

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
- Workup reagents
- Catalyst / Reagents
- Solvent
- 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-methyleneisoindolin-1-ones](#) have been recognized as core structures in natural compounds such as enterocarpam II, the [secophthalide-isoquinoline](#) ene-lactam fumaridine, [1-magallanesine](#), an [isoindolobenzazocine](#) isolated from the South-American plant *Berberis darwinii*.² [3-Methyleneisoindolin-1-ones](#) have shown a diverse range of bioactivities, such as vasorelaxant property³ and local anesthetic activity.⁴ In addition, [3-methyleneisoindolin-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-isoindolin-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)-isoindolin-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

Submit reaction

Save and annotate another reaction

☐ 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, Workup reagents, Catalyst / Reagents, Solvent, Temperature, Time).

Reactants
Products
Yield
Reaction type
Workup reagents
Catalyst / Reagents
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

Undo Reset

Reactants
Products
Yield
Reaction
Catalyst
Solvent
Temperature
Time

4. In case there are more than one entities belonging to an entity class (e.g. more than one reactant), repeat step 3, so that all of them are included in the entity 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

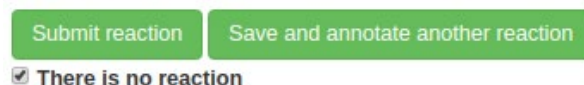
- Repeat steps 2 - 6
- If the current paragraph does not include additional reactions:
 - Click on 'Submit Reaction'

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:
 - Discard multi-step reactions.
 - If a paragraph describes multiple reactions, label them as separate reactions (e.g. 4a and 4b were reacted to form 5a and 5b, it should be two reactions: 4a → 5a and 4b → 5b). If it describes a reaction with multiple products, it should be annotated as a single reaction.
 - Annotate all entities explicitly linked to the reaction being annotated
 - Annotate as well those entities implicitly linked to the reaction being annotated, which are mentioned in other reactions within the paragraph.

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]
- For reversible reactions, annotate as two reaction if the reverse reaction is explicitly described (e.g. different conditions are used to reverse the reaction)
 - 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’
- Do annotate physical units. Example:

- '32 C', '32 °C', '25 F'
- '25 min', '8 h', '10 hours'

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

- ALL ENTITIES

- 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)
- Only label the chemicals, without additional details about concentration, state, etc. E.g. "1% aqueous FeCl₃", only label "FeCl₃"
- If the text mentions a range of chemicals, only annotate those explicit text (e.g. 4g – 4i were used to form 5a – 5c: only annotate two reactions 4g->5a and 4i->5c). If the range is not separable, e.g., 4a-c or 4a-4c (without space around the "-"), discard the reaction
- Default to reactant if unsure between reactant and catalyst/reagent. Default to catalyst/reagent if unsure between catalyst/reagent and solvent

- PRODUCTS AND REACTANTS

- 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~~'
- REAGENTS, CATALYSTS AND SOLVENTS
 - Annotate even if the text only describes the type of chemical (e.g. "Pd catalyst": annotate "Pd"; "in-situ generated catalyst": annotate "in-situ generated").

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 – Chemistry**
 - '**increased catalytic efficiency**'
 - '**improved reactivity**'
 - '**perfect selectivity**'
 - '**significant effect**'
 - '**highest conversion**'
 - '**no reactivity**'
 - '**no further reaction observed**'

5. Reaction type

- Annotate if the description is a verb (e.g. A is oxidized to B: annotate "oxidized" as the reaction type).

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, 8 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

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 °C

☐ There is no Temperature

Time

8 h,

☐ There is no Time[Submit reaction](#)[Save and annotate another reaction](#)☐ There is no reaction

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

61%

☐ 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 °C

☐ There is no Temperature

Time

8 h,

☐ There is no Time

Submit reaction

Save and annotate another reaction

☐ There is no reaction

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 °C

☐ There is no Temperature

Time

☒ There is no Time