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Titanium-Mediated Cross-Coupling Reactions of 1,3-Butadiynes with α-Iminonitriles to 3-Aminopyrroles: Observation of an Imino Aza-Nazarov Cyclization

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Abstract: Ti(OiPr)₄/2 nBuLi-mediated highly efficient cross-coupling reactions of 1,3-butadiynes with α-iminonitriles are described. The method provides a convenient access to functionalized 3-aminopyrroles with a wide diversity of substituents in a highly regioselective manner. When optically pure α-iminonitrile is employed in this reaction, chiral pyrrole derivative is obtained without loss of the enantiopurity. Mechanistic study indicates that the 3-aminopyrroles are formed upon treatment of the crude hydrolysis products with silica gel or Lewis acid. A novel imino aza-Nazarov cyclization reaction is proposed to account for the formation of the pyrrole products. Employing titanium-monoyne complex in this reaction resulted in the homo-coupling of α-iminonitriles, leading to the formation of 1,2-diimines.

3-Aminopyrroles are found in a variety of biologically active substances or natural
products,\(^1\) and are also useful building blocks in synthetic chemistry.\(^2\) For example, as shown in Figure 1, natural products such as distamycin and netropsin with 3-aminopyrrole skeletons are well-known DNA-minor groove binding agents with strong preference for adenine/thymine-rich sequences.\(^3\) The 3-aminopyrrole alkaloid solsodomine A, isolated from the fresh berries of solanum sodomaeum L., shows activity against *Mycobacterium intracellulare*.\(^4\) 3-Aminopyrrole-2-carboxylates, such as “a”, is identified as a common pharmacophore which exhibits potent anticonvulsant activity by blocking sodium channels in a frequency-dependent manner.\(^5\) Although a large number of pyrrole syntheses have been reported in recent years, the efficient synthetic routes to 3-aminopyroles are quite limited.\(^6-9\) General synthetic methods include: functional group transformation of pyrrole derivatives such as 3-nitropyrrle,\(^6a-d\) 3-arylazopyrroles,\(^6e\) pyrrol-3-carboxylic acids\(^6f\) etc.,\(^7\)

\[\text{Figure 1. Representative examples of bioactive 3-aminopyrrole derivatives}\]
intramolecular cyclization of enaminonitrile derivatives\textsuperscript{8} such as Thorpe-Ziegler type cyclization\textsuperscript{8e-j} etc.\textsuperscript{9} However, these methods usually restrict to special substituted substrates. Thus, the development of new methodologies using readily available starting materials is highly desired. On the other hand, titanium-mediated cross-coupling reactions have been proved to be highly efficient for the construction of carbon-carbon or carbon-heteroatom bonds, and the thus generated titanacycles are important intermediates for further selective transformations.\textsuperscript{10} During our continued studies on the chemistry of titanium-butadiyne complexes,\textsuperscript{11} we have developed the coupling reactions of titanium-butadiyne complexes with aldehydes or ketones, leading to the selective synthesis of stereodefined \textit{trans}-enynols\textsuperscript{11a} or trisubstituted [3]cumuleno\textsubscript{ls}.\textsuperscript{11b} Inspired by these results, we are next interested in the potential coupling reactions of titanium-butadiyne complexes with functionalized nitriles. In this paper, we report titanium-mediated cross-coupling reactions of 1,3-butadiynes with \(\alpha\)-iminonitriles, which provide a convenient one-pot synthesis of functionalized 3-aminopyrroles upon treatment of the crude hydrolysis products with silica gel or Lewis acid (Scheme 1). Interestingly, 3-aminopyrroles were formed likely via a rare imino aza-Nazarov cyclization of the diimines produced by hydrolysis of the \textit{in situ} generated azatitanacycles.

\textbf{Scheme 1}

\[ R^1 = \text{silyl, aryl, alkyl}; R^2, R^3 = \text{aryl or alkyl} \]
The reactivity of nitriles with group 4 metal complexes has been intensively studied during the last decades, in which C≡N insertion into a metal-carbon bond\textsuperscript{12} or a heterobimetallic complex,\textsuperscript{13} and formation of metal-keteniminate species\textsuperscript{14} have been observed. However, so far only one report by Sato \textit{et al.} related to titanium-mediated cross-coupling reactions of nitriles (restrict to $\alpha$-heterofunctionalized nitriles) with alkynes is precededent.\textsuperscript{15} They demonstrated that azatitanacyclopentadienes formed by cross-coupling reactions of alkynes with $\alpha$-methoxyacetonitriles could react with aldehydes, sulfonylacetylenes or second $\alpha$-methoxyacetonitrile to afford furans, pyridines and pyrroles, respectively.\textsuperscript{15} The $\alpha$-iminonitriles (imidoyl cyanides) are important synthetic precursors for the synthesis of $\alpha$-keto acids, diimines, amides, amidines \textit{etc.},\textsuperscript{16} and also serve as effective components in various cycloaddition reactions.\textsuperscript{17} Due to the enhanced reactivities of C=N and C≡N bond, both of these two unsaturated moieties in $\alpha$-iminonitriles might couple with alkynes in the presence of low-valent titanium species. We are therefore quite interested in exploring new reaction patterns using these substrates. $\alpha$-Iminonitriles can be readily prepared by the following two methods (Scheme 2): IBX/TBAB-mediated oxidative Strecker reaction (method a)\textsuperscript{18} and the reactions of imidoyl chlorides with CuCN (method b). Initially, we investigated the titanium-mediated coupling reactions of 1,4-bis(\textit{tert}-butyldimethylsilyl)buta-1,3-diyne 1\textit{a} with (Z)-N-(4-methoxyphenyl)benzimidoyl cyanide 3\textit{a}. The results are shown in Table 1. Based on our previous studies,\textsuperscript{11} titanium-butadiyne complex 2\textit{a} (also referred to as alkynyltitanacyclocpropene) was prepared \textit{in situ} by the reaction of diyne 1\textit{a} with 1.3 equiv of Ti(O\textit{Pr})\textsubscript{4}/2 $\textit{n}$BuLi reagent in THF. Addition of 1.1 equiv of 3\textit{a} to the mixture containing
Scheme 2

method a:

\[ \text{R}^1\text{CHO} + \text{R}^2\text{NH}_2 + \text{TMSCN} \rightarrow \begin{array}{c}
\text{cat. I}_2 \\
\text{IBX/TBAB}
\end{array} \begin{array}{c}
\text{CH}_3\text{CN}, \text{rt} \\
\text{Ref. 18}
\end{array} \xrightarrow{\text{3}} \begin{array}{c}
\text{R}^1\text{CN} \\
\text{N-R}^2
\end{array} \]

method b:

\[ \begin{array}{c}
\text{R}^1\text{CN} \\
\text{O}
\end{array} \xrightarrow{\text{SOCl}_2, \text{reflux}} \begin{array}{c}
\text{R}^1\text{Cl} \\
\text{N-R}^2
\end{array} \xrightarrow{\text{CuCN}} \begin{array}{c}
\text{R}^1\text{CN} \\
\text{N-R}^2
\end{array} \]

2a at -78 °C and stirred for 2 h resulted in the formation of 5-alkynyl-3-aminopyrrole 4a in 47% yield after quenching the mixture with 3 M HCl followed by silica gel purification. To our delight, the yield of 4a could be improved to 72% by quenching the reaction mixture with saturated aqueous NaHCO₃ solution. It was noted that in this case, in addition to 4a, one more byproduct could be detected in the crude reaction mixture. However, after the crude material was dissolved in CH₂Cl₂ followed by addition of silica gel and evaporation of the solvent, TLC analysis showed that only 4a remained. The results indicated that the observed byproduct converted to 4a on the silica gel. This conclusion was also confirmed by control experiments (vide infra). With the optimized reaction conditions in hand, substrate scope of this reaction was examined (Table 1). We first investigated the effect of the substituents on α-iminonitrides. When N-phenyl- or N-(p-bromophenyl)-substituted iminonitriles were employed, the corresponding 3-aminopyrroles 4b and 4c were obtained in 88% and 85% yields, respectively. The results indicated that the presence of electron-neutral or withdrawing N-aryl group on iminonitrile afforded higher product yields. N-alkyl-substituted iminonitriles such as N-(R)-(1-phenylethyl) or N-cyclohexyl-substituted one were also examined. Although the
Table 1. Synthesis of 3-aminopyrroles from 1,3-butadiynes and α-iminonitriles.\(^{a}\)

\[
\begin{array}{|c|c|}
\hline
\text{R}^1 & \text{Product} \\
\hline
\text{Ph} & \text{4a, 72\%} \\
\text{Ph} & \text{4b, 88\%} \\
\text{C}_6\text{H}_4\text{Br-p} & \text{4c, 85\%} \\
\text{Ph} & \text{4d, 73\%}\(^{b}\) \\
\text{p-ClC}_6\text{H}_4 & \text{4e, 75\%}\(^{b}\) \\
\text{p-CF}_3\text{C}_6\text{H}_4 & \text{4f, 84\%} \\
\text{ar} & \text{4g, 77\%} \\
\text{Ar} = 3,4,5-(\text{OME})\text{C}_6\text{H}_2 & \\
\text{C}_6\text{H}_4\text{Cl-p} & \text{4j, 79\%} \\
\text{Ph(CH)}_2\text{Ph} & \text{4k, 55\%}\(^{b,c}\) \\
\text{C}_6\text{H}_4\text{Me-p} & \text{4l, Ar} = \text{p-BrC}_6\text{H}_4, 48\%\(^{b,c}\) \\
\text{C}_6\text{H}_4\text{Me-p} & \text{4m, Ar} = \text{p-MeOC}_6\text{H}_4, 44\%\(^{b,c}\) \\
\text{C}_6\text{H}_4\text{Br-p} & \text{4n, 42\%}\(^{b,c}\) \\
\text{C}_6\text{H}_4\text{Br-p} & \text{4o, 39\%}\(^{b,c}\) \\
\text{C}_6\text{H}_4\text{Br-p} & \text{4p, 55\%}\(^{b,c}\) \\
\hline
\end{array}
\]

\(^{a}\) Isolated yields. \(^{b}\) The crude products were treated with BF\(_3\)-Et\(_2\)O. \(^{c}\) -78 °C to 0 °C, 3-5 h.
substrates with iminonitriles could occur at -78 °C, the desired products were not observed after silica gel purification. The results suggested that the silica gel was not effective in promoting the transformations to pyrroles in these cases. To our delight, further optimizations indicated that when the crude products obtained by quenching with saturated aqueous NaHCO₃ solution followed by normal work-up was stirred at 50 °C in THF for 1 h in the presence of 4.0 equiv of BF₃·Et₂O, the desired products 4d and 4e could be obtained in 73% and 75% yields, respectively. It was noted that the use of enantiomerically pure N-(R)-(1-phenylethyl)-substituted iminonitrile gave 4d without racemization, as determined by chiral-column HPLC analysis of 4d and (±)-4d. The iminonitriles bearing p-Cl, p-CF₃, 3,4,5-(MeO)₃ and 1-naphthyl substituents on the C-aryl rings (R³ group) reacted smoothly with 1a to afford 4e-4h in 72-84% yields. C-Heteroaryl-substituted iminonitriles such as (5-methyl-2-furanyl) or (2-thienyl)-substituted one were tolerated well during the reaction to afford 4i and 4j in 73% and 79% yields, respectively. The reaction was also compatible to C-alkyl substituted iminonitrile, furnishing 4k in 55% yield. Next, we made the effort to employ aryl- or alkyl-substituted 1,3-butadiynes as the diyne substrates. As shown in Table 1, when phenyl or p-tolyl-substituted butadiynes were used as the coupling components, the corresponding products 4l-4n could be formed in 42-48% yields by treatment of the crude products with BF₃·Et₂O in CH₂Cl₂ at room temperature. 4l-4n could also be formed without the need to use Lewis acid. The use of alkyl-substituted butadiynes such as Hex-C≡C-Hex and tBuC≡C-C≡CtBu were also suited for this reaction, furnishing the pyrrole products 4o and 4p in 39% and 55% yields, respectively. One of the reasons for the lower yields of 4l-4p derived from aryl- or
alkyl-substituted butadiynes might be due to the lower yields of the first step for the formation of the corresponding titanium-butadiyne complexes.\textsuperscript{11a} The structure and the regioselectivity of 3-aminopyrroles 4 were unambiguously confirmed by X-ray crystallographic analyses of the product 4a (Figure 1) and the N-tosylated derivatives of 4l and 4p.\textsuperscript{20}

![Figure 1. X-ray crystal structure of 3-aminopyrrole 4a](image)

To understand the reaction mechanism, we tried to isolate the possible intermediate before treating the crude products with silica gel. A diimine product 5, derived from the coupling reaction of titanium-butadiyne complex 2a with \(\text{N-}(4\text{-bromophenyl})\text{-3,4,5-trimethoxybenzimidoyl cyanide}\) 3g, was found to be stable upon isolation through neutral \(\text{Al}_2\text{O}_3\). The structure of 5 was also confirmed by X-ray crystallographic analysis.\textsuperscript{20} 5 converted to 3-aminopyrrole 4g in high yield of 85% upon loading on silica gel followed by column chromatography. The results indicated that
3-aminopyrrole 4 was formed during the silica gel purification process (Scheme 3).

Scheme 3

Based on the above results, we propose the following reaction mechanism for this novel transformation using butadiyne as the substrates (Scheme 4): First, addition of the C=N moiety of iminonitrile to the less hindered propargyl titanium moiety in complex 2 via $S_{E2}'$-type$^{21,22}$ reaction gives an azatitanacyclocumulene 7, which might isomerize to azatitanacyclopentadiene 8. 8 might also be formed by direct insertion of CN bond into the Ti-C(sp$^2$) bond close to R$^1$ group of 2. However, the attack of the nitrile from this side may encounter large steric hindrance. Hydrolysis of 8 affords the diimine product 5. Further transformation of 5 to 3-aminopyrroles 4 might proceed via an interesting imino aza-Nazarov cyclization promoted by silica gel due to its weak Lewis acidity.$^{23}$ As we know, imino$^{24}$ and aza-Nazarov$^{25}$ cyclizations are variations of the classical Nazarov reaction involving 4π electrocyclizations. Until now, the reports for imino-type Nazarov cyclizations are quite limited.$^{24}$ Calculations by Smith et al. indicated that the 3-imino-type Nazarov reaction is energetically disfavored due to the stabilization of 3-aminopentadienyl cation over the cyclic allylic cation by conjugation with the lone pair electrons on the nitrogen atom (Scheme 5).$^{26}$ To the best of our knowledge, the imino aza-Nazarov
cyclization has only been reported as a postulated reaction step in a diamine monotriflate-catalyzed asymmetric cyclization of ketoazirines. In our case, the allylic cation 11 could be more favored due to the stronger stabilization by an adjacent nitrogen atom on NR² group.

Scheme 4

Scheme 5

pentadienyl cations are favored in imino-Nazarov cyclization
We also investigated the reactions of titanium-monoyne complexes with \( \alpha \)-iminonitriles (Scheme 6). Interestingly, the expected 3-aminopyrroles were not obtained, instead, the diimine 15 was obtained in 59% yield, along with 74% of diphenylacetylene, after quenching the reaction mixture by water. In addition, one more byproduct was also observed, the structure of which was not defined yet. The reaction might proceed by first ligand exchange to give a titanium-imine complex 13, which undergoes homo-coupling with another \( \alpha \)-iminonitrile to give 14 by insertion of C=N moiety to azatitanacycle 13. This is followed by elimination of CN groups to deliver the desired product 15. Diimines are valuable ligands in transition-metal chemistry,\(^{28}\) for example, the diimine-Ni complex shows high catalytic activity in olefin polymerization.\(^{28\text{b-c}}\) Our reaction provides a simple and efficient method for the synthesis of diimines.

**Scheme 6**

In summary, we have developed a titanium-mediated regioselective cross-coupling reaction of 1,3-butadiynes with \( \alpha \)-iminonitriles. Functionalized 3-aminopyrroles were
efficiently constructed upon treatment of the crude hydrolysis products with silica gel or Lewis acid. The reaction likely proceeds via a novel imino aza-Nazarov type cyclization of the diimines produced by hydrolysis of the in situ generated azatitanacycles. Employing titanium-monoyne complex in this reaction resulted in homo-coupling of α-iminonitriles, leading to the formation of 1,2-diimines. Further studies to expand the reaction scope are in progress.

Electronic supplementary information (ESI) available: Experimental details, spectroscopic characterization of all new compounds, X-ray crystallography of compounds 3b, 4a, N-tosylated derivatives of 4l, 4p, 5, 15 and CIF files giving crystal data are given in the Supporting Information file.

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\[
\text{PhCHO} + \text{PhNH}_2 \xrightarrow{\text{TMSCN/IBX/TBAB}} \text{MeCN, rt, 5 h} \rightarrow \begin{cases} \text{3b} \quad & \text{1.1 : 1} \\ \text{3c} \quad \text{not obtained} \end{cases}
\]

(19) The use of CH$_2$Cl$_2$ as the solvent enables an efficient transformation to pyrrole on
silica gel.

(20) The X-ray crystal structures of compounds 3b, 4a, *N*-tosylated derivatives of 4l and 4p, 5 and 15 are shown in supporting information. CCDC-988139 (3b), CCDC-988138 (4a), CCDC-988137 (*N*-tosylated derivative of 4l), CCDC-988141 (*N*-tosylated derivative of 4p), CCDC-988140 (5) and CCDC-988142 (15) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


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