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Regioselective Pyrrole Synthesis from Asymmetric β-Diketone and Conversion to Sterically Hindered Porphyrin

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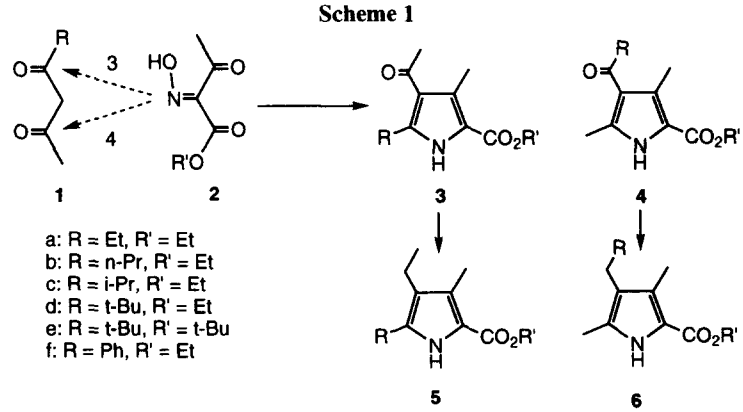
Abstract. The condensation of asymmetric β-diketones with α-oximinoacetoacetate esters affords pyrroles regioselectively. The mechanism of the regioselectivity is studied using ^{13}C-NMR spectroscopy. Pyrrole having a neopentyl group at the 4-position is synthesized by the method, and further converted to a steric hindered porphyrin in good yield.

Pyrrole and its derivatives are important heterocyclic compounds. They are not only a prolific source of interesting chemical reactions, but also an essential building block for many biologically active molecules, such as porphyrins, bile pigments, and vitamin B_{12}.[1] The Knorr reaction,[2] which is the condensation of ethyl α-oximinoacetoacetate with ethyl acetoacetate, was widely used for syntheses of pyrrole and its derivatives and, later, a number of useful variations of the reaction have been reported by several groups. Zanetti found that acetylacetone, instead of ethyl acetoacetate, reacts with α-oximinoacetoacetate to give a pyrrole that yields cryptopyrrole by diborane reduction.[3] Kleinspehn deduced that the substitution of diethyl oximinomalonate for ethyl α-oximinoacetoacetate forces this alternative mode to take place.[4] The condensation of diethyl α-oximinomalonate with 2,4-pentadione was found to give excellent yields of ethyl 3,5-dimethylpyrrole-2-carboxylate. However, in most cases, symmetric β-diketones, such as 2,4-pentadione (R=methyl), are used to avoid the formation of structural isomers (Scheme 1), and there are only few examples of asymmetric β-

Scheme 1



diketones. The Knorr reaction from asymmetric β-diketone would be useful to prepare functionalized porphyrin compounds because the reaction can introduce various substituents into the pyrrole β-position. For example, iron porphyrins having a sterically hindered substituent at the pyrrole β-position[5] have been shown to mimic reactive intermediates of several heme enzymes.[6] In this paper, we report a regioselective pyrrole synthesis from asymmetric β-diketone by the Knorr method. The reaction herein enables the preparation of pyrroles and porphyrins with steric hindered substituents at the pyrrole β-position easily and in high yield.

Asymmetric β-diketones of **1 a-f** were condensed with ethyl α-oximinoacetoacetate in the presence of zinc dust and sodium acetate in acetic acid.[7] The pyrroles were isolated by pouring the reaction solution into ice-water, then purified by crystallization from ethanol-water. The yields and isomer ratios of the reaction products are summarized in Table 1. For all asymmetric β-diketones, the corresponding pyrroles are synthesized in reasonable yields, which are comparable with those of the Knorr reaction from 2,4-pentadione. From **1a** (ethyl substituent), two structural isomers of **3a** and **4a** were detected with a ratio of 1 : 4 by ^{1}H-NMR measurement. Interestingly, the selectivity of **4** is improved (1 : 5) for the n-propyl group (**1b**) and **3** is not observed when the substituents are bulkier than the n-propyl group; **1c-1f**. These observations suggest that the steric effect of the substituent in β-diketone affects the selectivity of isomers of **3** and **4**.

To further confirm the structure, a carbonyl group at the pyrrole 4-position in **3** or **4** was reduced to methylene (**5** and **6**) by diborane reduction. The yields of the reactions are listed in Table 1. For all pyrroles, pyrroles (**5** or **6**) were isolated in excellent yield. The diborane reduction completed in 4 hr at room temperature, except for **4d** and **4e**. The diborane reduction of **4d** at room temperature afforded only an alcohol product in good yield and **6d** was obtained when the reduction was carried out at 60 °C for 24 hr. The structures of **6** were confirmed from hyperfine couplings in the ^{1}H-NMR signal.

Previously, introduction of an alkyl group at the pyrrole 4-position has been carried out by the Knorr condensation of meso-alkyl β-diketone with α-oximinoacetoacetate as shown in Scheme 2.[4] Although pyrroles

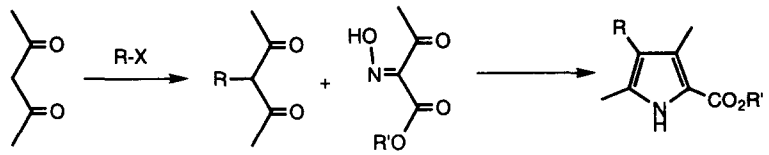
Table 1. The Knorr synthesis from asymmetric β-diketones and its diborane reduction.

Entry	R(**1**)	R'(**2**)	Yield of **3** (**4**)[a]	Ratio (**3** : **4**)[b]	Yield of **5** (**6**)[c]
a	Et	Et	38	20 : 80	84
b	n-Pr	Et	49	17 : 83	83
c	i-Pr	Et	45	0 : 100	66
d	t-Bu	Et	38	0 : 100	68[d]
e	t-Bu	t-Bu	38	0 : 100	65[d]
f	Ph	Et	46	0 : 100	70

a) Isolated yield. b) From ^{1}H-NMR. c) Reaction condition; room temperature for 4 hr. Isolated yield.
d) Reaction condition; reflux for 24 hr. Isolated yield.

of **6a**, **6b**, **6c**, and **6f** can be synthesized by this method, **6d** and **6e** can not be synthesized because the introduction of a neopentyl group at the 3-position of 2,4-pentadione hardly occurs. Thus, the present method is useful to synthesize pyrroles having bulky substituents, such as a neopentyl group, at the 4-position.

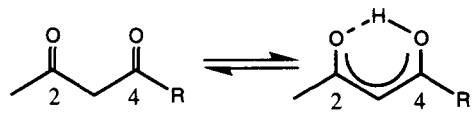
Scheme 2



Furthermore, to investigate the effect of electrophilicity of the carbonyl carbon on the regioselectivity, we measured ^{13}C-NMR spectra of β-diketones of **1a** - **1d**. The assignments of the signals were done by hetero 2D-NMR spectroscopies. The chemical shifts of the carbonyl carbon of β-diketones are summarized in Table 2. In $CDCl_3$ solution, the enol form is much more dominant than the keto form. Furthermore, for both the enol and keto forms, ^{13}C-NMR shifts of the carbonyl carbons at the 2-position are smaller than those at the 4-position. This means that the electrophilicity of the carbonyl carbon at the 2-position is weaker than that at the 4-position. Thus, pyrrole **3** would be dominant if electrophilicity of the carbonyl carbon is the cause of the regioselectivity. However, since the opposite results (pyrrole **4** is dominant) are observed in this study, this is not the case. The steric effect of β-diketone is more important than the electrophilicity of the carbonyl carbon.

We also examined the conversion of the sterically hindered pyrrole of **6d** to porphyrin having a neopentyl group at the pyrrole β-position. The condensation of 3-methyl-4-neopentyl-5-diethylaminomethyl-pyrrole-2-carboxylic acid, prepared from amination and hydrolysis of **6d**, afforded a porphyrinogen in excellent yield.[9] The oxidation of the porphyrinogen by air for 1 week gives porphyrin compound (**7**) in 24% yield (based on **6d**).

Table 2. ^{13}C-NMR shifts of asymmetric β-diketones of **1a** - **1d** in $CDCl_3$.



keto-form enol-form

β-Diketone	R	keto			enol		
		%	2	4	%	2	4
a	Et	23	202	205	77	191	195
b	n-Pr	17	202	204	83	191	194
c	i-Pr	12	202	208	88	191	198
d	t-Bu	14	200	208	86	193	200

The structure of **7** was confirmed by ^{1}H-NMR and FAB-MS spcetra.[8]

Iron was inserted into **7** by standard methods (e.g. $FeCl_2$ in hot acetic acid). The absorption and ^{1}H-NMR spectra of chloro iron(III) complex of **7**, **8**, were similar to those of hemin in natural heme enzymes.[8] The steric effect of the neopentyl group in **7** is evidenced by the fact that when a paramagnetic high-spin complex of **8** is treated with 1M NaOH, instead of the typical antiferromagnetically coupled, essentially diamagnetic μ-oxo dimer, a new paramagnetic species (^{1}H-NMR of ring Me at 37 ppm at 24°C; ESR of g = 6.2, 5.8, 2.0 at 77 K) is obtained, which is identical to the hydroxy iron(III) complex of **7**.[10] These data suggest that iron complex of **7** is suitable as models for rection intermediates in natural heme enzymes.[6]

Reference and Notes:

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7. Typical procedure: ethyl 3,5-dimethyl-4-neopentyl-pyrrole-2-carboxylate (**6d**): Preshly prepared ethyl α-oximinoacetoacetate(from 19 g of ethyl acetoacetate and 13 g of $NaNO_2$) was titrated into the mixture of 5,5-dimethyl-2,4-hexanedione(**1d**) (25 g), zinc dust (25 g), and sodium acetate (20 g) at 60 °C. The mixture was further stirred at 60 °C for 1hr, then refluxed for 2hr. The mixture was poured into ice-water while the solution was hot. Crude pyrrole was collected by filtration and purified by crystallization from ethanol-water. The pyrrole of **4d** (9 g) was dissolved in dry THF (200 ml) containing $NaBH_4$ (3.5 g), and BF_3 etherate solution (20 ml) was titrated at 0 °C. The mixture was refluxed for 24 hr, and treated with 5 % HCl solution followed by neutralization with $NaHCO_3$. The pyrrole was extracted by ether and evaporation of the ether exatract furnished white pyrrole(**6d**).
8. Spectroscopic data: ^{1}H-NMR in $CDCl_3$. **5a**; 8.6(s, 1H), 4.29(q, 2H), 2.59(t, 2H), 2.39(t, 2H), 2.34(s, 3H), 1.22(t, 3H), 1.06(t, 2H), 0.90(t, 3H). **6a**; 8.6(s, 1H), 4.28(q, 2H), 2.33(t, 2H), 2.26(s, 3H), 2.19(s, 3H), 1.45(m, 2H), 1.35(t, 3H), 0.90(t, 3H). **5b**; 8.6(s, 1H), 4.29(q, 2H), 2.51(t, 2H), 2.34(t, 2H), 2.28(s, 3H), 1.05(t, 3H), 0.96(t, 2H), 0.91(t, 3H). **6b**; 8.6(s, 1H), 4.28(q, 2H), 2.34(t, 2H), 2.26(s, 3H), 2.19(s, 3H), 1.35(m, 4H), 1.34(t, 3H), 0.91(t, 3H). **6c**; 8.8(s, 1H), 4.33(q, 2H), 2.30(s, 3H), 2.26(d, 2H), 2.23(s, 3H), 1.78(m, 1H), 1.39(t, 3H)), 0.92(d, 6H). **6d**; 8.6(s,1H), 4.28(q, 2H), 2.25(s, 5H), 2.20(s, 3H), 1.35(t, 3H), 0.89(s, 9H). **6e**; 8.6(s,1H), 2.25(d, 2H), 2.22(s, 3H), 2.18(s, 3H), 1.56(s, 9H), 0.89(s, 9H). **6f**; 8.7(s,1H), 7.2(m, 5H), 4.30(q, 2H), 3.77(s, 2H), 2.23(s, 3H), 2.18(s, 3H), 1.35(t, 3H). **7**; 10.2(s,4H), 4.0(s, 8H), 3.65(s, 12H), 1.3(s, 36H), -3.6(s, 2H). **8**; 50.0(s, 12H), 41.4(s, 8H), 3.6(s, 36H), -59.2(s, 4H). UV-vis. (nm) in CH_2Cl_2. **7**; 399, 499, 534, 568, 621. **8**; 380, 505, 536, 638. FAB-MS. **7**; M^+ = 647.7 (cal = 647.5).
9. (a) Paine III, J. B.; Kirsher, W. B.; Moskowitz, D. W.; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 385. (b) Nguyen, L. T. and Simth, K. M. *Tetraherdorn Lett.* **1996**, *37*, 7177.
10. Half of **8** formed its μ-oxo dimer from the reaction with NaOH and the hydroxy complex was not so stable to isolate. Because of flipping over the neopentyl group, the hydroxy complex slowly changed to the μ-oxo dimer.

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