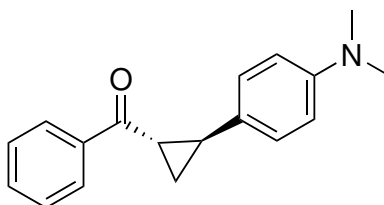


Synthesis of *trans*-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone



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Abstract

trans-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone was synthesised from 4-dimethylamino chalcone and trimethylsulfoxonium iodide using sodium hydride through a Corey-Chaykovsky reaction. 4-Dimethylamino chalcone was prepared from 4-dimethylamino benzaldehyde and acetophenone using sodium hydroxide through an Aldol condensation reaction. The atom economy of the reaction is 22% for the formation of 4-dimethylamino chalcone and 49% for the subsequent formation of *trans*-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone, resulting in a combined atom economy of 11%. It is as low since many heavy byproducts are obtained and potassium hydroxide is added in large excess. The reaction between 4-dimethylamino benzaldehyde and acetophenone is stirred over three days at 0 °C. The subsequent reaction between 4-dimethylamino chalcone is stirred over night at RT. The crude product is purified by recrystallisation from ethanol. The obtained yield for the intermediate was 43%. The obtained yield for the product was 15%. This resulted in an overall yield of 6.5%. The product and the intermediate were analyzed by melting point and IR.

D. Isler

Zurich, September 2, 2022

Daniel Isler

1 Introduction

trans-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone is synthesised from 4-dimethylamino chalcone and trimethylsulfoxonium iodide using sodium hydride. 4-Dimethylamino chalcone is prepared from 4-dimethylamino benzaldehyde and acetophenone using potassium hydroxide. Sulfur ylides have come a long way in organic

synthesis since the pioneer work of Corey and Chaykovsky in the 1960s. The Corey-Chaykovsky reaction is used to form compounds with three-membered rings. These can vary from epoxides over aziridines to cyclopropanes. Furthermore, usage of chiral sulfides in stoichiometric amounts results in an enantioselective behaviour. [1]

2 Chemical Properties

4-Dimethylamino chalcone was synthesised from 4-dimethylamino benzaldehyde (1) and acetophenone (2) using sodium hydroxide.

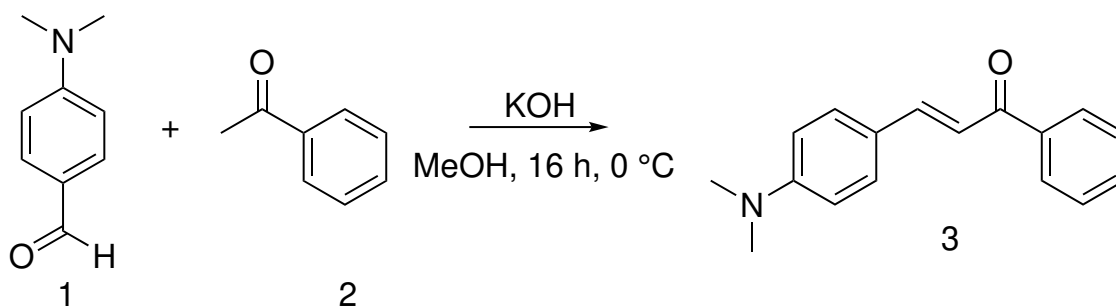


Figure 1: Performed aldol condensation reaction.

trans-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone (5) was synthesised from 4-dimethylamino chalcone (3) and trimethylsulfoxonium iodide using sodium hydride.

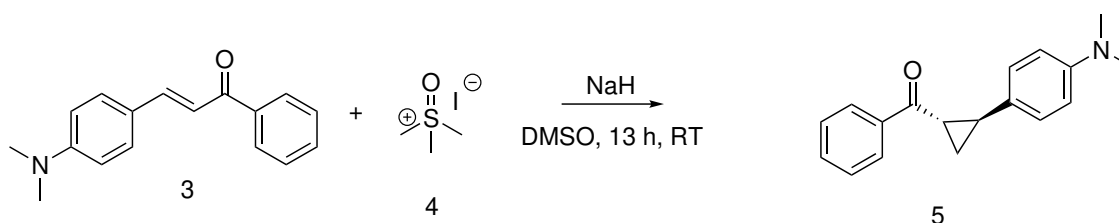







Figure 2: Subsequently performed Corey-Chaykovsky reaction.

Table 1: Chemical properties of the reactants and the product [2].

Reactants	MW in g/mol	Density	Melting Point	Boilingpoint
4-Dimethylamino benzaldehyde	149.19	-	74.5 °C	176-177 °C
Acetophenone	120.15	1.033 g/cm3 @ Temp: 15 °C	20.5 °C	202 °C
Potassium hydroxide	56.1	2.044 g/cm3	380 °C	1327 °C
Trimethylsulfoxonium iodide	220.07	-	200 °C @ Solvent: Water	-
Sodium hydride	24	1.396 g/cm3 @ Temp: 25 °C	-	-
Product	MW in g/mol	Density	Melting Point	Boilingpoint
<i>trans</i> -(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone	265.4	-	98 - 99.2 °C	-

All chemicals were provided by the Morandi-lab and used without further purification. The Hazard-&Precautionary-Phrases, for which the abbreviation H-&P will be used, are listed in the appendix. They were researched on [9].

Table 2: Safety regulations for the chemicals used during the experiment.

4-Dimethylamino benzaldehyde, CAS:100-10-7		H317-P261, P272, P280, P302+P352, P333+P313, P362+P364
Acetophenone, CAS:98-86-2		H302, H319-P264, P270, P280, P301+P312, P305+P351+P338, P337+P313
Potassium hydroxide, CAS:1310-58-3		H290, H302, H314, H318, H315, H319-P234, P260, P280, P301+P312, P303+P361+P353, P305+P351+P338
Methanol, CAS:67-56-1		H225, H301, H331, H311, H370, H301+H311+H331, H371, H301+H311-P210, P233, P280, P301+P310, P303+P361+P353, P304+P340+P311
Trimethylsulfoxonium iodide, CAS:1774-47-6		-
Sodium hydride, CAS:7646-69-7		H228, H260, H290, H314- P210, P231+P232, P260, P280, P303+P361+P353, P305+P351+P338
4-(Dimethylamino)chalcone, CAS:1030-27-9		H302, H414-P264, P270, P273, P301+P317, P330, P501
DMSO, CAS:67-68-5		-
Sodium bicarbonate, CAS:144-55-8		-
Magnesium sulfate, CAS:7487-88-9		-

2.1 Disposal

The organic waste is disposed in the waste for non-chlorinated organic solvents. The aqueous solutions are disposed in the aqueous basic/acidic waste respectively. The filtered solid and other contaminated solids are disposed in the solid waste.

3 Reaction mechanism

This section describes the mechanism of the synthesis in detail. Acetophenone (2) is deprotonated by potassium hydroxide. The formed enolate (6) attacks the electrophilic 4-dimethylamino benzaldehyde (1). By protonation of the resulting alkoxide (7), then deprotonation of the CH₂ group and elimination of OH⁻ 4-dimethylamino chalcone (3) is obtained.

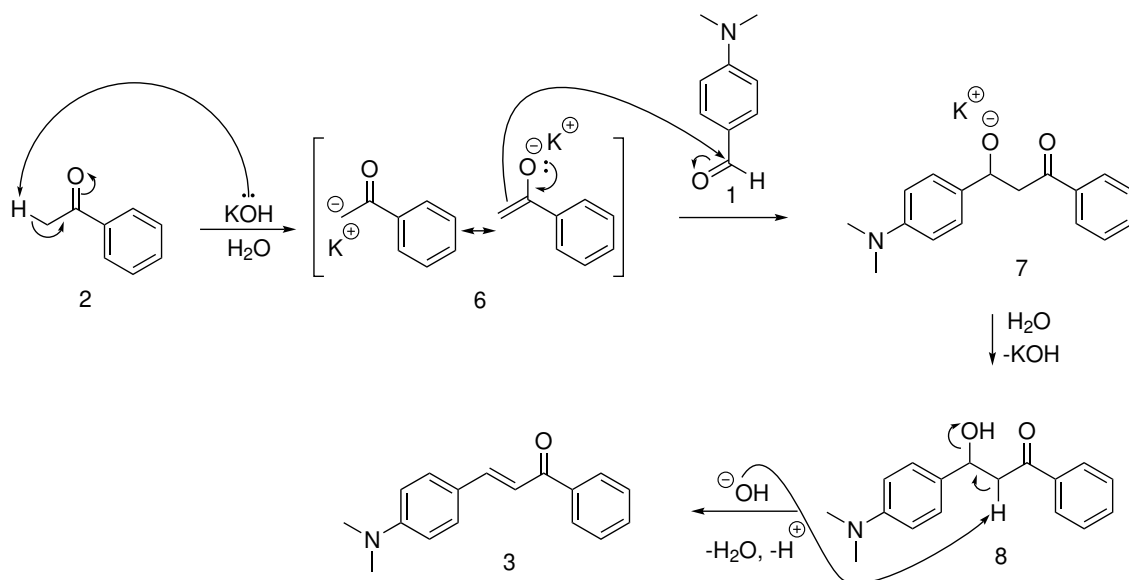


Figure 3: Reaction mechanism of the performed aldol condensation to obtain of 4-dimethylamino chalcone.

Through deprotonation by sodium hydride, Me₃SOI (4) forms the activated dimethylloxosulfonium methyllide (11). 4-Dimethylamino chalcone (3) is attacked to form intermediate (12) through a 1,4-addition. Through an intramolecular S_N2 like reaction with DMSO as leaving group and the enolate as nucleophile, *trans*-(4-(dimethylamino)phenyl)(2-phenylcyclopropyl)methanone is obtained. Due to the reversibility of the 1,4-addition, the thermodynamically more stable *trans* product is formed.

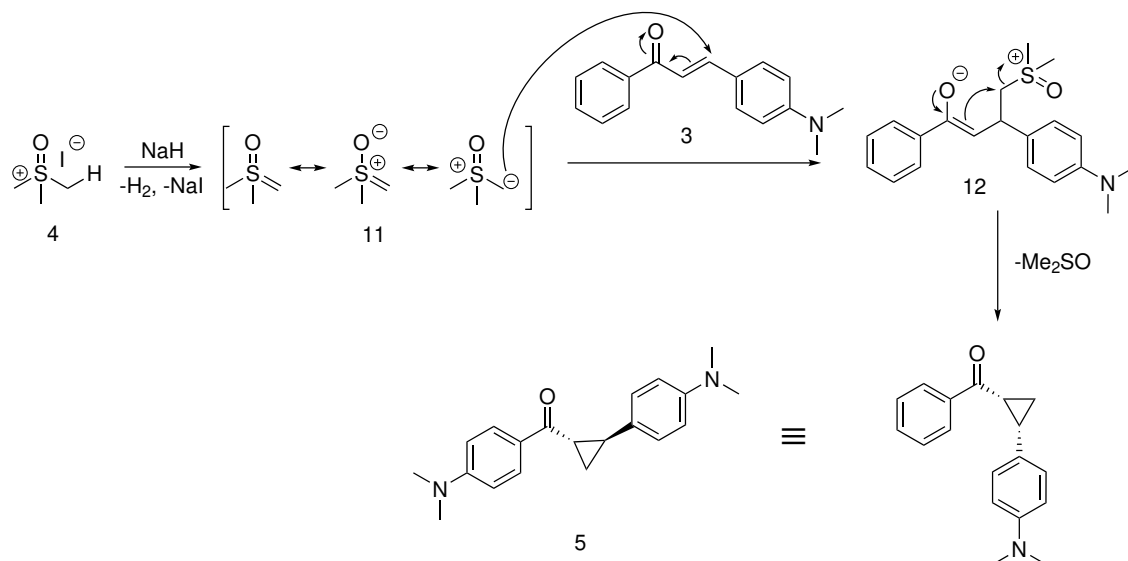


Figure 4: Reaction mechanism of the synthesis of *trans*-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone.

4 Atom Economy

$$AE_1 = \frac{M_{Product}}{M_{Reactants}} = \frac{251.3 \frac{\text{g}}{\text{mol}}}{(149.2 + 120.2 + 4 \cdot 56.11) \frac{\text{g}}{\text{mol}}} \cdot 100\% = 22\%$$

$$AE_2 = \frac{M_{Product}}{M_{Reactants}} = \frac{267.4 \frac{\text{g}}{\text{mol}}}{(1.2 \cdot 24 + 1.2 \cdot 220.07 + 251.3) \frac{\text{g}}{\text{mol}}} \cdot 100\% = 49\%$$

$$AE_{tot} = AE_1 \cdot AE_2 = 11\%$$

5 Procedure

In 100 mL flask equipped with a stirring bar 4-dimethylamino benzaldehyde (2.5 g, 17 mmol, 1.0 eq) and acetophenone (2.1 g, 17 mmol, 1.0 eq) were dissolved in methanol (43 mL, 0.4 M) and cooled to 0 °. Potassium hydroxide (3.8 g, 68 mmol, 4.0 eq) was added and the reaction was stirred over three days at RT, then stored in fridge for one day. The precipitate was collected by filtration, washed with H₂O and little methanol. The crude product was purified by recrystallisation from methanol to yield 4-dimethylamino chalcone (1.8 g, 7.3 mmol, 43%) as a light yellow solid.

A 100 mL flask was charged with trimethyl-

sulfonium iodide (1.1 g, 4.8 mmol, 1.2 eq) and sodium hydroxide (0.18 g, 4.8 mmol, 1.0 eq, 60%). After exchange of the atmosphere with nitrogen, dry DMSO (16 mL, 0.25 M) was added dropwise and the reaction was stirred for 30 min at RT. The previously prepared 4-dimethylamino chalcone (1.0 g, 4.0 mmol, 1.0 eq) was added as solid and the reaction was stirred overnight at RT. TLC analysis (9 : 1 hexane : ethylacetate) showed complete consumption of the reactant 4-dimethylamino chalcone. The reaction was quenched with H₂O and the aqueous layer was extracted with DCM (2 times, 40 mL). The combined organic layers were

washed with H₂O, saturated NaHCO₃, brine and dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by recrystallisation from ethanol to yield *trans*-(4-(dimethylamino)phenyl)(2-phenylcyclopropyl)methanone (0.15 g, 0.6 mmol, 15%) as a light yellow solid.

6 Characterisation

6.1 Melting point

6.1.1 4-Dimethylamino chalcone

Literature value [7]: 111 – 113 °C

Measured value: 113 °C

6.1.2 *trans*-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone

Literature value [3]: 98 – 99.2 °C

Measured value: 160 °C

6.2 Infrared spectrum

6.2.1 4-Dimethylamino chalcone

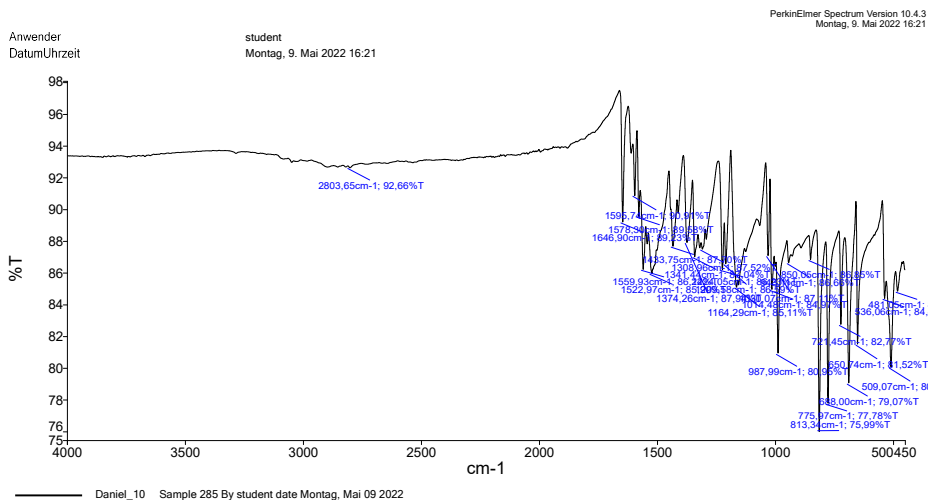


Figure 5: Measured infrared spectrum of the purified product from the synthesis of 4-dimethylamino chalcone.

Table 3: Interpretation of the stretches in the measured IR characteristic for 4-dimethylamino chalcone [6].

Wave number [cm^{-1}]	Interpretation
2804 (w)	C-H stretching
1647 (m)	C=O stretching
1596 (m)	C=C stretching, aromatic
1523 (m)	C=C stretching, aromatic
1341 (m)	C-N stretching, aryl
1309 (m)	C-N stretching, aryl

By comparing the measured IR spectrum to the literature spectrum [5], shown in Fig. 6, the product could be clearly identified. The C=O, the aromatic C=C and the Ar-N stretches are characteristic for 4-dimethylamino chalcone. The peaks in the fingerprint area are in agreement with the reported spectrum. From the absence of additional peaks it can be deduced that 4-dimethylamino chalcone was obtained in sufficient purity.

The yield of 43% is very low, compared to the literature value of 88% [8]. A likely cause for that would be that the starting material was obtained from a previous synthesis and might not have been as pure as expected.

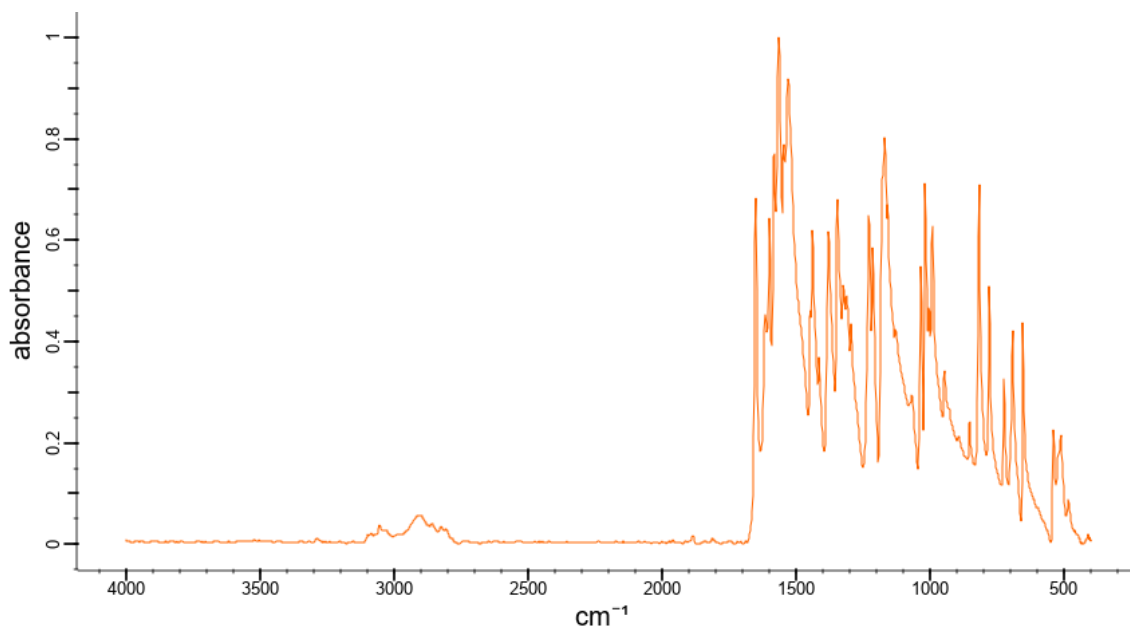


Figure 6: Literature IR of 4-dimethylamino chalcone from [5]

6.2.2 *trans*-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone

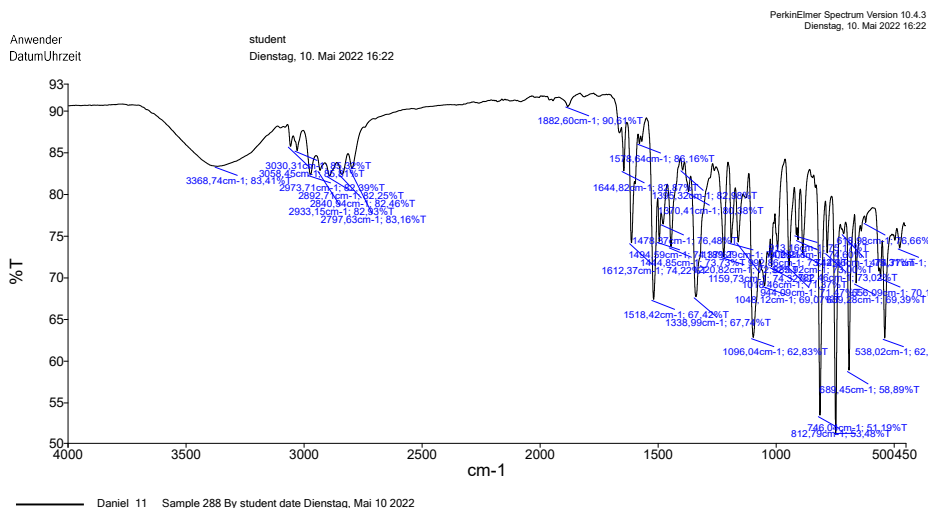


Figure 7: Measured infrared spectrum of the purified product from the synthesis of *trans*-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone.

Table 4: Interpretation of the stretches in the measured IR characteristic for *trans*-(4-(Dimethylamino)phenyl)(2-phenylcyclopropyl)methanone [6].

Wave number [cm ⁻¹]	Interpretation
3369 (m, b)	O–H stretching, probably solvent
2974 (m)	C–H stretching, alkyl
2798 (m)	C–H stretching
1612 (s)	C=C stretching, aromatic
1518 (s)	C=C stretching, aromatic

Unfortunately no full spectrum could be found in literature and therefore the fingerprint area could not be compared. However, a paper was obtained where the most important peaks were listed as follows [5]. IR (in cm⁻¹): 2921, 1603, 1396, 1196.

Due to the great difference of the referenced melting point and the disagreement of the literature infrared spectra it can be deduced that the wrong product was obtained from the conducted synthesis.

Even if the right product was been obtained, the yield of 15% is very low, compared to the literature value of 97% [4]. A likely cause for that would be that the nitrogen atmosphere was removed to add 4-dimethylamino chalcone as solid and not dissolved in DMSO as in

[4]. Another possible cause would be that only an impurity was obtained through the recrystallisation while the product remained in solution.

References

- [1] Clarice A. D. Caiuby, Lucas G. Furniel, and Antonio C. B. Burtoloso. "Asymmetric transformations from sulfoxonium ylides". In: *Chem. Sci.* 13 (5 2022), pp. 1192–1209. DOI: 10.1039/D1SC05708A. URL: <http://dx.doi.org/10.1039/D1SC05708A>.
- [2] CAS API. URL: <https://commonchemistry.cas.org/api/>. (accessed: 02.03.2022).
- [3] Chenhui Chen et al. "Iron-Catalyzed Hydroboration of Vinylcyclopropanes". In: *Organic Letters* 19.19 (2017). PMID: 28953399, pp. 5422–5425. DOI: 10.1021/acs.orglett.7b02691. eprint: <https://doi.org/10.1021/acs.orglett.7b02691>. URL: <https://doi.org/10.1021/acs.orglett.7b02691>.
- [4] Chenhui Chen et al. "Iron-Catalyzed Hydroboration of Vinylcyclopropanes". In: *Organic Letters* 19.19 (2017). PMID: 28953399, pp. 5422–5425. DOI: 10.1021/acs.orglett.7b02691. eprint: <https://doi.org/10.1021/acs.orglett.7b02691>. URL: <https://doi.org/10.1021/acs.orglett.7b02691>.
- [5] Inc. John Wiley & Sons. *Spectra-Base*. URL: <https://spectrabase.com/spectrum/3PcCrMu0ilF>. (accessed: 11.05.2022).
- [6] Jürgen Popp Manfred Reichenbacher. *Strukturanalytik organischer und anorganischer Verbindungen*. Teubner, 2007. ISBN: 978-3-8351-9204-1.
- [7] Kieran Nicholson, Thomas Langer, and Stephen P. Thomas. "Borane-Catalyzed, Chemoselective Reduction and Hydrofunctionalization of Enones Enabled by B–O Transborylation". In: *Organic Letters* 23.7 (2021). PMID: 33724859, pp. 2498–2504. DOI: 10.1021/acs.orglett.1c00446. eprint: <https://doi.org/10.1021/acs.orglett.1c00446>. URL: <https://doi.org/10.1021/acs.orglett.1c00446>.
- [8] Kieran Nicholson, Thomas Langer, and Stephen P. Thomas. "Borane-Catalyzed, Chemoselective Reduction and Hydrofunctionalization of Enones Enabled by B–O Transborylation". In: *Organic Letters* 23.7 (2021). PMID: 33724859, pp. 2498–2504. DOI: 10.1021/acs.orglett.1c00446. eprint: <https://doi.org/10.1021/acs.orglett.1c00446>. URL: <https://doi.org/10.1021/acs.orglett.1c00446>.
- [9] Web Site sigma-aldrich.com. URL: <https://sigma-aldrich.com>. (accessed: 24.03.2022).

A Appendix

A.1 Safety

A.1.1 H-Phrases

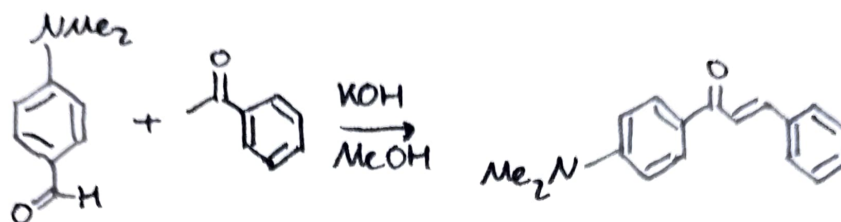
H317: May cause an allergic skin reaction.
H302: Harmful if swallowed.
H319: Causes serious eye irritation.
H290: May be corrosive to metals.
H314: Causes severe skin burns and eye damage.
H318: Causes serious eye damage.
H315: Causes skin irritation.
H225: Highly flammable liquid and vapour.
H301: Toxic if swallowed.
H331: Toxic if inhaled.
H311: Toxic in contact with skin.
H370: Causes damage to organs.
H301+H311+H331: Toxic if swallowed, in contact with skin or if inhaled
H371: May cause damage to organs.
H301+H311: Toxic if swallowed or in contact with skin.

A.1.2 P-Phrases

P261: Avoid breathing dust/fume/gas/mist/vapours/spray.
P272: Contaminated work clothing should not be allowed out of the workplace.
P280: Wear protective gloves/protective clothing/eye protection/face protection.
P302+P352: IF ON SKIN: Wash with plenty of water
P333 + P313: If skin irritation or rash occurs: Get medical advice/attention.
P362+P364: Take off contaminated clothing. And wash it before reuse.
P264: Wash ... thoroughly after handling.
P270: Do not eat, drink or smoke when using this product.
P301 + P312: IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell.
P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P337 + P313: If eye irritation persists: Get medical advice/attention.
P234: Keep only in original container.
P260: Do not breathe dust/fume/gas/mist/vapours/spray.
P303 + P361 + P353: IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower.
P210: Keep away from heat/sparks/open flames/hot surfaces. — No smoking.
P233: Keep container tightly closed.
P301 + P310: IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician.
P304+P340+P311: IF INHALED: Remove person to fresh air and keep comfortable for breathing. Call a POISON CENTER or doctor.

A.2 Lab journal copies

Experiment 10, 4-Dimethylamino chalcone



Reactant	MW/ $\frac{g}{mol}$	Eq.	Moles	Mass/g	V/ml
4-Dimethylamino benzaldehyde	149.19	1.0	0.017	2.5483	-
Acetophenone	120.15	1.0	0.017	2.05g	1.99 $1.03 \frac{g}{ml}$
KOH	56.1	4.0	0.068	3.83g	-
MeOH	32.04	0.4M			42.5
Product	MW/ $\frac{g}{mol}$	Yield	Moles	Mass/g	
4-Dimethylamino chalcone	257.32g	43%	7.25mmol	1.8225g	

Procedure:

- Dissolve 4-Dimethylamino & Acetophenone in MeOH
- Cool to 0°C
- Add KOH \Rightarrow vigorously stirring over ~~night~~ 3 days
- Cool to 0°C
- Collect precipitate via filtration
 - \hookrightarrow wash with H₂O, little cold MeOH
- If not pure:
 - purification by recrystallisation from MeOH

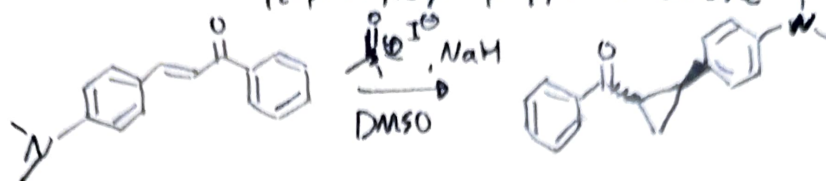
Characterisation:

- MP \Rightarrow 113°C
- IR

Date of exp.

05.05./10.05.2022

Experiment 11: trans-(4-(Dimethylamino)phenyl) (2-phenylcyclopropyl) methanone



Reactant	MW/ $\frac{g}{mol}$	Moles	Mass	V/ml	Eq. Parts
4-Dimethylamino chalcone	257.32	4mmol	1g	-	1.0
Me ₃ SOI	220.07	4.8mmol	1.7g	-	1.2 ^{30%}
NaH	24	4.8mmol	0.18g	-	1.2 ^{60%}
DMSO				16ml	0.25M
Product	MW/ $\frac{g}{mol}$	Yield	Moles	Mass	
trans *	256.4	15%	0.6mmol	0.15g	
$m_0 = 6.7048g, m_1 = 6.8584g$					

Procedure:

- Charge flask with Me₃SOI, NaH
- Apply N₂ atmosphere
- Add dry DMSO slowly, stir at RT for 30 min
- Add solid Chalcone in portions
- Stir for 20h until TLC shows starting material consumed (70:1 hex/EA)
- Quenche with H₂O (carefully)
- Extract with DCM 2x 40ml ^{prime}
- Wash with H₂O, sat. NaHCO₃, dry over MgSO₄, filter and concentrate

Purification by recrystallisation from EtOH

Characterisation:

MP:
IR

Date of exp.:

B Acknowledgment

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