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**Synthesis of N-substituted 2-arylpyrroles by the reaction of (η²-imine)titanium complexes with 3,3-diethoxypropyne**

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Synthesis of N-substituted 2-arylpyrroles by the reaction of \((\eta^2\text{-imine})\text{titanium complexes with 3,3-diethoxypropyne}\)

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Abstract—\((\eta^2\text{-Imine})\text{Ti(O-Pr)}_2\) complexes generated from arylaldehyde imines and a divalent titanium reagent, \(\text{Ti(O-Pr)}_4/2\text{-PrMgCl}\), reacted with 3,3-diethoxypropyne to afford 2-arylpyrroles. © 2011 Elsevier Science. All rights reserved

We have reported that \((\eta^2\text{-imine})\text{Ti(O-Pr)}_2\) complexes (3) generated from arylaldehyde imines 2 and a divalent titanium reagent, \(\text{Ti(O-Pr)}_4/2\text{-PrMgCl}\) (1), reacted with 1-alkynes or propargyl alcohol derivatives to provide \(\alpha\)-aryl allylamines 4 and \(\alpha\)-allenylamines 5, respectively (Scheme 1).  

\[ 
\begin{align*}
\text{R'} & \quad \text{H}^+ \\
\text{N} & \quad \text{R} \\
\text{Til}_2 & \quad \text{Ar} \\
\text{Ar} & \quad \text{1} \\
\text{R} & \quad \text{2} \\
\text{2} & \quad \text{3} \\
\text{L} = \text{O-Pr} \\
\end{align*}
\]

Scheme 1. Formation of azatitanacyclopropanes 3 from 1 and 2 and their reactions with alkynes.

Based on these results, we planned and investigated synthesis of pyrroles 6 as illustrated in Scheme 2, assuming that allenyamines 8 having a leaving group X might be obtained by the reaction of 2 with a propargylic compound 7 with two leaving groups at the propargyl position and the cyclization of the resulting 8 would provide 6 by elimination of HX.

Since substituted pyrroles are of importance in synthesis of natural and artificial biologically active compounds, numerous methods for their synthesis have been developed, and recently metal-mediated and –catalyzed approaches have been focused on. The 2-arylpyrrole nucleus such as 6 is widely distributed in many natural and artificial biologically important compounds such as pentalenopseudalin and selective COX-2 inhibitors, and also attracts interest as a substructure of organic electronic materials.  

\[ 
\begin{align*}
\text{X} & \quad \text{R} \\
\text{N} & \quad \text{H} \\
\text{Ar} & \quad \text{8} \\
\end{align*}
\]

Scheme 2. Synthetic plan for pyrroles 6 from azatitanacyclopropanes 3.

According to the plan mentioned above, we chose commercially available 3,3-diethoxypropyne as 7 and tried to prepare 8. Thus, the imine 2a, derived from benzaldehyde and benzylamine, was treated with a divalent

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titanium reagent 1 (1.5 equiv) at −40 °C for 1.5 h to produce the corresponding (η2-imine)Ti(O-i-Pr) complexes in situ. To this was added 3,3-diethoxypropyne (2.0 equiv) at −40 °C and the mixture was gradually warmed to room temperature over 3 h. Aqueous work-up and concentration of the resulting mixture did not yield the corresponding allenylamine 8 but, interestingly, the procedure gave 2-arylpyrroles 6a in 74% isolated yield after column chromatography (Scheme 3). The direct formation of 6a can be explained by assuming that the allenylamine 8 was unstable and could easily cyclize and eliminate an ethoxy group from the resulting pyrrole 10 during the work-up.

Another possible pathway may involve intramolecular aminotitanation of 9 to 11, which can be protonated to give 10 and/or eliminate EtOH to generate titanated pyrrole 12 (Scheme 3). To confirm this possibility, we carried out the following reactions (Scheme 4). Thus, the addition of $^2$H2O to the reaction mixture of 1, 2a and 3,3-diethoxypropyne afforded deuterated pyrrole $^2$H-6a with 24% $^2$H-incorporation at the C-4 position. Meanwhile, the reaction of deuterated imine $^2$H-2a (98% $^2$H-incorporation) provided 6a with 46% or 73% $^2$H-incorporation after quenching with H2O or $^2$H2O, respectively. These results might indicate generation of the metalated pyrrole of the type 12, however, its formation may be incomplete and the compound of the type 9 may remain. It can be assumed that ethoxypyrrroles such as 10 and 11 are unstable and quickly eliminate EtOH to provide the corresponding pyrroles 6a and 12, respectively. Generated 12 could be protonated in situ by eliminated EtOH or EtO2H to give 6a and $^2$H-6a, respectively, but the protonation may occur partially because EtOH or EtO2H can competitively react in situ with other compound(s) having a metal-carbon bond(s) such as Ti-C and Mg-C. The reason for the incomplete conversion of 9 to 12 is unclear at this time.

Next, we applied the method to one-pot synthesis of 6 from aldehyde and amine. Thus, the imine 2 was prepared from the corresponding arylaldehyde (1.0 mmol) and amine (1.0 mmol) in situ by dehydrative condensation and then sequentially treated with 1 (1.5 mmol) and 3,3-diethoxypropyne (2.0 mmol). Figure 1 shows the yield of 6 synthesized by this one-pot procedure. As revealed from the results, a variety of 2-arylpyrroles could be synthesized in moderate to good yield, where a functional group such as bromo and trifluoromethyl moieties tolerated the reaction conditions. Substituted and unsubstituted phenyl-pyrroles as well as 2-furyl- and -naphthyl-pyrroles could also be prepared. Regarding the N-substituent, a variety of alkyl groups such as n-propyl, i-propyl, benzyl, p-methoxybenzyl, and 2-methoxyethyl moieties afforded the corresponding pyrroles, albeit 6g was obtained in poor yield due to low solubility of the corresponding imine intermediate in the solvent (ether).

The results shown in Scheme 5 indicate the limitation of the present method: the method is restricted to the preparation of N-alkyl-2-arylpyrroles. Thus, the reaction of 2k and 2l gave low yield or a trace amount of the corresponding 6k and 6l, respectively. An attempt to synthesize 3-substituted pyroles such as 6m using 13 instead of 3,3-diethoxypropyne also failed, where dibenzylamine, reduction product of 2a, was obtained as a major product.

In summary, we developed a one-pot, convergent method for preparing N-alkyl-substituted 2-arylpyrroles 6 from three components of arylaldehydes, primary alkylamines and commercially available 3,3-diethoxypropyne. The results of the reactions with $^2$H-2a and/or quenching with $^2$H2O pointed out the formation of metalated pyrroline and/or pyrrole of the type 11 and 12 through an intramolecular aminotitanation of a titanium amide 9.

Scheme 3. Synthesis of pyrrole 6a from imine 2a and its proposed mechanism.

Scheme 4. Reaction of $^2$H-2a with 1 and 3,3-diethoxypropyne.
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Acknowledgments

References and Notes


7. 2H-2a was prepared according to the procedure illustrated in the following scheme:

8. Typical procedure: A mixture of benzaldehyde (0.101 mL, 1.0 mmol), benzylamine (0.109 mL, 1.0 mmol) and THF (5 mL) was stirred for 2 h at room temperature and then concentrated in vacuo. To this was added THF (5 mL) and the mixture was concentrated under reduced pressure for azeotropical removal of water. After purging the flask with argon gas, to this were added ether (8 mL) and Ti(O-i-Pr)4 (446 µL, 1.5 mmol). To this solution was added i-PrMgCl (3.95 mL, 0.76 M in ether, 3.0 mmol) at -40 °C. After being stirred for 1.5 h at -40 °C, 3,3-diethoxypropyne (0.29 mL, 2.0 mmol) was added and the mixture was gradually warmed to room temperature over 3 h. After addition of aqueous saturated NaHCO3 (0.2 mL), NaF (~1 g) and Celite (~1 g), the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and chromatographed on silica gel to give 1a (158 mg) in 68% yield.

9. Reductive homocoupling product from 2k and benzyl[1-isopropyl]butylamine from 2l were produced as major products.

10. 1H NMR data (in CDCl3) of 6a: (500 MHz) δ 5.17 (s, 2H), 6.30 (d, J = 2.3 Hz, 2H), 6.76 (t, J = 2.4 Hz, 1H), 7.02-7.07 (m, 2H), 7.25-7.37 (m, 8H). 6b: (300 MHz) δ 5.14 (s, 2H), 6.29-6.31 (m, 2H), 6.78-6.80 (m, 1H), 7.0-7.49 (m, 9H). 6c: (500 MHz) δ 0.81 (t, J = 7.5 Hz, 3H), 1.62-1.69 (m, 2H), 3.87 (t, J = 6.5 Hz, 2H), 6.16-6.19 (m, 2H), 7.6 (d, J = 2.3 Hz, 1H), 7.25 (d, J = 7.3 Hz, 2H), 7.51 (d, J = 7.3 Hz, 2H). 6d: (300 MHz) δ 3.64 (s, 3H), 3.89 (s, 3H), 5.15 (s, 1H), 6.26 (dd, 2H, J = 9.0 Hz).

gg
$J = 1.8, 3.6 \text{ Hz, 1H}$, 6.30 (dd, $J = 2.7, 3.6 \text{ Hz, 1H}$), 6.76-7.36 (m, 9H). 6e: (270 MHz) δ 3.84 (s, 3H), 3.92 (s, 3H), 5.51 (s, 1H), 6.86 (d, $J = 1.8 \text{ Hz, 1H}$), 7.34-7.46 (m, 17H). 6f: (300 MHz) δ 5.19 (s, 1H), 6.33 (dd, $J = 2.7, 3.6 \text{ Hz, 1H}$), 6.38 (dd, $J = 2.1, 3.6 \text{ Hz, 1H}$), 6.83 (dd, $J = 1.8, 2.7 \text{ Hz, 1H}$), 7.05-7.10 (m, 2H), 7.25-7.36 (m, 3H), 7.44 (d, $J = 7.8 \text{ Hz, 2H}$), 7.59 (d, $J = 7.8 \text{ Hz, 2H}$). 6g: (270 MHz) δ 3.52 (s, 3H), 3.51 (m, 4H), 6.21 (m, 2H), 6.83 (dd, $J = 1.8, 2.7 \text{ Hz, 1H}$), 7.44 (d, $J = 7.8 \text{ Hz, 2H}$), 7.59 (d, $J = 7.8 \text{ Hz, 2H}$). 6h: (300 MHz) δ 3.52 (s, 3H), 3.51 (m, 4H), 6.21 (m, 2H), 6.83 (dd, $J = 1.8, 2.7 \text{ Hz, 1H}$), 7.44 (d, $J = 7.8 \text{ Hz, 2H}$), 7.59 (d, $J = 7.8 \text{ Hz, 2H}$), 7.05-7.10 (m, 2H), 7.25-7.36 (m, 3H), 7.38 (d, $J = 7.8 \text{ Hz, 2H}$), 7.75-7.90 (m, 3H).