparation of Dipyrrolyl Sulfides.

entry	substrates	condi-tions	reaction sym. dipyrroles	products[a] unsym. dipyr.	(yield,%) by-products
1	**4a**	A	**8** (41) + **9** (38)	-	**4c** (14)
2	**4a**	B	**8** (40) + **9** (36)	-	**4c** (10)
3	**5a**	A	**10** (76)	-	**5c** (9)
4	**5a**	B	**10** (86)	-	**5c** (8)
5	**6a**	A	**11** (80)	-	**6c** (3)
6	**6a**	B	**11** (70)	-	**6c** (2)
7	**4a** + **5a**	A	**8** (20) + **9**[b] + **10** (49)	**13** (24)	**5c** (10) + **4c**[b]
8	**4a** + **5a**	B	**8** (15) + **9** (7) + **10** (36)	**13** (28)	**5c** (7) + **4c** (3)
9	**4a** + **5a**	C	**8** (28) + **9**[b] + **10** (58)	**13** (13)	**5c** (7) + **4c**[b]
10	**4a** + **5a**	D_A,D_C	**8**[b] + **9**[b] + **10**[b]	**13** (26,18)	**5c**[b] + **4c**[b]
11	**4a** + **6a**	A	**8** (21) + **9** (10) + **11** (25)	**14** (21)	**6c**[b] + **4c** (23)
12	**4a** + **6a**	B	**8** (18) + **9** (16) + **11** (31)	**14** (23)	**6c** (10) + **4c** (11)
13	**4a** + **6a**	E	**8** (15) + **9** (4) + **11** (27)	**14** (26)	**6c** (7) + **4c** (11)
14	**5a** + **7a**	C	**10** (55) + **12** (29)	**15** (26)	**5c**[b] + **7c**[b]
15	**5a** + **7a**	B	**10** (47) + **12** (25)	**15** (29)	**5c** (5) + **7c** (9)

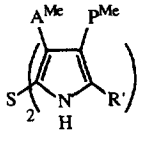
A: see a.
B: A + addition of neutral Al_2O_3 to SCl_2 solution.
C: addition of a solution of **5a** to SCl_2 solution, then addition of the solution of the second substrate (**4a** or **7a**).
D_A: A + 0.2 eq. $SnCl_2$ added to the SCl_2 solution; D_C: C + 0.2 eq $SnCl_2$ added to the SCl_2 solution.
E: 1 eq. 1M SCl_2 in CH_2Cl_2 was added to a solution of the substrates followed by 2 eq. anh. $CaCO_3$ at the end of the addition.

a: Typical procedure (condition A): The 2 substrates (0.2 mmol each) in anh. CH_2Cl_2 (0.4 M) were added dropwise during 15 min to a solution of SCl_2 (1M in CH_2Cl_2, 0.2 mmol). The reaction was stirred in the dark at RT under N_2 for 8 h. The solution was washed with $NaHCO_3$, the organic solution dried over $MgSO_4$, filtered and the solvent evaporated. The different products were isolated by preparative TLC (AcOEt/Hexanes, 1/1). For conditions B and E, the reaction mixture was filtered through Celite and the solid washed with CH_2Cl_2 + 5% MeOH prior washing with $NaHCO_3$. All products were satisfactorily characterized by ^1H-, ^{13}C-NMR and mass spectroscopy.

b: observed by TLC, but the yield was not determined.

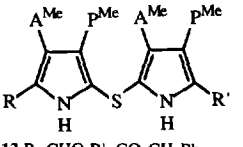


8 R=CHO X=S
9 R=CHO $X=S_2$
12 R=$CO_2{}^tBu$ X=S



10 R'=CO_2CH_2Ph
11 R'=$CO_2{}^tBu$

A^{Me}=CH_2CO_2Me P^{Me}=$CH_2CH_2CO_2Me$



13 R=CHO R'=CO_2CH_2Ph
14 R=CHO R'=$CO_2{}^tBu$
15 R=$CO_2{}^tBu$ R'=CO_2CH_2Ph

slightly by its addition (entries 8, 12 and 15) or the addition of solid calcium carbonate (entry 13) after reagent addition to the substrates. This could be easily explained in both cases by the elimination of the hydrogen chloride formed during the course of the reaction, thus allowing the reaction to proceed at nearly neutral pH.

In summary, this represents the first account of preparation of unsymmetrical dipyrrolyl sulfides bearing electron-withdrawing groups at the α-position and could open the way to a variety of new polypyrroles and porphyrinoid compounds. In particular, the synthesis of a bilane with a meso sulfur bridge (**2**), a substrate analog for Uroporphyrinogen III synthase, is now in progress.

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