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

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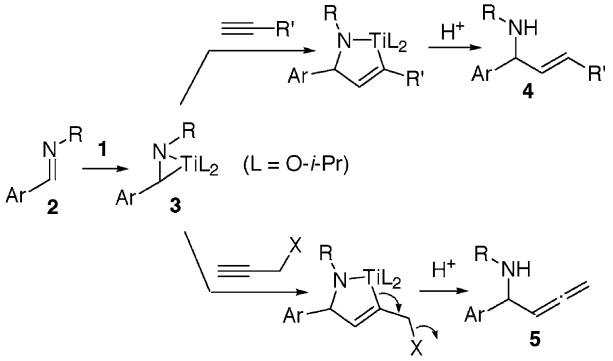
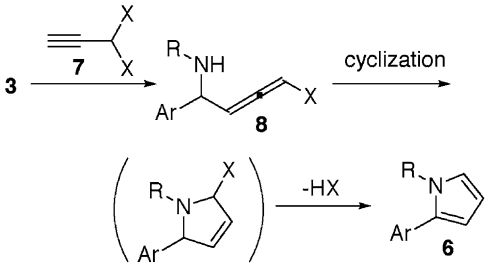
Abstract—(η^2-Imine)Ti(O-*i*-Pr)$_2$ complexes generated from arylaldehyde imines and a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, reacted with 3,3-diethoxypropyne to afford 2-arylpyrroles.

We have reported that (η^2-imine)Ti(O-*i*-Pr)$_2$ complexes (**3**) generated from arylaldehyde imines **2** and a divalent titanium reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl (**1**),[1] reacted with 1-alkynes or propargyl alcohol derivatives to provide α-aryl allylamines **4** and α-allenylamines **5**, respectively (Scheme 1).[2]

Based on these results, we planned and investigated synthesis of pyrroles **6** as illustrated in Scheme 2, assuming that allenylamines **8** having a leaving group X might be obtained by the reaction of **3** 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.



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



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

Since substituted pyrroles are of importance in the synthesis of natural and artificially biologically active compounds, numerous methods for their synthesis have been developed, and recently metal-mediated and-catalyzed approaches have been focused on.[3] The 2-arylpyrrole nucleus such as **6** is widely distributed in many natural[4] and artificially[5] biologically important compounds such as pentabromopseudilin and selective COX-2 inhibitors, and also attracts interest as a substructure of organic electronic materials.[6]

According to the plan mentioned above, we chose commercially available 3,3-diethoxypropyne as **7** and tried

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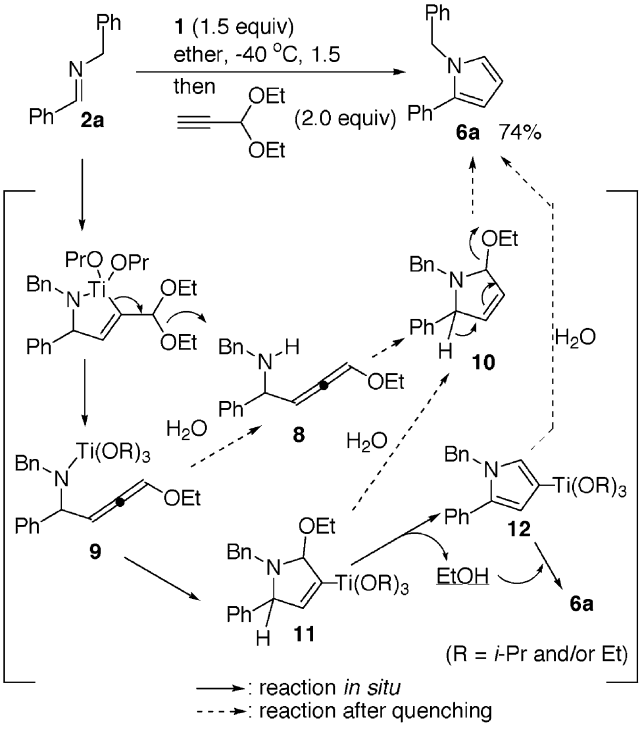
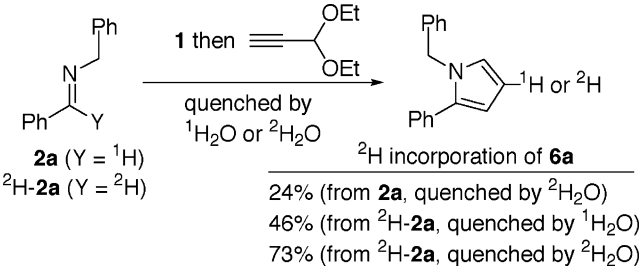
to prepare **8**. Thus, the imine **2a**, derived from benzaldehyde and benzylamine, was treated with a divalent titanium reagent **1** (1.5 equiv) at −40 °C for 1.5 h to produce the corresponding (η^2-imine)Ti(O-*i*-Pr)$_2$ complexes in situ. To this was added 3,3-diethoxypropyne (2.0 equiv) at −40 °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 pyrroline **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,



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.

the addition of ^2H_2O 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**[7] (>98% ^{2}H-incorporation) provided **6a** with 46% or 73% ^{2}H-incorporation after quenching with H_2O or ^2H_2O, 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 ethoxypyrrolines 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 EtO^{2}H to give **6a** and ^{2}H-**6a**, respectively, but the protonation may occur partially because EtOH or EtO^{2}H 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.[8] 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

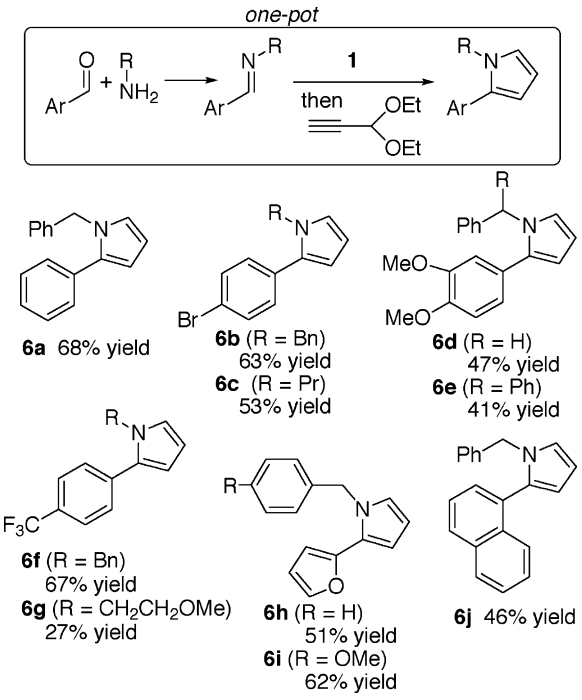
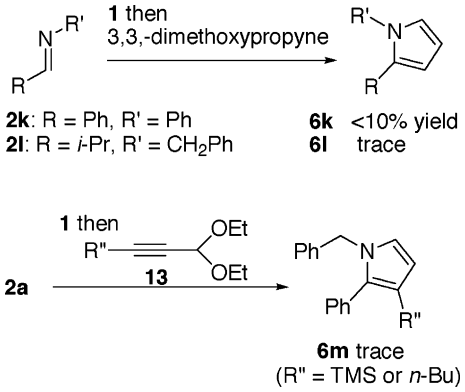


Figure 1. Yield of **6** prepared from arylaldehyde, amine and 3,3-diethoxypropyne by one-pot method.



Scheme 5. Limitations of the present pyrrole synthesis.

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.[9] An attempt to synthesize 3-susbstituted pyrroles 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**[10] from three components of arylaldehydes, primary alkylamines and commercially available 3,3-diethoxypropyne.[11] The results of the reactions with ^{2}H-**2a** and/or quenching with $^{2}H_2O$ pointed out the formation of metalated pyrroline and/or pyrrole of the types **11** and **12** through an intramolecular aminotitanation of a titanium amide **9**.

Acknowledgements

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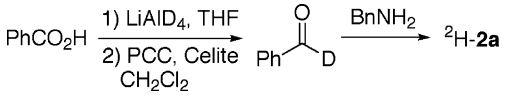
7. ^{2}H-**2a** was prepared according to the procedure illustrated in the following scheme:



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 $NaHCO_3$ (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-isopropylbutyl)amine from **2l** were produced as a major product.[2a]
10. ^{1}H NMR data (in $CDCl_3$) of **6**. Compound **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). Compound **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). Compound **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), 6.76 (d, $J = 2.3$ Hz, 1H), 7.25 (d, $J = 7.3$ Hz, 2H), 7.51 (d, $J = 7.3$ Hz, 2H). Compound **6d**: (300 MHz): δ 3.64 (s, 3H), 3.89 (s, 3H), 5.15 (s, 2H), 6.26 (dd, $J = 1.8$, 3.6 Hz, 1H), 6.30 (dd, $J = 2.7$, 3.6 Hz, 1H), 6.76–7.36 (m, 9H). Compound **6e**: (270 MHz): δ 3.84 (s, 3H), 3.92 (s, 3H), 5.51 (s, 1H), 6.86 (d, $J = 1.8$ Hz, 1H), 7.34–7.46 (m, 17H). Compound **6f**: (300 MHz): δ 5.19 (s, 1H), 6.33 (dd,

$J = 2.7$, 3.6 Hz, 1H), 6.38 (dd, $J = 2.1$, 3.6 Hz, 1H), 6.83 (dd, $J = 1.8$, 2.7 Hz, 1H), 7.05–7.10 (m, 2H), 7.25–7.36 (m, 3H), 7.44 (d, $J = 7.8$ Hz, 2H), 7.59 (d, $J = 7.8$ Hz, 2H). Compound **6g**: (270 MHz): δ 3.52 (s, 3H), 3.51 (m, 4H), 6.21 (m, 2H), 6.83 (dd, $J = 1.8$, 2.7 Hz, 1H), 7.44 (d, $J = 7.8$ Hz, 2H), 7.59 (d, $J = 7.8$ Hz, 2H). Compound **6h**: (300 MHz): δ 5.29 (s, 2H), 6.19 (d, $J = 3.3$ Hz, 1H), 6.24 (dd, $J = 2.7$, 3.6 Hz, 1H), 6.36 (dd, $J = 1.8$, 3.3 Hz, 1H), 6.48 (dd, $J = 1.8$, 3.9 Hz, 1H), 6.73 (dd, $J = 1.8$, 2.7 Hz, 1H), 7.03–7.34 (m, 5H), 7.38 (dd, $J = 0.6$, 2.4 Hz, 1H). Compound **6i**: (500 MHz): δ 3.77 (s, 3H), 5.21 (s, 2H), 6.21–6.22 (m, 2H), 6.37 (d, $J = 1.7$ Hz, 1H), 6.48 (d, $J = 1.8$ Hz, 1H), 6.70 (t, $J = 1.8$ Hz, 1H), 6.83 (d, $J = 7.1$ Hz, 2H), 7.01 (d, $J = 8.3$ Hz, 2H), 7.40 (d, $J =$ 1.2 Hz, 1H). Compound **6j**: (300 MHz): δ 4.86 (s, 2H), 6.31 (dd, $J = 1.8$, 3.6 Hz, 1H), 6.37 (dd, $J = 2.7$, 3.6 Hz, 1H), 6.83–6.88 (m, 3H), 7.14–7.21 (m, 3H), 7.35–7.52 (m, 4H), 7.75–7.90 (m, 3H).

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