Conversion of Aryl Methyl Ketimines to 2,5-Diarylpyrroles Using $TiCl_4/Et_3N$

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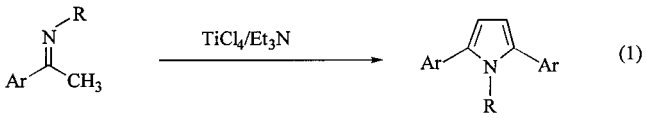
The 2,5-diarylpyrroles are generally synthesized by following the classical Paal−Knorr synthesis involving the reaction of 1,4-diketone with amines.[1] Some of the shortcomings in this reaction were overcome by a later method reported by McEwen.[2] Other methods available for pyrrole synthesis are Hantzsch synthesis using chloroacetone and 3-amino ethyl crotonate,[3] 1,3-dipolar cycloaddition reactions involving azalactones, oxazolones, and alkynes followed by carbon dioxide elimination,[4] 1,3-dipolar cycloaddition reaction of nitrile ylides with electron deficient alkynes and alkenes,[5] and $TiCl_3/C_8K$-induced cyclization of amido-enones to substituted pyrroles.[6] However, all these methods of synthesis of pyrroles involve multistep synthetic operations. Herein, we wish to report a one-pot synthesis of 2,5-diarylpyrroles from the ketimines using the $TiCl_4/Et_3N$ reagent combination (eq 1).



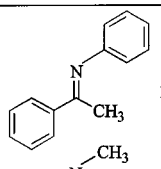
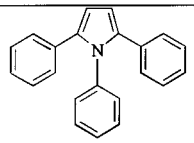
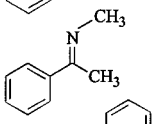
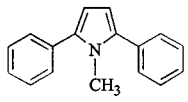
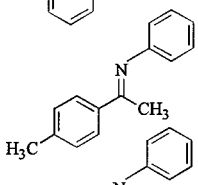
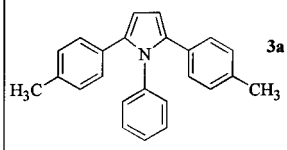
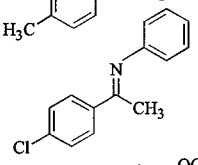
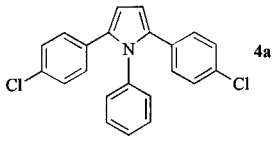
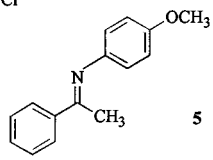
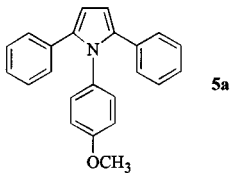
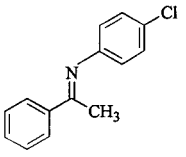
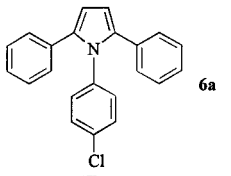
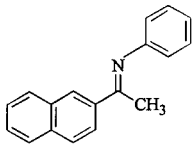
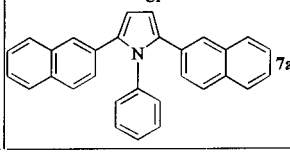
(1)

In connection with efforts toward the synthesis of the C2-chiral 2,5-diarylpyrrolidine system, we were looking for a simple convenient method of preparation of the corresponding 1,4-diketones. Preliminary studies revealed that the reaction of aryl methyl ketones with $TiCl_4/Et_3N$ results in the corresponding 1,4-diketone in ~20% yield in addition to the undesired aldol condensation product.[7] It was thought that the corresponding imines would not lead to such aldol-type reactions. Hence, we have examined the reaction using the imines. Surprisingly, the corresponding 2,5-diarylpyrroles were formed directly with these substrates (eq 1). The transformation was found to be general for several ketimines, and the results are summarized in Table 1.

Whereas ketimines derived from acetophenone and the *N*-alkylamines (*N*-benzyl, *N*-ethyl, *N*-octyl, and *N*-butyl) gave lower yields of pyrrole (8%, 15%, 10% and 12%, respectively), the anils of cyclohexanone and cyclopentanone gave several unidentified products and the reactions were not clean. The anils derived from propiophenone, isobutyrophenone, and camphor remained unreacted under these conditions. In the case of the anil of *p*-methoxyacetophenone, one more equivalent of titanium tetrachloride was necessary to obtain optimum yield (75%, Table 1, entry 5) of the corresponding pyrrole. The reaction goes well at 0−25 °C. Also, change in the order of addition of the reagents did not have any effect on the course of the reaction.

Since the $TiCl_4$ is known to mediate the formation of imines from ketones in the presence of excess primary amine, we have decided to examine the pyrrole synthesis by preparing the anil of acetophenone *in situ*, followed by reaction with additional amounts of $TiCl_4/Et_3N$. Surprisingly, the reaction did not proceed beyond the ketimine stage in this case. Only the ketimines were isolated in very good yields. We find that this method of preparation of imines is operationally simple compared to the hitherto reported methods of synthesis of imines.[8,9] Also, this method is advantageous since the reaction is

Table 1. the Reaction of Ketimines with $TiCl_4/Et_3N$

No.	Substrate	Products	Yield[b] (%)
1.	 1	 1a	90
2	 2	 2a	63
3.	 3	 3a	82
4.	 4	 4a	68
5.	 5	 5a	75
6.	 6	 6a	86
7.	 7	 7a	72

a. The products were identified using ^{1}H-NMR, ^{13}C-NMR and mass spectral data and comparison with physical constant data.[2,12] Satisfactory elemental analyses (≤±0.36 for C, H and N) were also obtained for unknown compounds **3**, **4** and **7**.

b. Yields are based on the imines used.

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(3) Hantzsch, A. *Chem. Ber*. **1890**, *23*, 1474.
(4) (a) Bayer, H. O.; Gotthardt, H.; Huisgen, R. *Chem. Ber*. **1970**, *103*, 2356. (b) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefter, F. C. *Chem. Ber*. **1970**, *103*, 2611.
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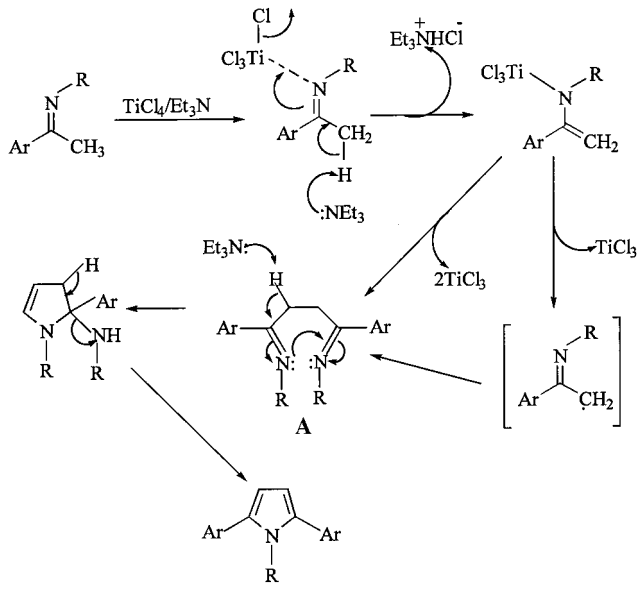
Scheme 1



carried out under mild conditions, at 0−25 °C in CH_2Cl_2. This modified procedure was adopted for the preparation of the ketimines used.

The interesting feature of the transformation reported here is that there is no need to prepare a 1,4-diketone intermediate. Recently, Matsumara *et al.*[10] reported that methyl phenylacetate undergoes oxidative coupling with $TiCl_4/Et_3N$ to give the corresponding 2,3-diphenylsuccinate ester. Presumably, the aryl methyl ketimines also undergo a similar oxidative coupling on reaction with $TiCl_4/Et_3N$ followed by cyclization to give the corresponding pyrroles. Accordingly, the transformation can be visualized by a tentative mechanism outlined in Scheme 1.

Coordination of $TiCl_4$ to the imine nitrogen would make the methyl proton acidic enough to be pulled by Et_3N. The resulting complex could produce a radical on decomposition that can undergo coupling to give the diimine (**A**) followed by aromatization leading to pyrrole (Scheme 1). Alternatively, the intermediate can dimerize to give two $TiCl_3$ and the diketimine. We have observed that neither $TiCl_4$ nor Et_3N alone effects this transformation.

In conclusion, the simple, convenient method described here for the conversion of ketimines to the corresponding pyrroles using $TiCl_4/Et_3N$ should be attractive for synthetic applications as the transformation requires ambient conditions.

Experimental Section:

General. ^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 ($\delta = 0$ ppm). The chemical shifts are reported in ppm on the δ scale relative to $CDCl_3$ (77.0 ppm). Melting points are uncorrected. Dichloromethane was distilled over calcium hydride and dried over molecular sieves. Triethylamine was distilled over CaH_2. All imines were prepared by the method developed in this laboratory.[11] 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, adjusted homogeneous by TLC analysis.

Representative Procedure. Dichloromethane (25 mL), Et_3N (15 mmol), and ketimine (10 mmol) were taken under an N_2 atmosphere. $TiCl_4$ (10 mmol) in CH_2Cl_2 (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 7−8 h at 25 °C. It was quenched with a saturated K_2CO_3 solution (30 mL), and the reaction mixture was filtered through a Buchner funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with a brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column. Hexane eluted the corresponding pyrrole.

1a. 1,2,5-Triphenylpyrrole: mp 233−234 °C (lit.[2] mp 234−236 °C); ^{13}C NMR 138.0, 135.0, 133.29, 128.93−126.20, 109.93; ^1H NMR 7.05−7.35 (15H, m), 6.5 (2H, s).

2a. 1-Methyl-2,5-diphenylpyrrole: mp 197−199 °C (lit.[12] mp 200−202 °C); ^{13}C NMR 136.92, 133.67, 128.78, 128.42, 126.81, 108.75, 34.21; ^1H NMR 7.3−7.6 (10H, m), 6.4 (2H, s), 3.65 (3H, s). Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.86; H, 6.84; N, 6.17. Mass: M^+ (*m/e*) 233.

3a. 1-Phenyl-2,5-bis(*p*-tolyl)pyrrole: mp 208−210 °C; ^{13}C NMR 139.24, 135.79, 130.52, 129.0, 128.62, 127.10, 109.50, 21.06; ^1H NMR 6.85−7.3 (13H, m), 6.4 (2H, s), 2.3 (6H, s). Anal. Calcd for $C_{24}H_{21}N$: C, 89.13; H, 6.54; N, 4.33. Found: C, 89.32; H, 6.58; N. 4.35. Mass: M^+ (*m/e*) 323.

4a. 1-Phenyl-2,5-bis(*p*-chlorophenyl)pyrrole: mp 264−265 °C; ^{13}C NMR 134.97, 132.35, 131.58, 129.79−128.33, 127.69, 110.28; ^1H NMR 6.9−7.4 (13H, m). 6.45 (2H, s). Anal. Calcd for $C_{22}H_{15}NCl_2$: C, 72.54; H, 4.15; N, 3.85. Found: C, 72.80; H, 4.20; N, 3.90. Mass: M^+ (*m/e*) 364.

5a. 1-(*p*-Methoxyphenyl)-2,5-diphenylpyrrole: mp 229−230 °C (lit.[2] mp 227−229 °C); ^{13}C NMR 158.52, 135.97, 133.39, 131.96, 129.84−126.13, 113.95, 109.66, 55.35; ^1H NMR 6.8−7.2 (14H, m), 6.5 (2H, s), 3.8 (3H, s); (imine 10 mmol, $TiCl_4$ 20 mmol, and Et_3N 30 mmol were used).

6a. 1-(*p*-Chlorophenyl)-2,5-diphenylpyrrole: mp 227−228 °C (lit.[2] mp 226−227 °C); ^{13}C NMR 137.58, 135.83, 133.0, 130.0−126.48, 110.28; ^1H NMR 7.3−6.9 (14H, m), 6.45 (2H, s).

7a. 1-Phenyl-2,5-bis(2-naphthyl)pyrrole: mp 222−224 °C; ^{13}C NMR 139.5, 136.03, 133.2, 131.9, 130.7, 129.88−125.66, 123.9, 110.67; ^1H NMR 7.8−7.1 (19H, m), 6.65 (2H, s). Anal. Calcd for $C_{30}H_{21}N$: C, 91.11; H, 5.35; N, 3.54. Found: C, 91.12; H, 5.36; N, 3.58. Mass: M^+ (*m/e*) 395.

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Supporting Information Available: ^{13}C NMR spectra for compounds **1**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **Preparation of Aryl Methyl Ketimines.** Dichloromethane (25 mL), Et_3N (20 mmol), ketone (10 mmol), and amine (12 mmol) were taken under an N_2 atmosphere. $TiCl_4$ (5 mmol) in CH_2Cl_2 (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 7−8 h at 25 °C. It was quenched with a saturated K_2CO_3 solution (30 mL), and the reaction mixture was filtered through a Buchner funnel. The organic layer was separated from the filtrate, and the remaining aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was washed with a brine solution (10 mL) and dried over anhydrous Na_2CO_3. The solvent was removed, and the ketimine was recrystallized from ethanol. The yields of the ketimines: **1**. 91%, **3**. 93%, **4**. 89%, **5**. 90%, **6**. 92%, **7**. 88%.

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