Two Titanium-Catalyzed Reaction Sequences for Syntheses of Pyrroles from \((E/Z)\)-Chloroenynes or \(\alpha\)-Haloalkynols

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Biological Importance of Pyrroles

Pharmaceuticals:
- Lipitor is the largest selling drug in the world (2006 $12.9 billion)

Biology:
- Porphyrins (Heme, Chlorophyl, and Vitamin B$_{12}$)

Hemoproteins:
- transport diatomic gases
- chemical catalysis
- diatomic gas detection
- electron transfer

Chlorophyl:
- vital to photosynthesis

Material Science:
- Polypyrrole
  - fast-charging and discharging batteries
  - bio-sensors for metals (such as Li)

http://www.greencarcongress.com/2006/09/brown_universit.html#more
History of Pyrrole

- 1834, Runge noted that a component of coal tar and bone oil imparted a red color to pine splinters which had been moistened with mineral acid, naming the compound pyrrole (from the Greek meaning red oil)

- 1857, Anderson isolates the pure compound via distillation of bone oil

- 1870, Beyer determines its structural formula

- 1884, Paal and Knorr almost simultaneously report synthesis of pyrrole from 1,4-diketones

- Useful nomenclature

Classical Syntheses

- **Paal-Knorr Pyrrole Synthesis (1884)**

  ![Paal-Knorr Pyrrole Synthesis Diagram](image)

- **Knorr Synthesis (1886)**

  ![Knorr Synthesis Diagram](image)

- **Hantzsch Pyrrole Synthesis (1890)**

  ![Hantzsch Pyrrole Synthesis Diagram](image)
T.M. Catalyzed C-N Bond Formation


Toste, *JACS.*, 2005, 127, 11260-11261
Previous Work

-Pitfalls:
1) requires diastereomerically pure (Z)-iodo or (Z)-bromo enynes
2) requires less basic N-nucleophile Boc-NH$_2$ or Boc-NH-NH-Boc

Buchwald, ACIE, 2006, 45, 7079-7082
Optimization

\[ \text{Cl} \quad \text{Hex} + \quad \text{NH}_2 \quad [\text{Ti}] \quad (20 \text{ mol } \%) \quad \xrightarrow{\text{PhMe}} \quad \text{Hex} \quad \text{P-Tol} \]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Diastereomer} & [\text{Ti}] & T \quad (^\circ \text{C}) & \text{Yield} \quad (%) \\
\hline
Z & \text{TiCl}_4/\text{t-BuNH}_2 & 105 & 80 \\
E & \text{TiCl}_4/\text{t-BuNH}_2 & 105 & 83 \\
E/Z & \text{TiCl}_4/\text{t-BuNH}_2 & 105 & 86 \\
E/Z & \text{TiCl}_4 & 105 & 22 \\
E/Z & \text{Ti(NMe}_2)_4 & 105 & 82 \\
E/Z & & 105 & \\
E/Z & \text{TiCl}_4/\text{t-BuNH}_2 & 80 & 84 \\
E/Z & \text{TiCl}_4/\text{t-BuNH}_2 & 25 & \\
\hline
\end{array}
\]
New Reactions

Removes need for diastereomerically pure starting material, expands scope of Nitrogen substitution to include more basic N-nucleophiles allowing for the use of chlorine.

Allows for readily accessible starting material and a one-pot procedure, utilizing TiCl₄ as both a dehydrating agent as well as a catalyst in the hydroamination.
Scope

\[ \text{Cl} \quad \text{C} = \text{C} \quad R^1 \]

+ \[ \text{NH}_2 \quad R^2 \]

\[ \text{TiCl}_4 \text{ (20 mol %)} \]

t-BuNH\_2, PhMe

105º C, 18 hr

\[ \rightarrow \]

\[ \text{R}^1 \quad \text{N} \quad \text{R}^2 \]

1) TiCl\_4, t-BuNH\_2, PhMe, 105º C, 24 hr

2) AcCl, TiCl\_4

\[ \rightarrow \]

\[ \text{Ac} \quad \text{R}^1 \quad \text{N} \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^4 \]

Bu

86%

p-Tol

71%

Hex

76%

Mes

39%

Bu

63%

Bu

87%

Bu

51%

Bu

51%

Bu

59%

Ac

81%

Ac

65%

Ac

49%

Ac

59%

Ac

65%

Ac

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Ac

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Ac

49%
Conclusions

- Efficient one-pot pyrrole synthesis through a reaction sequence of dehydration, intermolecular hydroamination, [1,5]H sigmatropic shift, and an intramolecular nucleophilic substitution.

- Providing access to di-, tri-, tetra-, and pentasubstituted pyrroles in a highly modular, yet regioselective, fashion

- Improved scope over previous methodology to included more basic $N$-nucleophiles, allowing for the use of chlorides

- Utilizes readily accessible starting materials and an inexpensive catalyst