Synthesis of 2,3,4,5-tetrasubstituted pyrroles from aromatic ketoximes using the $TiCl_4/Et_3N$ reagent system

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Aryl alkyl ketoximes react with the $TiCl_4/Et_3N$ reagent to give 2,3,4,5-tetrasubstituted pyrroles in moderate to good yields (55–81%).

Keywords: ketoximes, pyrroles, titanium tetrachloride, oxidative coupling

Pyrroles are an important class of heterocycle.[1] Symmetrically substituted pyrroles are usually prepared through methods involving the corresponding ketazine intermediate,[2] rearrangement of ketazine dianions,[3] and using ketones and alkyl hydrazines.[4] In the course of studies on the synthetic applications of the $TiCl_4/Et_3N$ reagent system,[5] we have discovered, and report here, a convenient one-pot synthesis of 2,3,4, 5-tetrasubstituted pyrroles from aromatic ketoximes (Scheme 1).

We have examined the reaction of ketoximes (**1**) with $TiCl_4$ and Et_3N in CH_2Cl_2 at 0-25 °C. It was observed that the 2,3,4,5-tetrasubstituted pyrroles (**2**) are obtained as products. This transformation is found to be general for several aromatic ketoximes, and the pyrroles are obtained in 55 to 81% yields. The results are summarised in Table 1.

It was observed that the order of addition of the reagents affects the course of the reaction. The results were better when the $TiCl_4$ was added to the mixture of oxime and Et_3N. When the oxime was added to a mixture of Et_3N and $TiCl_4$, the yield was decreased by 10–15%. Also, when the oxime and $TiCl_4$ were mixed first and Et_3N was added later, the ketone was recovered. We have found that neither $TiCl_4$ nor Et_3N alone effects this transformation.

In the case of α-tetralone oxime (**3**), besides the 12,13-dihydro-7*H*-dibenzo[*a*,*g*]carbazole (**3a**) (27%), 1-naphthylamine (**3b**) was also obtained in 50% yield. Further, we have observed that the 12,13-dihydro-7*H*-dibenzo[*a*,*g*]carbazole (**3a**) is readily oxidised to the 7*H*-dibenzo[*a*,*g*]carbazole (**3c**) under the reaction conditions[6] (Scheme 2).

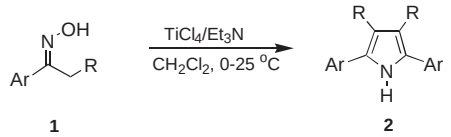
The oxime of acetophenone gave only unidentified products under the reaction conditions. Also, the reaction using one equivalent of $TiCl_4$ (5 mmol) and 1.2 equivalents of Et_3N (6 mmol) gave the Beckmann rearrangement product *N*-methylbenzamide (53% yield).

We have also examined the reactivity of the aliphatic ketoximes cyclohexanone oxime and camphor oxime. In both cases the reagent did not lead to a clean reaction. When the oxime was treated with the $TiCl_4$ / Et_3N reagent in 1 : 1 . 2 ratio, cyclohexanone oxime gave ε-caprolactam, and the fragmentation product **4b** was obtained from camphor oxime (**4**). Previously, such fragmentation of camphor oxime has been reported using polyphosphoric acid (Scheme 3).[7]

The formation of pyrroles from aryl alkyl ketoximes can tentatively be explained through a mechanism involving oxidative coupling and cyclisation as shown in Scheme 4. A similar mechanism has been previously considered for the conversion of aryl alkyl ketimines to the corresponding pyrroles.[5a]

The crucial step in the mechanism involves coupling of the initially formed titanium complex to give the dioxime derivative **6** and $TiCl_3$. Previously, it has been reported that 1,4-diketones react with some primary amines in the presence of $TiCl_4$ to give the corresponding pyrroles.[8] A mechanism similar to that visualized in Scheme 4, involving cyclisation of an enamine intermediate, was proposed by these authors.[8] Accordingly, to examine whether the present transformation of oximes to the corresponding pyrroles involves such dioxime intermediates, we have carried out the reaction of the corresponding dioxime derived from 1,4-diphenylbutane-1, 4-dione. In this case, 2,5-diphenylpyrrole was obtained, although in somewhat low yield (24% yield) besides some unidentified products (Scheme 5).

The formation of pyrrole from the ketoximes could involve the reduction of the N-O bond by the Ti^{3+} species produced *in situ* at some stage via the intermediacy of the species such as **7–9.** However, the mechanism outlined in Scheme 4 is only



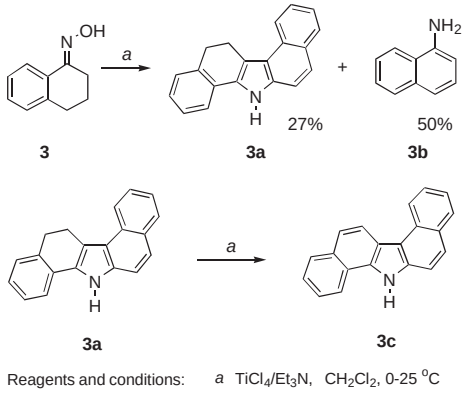
1 **2**

Scheme 1

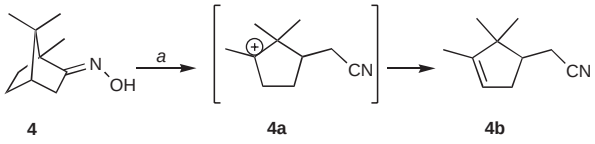
Table 1 Conversion of aromatic ketoximes into 2,3,4, 5-tetrasubstituted pyrroles

Oxime	Ar	R	Product[a]	Yield[b]/%
1a	Ph	Ph	2a	81
1b	CH_2Ph	Ph	2b	62
1c	Ph	CH_3	2c	57
1d	*p*-$C_6H_4CH_3$	CH_3	2d	55
1e	Ph	C_2H_5	2e	58

[a]See Experimental; [b]yields are based on the isolated products.



Scheme 2



Scheme 3 Reagents and conditions: see Scheme 2.

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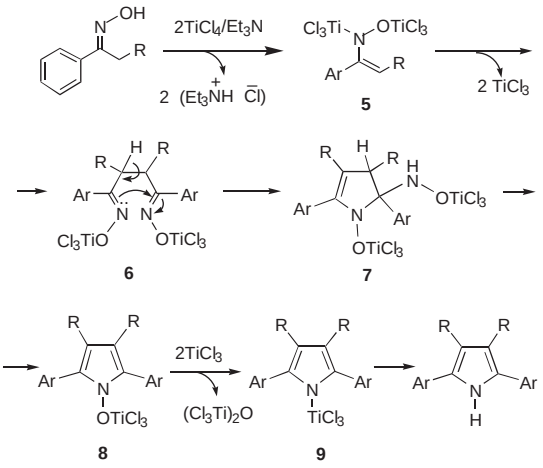
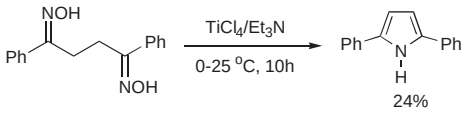


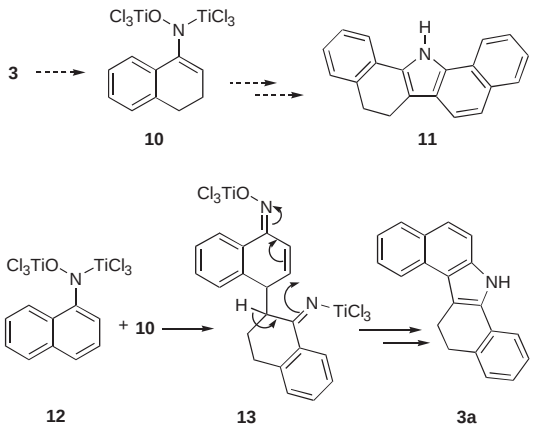
Scheme 4

tentative and we do not have evidence in support of species such as **7–9**. Another interesting aspect is the formation of the 1-naphthylamine **3b** and the dihydrocarbazole **3a** derivative in the reaction of the α-tetralone oxime with the $TiCl_4/Et_3N$ reagent system (Scheme 2). Previously, aromatisation of some cyclic enamines has been reported[9] using the $TiCl_4/Et_3N$ reagent system and hence the formation of 1-naphthylamine is not unexpected under the reaction conditions. However, interestingly, the dihydrocarbazole **3a** is formed instead of the dihydro derivative **11** expected considering a 2,2'-type coupling of the corresponding enamine-type intermediates (Scheme 6).

Presumably, the enamine-type intermediate **10** formed *in situ* would initially undergo dehydrogenation by the $TiCl_4/Et_3N$ reagent system[9] to produce species **12,** a likely precursor of the major product **3b,** that could react with the species **10** via a 2,4'-type coupling to give a species of type **13,** which in turn could give the observed product **3a** in several steps involving 1,4-addition-cyclisation followed by hydrogen shifts and elimination of an amine derivative (Scheme 6). However, this rationalisation can at best be only a working hypothesis and we do not have evidence for the involvement of such intermediates.



Scheme 5



Scheme 6

In conclusion: although the mechanism and intermediates involved in the conversion of aromatic ketoximes to 2,3,4,5-tetrasubstituted pyrroles are not fully understood, this simple one-pot method of synthesis of pyrroles using readily accessible ketoximes has good synthetic potential.

Experimental

^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ unless otherwise stated and TMS was used as reference (δ = 0 ppm). The ^{13}C chemical shifts are reported in ppm on the δ scale relative to $CDCl_3$ (77.0 ppm).

Dichloromethane was distilled over calcium hydride and dried over molecular sieves. Oximes were prepared following a reported procedure.[10] Chromatographic purification was conducted by column chromatography using 100–200 mesh silica gel obtained from Acme Synthetic Chemicals, India. All reactions and manipulations were carried out under a dry nitrogen atmosphere. All yields reported are isolated yields of materials, adjudged homogeneous by TLC analysis.

Reaction of ketoximes with the $TiCl_4/Et_3N$ reagent system. Representative experimental procedure

Dichloromethane (25 ml), Et_3N (15 mmol, 2.1 ml) and oxime (5 mmol) were taken under N_2. $TiCl_4$ (10 mmol) in dichloromethane (10 ml) was added drop wise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 7–8 h at 25°C. It was quenched with saturated K_2CO_3 solution (30 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 25 ml). The combined organic extract was washed with brine solution (10 ml) and dried over anhydrous K_2CO_3. The solvent was removed and the residue was chromatographed on a silica gel column with 2% EtOAc/hexane mixture as eluent.

2,3,4,5-Tetraphenylpyrrole (**2a**) m.p. 213–214 °C (lit.[2b] m.p. 214–215 °C); *2,5-Dibenzyl-3,4-diphenylpyrrole* (**2b**) m.p. 170–172 °C; ^{13}C NMR δ 32.4, 121.9, 125.5, 126.4, 127.9, 128.5, 128.7, 130.3, 136.1, 139.9; MS: M^+ (m/e) 308. Anal: calcd for $C_{30}H_{25}N$: C, 90.20; H, 6.26; N, 3.50. Found: C, 90.25; H, 6.35; N, 3.58 %. *3,4-Dimethyl-2,5-diphenylpyrrole* (**2c**) m.p. 136–137 °C; (lit.[3b] m.p. 138–139 °C); *3,4-Dimethyl-2,5-di p-tolylpyrrole* (**2d**) m.p. 140–142 °C, ^{13}C NMR δ 10.5, 21.2, 117.0, 126.6, 128.3, 129.4, 131.0, 135.7; MS: M^+ (*m/e*) 275; Anal. calcd for $C_{20}H_{21}N$: C, 87.27; H, 7.6; N, 5.09; Found: C, 87.12; H, 7.71; N, 5.15 %. *3,4-Diethyl-2,5-diphenylpyrrole* (**2e**) m.p. 82–84 °C, (lit.[3b] m.p. 81–85 °C); *12,13-Dihydro-7H-dibenzo[a,g]carbazole* (**3a**) m.p. 197–198 °C, (lit.[6] m.p. 197 °C). *7H-dibenzo[a,g]carbazole* (**3c**)**.** m.p. 234–236 °C, (lit.[6] m.p. 237–238 °C).

Conversion of 1,4-diphenylbutane-1,4-dione oxime into 2,5-diphenylpyrrole

Dichloromethane (30 ml), Et_3N (10 mmol, 1.4 ml) and the dioxime (2 mmol, 0.516 g) were taken under N_2. $TiCl_4$ (8.8 mmol, 1.8 ml of 1 : 1 solution of $TiCl_4$ in DCM)) in further dichloromethane (10 ml) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 10 h at 25 °C. It was quenched with saturated K_2CO_3 solution (30 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 25 ml). The combined organic extract was washed with brine solution (10 ml) and dried over anhydrous K_2CO_3. The solvent was removed and the residue was chromatographed on a silicagel column with 2% EtOAc / hexane mixture as eluent to obtain 2,5-diphenylpyrrole (0.105 g, 24% yield), m.p. 142–144 °C (lit[3b]. m.p. 142–143 °C).

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