Recent Developments in Alkynylation

--New approaches to introduce an alkynyl group

Reporter: Zhao-feng Wang
Supervisor: Yong Huang
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Recent Developments in Alkynylation

Contents

1. Introduction of Acetylene Chemistry
2. Nucleophilic alkynylation: Classic text book approach
3. Electrophilic alkynylation: The dark side of acetylene chemistry
4. Radical C-alkynylation
5. Summary and outlook
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Introduction -- Structure and Bonding

Linear Acetylenic Scaffolds

\[ pK_a \approx 25 \]

Total bond strength: 839 kJ/mol
- C-C_σ bond: 369 kJ/mol
- 1st C-C_π bond: 268 kJ/mol
- 2nd C-C_π bond: 202 kJ/mol

Picture downloaded from http://en.wikipedia.org
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**Introduction -- Why we need to introduce an alkynyl group?**

Heterocycles

\[ R_1 \quad \text{X} \quad R_2 \]

Meta catalyzed cyclization

etc...

\[ R_1 \quad \text{C} \quad R_2 \]

Enyne Metathesis

Diels-Alder reaction

versatile building blocks in organic synthesis

Arylene-Acetylene nanostructure

\[ \text{Cu(II)} \quad \text{Ligand} \]

\[ N_3^- + \quad \text{Cu(II)} \quad \text{Ligand} \]

= Biomolecule

= Fluorophore

click chemistry for biomolecular labeling


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Nucleophilic alkynylation: Classic text book approach

Addition of Alkyne Nucleophiles to Carbonyl Groups

\[ \text{X=O, NPG} \]

Sonogashira coupling of aryl halides and acetylides

\[ \text{Cu cat., Pd cat. base} \]

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Nucleophilic alkynylation

Asymmetric alkynylation of α-imino esters via synergistic catalysis strategy

Combined enantioselective Brønsted acid and metal-catalyzed alkynylation of α-imino esters

M. Rueping et al. Angew. Chem., Int. Ed. 2007, 46, 6903-6906
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Nucleophilic alkynylation

The first applications of carbene ligands in sonogashira reactions of unactivated alkyl halides

M. Eckhardt, G.-C. Fu et al. J. Am. Chem. Soc. 2003, 125, 13642-13643
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Electrophilic alkynylation: The dark side of acetylene chemistry

Addition of alkynes on a nucleophilic position

Electrophilic alkynylation reagents

Halogens

\[ R_2 \equiv X \]

X = F, Cl, Br, I

Hypervalent Iodine

\[ R_2 \equiv I \equiv X \]

X = OTs, OTf, BF$_4$...

Sulfur Reagents

\[ R_2 \equiv SO_2 R_1 \]

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Electrophilic alkynylation: Heteroatom alkynylation

C-N bond formation: first ynamine synthesis

Extended methodology to ynamide

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Electrophilic alkynylation: Heteroatom alkynylation

C-S bond formation: regiospecific thiazole synthesis using alkynyliodonium salts

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**Electrophilic alkynylation: Enolate alkynylation**

First alkynyliodonium salt reacted with the enolate

![Chemical structure](image)

yield 73%

Improvement of the methodology involving novel hypervalent iodine reagents

![Chemical structure](image)

EWG= COX, CN, NO₂

R₁ = alkyl, aryl

TMS-EBX

terminal acetylenes obtained

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Electrophilic alkynylation: Enolate alkynylation

Alkynylation of non-stabilized enolates using chloroacetylenes

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Electrophilic alkynylation: Enolate alkynylation

Highly enantioselective electrophilic alkynylation

Electrophiles approach from Si-face (above)

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**Electrophilic alkynylation**: Alkynylation of organometallic nucleophiles

Pioneering work using alkynyl sulfones

\[
\begin{align*}
R_1&=\equiv\text{SO}_2\text{Ar} + M\text{R}_2 & \text{THF} & \text{78°C to rt} & R_1&=\equiv\text{R}_2 \\
M&=\text{Li, MgX} \\
R_1, R_2&=\text{aryl, tertiary alkyl}
\end{align*}
\]

Efficient synthesis of aliphatic acetylenes based on a mixed Zn–Cu reagent

\[
\begin{align*}
\text{ZnI}\&\text{R}_1 & \text{CuCN} & 2\text{LiCl} & \text{THF, -65°C} & X=\text{Br, I} & R_1&=\equiv\text{R}_2 \\
& & & & & \\
R_2&=\equiv\ X & \text{ZnI(CN)Cu}\&\text{R}_1 & X=\text{Br, I} & R_1&=\equiv\text{R}_2
\end{align*}
\]

Organocopper reagent as nucleophile in total synthesis


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Electrophilic alkynylation: Alkynylation of C(sp)–H

Cadiot–Chodkiewicz alkynylation of terminal alkynes

\[
R_1\equiv\equiv\text{Br} + H\equiv\equivR_2 \xrightarrow{\text{Cul, EtNH}_2} R_1\equiv\equiv\equivR_2
\]

non-symmetric diynes

Palladium could be a superior catalyst

\[
R_1\equiv\equiv\text{Br} + H\equiv\equivR_2 \xrightarrow{\text{Pd(dba)}_2/L\text{NEt}_3, \text{Cul, DMF, rt, 2-9h}} R_1\equiv\equiv\equivR_2
\]

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Electrophilic alkynylation: Alkynylation of C(sp²)–H

Gold-catalyzed alkynylation of indoles and pyrroles using alkynyl benziodoxolone

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Electrophilic alkynylation: Alkynylation of C(sp³)–H

First Palladium(II)-catalyzed β-C(sp³)–H bond alkynylation

Palladium(0)-catalyzed primary β-C(sp³)–H bond alkynylation

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Radical C-alkynylation

Overview of radical C-alkynylation reactions

P. Renaud et al. Angew. Chem., Int. Ed. 2006, 45, 5847-5849
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Radical C-alkynylation
Radical-mediated C(sp³) - C(sp) coupling

R−COOH + G= Ar, TIPS
R= 1°, 2°, 3°, alkyl

\[
\text{Cl} \quad \text{CO}_2\text{H} + \text{TIPS-EBX} \quad \text{CH}_3\text{CN/H}_2\text{O} \\
50 \degree \text{C}, 10\text{h} \quad \text{74\% yield}
\]

AgNO₃ (cat.) K₂S₂O₈
\[
\text{R} \quad \equiv \quad \text{G} \quad \text{Yield: 60-94\%}
\]

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Summary
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Acknowledgement

Prof. Yong Huang

All my labmates in E201

All the members in SCBB
Thank you! 
Scheme 2. Possible reaction mechanisms.
**Scheme 2. Proposed Pathways of Palladium-Catalyzed C(sp)–C(sp) Coupling**

- **Path A**: $X \equiv R^1 \overset{Pd}{\rightarrow} X \equiv R^1 \rightarrow M \equiv R^2 \rightarrow R^2 \equiv R^1$
- **Path B**: $R^1 \equiv Pd \equiv R^1 \downarrow \rightarrow R^1 \equiv \rightarrow \rightarrow M \equiv R^1 \downarrow \rightarrow M \equiv R^2 \rightarrow R^2 \equiv R^2$
- **Path C**: $R^1 \equiv \rightarrow \rightarrow \rightarrow R^1 \downarrow \rightarrow R^1 \equiv \rightarrow \rightarrow M \equiv R^1 \downarrow \rightarrow M \equiv R^2 \rightarrow R^2 \equiv R^2$

- $X = \text{Cl, Br, I}$
- $M = \text{Cu}$
General Procedures for the Coupling Reactions.
To an ovendried Schlenk tube with a magnetic stir bar were added Pd(dba)$_2$ (11.5 mg, 0.02 mmol), L1 ligand (7.9 mg, 0.02 mmol), and CuI (1.9 mg, 0.01 mmol). DMF (1 mL) was added via a syringe. The system was vacuumed with an oil pump at 0 °C and filled with nitrogen, and this was repeated five times. After the mixture was stirred under nitrogen for about 10 min, alkyne (0.6 mmol) was added via a microliter and stirred for another 5 min. 1-Bromoalkyne was added last via a microliter syringe. The system was stirred at room temperature for 10 h. Upon completion, 4 mL of brine was added, and the mixture was extracted by ethyl acetate (3 mL × 3). The product was obtained by flash column chromatography.
Scheme 3. Possible mechanisms for the ethynylation reaction and labeling experiment (Ar = phenyl-2-carboxylate).
Scheme 65  Radical alkynylation of sp³ C–H bonds using alkynyl triflones.

Scheme 66  Mechanism of the radical alkynylation.