Project ChEMU

Guidelines for Annotating Chemical Entities related to Chemical Reactions

Version <1.02.1>

Revision History

Version Number, Date	Revision made by	Change Summary
1.00	Christian Druckenbrodt	created
1.01	Christian Druckenbrodt	adjusted
1.02.1	Christian Druckenbrodt	adjusted

Contents

SCOPE OF THE GUIDELINE

This document is the manual for the Full-Text Patent Annotation (FTPA) project and should advise how to annotate manually (or check pre-annotated) parts of a chemical reaction, e.g. chemical entities, reaction conditions etc. in patents correctly. It will provide definitions in which cases and how a string of characters embedded in text of patents must be annotated accordingly. The resulting manually annotated BRAT files can be used as a so-called "gold standard" in order to determine Recall and Precision values regarding corresponding automatic annotations, produced by state-of-the-art text mining tools.

OVERVIEW

The recognition of chemical reactions is an essential step in the extraction of chemical information from any kind of document. This goes beyond the annotation of chemical entities as it also covers their role within the context of a chemical reaction. In addition, some typical conditions should be annotated which provide contextual hints to the presence of a chemical reaction, whilst also providing additional information beyond a simple starting material/product relationship. In the current FTPA project we only focus on representations of entities and conditions as strings in snippets of running text. Drawn chemical entities/structures and conditions in pictures, schemes or tables are excluded, as state-of-the-art technologies are currently not able to reach enough quality in such regions of documents.

Determination of acceptability for chemical entity strings in a reaction derived from snippets of running text is often quite difficult. The complexity originates from the matter of fact, that chemical entities present in a reaction snippet may or not may not play a certain role in a reaction. The problem here is to identify all chemical entities playing a role in the reaction in the first place followed by the classification of these chemical entities according to the role they have in the chemical reaction.

An additional problematic issue is that strings used in snippets often refer to context beyond the individual snippet. The string used in the snippet may only be a representative of the complete chemical entity. Strings of chemical entities themselves can be detected, annotated, and to some extend resolved by state-of-the-art name-to-structure tools. Representatives, be it a label or a reference to the "product of a certain reaction", can be detected and annotated within this context but they cannot be resolved without any coreference.

As the basically only snippets of reaction texts will be part of the to be annotated text one further issue is not so prominent but is still present: in context/within natural language may change their intrinsic meaning depending on the different environments. That means, from an atomistic point of view, a string/word/term/group of characters may have an intrinsic unique meaning in the chemical domain (e.g. “Glucose”; “gold”), but embedded in running text it might mean something different (e.g. “Glucose transporters are a wide group of membrane proteins”) although it is still the same domain or even in other domain (“The exchange rate under the gold standard monetary system…”). As a consequence, documents, frequently annotated automatically by machines, will contain a huge amount of strings annotated as chemical entities. Although all of these annotations are somehow related to chemistry, only a certain amount of them are actually contextual chemical entities. Due to the above explained contextual constraints, the embedded meaning for the rest of the annotated strings in running text is not a chemical entity but something else.

INTRODUCTION TO PATENTS

A patent is a right granted to the owner of an invention that prevents others from making, using, importing or selling the invention without his permission. A patentable invention can be a product or a process that gives a new technical solution to a problem. It can also be a new method of doing things, the composition of a new product, or a technical improvement on how certain objects work. For an invention to be patentable, it must, in general, satisfy three key criteria: New, inventive step, and industrial application.

The sections of patents are quite conserved: title, bibliographic information (patent number, dates, inventors, assignees, IPC classes, …), abstract, description, and claims. Most of the chemical data will be found in the experimental section of the description, while compounds claimed (protected) are available in the claims section. Drawings, sequences, or other additional information will normally be found at the very end of a patent.

This particular project concentrates exclusively on the experimental section in the description as the source of reaction text snippets.

HIGH LEVEL RULES

In general, chemical reaction is a process leading to the transformation of one set of chemical substances to another. Here, the task is to identify specific types of chemical compounds, i.e. to assign the label of a chemical compound according to the role the chemical compound plays within a chemical reaction. Mostly the reaction full text can be divided into actual reaction and the following work-up – in the reaction the product is completely formed. In the work-up the product remains unchanged and steps undergone are for isolation of the product only. The actual reaction and the following workup must be kept separate in the annotation. The presence of a chemical entity in one of the separate parts has consequences for the annotation.

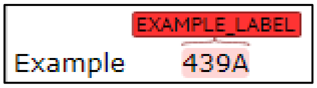
All snippets represent reaction full texts and are already pre-tagged. All tags must be revised and – if necessary – corrected. Missing tags must be set. Entities present more than once – also in different representations – must be annotated at each occurrence.

Part 1: Entity Annotation

We define 10 different entity types, including:

EXAMPLE_LABEL, REACTION_PRODUCT, STARTING_MATERIAL, REAGENT_CATALYST, SOLVENT, TIME, TEMPERATURE, YIELD_PERCENT, YIELD_OTHER and OTHER_COMPOUND.

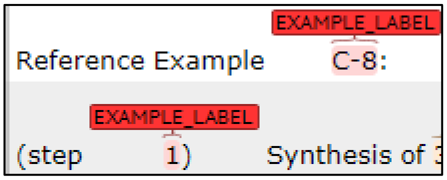
EXAMPLE_LABEL


EXAMPLE_LABEL

Example 439A

If a reaction label is given in the snippet this must be annotated with this tag.

Words like “Example”, “Step”, “Intermediate”, “Core” and “Reference example” must not be annotated, neither are parentheses, brackets or braces. Do not confuse reaction labels and compound labels. This tag must only be annotated to reaction labels.


EXAMPLE_LABEL

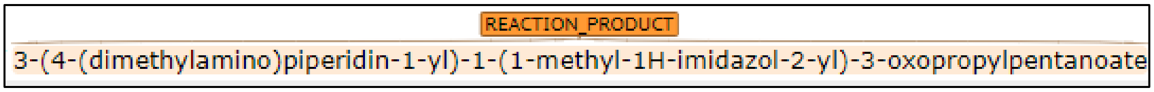
Reference Example C-8:

EXAMPLE_LABEL

(step 1) Synthesis of 3

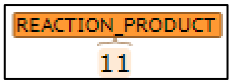
There can be more than one reaction label in a snippet as reaction labels consider both the label of the finally generated product, as well as, the described intermediate product.

REACTION_PRODUCT


REACTION_PRODUCT

3-(4-(dimethylamino)piperidin-1-yl)-1-(1-methyl-1H-imidazol-2-yl)-3-oxopropylpentanoate

, or

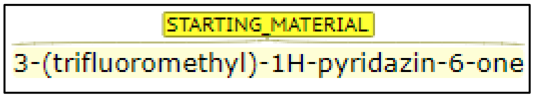

REACTION_PRODUCT

11

A product is a substance that is formed during a chemical reaction and must be annotated with this tag.

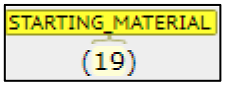
As REACTION_PRODUCT all representations of the product must be annotated, product name and/or label but also representatives like “title compound” generally pointing to the title of the reaction snippet. All such variants of the reaction product must be annotated in the snippet.

STARTING_MATERIAL


STARTING_MATERIAL

3-(trifluoromethyl)-1H-pyridazin-6-one

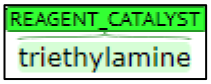
, or


STARTING_MATERIAL

(19)

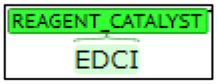
A substance that is consumed in the course of an organic chemical reaction providing carbon atoms to products is considered as starting material and must be annotated with this tag. In inorganic reactions the prerequisite is that the starting material provides any atoms to the product.

REAGENT_CATALYST



triethylamine

, or

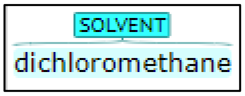


EDCI

A reagent is a compound added to a system to cause or help with a chemical reaction. Compounds like catalysts, bases to remove protons or acids to add protons must be annotated with this tag. In organic reactions compounds providing non carbon atoms to a product are also considered REAGENT_CATALYST.

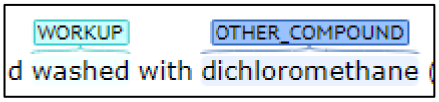
Reagents must be involved in the reaction. Compounds given in the course of work-up, like MgSO4 for drying must not be annotated with this tag. These must be annotated as OTHER_COMPOUND. It may well be that within the same snippet compounds may have a role as REAGENT_CATALYST and OTHER_COMPOUND.

SOLVENT



dichloromethane

A solvent is a chemical entity that dissolves a solute resulting in a solution. The solvents used in the reaction must be annotated with this tag. In case of solvent mixtures all individual solvents must be annotated. Solvents that also have the role as STARTING_MATERIAL must only be annotated as such. Solvents used in the work-up must not be annotated as SOLVENT but as OTHER_COMPOUND.

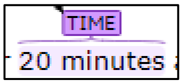


d washed with dichloromethane (

It may well be that within the same snippet compounds may have a role as SOLVENT and OTHER_COMPOUND.

Alternatively used solvents must not be annotated (e.g. in case of ‘dichloromethane or chloroform was used’ none of the mentioned solvents must be annotated).

TIME

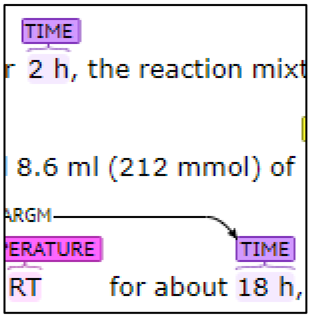


20 minutes

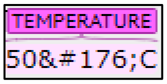
The reaction time of the reaction must be annotated with this tag.

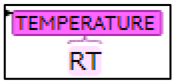
If just one particular time information is given (e.g. 20 min, 2 h or 3 d), that time information must be annotated.

If different procedures with different reaction times were carried out consecutively (e.g. 30 min stirring at 20 °C, then 2 h reflux) the individual times must be annotated.



TEMPERATURE



, or


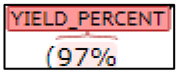
The temperature (range) at which the reaction was carried out must be annotated with this tag.

In case a reaction was carried out at more than one temperature, the given lowest and the given highest temperature must be annotated. Temperatures within this range must not be annotated.

The temperature range can be given with (1) numerical values or (2) by a specific keyword. “room temperature (RT)”. This keyword must be annotated if the temperature is not specified by a concrete value. “Room temperature” is representing 20 °C here. This must be considered when setting ranges and entering only the minimum and maximum temperature.

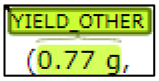
It must be kept in minds that the xml expression for °C is given as “&#176;”.

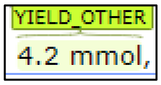
YIELD_PERCENT



Yield given in percent values must be annotated with this tag. Only isolated yields must be annotated with this particular tag.

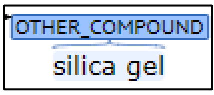
YIELD_OTHER

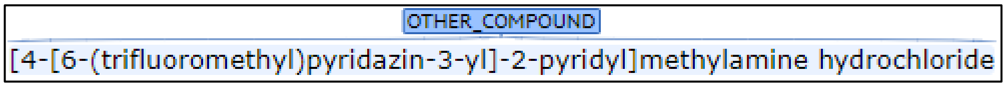


, or


Yields provided in other units than % must be annotated with this tag. YIELD_OTHER can be given as amount of substance (in mol or mmol) received mass of substance (in g or mg)

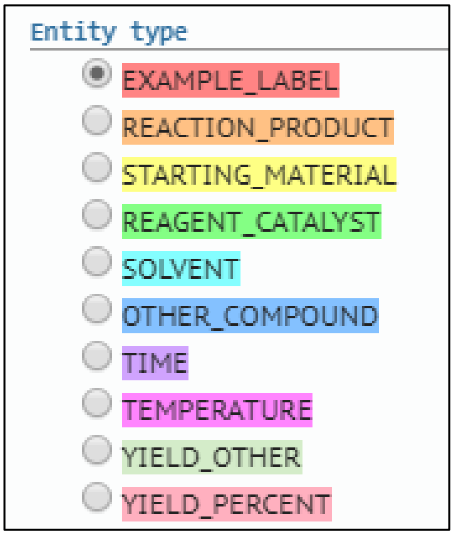
OTHER_COMPOUND



, or

OTHER_COMPOUND
[4-[6-(trifluoromethyl)pyridazin-3-yl]-2-pyridyl]methylamine hydrochloride

Other chemical compounds, which are not the products, starting materials, reagents and solvents, must be annotated with this tag. This can be standard chemicals used for drying but also the overall title compound of a set of reactions present in the snippet.

The following colors are used to distinguish different entity types in BRAT.



Entity type

● EXAMPLE_LABEL
○ REACTION_PRODUCT
○ STARTING_MATERIAL
○ REAGENT_CATALYST
○ SOLVENT
○ OTHER_COMPOUND
○ TIME
○ TEMPERATURE
○ YIELD_OTHER
○ YIELD_PERCENT

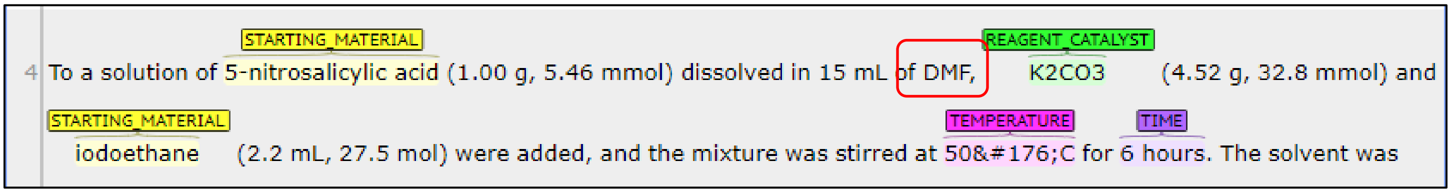
Real Live Problematic Examples

All the above entities are generally pre-tagged either by correlation with Reaxys content or by a chemical entity recognition process. Some mistakes are intrinsically present in the underlying processes. Therefore, the main aspect of the chemical entity annotation will be a thorough check of existing tags. Greatest care must be taken to ensure consistency and correctness.

In general, three aspects have to be considered here:

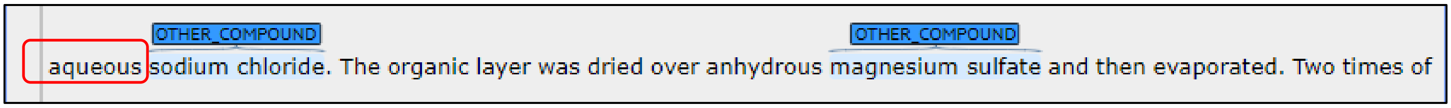
- Missing tags – that must be annotated
- Wrong tags – that must be changed
- Wrong tags - that must be deleted

Missing tags



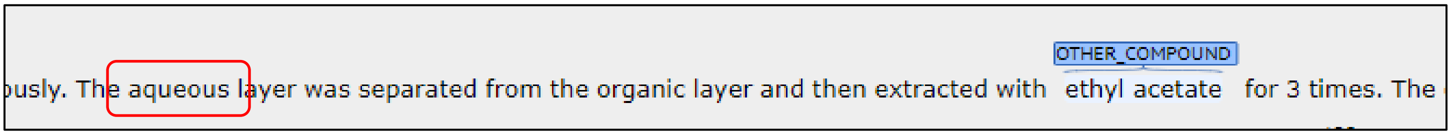
4 To a solution of 5-nitrosalicylic acid (1.00 g, 5.46 mmol) dissolved in 15 mL of DMF, K2CO3 (4.52 g, 32.8 mmol) and iodoethane (2.2 mL, 27.5 mol) were added, and the mixture was stirred at 50&#176;C for 6 hours. The solvent was

The solvent DMF – dimethylformamide is missing in the original annotation. The mapping process, as well as, the chemical entity recognition are mostly depending on systematic names. Abbreviations like DMF here may cause problems and remain un-tagged.



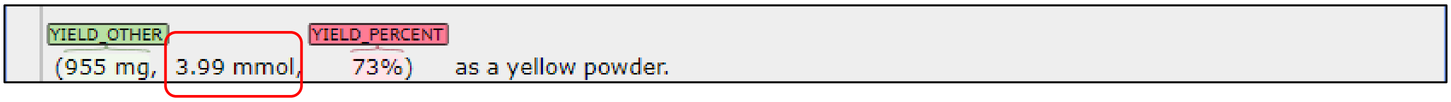
aqueous sodium chloride. The organic layer was dried over anhydrous magnesium sulfate and then evaporated. Two times of

The solvent water is “hidden” in this specific term. It is not detected by chemical entity recognition.



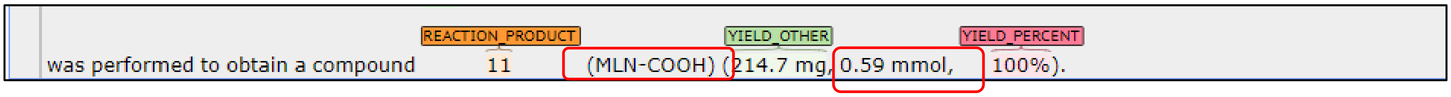
usly. The aqueous layer was separated from the organic layer and then extracted with ethyl acetate for 3 times. The

The term “aqueous” can be ambiguous. Only in cases where this word is used as a placeholder for the compound annotation must be done. In the above case the “aqueous” is only further identifying the layer and must therefore not be annotated.



(955 mg, 3.99 mmol, 73%) as a yellow powder.

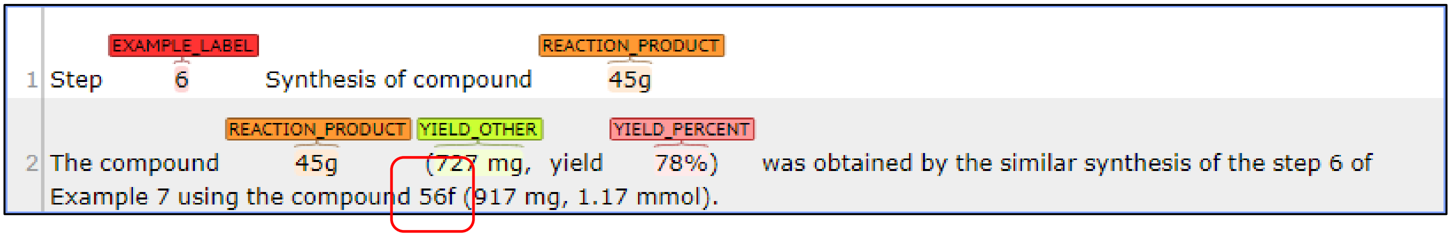
The absolute yield provided in mmol is not pre-annotated. Please add further annotation YIELD_OTHER.



was performed to obtain a compound 11 (MLN-COOH) (214.7 mg, 0.59 mmol, 100%).

The second label provided for the product is missing and must be annotated. In addition, the absolute yield in mmol is missing.

In case the reaction is missing the starting material and shows only the REACTION_PRODUCT as indirect entry the STARTING_MATERIAL should be identified semantically.

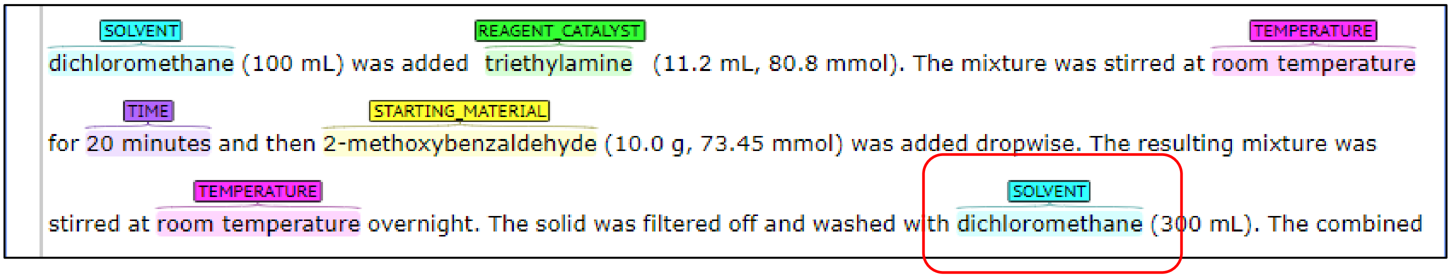


Step 6 Synthesis of compound 45g

The compound 45g (727 mg, yield 78%) was obtained by the similar synthesis of the step 6 of Example 7 using the compound 56f (917 mg, 1.17 mmol).

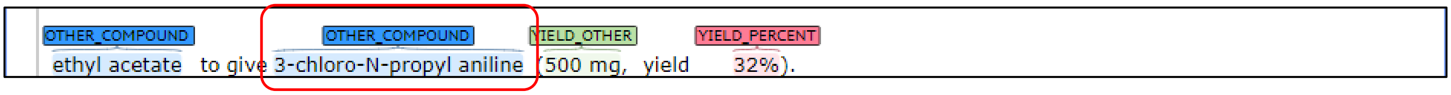
Here no STARTING_MATERIAL was pre-tagged. By semantic analysis of the snippet 56f can be identified as STARTING_MATERIAL.

Wrong tags - that must be changed



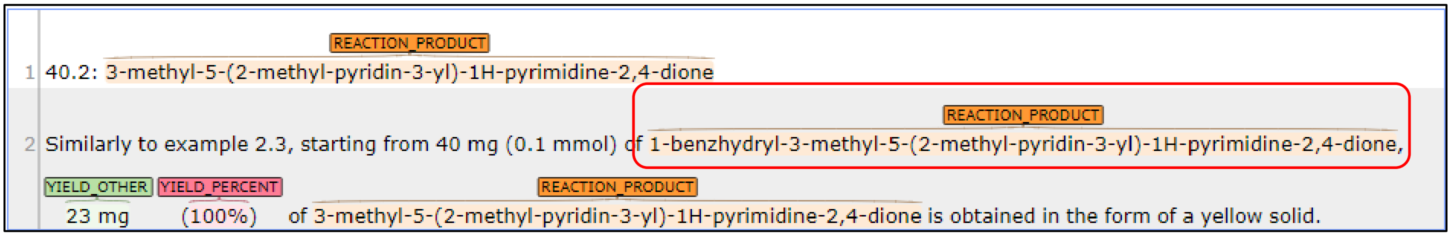
dichloromethane (100 mL) was added triethylamine (11.2 mL, 80.8 mmol). The mixture was stirred at room temperature for 20 minutes and then 2-methoxybenzaldehyde (10.0 g, 73.45 mmol) was added dropwise. The resulting mixture was stirred at room temperature overnight. The solid was filtered off and washed with dichloromethane (300 mL). The combined

Dichloromethane is present in two instances. Whilst the first instance is correctly tagged as SOLVENT the second instance is clearly part of the workup (washed with…) and must therefore be annotated as OTHER_COMPOUND.



ethyl acetate to give 3-chloro-N-propyl aniline (500 mg, yield 32%).

3-chloro-N-propyl aniline has been tagged as OTHER_COMPOUND but must have been annotated as REACTION_PRODUCT



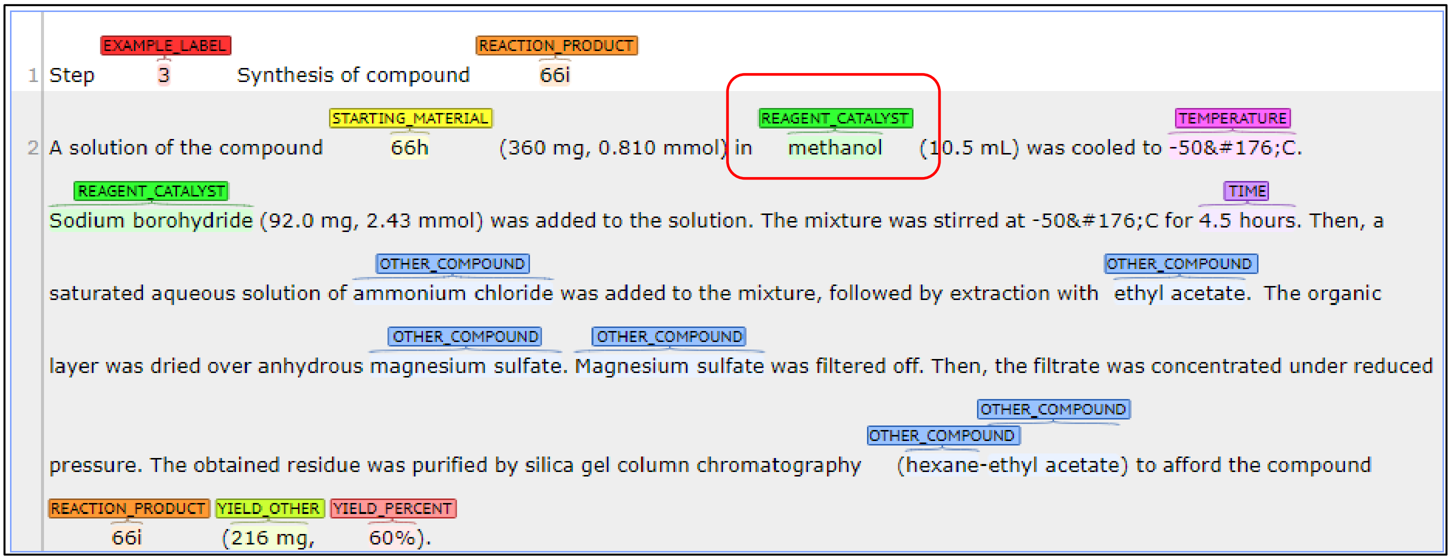
40.2: 3-methyl-5-(2-methyl-pyridin-3-yl)-1H-pyrimidine-2,4-dione

Similarly to example 2.3, starting from 40 mg (0.1 mmol) of 1-benzhydryl-3-methyl-5-(2-methyl-pyridin-3-yl)-1H-pyrimidine-2,4-dione, 23 mg (100%) of 3-methyl-5-(2-methyl-pyridin-3-yl)-1H-pyrimidine-2,4-dione is obtained in the form of a yellow solid.

1-benzhydryl-3-methyl-5-(2-methyl-pyridin-3-yl)-1H-pyrimidine-2,4-dione has been tagged as REACTION_PRODUCT but must have been annotated as STARTING_MATERIAL

Notes:

- In case the reaction in the snippet holds annotations for main STARTING_MATERIAL and REACTION_PRODUCT which are not directly given no changes regarding assignment of the chemical entities must be made within the reaction regarding REAGENT_CATALYST, SOLVENT and further STARTING_MATERIALS. These entities are pre-tagged by match with data excerpted for Reaxys. Without any context present there practically no chance to clear up matters.

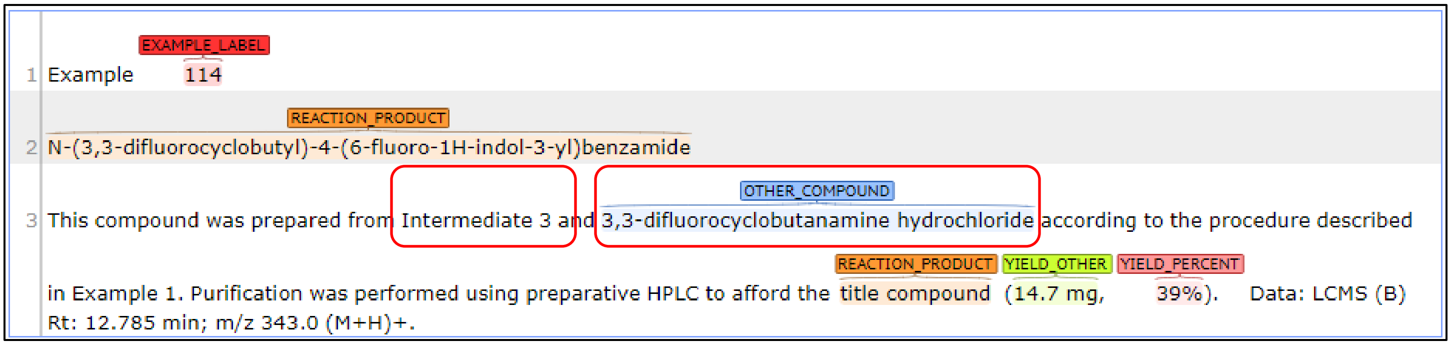


Step 3 Synthesis of compound 66i

A solution of the compound 66h (360 mg, 0.810 mmol) in methanol (10.5 mL) was cooled to -50&#176;C. Sodium borohydride (92.0 mg, 2.43 mmol) was added to the solution. The mixture was stirred at -50&#176;C for 4.5 hours. Then, a saturated aqueous solution of ammonium chloride was added to the mixture, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. Magnesium sulfate was filtered off. Then, the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane-ethyl acetate) to afford the compound 66i (216 mg, 60%).

Methanol is also a typical SOLVENT but according to pre-tagging it is a REAGENT_CATALYST. No changes can be made here.

- If either STARTING_MATERIAL or REACTION_PRODUCT is given directly necessary changes must be made. These changes are often necessary when the reaction used for pre-tagging was an “analogue reaction”. As for these no starting materials are entered by default starting materials are tagged by the chemical entity recognition only as OTHER_COMPOUND.



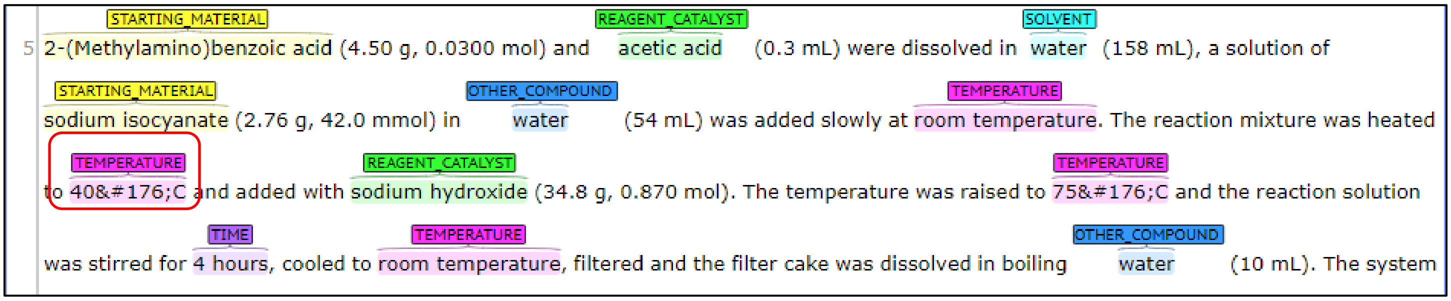
Example 114

N-(3,3-difluorocyclobutyl)-4-(6-fluoro-1H-indol-3-yl)benzamide

This compound was prepared from Intermediate 3 and 3,3-difluorocyclobutanamine hydrochloride according to the procedure described in Example 1. Purification was performed using preparative HPLC to afford the title compound (14.7 mg, 39%). Data: LCMS (B) Rt: 12.785 min; m/z 343.0 (M+H)+.

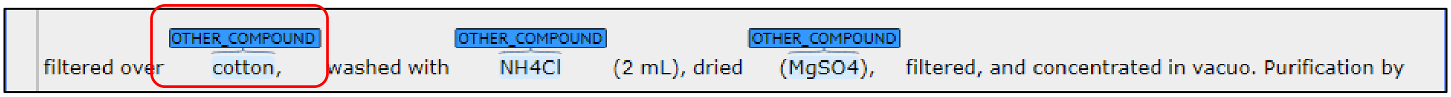
Intermediate 3 has not been detected at all and 3,3-difluorocyclobutanamine hydrochloride only as OTHER_COMPOUND. Both must have been tagged as STARTING_MATERIALS

Wrong tags - that must be deleted



2-(Methylamino)benzoic acid (4.50 g, 0.0300 mol) and acetic acid (0.3 mL) were dissolved in water (158 mL), a solution of sodium isocyanate (2.76 g, 42.0 mmol) in water (54 mL) was added slowly at room temperature. The reaction mixture was heated to 40&#176;C and added with sodium hydroxide (34.8 g, 0.870 mol). The temperature was raised to 75&#176;C and the reaction solution was stirred for 4 hours, cooled to room temperature, filtered and the filter cake was dissolved in boiling water (10 mL). The system

40&#176;C was tagged as TEMPERATURE. In this case a range is given with the lowest temperature at 20 °C (room temperature) the highest point with 75 °C. Therefore, the tag for 40&#176;C must be deleted.



filtered over cotton, washed with NH4Cl (2 mL), dried (MgSO4), filtered, and concentrated in vacuo. Purification by

Cotton is no chemical compound. This wrongly assigned tag must be deleted.