A Synthesis of Pyrrole Derivatives from *O*-(2-Hydroxyethyl)-ketoximes

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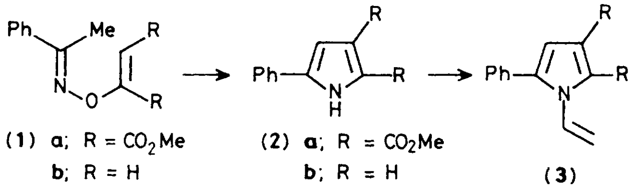
Acetophenone, cyclohexanone, cycloheptanone, cyclo-octanone, and heptan-4-one were converted, *via* their *O*-(2-hydroxyethyl)-oximes [(**5**), (**6a**), (**6b**), (**6c**), and (**8**)] into the pyrrole derivatives [(**2b**), (**7a**), (**7b**), (**7c**), and (**9**), respectively] in satisfactory overall yields.

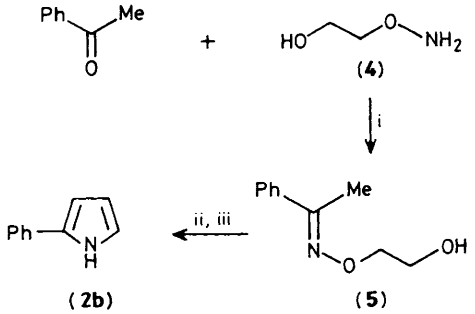
A number of years ago, Sheradsky reported[1] that when the base-catalysed addition products [(**1a**) and its *trans*-isomer] of acetophenone oxime and dimethyl acetylenedicarboxylate were heated together (Scheme 1), the pyrrole derivative (**2a**) was obtained. Trofimov *et al.* have since reported[2] that when the *O*-vinyl derivative (**1b**) of acetophenone oxime was heated with potassium hydroxide in dimethyl sulphoxide solution, 2-phenylpyrrole (**2b**) was obtained (Scheme 1) in high yield. The Russian workers[2] prepared (**1b**) by heating acetophenone oxime, acetylene, and potassium hydroxide together in dimethyl sulphoxide solution, under conditions which can lead[3] to the formation both of 2-phenylpyrrole (**2b**) and its 1-*N*-vinyl derivative (**3**; R = H). In connection with another study, we required certain 2,3-cycloalkeno-pyrroles (see below) and, mainly in order to avoid their possible contamination with the corresponding 1-*N*-vinylpyrrole derivatives, we sought an alternative and more convenient method for the generation of intermediate *O*-vinyl-ketoximes and their conversion into pyrrole derivatives.

The procedure that we have developed for the conversion of ketones into pyrrole derivatives is illustrated for acetophenone in Scheme 2. When acetophenone was heated, under reflux, with *O*-(2-hydroxyethyl)-hydroxylamine† (*ca.* 2 mol equiv.) in the presence of 2 mol equiv. each of acetic acid and pyridine in ethanol solution, the corresponding *O*-(2-hydroxyethyl)-oxime (**5**) was obtained in 80% yield (Table 1, entry 1). When (**5**) was then treated with a slight excess (*ca.* 1.4 mol equiv.) of methyltriphenoxyphosphonium iodide[4] in dry acetonitrile for 20 min at room temperature, the corresponding *O*-(2-iodoethyl)-ketoxime was obtained. The latter product was isolated without purification and was heated, under reflux, with an excess (6 mol equiv.) of *ca.* 1.7 M potassium t-butoxide in t-butyl alcohol for 5 h. After work-up, 2-phenylpyrrole (**2b**) was isolated, following Kugelrohr distillation, as a crystalline solid in 74% yield. When (**5**) was treated with methyltriphenoxyphosphonium iodide, and the resulting *O*-(2-iodoethyl)-oxime was then heated, under reflux, with 5 mol equiv. of 0.4 M potassium t-butoxide in t-butyl alcohol for 20 min, the *O*-vinyl-oxime (**1b**) was obtained. The latter compound (**1b**)‡ was isolated in 41% yield, following chromatography of the products on silica gel; when it was further heated with potassium t-butoxide under the same conditions for 5 h, 2-phenylpyrrole (**2b**) was obtained in 89% yield.

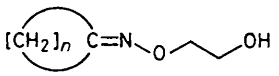


Scheme 1

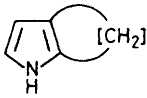
The procedure described above (Scheme 2) in the preparation of 2-phenylpyrrole (**2b**) was also used successfully to convert cyclohexanone (Table 1, entry 2), *via* its *O*-(2-hydroxyethyl)-oxime (**6a**), into (**7a**).[5] Cycloheptanone, cyclo-octanone, and heptan-4-one (entries 3, 4, and 5) were



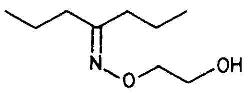
Scheme 2. *Reagents:* i, acetic acid, pyridine–ethanol, reflux; ii, $(PhO)_3P^+MeI^-$/acetonitrile, room temp., 20 min; iii, $KOBu^t$–Bu^tOH, reflux, 5 h.



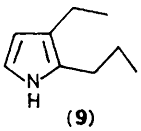
(**6**)
a; *n* = 5
b; *n* = 6
c; *n* = 7



(**7**)
a; *n* = 4
b; *n* = 5
c; *n* = 6



(**8**)



(**9**)

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† We are unaware of a procedure in the literature for the preparation of *O*-vinylhydroxylamine, and the literature preparation [I. Bruno, J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, 1962, **45**, 358] of *O*-(2-hydroxyethyl)-hydroxylamine (**4**) is cumbersome and leads to unsatisfactory yields. However, the following procedure for the preparation of (**4**) proved to be very convenient: *N*-hydroxyphthalimide (1 mol equiv.), 2-bromoethanol (3 mol equiv.), anhydrous potassium carbonate (3 mol equiv.), and dimethyl sulphoxide (10 ml/g *N*-hydroxyphthalimide) were stirred together at 70 °C for 20 min. The cooled products were partitioned between dichloromethane and water to give *N*-(2-hydroxyethoxy)phthalimide (m.p. 73 °C, after recrystallisation from aqueous ethanol) in 79% yield. A solution of the latter compound (1 mol equiv.), hydrazine hydrate (1.5 mol equiv.), and absolute ethanol [2 ml/mmol of *N*-(2-hydroxyethoxy)phthalimide] were heated, under reflux, for 2 h and the cooled products were filtered. The filtrate was concentrated and distilled under reduced pressure to give *O*-(2-hydroxyethyl)-hydroxylamine (**4**) as a colourless liquid, b.p. 55 °C/0.07 mmHg, in 86% yield.

‡ (**1b**) was identified on the basis of its ^1H [$\delta(CDCl_3$, 250 MHz): 2.35 (3H, s), 4.21 (1H, dd, *J* 1.8, 6.8 Hz), 4.73 (1H, dd, *J* 1.5, 14.2 Hz), 7.08 (1H, dd, *J* 6.5, 14.2 Hz), 7.42 (3H, m), 7.71 (2H, m)] and ^{13}C [δ ($CDCl_3$, 62.9 MHz): 13.31, 88.12, 126.36, 128.47, 129.66, 135.73, 152.80, 157.25] n.m.r. spectra.

Table 1. Conversion of ketones into pyrrole derivatives.

Entry	Ketone	Oxime derivative	% Yield[a]	Pyrrole derivative[b]	M.p./°C	% Yield
1	Acetophenone	(**5**)	80	(**2b**)	129	74
2	Cyclohexanone	(**6a**)	95	(**7a**)		65
3	Cycloheptanone	(**6b**)	82	(**7b**)	99	70
4	Cyclo-octanone	(**6c**)	87	(**7c**)	35—36	70
5	Heptan-4-one	(**8**)	82	(**9**)		71

[a] The *O*-(2-hydroxyethyl)-ketoximes were isolated by Kugelrohr distillation. [b] Satisfactory microanalytical data were obtained for the crystalline solids [(**2b**), (**7b**), and (**7c**)] and satisfactory exact mass measurements were obtained for the liquids [(**7a**) and (**9**)].

similarly converted into (**7b**), (**7c**), and (**9**) in *ca.* 57, 61, and 58% overall yields, respectively. The possibility of converting aldehydes, *via* their *O*-(2-hydroxyethyl)-oximes, into pyrrole derivatives is currently under investigation.

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