An Efficient Synthesis of Substituted Pyrroles with the Aid of a Low-Valent Titanium Reagent

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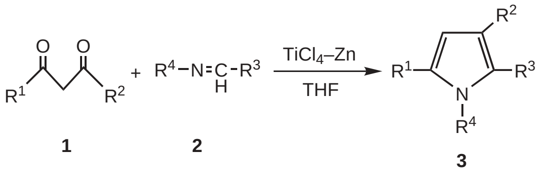
Abstract: A short and efficient synthesis of substituted pyrroles was accomplished in good yields via the novel coupling cyclization reaction of 1,3-diketones with imines or oximes promoted by $TiCl_4$/Zn system.

Key words: pyrrole, low-valent titanium reagent, synthesis

The pyrrole ring constitutes a basic heteroaromatic structure. It is a vital building block for the construction of porphyrins and alkaloids.[1] Several substituted pyrroles have potential as fungicids and bactericides and as active components of nonsteroidal anti-inflammatory drugs inhibiting human cyclooxygenase.[2] Although there are a number of potentially useful methods for the synthesis of pyrroles,[3] the Knorr[4] method is a classical method. Recently, several methods have been developed for the synthesis of this heterocyclic system, e.g. Ishii et al. have reported the synthesis of pyrroles via samarium-catalyzed three-component coupling reaction of aldehydes, amines and nitroalkanes,[5] and one-pot synthesis of pyrroles via three-component condensation of a carbonyl compound, an amine and a nitroalkene in a molten ammonium salt.[6] Ranu et al.[7] have also reported the synthesis of pyrroles on the surface of silica gel and alumina under microwave irradiation. Some one-pot pyrroles synthesis starting from imines have been reported recently, e.g. Gao et al. have reported the synthesis of substituted pyrroles from alkynes, imines, carbon monoxide via an organotitanium intermediate[8] or from alkynes, nitriles, imines and titanium-imine complexes.[9] Lee et al. have reported a one-pot synthesis of substituted pyrroles from propargylic dithioacetals,[10] and Katritzky et al. have also reported the synthesis of 1,2,3-triarylpyrroles from 1-benzylbenzotriazoles via [1+2+2] annulation.[11] However, these are not always satisfactory with respect to ease of operation, yield and general applicability. Therefore, the development of novel and convenient synthetic methods for the preparation of pyrrole derivatives still remains as active research area.

Low-valent titanium reagents have an exceeding high ability to promote reductive coupling of carbonyl compounds and are attracting increasing interest in organic synthesis.[12] Many other functional groups can be reacted.[13] Recently, we have reported the low-valent titanium-induced intermolecular reductive coupling reaction of carboxylic derivatives with aromatic ketones,[14] the intramolecular reductive coupling reaction of 4,4-dicyano-1,3-diaryl-1-butanone[15] and the cyclodimerization of α,β-unsaturated ketones.[16] In the course of our work on the application of low-valent titanium reagents in the preparation of bioactive heterocyclic compounds, we have reported the synthesis of quinazolin-4(3*H*)-ones, quinazolines and imidazo[1,2-*c*]quinazolines with the aid of low-valent titanium reagent.[17] Here we wish to describe a method induced by the $TiCl_4$/Zn system for the preparation of pyrroles using 1,3-diketones, imines and oximes as the starting materials.

When 1,3-diketone **1** and imine **2** were treated with low-valent titanium prepared from titanium tetrachloride and zinc powder in anhydrous THF, the coupling cyclization products 1,2,3,5-tetrasubstituted pyrroles **3**[18] were obtained in good yields (Scheme 1). The results are summarized in Table 1.



Scheme 1

From Table 1, it was found that the $TiCl_4$/Zn system could efficiently promote the reductive cyclization of 1,3-diketone and imine to give pyrroles with different substitution patterns. In particular, the substituents at N and C-2 on the newly formed heteroatomic ring can be easily varied by condensation of aromatic aldehydes with different aromatic amines. Unfortunately, when 2,4-pentanedione (**3k**) or ethyl acetoacetate (**3l**) and **2a** was treated with $TiCl_4$/Zn system under the same reaction conditions they failed to give the desired pyrrole products and only the self-coupling product of imine was obtained. It seems that both, R^1 and R^2, should be aryl groups; otherwise, the reductive cross-coupling process could not take place. The inertness of these two substrates toward $TiCl_4$/Zn system may be

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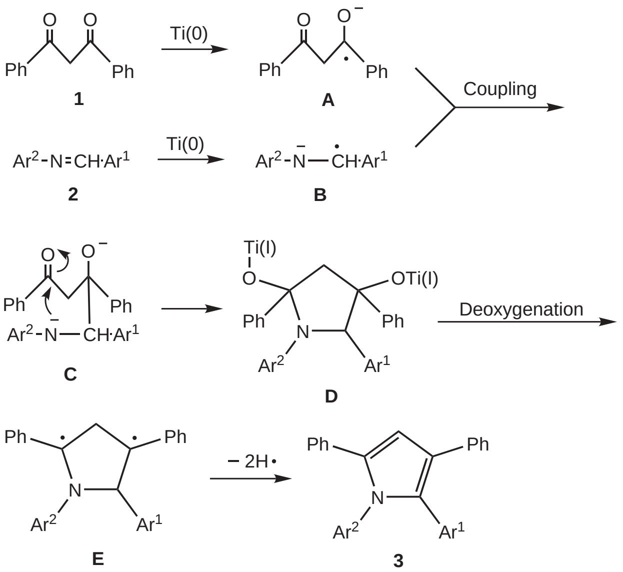
Table 1 The Synthesis of 1,2,3,5-Tetrasubstituted Pyrroles Promoted by Low-Valent Titanium

Product	R^1	R^2	R^3	R^4	Isolated yield (%)
3a	C_6H_5	C_6H_5	C_6H_5	C_6H_5	75
3b	C_6H_5	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	70
3c	C_6H_5	C_6H_5	4-ClC_6H_4	C_6H_5	71
3d	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	C_6H_5	80
3e	C_6H_5	C_6H_5	4-ClC_6H_4	4-$CH_3C_6H_4$	79
3f	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	81
3g	C_6H_5	C_6H_5	4-ClC_6H_4	4-ClC_6H_4	77
3h	C_6H_5	C_6H_5	4-$CH_3C_6H_4$	C_6H_5	75
3i	C_6H_5	C_6H_5	4-$CH_3C_6H_4$	4-ClC_6H_4	68
3j	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	4-ClC_6H_4	69
3k	CH_3	CH_3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	0
3l	CH_3	OC_2H_5	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	0

due to the instability of the possibly formed ketyl intermediate resulting from an acetyl.

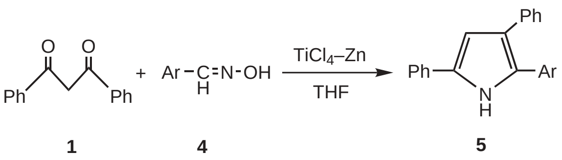
A plausible mechanistic pathway to pyrrole is illustrated in Scheme 2, though the details are unclear as yet.



Scheme 2

$TiCl_4$ is reduced by Zn dust to give low-valent titanium. In the initial steps, and electron is transferred from low-valent titanium to 1,3-diketone **1** or imine **2** to give radical anion **A** and **B**, respectively, the two radical anions then couple to form the carbon-carbon bond and generates intermediate **C**. The latter then takes place by nucleophilic addition to give the intermediate **D,** which occurs deoxygenation to form radical **E**. The radical **E** loses two hydrogen atoms to form the pyrrole **3**.

Moreover, treatment of dibenzoylmethane **1** and oximes **4** with $TiCl_4$/Zn system in anhydrous THF under the same reaction conditions, the cross-coupling products 2,3,5-trisubstituted pyrroles **5** were obtained in moderated yields (Scheme 3). The results are summarized in Table 2.



Scheme 3

Table 2 The Synthesis of 2,3,5-Trisubstituted Pyrroles Promoted by Low-Valent Titanium

Product	Ar	Isolated yield (%)
5a	3,4-$(CH_3O)_2C_6H_3$	72
5b	3,4-$OCH_2OC_6H_3$	69
5c	2,4-$Cl_2C_6H_3$	65
5d	4-BrC_6H_4	62

The structures **3** and **5** were identified by IR, ^{1}H NMR, MS and elemental analysis.[19] The structure of **3g** was further confirmed by X-ray analysis (Figure 1).[20]

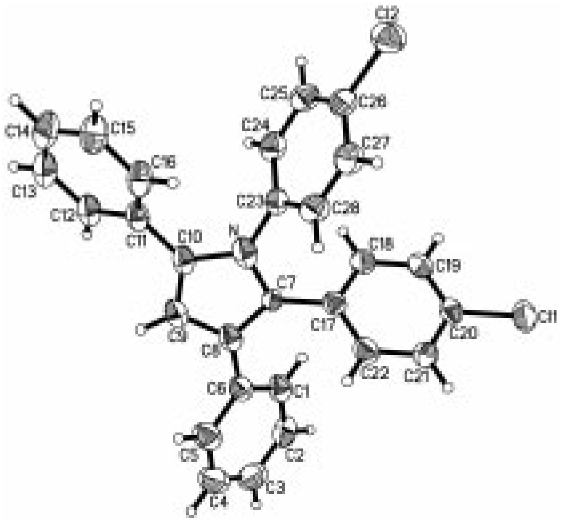


Figure 1 ORTEP diagram of **3g**

In summary, a series of 1,2,3,5-tetrasubstituted pyrroles and 2,3,5-trisubstituted pyrroles were synthesized via coupling cyclization of 1,3-diketones with imines or oximes induced by the $TiCl_4$/Zn system. The advantages of our method are the easily accessible starting materials, convenient manipulation and moderate to high yields.

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(18) The general procedure is represented as follows: $TiCl_4$ (1.65 mL, 15 mmol) was added dropwise using a syringe to a stirred suspension of Zn powder (1.95 g, 30 mmol) in freshly distilled dry THF (20 mL) at r.t. under a N_2 atmosphere. The mixture was refluxed for 2 h. The suspension of low-valent titanium reagent formed was cooled to r.t. and a solution of 1,3-diketone(**1**) (5 mmol) and imine **2** (5 mmol) in THF (5 mL) was added carefully. The reaction mixture was stirred for 4 h at r.t. On completion of the reaction most of the solvent was removed in vacuo. The residue was poured into 5% HCl (100 mL) and extracted with $CHCl_3$ (4×30mL). The combined organic layer was washed with H_2O (4×30 mL), dried (Na_2SO_4), and the solvent was removed to give the crude product, which was purified by column chromatography [silica gel, acetone–petroleum ether (bp 60–90°C), 1:6] to give pure **3**.

(19) Typical data for representative compounds: Compound **3a**, 1,2,3,5-tetraphenylpyrrole: mp 202–204 °C. IR: ν_{max} = 3050, 1600, 1495, 1450, 1370, 1075, 1030, 915, 760, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): = 6.71 (1 H, s, C^4-H), 6.98–6.99 (2 H, m, ArH), 7,03–7.05 (2 H, m, ArH), 7.11–7.26 (16 H, m, ArH). MS: *m*/*z* (%) = 371 (100). Anal. Calcd for $C_{28}H_{21}N$: C, 90.53; H, 5.70; N, 3.77%. Found: C, 90.56; H, 5.59; N, 3.74%. Compound **5a**, 3,5-diphenyl-2-(3′,4′-dimethoxyphenyl)pyrrole: mp 184–185 °C. IR: ν_{max} = 3350, 3030, 1600, 1515, 1495, 1460, 1245, 1220, 1140, 1025, 855, 815, 760, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.66$ (6 H, s, $2 \times CH_3O$), 6.47 (1 H, s,C^4-H), 6.87–7.40 (13 H, m, ArH), 8.43 (1 H, s, NH). MS: *m*/*z* (%) = 355 (100), 340 (22). Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94%. Found: C, 81.28; H, 5.82; N, 3.85%.

(20) X-Ray data for **3g**: $C_{28}H_{19}Cl_2N$; *M* = 440.34, colorless block crystals, $0.54 \times 0.50 \times 0.50$ mm, monoclinic, space group P2$_1$/c, *a* = 9.952 (2), *b* = 9.863 (2), *c* = 23.460 (6) Å, β = 99.62 (2)°, *V* = 2270.4 (9) Å^3, *Z* = 4, *Dc* = 1.288 gcm^{-3}. *F*(000) = 912, μ(MoKα) = 0.301 mm^{-1}. Intensity data were collected on a Siemens P4 diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å), using scan mode with $1.76° < \theta < 25.50°$. 4205 unique reflections were measured and 2267 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and expanded using Fourier techniques. The final refinement was converged to *R* = 0.0387 and *wR* = 0.0793.