

Annotation Instructions

A. INTRODUCTION

The goal of the Chemical Literature Annotation is the identification (annotation) of the following entities and their roles, related to specific chemical reactions in scientific literature:

- Reactants
- Products
- Yield
- Reaction type
- Catalyst(s)
- Solvent(s)
- Temperature
- Time (duration)

Tagging Instructions (Click to expand)

Highlight the **Reactants** in the description

and medicinal chemistry due to their prevalence in numerous synthetic and naturally occurring bioactive molecules. In particular, [3-methyleneisindolin-1-ones](#) have been recognized as core structures in natural compounds such as enterocarpam II, the [secophthalide-isoquinoline](#) ene-lactam fumaridine, [1-magallanesine](#), an [isindolobenzazocine](#) isolated from the South-American plant *Berberis darwinii*.² [3-Methyleneisindolin-1-ones](#) have shown a diverse range of bioactivities, such as vasorelaxant property³ and local anesthetic activity.⁴ In addition, [3-methyleneisindolin-1-ones](#) are also important the synthesis of other useful alkaloids.⁵ Owing to their great importance, many methods have been developed for the preparation of [3-methylene-isindolin-1-ones](#). These methods mainly involved the traditional condensation reaction of [phthalimides](#) with stabilized phosphoranes,⁶ or addition of organometallic reagents, followed by dehydration of the resulting 3-hydroxyphthalimides,⁷ the Horner condensation of 3-(diphenylphosphinoyl)-isindolin-1-ones with [aldehydes](#),⁸ ortholithiation-anionic cyclization of [N-acyl-2-bromobenzamides](#),⁹ electrophilic cyclizations of 2-alkynylbenzamides,¹⁰ and recently developed metal-catalyzed cascade reactions.¹¹ However, most of the present procedures suffer from one or more drawbacks such as intermediates for

Undo Reset

| Reactants |
|-------------|
| Products |
| Yield |
| Reaction |
| Catalyst |
| Solvent |
| Temperature |
| Time |

Reactants

☐ There is no Reactants

Products

☐ There is no Products

Yield

☐ There is no Yield

Reaction

☐ There is no Reaction

Catalyst

☐ There is no Catalyst

Solvent

☐ There is no Solvent

Temperature

☐ There is no Temperature

Time

☐ There is no Time

☐ There is no reaction

B. ANNOTATION PROCESS

1. The text paragraph to be annotated will be shown in the text window on the left side of the screen.
 - The paragraph shown may include from none to multiple chemical reactions.
 - Only one reaction at a time must be annotated.
 - Most chemical entities are automatically highlighted in order to facilitate annotation. Nevertheless, some relevant entities might not be identified automatically so that they should be manually identified by the user.

Highlight the **Reactants** in the description

ABSTRACT: Highly stereoselective intermolecular reactions of electron-deficient [alkynes](#) with [N-hydroxyphthalimides](#) for efficient construction of [N-unprotected 3-methyleneisoindolin-1-ones](#) have been developed through base catalytic strategies. The reaction of [alkynoates](#) with [N-hydroxyphthalimides](#) catalyzed by [Bu3P](#) in [DMF](#) at 150 °C gave the corresponding [3-methyleneisoindolin-1-ones](#) with a (Z)-configuration, while the reaction of [alkynoates](#) with [N-hydroxyphthalimides](#) catalyzed by [K2CO3](#) in [DMF](#) at 60 °C gave the corresponding [3-methyleneisoindolin-1-ones](#) with an (E)-configuration, and (Z)-3-methyleneisoindolin-1-ones were obtained when [alkyne ketones](#) reacted with [N-hydroxyphthalimide](#).

FOR EACH REACTION IN THE PARAGRAPH REPEAT SETPS 2 – 6 BELOW :

2. Select (highlight in green) in the window on the right the entity class to be annotated (Reactants, Products, Yield, Reaction type, Catalyst, Solvent, Temperature, Time).

| |
|-------------|
| Reactants |
| Products |
| Yield |
| Reaction |
| Catalyst |
| Solvent |
| Temperature |
| Time |

3. Select the relevant word or span in the paragraph so that it is included in the entity field.

Highlight the **Reactants** in the description

ABSTRACT: Highly stereoselective intermolecular reactions of electron-deficient **alkynes** with **N-hydroxyphthalimides** for efficient construction of **N-unprotected 3-methyleneisindolin-1-ones** have been developed through base catalytic strategies. The reaction of **alkynoates** with **N-hydroxyphthalimides** catalyzed by **Bu3P** in **DMF** at 150 °C gave the corresponding **3-methyleneisindolin-1-ones** with a (Z)-configuration, while the reaction of **alkynoates** with **N-hydroxyphthalimides** catalyzed by **K2CO3** in **DMF** at 60 °C gave the corresponding **3-methyleneisindolin-1-ones** with an (E)-configuration, and (Z)-3-methyleneisindolin-1-ones were obtained when **alkyne ketones** reacted with **N-hydroxyphthalimide**.

Reactants

☐ There is no Reactants

| Reactants |
|-------------|
| Products |
| Yield |
| Reaction |
| Catalyst |
| Solvent |
| Temperature |
| Time |

4. In case there is more than one entity belonging to an entity class (e.g. more than one reactant), repeat step 3, so that all of them are included in the entity class field.
5. In case there are no entities related to the entity class being annotated, check the 'There is no [Item]' box next to the entity class field.

☒ There is no Catalyst

6. Once the current reaction has been annotated:
- If the current paragraph includes additional reactions:
 - Click on 'Save and annotate another reaction'

Save and annotate another reaction

- Repeat steps 2 - 6
- If the current paragraph does not include additional reactions:
 - Click on 'Submit Reaction'

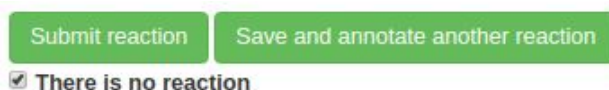
Submit reaction

- If there are more paragraphs to annotate: Repeat steps 1 - 7 for the subsequent paragraphs

7. Once there are no more paragraphs to annotate, the tool will show a 'DONE' message and no more paragraphs will be shown.

C. MISSING REACTIONS

- The annotation tool extracts those paragraphs which may be describing chemical reactions most likely. Nevertheless, some paragraphs may not include any reaction. In this case, the '**There is no reaction**' box should be checked, followed by the '**Submit Reaction**' button in order to start the annotation of the next paragraph.



D. CORRECTIONS

The '**Undo**' and '**Reset**' buttons allow to make corrections during the annotation process:

- Undo: Undoes the last action
- Reset: Clears the active entity field



E. GENERAL ANNOTATION RULES

This section describes the general annotation rules for the different types of entities.

Legend:

- 'Annotate'
- '~~Do not annotate~~'

1. General

- In case a paragraph is describing more than one reaction:
 - Annotate all entities explicitly linked to the reaction being annotated
 - In case an entity is not explicitly mentioned in the reaction being annotated but it is implicitly linked to it by being mentioned in other reaction within the paragraph, annotate it.

Example:

"On the basis of conventional Knoevenagel reactions, we initially investigated reaction conditions using benzaldehyde (1a) and dimethyl malonate (2a) as a model substrate (Table 1). When a reaction was performed with 10 mol % of InBr₃ in toluene at 60 °C for

8 h, only 3% of Knoevenagel product 3aa was detected (entry 1) [Reaction 1]. Thus, to promote the initial abstraction of the activated proton, the addition of 1 equiv of several bases to the reaction mixture was examined. Consequently, when the primary amine 2-aminoethanol was added, the yield was remarkably increased to 61% (entry 2) [Reaction 2]."

Annotate [Reaction 2] as follows:

- **Reactants:** benzaldehyde, (1a), dimethyl malonate, (2a) [Reaction 1]
 - **Products:** Knoevenagel, 3aa [Reaction 1]
 - **Yield:** 61% [Reaction 2]
 - **Reaction:** Knoevenagel [Reaction 1]
 - **Catalyst:** InBr₃ [Reaction 1], primary amine 2-aminoethanol [Reaction 2]
 - **Solvent:** toluene [Reaction 1]
 - **Temperature:** 60 [Reaction 1]
 - **Time:** 8h [Reaction 1]
- Do not annotate expected results but actual results. Example:
 - 'Since CuCl(PPh₃) is a widely studied and common copper salt, the active catalytic species was expected to be ~~CuCN-(PPh₃)~~ in our optimized reaction condition'
 - Annotate not only the reactions obtained in the actual experiments but also past reactions described. Example:
 - 'Both the Ullmann and Buchwald-Hartwig aminations are well-known copper-catalyzed crosscoupling reactions between an aryl halide and an amine'

2. Conditions

- Do annotate compound expressions when they form a single word. Examples:
 - 'Copper-catalyzed crosscoupling reactions'
 - 'Phosphine-catalyzed [3 + 2] annulation'
- Do not annotate references to reaction conditions. Examples:
 - '~~condition A~~ shows the highest reactivity'
- Do annotate generic reaction conditions. Example:
 - 'Elevated temperature'

3. Chemical entities (reactants, products, catalysts, and solvents)

- Annotate both the entity and its corresponding reference when they are shown together. Example:

- 'We started our investigation by examining the Bu₃P catalyzed reaction of 2-hydroxyisoindoline-1,3-dione (1a) and ethyl propiolate (2a)'
- Annotate references (to Schemes, Tables, Figures, etc.) to entities. Example:
 - 'The reaction of 1a with 2a in the presence of Bu₃P in DMF...'
- Annotate all references to an entity when shown together. Example:
 - pivalonitrile (2,2,-dimethylpropanenitrile, bp 105 °C)
- Do not annotate references to entity types but to specific entities. Examples:
 - 'the initial ~~hexameric PPh₃-bounded copper-cyanide~~ species'
 - 'the expected ~~alcohols~~'
 - 'the corresponding ~~alkene 3aa~~'
 - 'however, only ~~colorless-crystals~~ were obtained'
- Do not annotate generic references to entities. Examples:
 - '~~the-product~~', '~~final-product~~', '~~the-reactant~~'
 - '~~the-corresponding-product~~'
 - '~~same-starting-materials~~'
- Do not annotate entity classes but only specific entities. Examples:
 - 'While the ~~C-2-arylated-product (4aa)~~ was the major product'
 - '~~Benzoxazoles-bearing-substituents-with-diverse-electronic-properties-such-as-methyl (1b-1d), phenyl (1e), and chloro (1f) groups~~'
 - 'effectively promotes the Knoevenagel condensation of ~~aromatic-/aliphatic-/heteroaromatic aldehydes~~ with a ~~variety-of-activated-methylene-compounds~~'

4. Yields

- Annotate generic yield expressions. Examples:
 - 'similar yield', 'lower yield', 'higher yield', 'diminished yield', 'improved reaction yield'
- Annotate all yield measures in case more than one is provided. Examples:
 - 'Higher yield (62%)'
- Alternative expressions of yield: **TBD – Ask Thomas**
 - 'increased catalytic efficiency'
 - 'improved reactivity'
 - 'perfect selectivity'
 - 'significant effect'
 - 'highest conversion'
 - 'no reactivity'
 - 'no further reaction observed'

F. EXAMPLE 1

The following example shows the annotation of two different reactions present in a single paragraph and with no missing entity classes.

Reaction #1:

On the basis of conventional [Knoevenagel](#) reactions, we initially investigated reaction conditions using [benzaldehyde](#) (1a) and [dimethyl malonate](#) (2a) as a model substrate (Table 1). When a reaction was performed with 10 [mol](#) % of [InBr3](#) in [toluene](#) at 60 °C for 8 h, only 3% of [Knoevenagel](#) product [3aa](#) was detected (entry 1). Thus, to promote the initial abstraction of the activated proton, the addition of 1 equiv of several bases to the reaction mixture was examined. Consequently, when the [primary amine 2-aminoethanol](#) was added, the yield was remarkably increased to 61% (entry 2). The addition of a [secondary](#) or [tertiary amine](#), however, was ineffective for the present condensation (entries 3 and 4). Upon further screening several additives for the condensation reaction, 1 equiv of [acetic anhydride](#) showed the best additive effect to afford corresponding product [3aa](#) in 89% yield (entry 5). Then, a counteranion effect of the [indium](#) catalyst was investigated in the presence of [Ac2O](#). [InCl3](#) produced the best yield of [Knoevenagel](#) product [3aa](#) in 94% NMR yield (86% isolated yield) along with the formation of a small amount (4%) of [geminal diacetate](#) 4a. Stronger [Lewis acids](#), [InI3](#) and [In\(OTf\)3](#), showed a similar catalytic effect and provided [alkene 3aa](#) in 79% (with 8% of [diacetate](#) 4a) and 82% yields, respectively (entries 7 and 8); however, [In\(OH\)3](#) and [In\(OAc\)3](#) produced neither the corresponding [alkene 3aa](#) nor [diacetate](#)

Undo

Reset

| |
|-------------|
| Reactants |
| Products |
| Yield |
| Reaction |
| Catalyst |
| Solvent |
| Temperature |
| Time |

Reactants

benzaldehyde (1a) dimethyl (2a)

☐ There is no Reactants

Products

Knoevenagel 3aa

☐ There is no Products

Yield

3%

☐ There is no Yield

Reaction

Knoevenagel

☐ There is no Reaction

Catalyst

InBr3

☐ There is no Catalyst

Solvent

toluene

☐ There is no Solvent

Temperature

60

☐ There is no Temperature

Time

8

☐ There is no Time

Reaction #2:

On the basis of conventional [Knoevenagel](#) reactions, we initially investigated reaction conditions using [benzaldehyde \(1a\)](#) and [dimethyl malonate \(2a\)](#) as a model substrate (Table 1). When a reaction was performed with 10 [mol](#) % of InBr₃ in [toluene](#) at 60 °C for 8 h, only 3% of [Knoevenagel](#) product [3aa](#) was detected (entry 1). Thus, to promote the initial abstraction of the activated proton, the addition of 1 equiv of several bases to the reaction mixture was examined. Consequently, when the [primary amine 2-aminoethanol](#) was added, the yield was remarkably increased to 61% (entry 2). The addition of a [secondary](#) or [tertiary amine](#), however, was ineffective for the present condensation (entries 3 and 4). Upon further screening several additives for the condensation reaction, 1 equiv of [acetic anhydride](#) showed the best additive effect to afford corresponding product [3aa](#) in 89% yield (entry 5). Then, a counteranion effect of the [indium](#) catalyst was investigated in the presence of [Ac₂O](#). [InCl₃](#) produced the best yield of [Knoevenagel](#) product [3aa](#) in 94% NMR yield (86% isolated yield) along with the formation of a small amount (4%) of [geminal diacetate](#) 4a. Stronger [Lewis acids](#), InI₃ and In(OTf)₃, showed a similar catalytic effect and provided [alkene 3aa](#) in 79% (with 8% of [diacetate](#) 4a) and 82% yields, respectively (entries 7 and 8); however, In(OH)₃ and In(OAc)₃ produced neither the corresponding [alkene 3aa](#) nor [diacetate](#)

Undo
Reset

| |
|-------------|
| Reactants |
| Products |
| Yield |
| Reaction |
| Catalyst |
| Solvent |
| Temperature |
| Time |

Reactants

benzaldehyde (1a) dimethyl malonate (2a)

☐ There is no Reactants

Products

Knoevenagel 3aa

☐ There is no Products

Yield

89%

☐ There is no Yield

Reaction

Knoevenagel

☐ There is no Reaction

Catalyst

InBr₃ primary amine 2-aminoethanol

☐ There is no Catalyst

Solvent

toluene

☐ There is no Solvent

Temperature

60

☐ There is no Temperature

Time

8

☐ There is no Time

G. EXAMPLE 2

The following example shows the annotation of a reactions with missing entity classes (yield, reaction type and time).

ABSTRACT: Highly stereoselective intermolecular reactions of electron-deficient alkynes with N-hydroxyphthalimides for efficient construction of N-unprotected 3-methyleneisindolin-1-ones have been developed through base catalytic strategies. The reaction of alkynoates with N-hydroxyphthalimides catalyzed by Bu3P in DMF at 150 °C gave the corresponding 3-methyleneisindolin-1-ones with a (Z)-configuration, while the reaction of alkynoates with N-hydroxyphthalimides catalyzed by K2CO3 in DMF at 60 °C gave the corresponding 3-methyleneisindolin-1-ones with an (E)-configuration, and (Z)-3-methyleneisindolin-1-ones were obtained when alkyne ketones reacted with N-hydroxyphthalimide.

Undo Reset

| |
|-------------|
| Reactants |
| Products |
| Yield |
| Reaction |
| Catalyst |
| Solvent |
| Temperature |
| Time |

Reactants

alkynoates N-hydroxyphthalimides

☐ There is no Reactants

Products

3-methyleneisindolin-1-ones

☐ There is no Products

Yield

☒ There is no Yield

Reaction

☒ There is no Reaction

Catalyst

Bu3P

☐ There is no Catalyst

Solvent

DMF

☐ There is no Solvent

Temperature

150

☐ There is no Temperature

Time

☒ There is no Time