Low-valent Titanium Induced Intramolecular Reductive Coupling of Keto-enamines: A Facile Synthesis of 2,3,5-Trisubstituted Pyrroles

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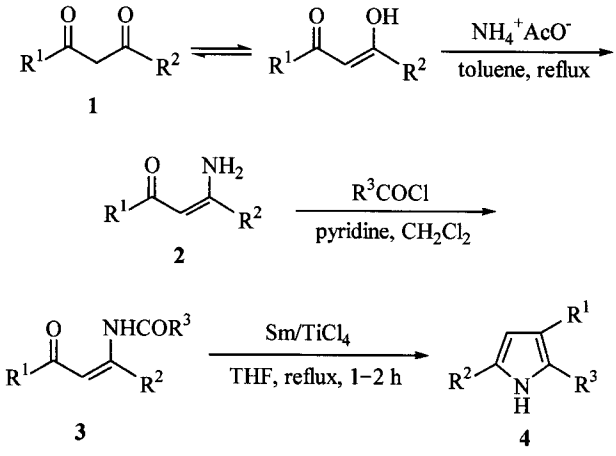
Promoted by low-valent titanium reagent which was generated *in situ* from Sm/$TiCl_4$ system, keto-enamine derivatives underwent efficient intromolecular deoxygenative coupling reactions and afforded the corresponding 2,3,5-trisubstituted pyrroles in moderate to good yields under mild reaction conditions.

Keywords low-valent titanium, metallic samarium, pyrrole, reductive cyclization

The synthesis of pyrroles is an important area of heterocyclic chemistry due primarily to the fact that many pyrroles are subunits of natural products, pharmaceutical agents and polymers.[1] A wide variety of reactions have been reported for the preparation of pyrroles,[2] but most of the available methods lead to pyrroles which are substituted at various positions with functional groups and thus require further synthetic operations to afford simple alkyl or aryl substituted pyrroles. Therefore, the development of novel and convenient synthetic methods for the preparation of pyrrole derivatives still remains an active research area.

Low-valent titanium as reagent combines a high reducing ability with a pronounced oxophilicity. This alliance undoubtedly constitutes the driving force for the reductive coupling of carbonyl compounds to alkenes. Generally referred as the McMurry reaction,[3] this transformation has witnessed its potential in many natural product syntheses, in the formation of strained olefins and in the preparation of cycloalkenes. Recently, the scope of this transformation has been extended beyond aldehydes and ketones as the traditional starting materials by reductively cyclizing amido-enones to substituted pyrrole derivatives,[4] although amides were hitherto considered to be essentially inert towards low-valent titanium.[5] Unfortunately, this process necessitates the using of hazardous compounds such as potassium or potassium-graphite laminate (C_8K) to prepare the active titanium species. What is more, 4 equiv. of titanium reagent relative to the substrates must be employed to obtain the desired products in reasonable yields. Thus, this method seems to be unsuitable for an up-scaling process. In our previous work, we found that low-valent titanium reagent could be prepared from Cp_2TiCl_2-Sm[6] or $TiCl_4$-Sm[7] system and the low-valent titanium reagent so formed has been successfully used in various reductive coupling processes. Herein we wish to report that low-valent titanium reagent prepared from metallic samarium and $TiCl_4$ can efficiently promote readily accessible amido-enones to undergo intramolecular reductive cyclization to give 2,3,5-trisubstituted pyrrole derivatives in moderate to good yields under mild reaction conditions. The reaction was shown in Scheme 1.

Scheme 1



When 1 mmol of 2-benzamido-4-phenyl-2-buten-4-one (**3a**) was treated with 2 equiv. of low-valent titanium reagent derived from 0.30 g of metallic samarium and 0.22 mL $TiCl_4$ under reflux in THF, the deep dark color of the solution changed into a brownish red gradually. The result of TLC showed that **3a** was consumed within 1 h. Subsequent handling of the reaction mixture gave 2,3-diphenyl-5-methylpyrrole (**4a**) in 78% yield, the structure of which was unam-

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biguously assigned based on its spectral data (IR, ^{1}H NMR, MS and elemental analysis). Several other substrates were also treated with our $TiCl_4$-Sm system. The results are listed in Table 1.

From Table 1, it was found that Sm/$TiCl_4$ system can efficiently promote the reductive cyclization of keto-enamines to give pyrroles with different substitution patterns. In particular the substituent at C-2 on the newly formed heteroarene ring can be easily varied by acylating a parent keto-enamine with different aroyl chlorides. Unfortunately, when 2-acetamido-4-phenyl-2-buten-4-one (**3g**, Entry 7, Table 1), which was prepared from acetyl chloride and the corresponding keto-emamine, was treated with Sm/$TiCl_4$ under reflux for 4 h, no reaction took place and only the starting material was recovered. In order to investigate the scope of this reductive coupling process further, substrates **3h** and **3i** (Entries 8 and 9, Table 1) were also prepared and treated with the Sm/$TiCl_4$ system and it has been demonstrated that they failed to give the desired pyrrole products. It seems that both R^1 and R^3 should be aryl groups; otherwise, the reductive coupling process could not take place. The inertness of these three substrates toward our Sm/$TiCl_4$ system may be due to the instability of the possibly formed ketyl intermediate resulting from an acetyl. Certainly, more works should be done to clarify the detailed mechanism of this reductive coupling process.

It is also worth noting that in contrast with the method reported in the literature,[4] in which 4 equiv. of titanium relative to the substrates should be employed, only 2 equiv. of titanium is enough to push the reductive cyclization process to be completed in our process. Furthermore, the use of hazardous compounds such as potassium or potassium-graphite laminate (C_8K) to prepare the active titanium species is also avoided. All these features make our process more economical and environmentally benign, thus more practical for an up-scaling process.

In addition, the results in Table 1 also showed that both keto-enamines bearing electron donating groups (4-Me and 4-OMe, Entries 2 and 3, Table 1) and keto-enamines bearing electron withdrawing groups (4-Cl and 4-F, Entries 4 and 5, Table 1) underwent smooth reduction under the same reaction conditions. No substituent effect and the chemo-selectivity in those reducible groups, such as chloro, fluoro groups, was observed. Thus it is suggested that this method may afford a general method for the preparation of 2, 3, 5-trisubstituted pyrroles bearing various substituents on the aryl rings.

In summary, with its mildness, convenience and environmental benignancy, the method presented above may be used as an attractive alternative to the previously reported methods for the preparation of pyrrole derivatives. Further work to clarify the mechanism of this process and to find other new uses of Sm/$TiCl_4$ system in the synthesis of heterocyclic compounds are now in progress in our laboratory.

Experimental

Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately prior to use. Metallic samarium and $TiCl_4$ solution were purchased and used as received. Enaminones (**2**) and substrates **3a**—**3i** were prepared as depicted in Scheme 1 according to the literature.[8,9]

Melting points were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer with absorption in cm^{-1}. ^{1}H NMR spectra were determined on a Bruker AC-400 spectrometer as $CDCl_3$ solutions. Chemical shifts were downfield from the internal standard tetramethylsilane. Mass spectra were recorded on an HP 5989B mass spectrometer. Elemental analyses were carried out on a Carlo-Erba EA 1110 instrument.

General procedure for the preparation of 2,3,5-trisubstituted pyrroles

Under anhydrous conditions, titanium tetrachloride (0.22 mL, 2 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.30 g, 2 mmol) in THF (15 mL) at room temperature under a nitrogen atmosphere. After the completion of addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to room temperature and a solution of substrates **3** (1 mmol) in anhydrous THF (2 mL) was added via a syringe. The mixture was refluxed for 1 h, and the deep dark color of the solution changed into a brownish

Table 1 Preparation of 2,3,5-trisubstituted pyrroles through low-valent titanium induced intramolecular reductive coupling of keto-enamines

Entry	Substrate	R^1	R^2	R^3	Reaction time (h)	Product	Yield[a] (%)
1	**3a**	C_6H_5	CH_3	C_6H_5	1	**4a**	78
2	**3b**	C_6H_5	CH_3	4-$CH_3C_6H_4$	1	**4b**	75
3	**3c**	C_6H_5	CH_3	4-$CH_3OC_6H_4$	1	**4c**	66
4	**3d**	C_6H_5	CH_3	4-ClC_6H_4	1	**4d**	82
5	**3e**	C_6H_5	CH_3	4-FC_6H_4	1	**4e**	83
6	**3f**	C_6H_5	C_6H_5	C_6H_5	1	**4f**	79
7	**3g**	C_6H_5	CH_3	CH_3	4	—	—
8	**3h**	CH_3	CH_3	C_6H_5	4	—	—
9	**3i**	CH_3	CH_3	CH_3	4	—	—

[a] Isolated yields based on keto-enamines.

red gradually. After completion (the reaction was monitored by TLC), the reaction was quenched with dilute HCl and extracted with ether (3 × 20 mL). The combined extract was washed with saturated brine (15 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the resulting crude product was purified by preparative TLC using ethyl acetate and cyclohexane (1:6) as eluant.

2,3-*Diphenyl*-5-*methylpyrrole* (**4a**) Syrup, IR (film) ν: 3416 (NH), 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H, CH_3), 6.07 (s, 1H), 7.17—7.35 (m, 10H), 8.05 (s, br, 1H); MS *m/z* (%): 233 (M^+, 100). Anal. calcd for $C_{17}H_{15}N$: C 87.52, H 6.48, N 6.00; found C 87.67, H 6.36, N 6.05.

2-(4-*Methylphenyl*)-3-*phenyl*-5-*methylpyrrole* (**4b**) Syrup, IR (film) ν: 3417 (NH), 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 6.07 (s, 1H), 7.15—7.35 (m, 9H), 8.00 (s, br, 1H); MS *m/z* (%): 247 (M^+, 100). Anal. calcd for $C_{18}H_{17}N$: C 87.41, H 6.93, N 5.66; found C 87.55, H 6.83, N 5.62.

2-(4-*Methoxyphenyl*)-3-*phenyl*-5-*methylpyrrole* (**4c**) Syrup, IR (film) ν: 3416 (NH), 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 6.04 (s, 1H), 7.16—7.30 (m, 9H), 7.96 (s, br, 1H); MS *m/z* (%): 263 (M^+, 100). Anal. calcd for $C_{18}H_{17}NO$: C 82.10, H 6.51, N 5.32; found C 82.24, H 6.40, N 5.38.

2-(4-*Chlorophenyl*)-3-*phenyl*-5-*methylpyrrole* (**4d**) Syrup, IR (film) ν: 3410 (NH), 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H, CH_3), 6.03 (s, 1H), 7.16—7.31 (m, 9H), 8.08 (s, br, 1H); MS *m/z* (%): 267 (M^+, 100). Anal. calcd for $C_{17}H_{14}ClN$: C 76.26, H 5.27, N 5.23; found C 76.24, H 5.25, N 5.22.

2-(4-*Fluorophenyl*)-3-*phenyl*-5-*methylpyrrole* (**4e**) Syrup, IR (film) ν: 3406 (NH), 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 6.14 (s, 1H), 6.99—7.03 (m, 2H), 7.20—7.39 (m, 7H), 8.14 (s, br, 1H); MS *m/z* (%): 251 (M^+, 100). Anal. calcd for $C_{17}H_{14}FN$: C 81.25, H 5.62, N 5.57; found C 81.34, H 5.55, N 5.52.

2,3,5-*Triphenylpyrrole* (**4f**) Crystal, m.p. 133—135 ℃ (lit.[4] 135—137 ℃); IR (KBr) ν: 3413 (NH), 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.58 (s, 1H), 7.16—7.38 (m, 13H), 7.50 (d, 2H, J = 8.0 Hz), 8.28 (s, br, 1H); MS *m/z* (%): 295 (M^+, 100).

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