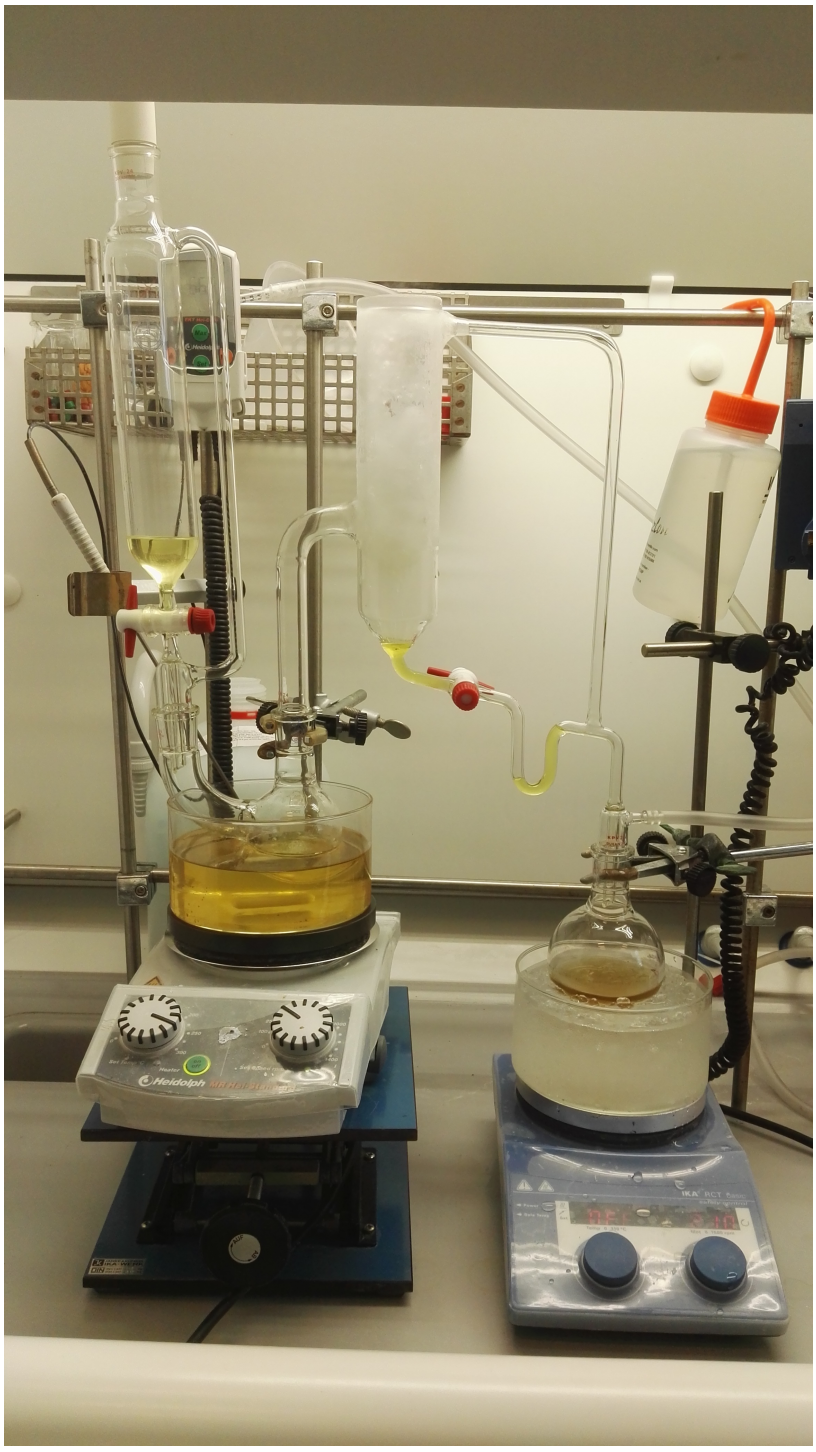
# Cyclopropanation of *tert*-butyl 3-butenoate with freshly distilled diazomethane.

Exam assignment for *Syntesekemiske Metoder*, August 2016.

PhD student Jakob Blom (Blom@chem.au.dk)

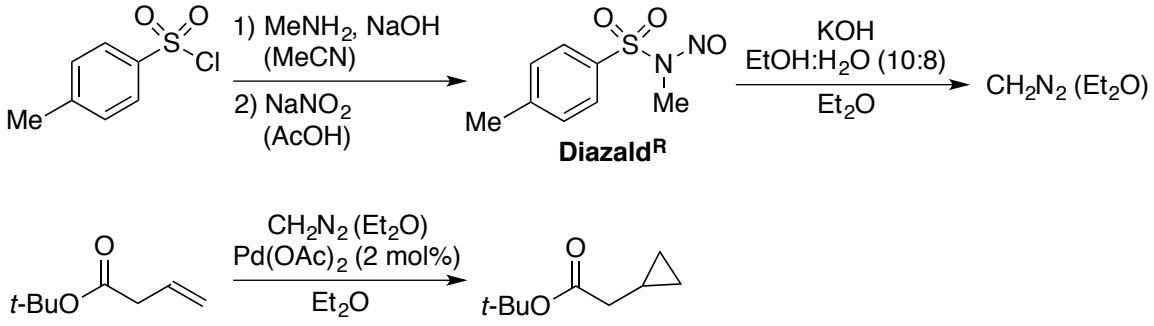


*PhD student Jakob Blom*
*Blom@chem.au.dk*

# 1. A brief presentation.

The German chemist Hans Von Pechmann first described the formation of diazomethane in 1884.[1] Over the last 130 years, diazomethane has proven to be a versatile reagent for *e.g.* the methylation of acidic hydroxyl functionalities, homologation of acyl chlorides and lately cyclopropanations of alkenes. Though, due to safety concerns regarding the vicious nature of the reagent, alternative protocols using more handily reagents have been developed for most of the formerly mentioned transformations.
It is the authors' personal opinion that despite the opportunity for alternative strategies, synthesis and handling of diazomethane should be in the repertoire of every organic chemist. Especially as treatment of alkenes with diazomethane in the presence of a palladium catalyst, allows for the formation of unfunctionalized cyclopropanes, which the author finds most useful for the synthesis of a starting material in an ongoing project.

In this report, the synthesis of the diazomethane precursor *N*-Methyl-*N*-(*p*-tolylsulfonyl)nitrosamide (Diazald®) is disclosed, followed by the formation and distillation of diazomethane which is used in the cyclopropanation of *tert*-butyl 3-butenoate.




# 2. Synthetic procedures.

*Preparation of Diazald®.*[2]

In a 100 mL round-bottomed flask was added a 40% aqueous solution of methyl amine (4.00 mL, 50 mmol, 2.5 equiv) to a solution of *p*-toluene sulphonyl chloride (3.8 g, 20 mmol, 1.0 equiv) in acetonitrile (40 mL). The mixture was allowed to react for 2 hours at rt, after which aqueous sodium hydroxide (1 g in 20 mL water) was added and the mixture was concentrated to dryness *in vacuo*. The remaining white solid was dissolved in warm acetic acid (glacial, 20 mL) and then the mixture was cooled to 0 °C. An aqueous solution of sodium nitrite (2 g in 4 mL water, 29 mmol, 1.5 equiv) was added dropwise to the cooled mixture, which was then allowed to warm to rt. After the formation of a heavy precipitate, an ice-water slurry (20 mL) was added to mixture which again was cooled to 0 °C. The crude mixture was filtered and the filter cake was washed with cold water (0 °C, 40 mL) to give the desired product as pale yellow crystalline solid (3.7 g, 17.4 mmol, 87 %).
**$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.86 (d, *J*=8.4 Hz, 2 H), 7.37 (d, *J*=8.4 Hz, 2 H), 3.12 (s, 3 H), 2.45 (s, 3 H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 146.3 (1 C), 134.2 (1 C), 130.5 (2 C), 128.1 (2 C), 29.0 (1 C), 21.9 (1 C).

[1] Pechmann, H. V. *Berichte der Deutschen Chemischen Gesellschaft*, **1894**, *27*, 1888.
[2] Mauraya, R. A.; Park, C. P.; Lee, J. H.; Kim, D.-P. *Angew. Chem. Int. Ed.* **2011**, *50*, 5952.

*Formation and distillation of diazomethane and cyclopropanation of tert-butyl 3-butenoate.*[3]

A Macro Diazald Kit® (Sigma Aldrich) with Clear-Seal Joints® was thoroughly rinsed in $Et_2O$ and inspected for defects. The reaction flask was charged with potassium hydroxide (5 g), water (10 mL) and ethanol (abs., 8 mL). In the receiver flask was added $Pd(OAc)_2$ (27 mg, 0.12 mmol, 0.02 equiv) to a solution of *tert*-butyl 3-butenoate (1.00 mL, 6.0 mmol, 1.0 equiv) in $Et_2O$ (60 mL). The Macro Diazald Kit® was assembled and the cold-finger trap was loaded with a dry ice-acetone slurry. The addition funnel was charged with $Et_2O$ (20 mL), which was added to the reaction flask and replaced by an ethereal solution of Diazald® (2.5 g in 30 mL $Et_2O$, 11.7 mmol, 1.9 equiv). The receiver flask was placed in an ice-water cooling bath and the reaction flask was placed in an oil bath, which was allowed to gradually warm to 60 °C. As condensation and dripping of $Et_2O$ into the receiver flask was observed, the Diazald® solution was added dropwise to the receiver flask, in the same rate as the distillation (Note 1). The yellow ethereal distillate of diazomethane was added dropwise to the receiver flask in the same rate as the distillation to avoid accumulation of the diazomethane solution in the cold-finger trap.
After the last drop of Diazald® solution was added to the reaction flask (30 minutes) the addition funnel was washed with $Et_2O$ (2 mL), which was allowed to add to the reaction flask mixture. Then the funnel was recharged with $Et_2O$ (ca. 20 mL) which was added dropwise to the reaction flask until the distillate became colorless and all the diazomethane was collected in the receiver flask.
Heating of the reaction flask was discontinued and the ice-water cooling bath was removed from the receiver flask, allowing it to gradually warm to rt. After 3 hours the Macro Diazald Kit® was gently disassembled and the mixture in the receiver flask was concentrated under a steam of $N_2$ (Note 2). The remaining heterogeneous black oil was distilled to yield the desired product as a colorless oil with a powerful odor (0.33 g, 34 %, bp. 43 °C (20 torr)).
**$^1$H NMR (400 MHz, $CDCl_3$):** δ 2.11 (d, *J*=7.2 Hz, 2 H), 1.45 (s, 9 H), 0.94-1.07 (m, 1 H), 0.48-0.55 (m, 2 H), 1.14 (q, *J*=4.8 Hz, 2 H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 172.9 (1 C), 80.2 (1 C), 40.8 (1 C), 28.3 (3 C), 7.2 (1 C), 4.3 (2 C).

Note 1: From this point forward and until the crude was concentrated, the synthesis ensemble was enclosed behind a blast screen.
Note 2: A longer reaction time might have been beneficial, as full consumption of the *tert*-butyl 3-butenoate was not achieved in this experiment.

## 3. Chemicals to be used in the synthesis.

*p*-Toluene sulphonyl chloride
40% aqueous solution of methyl amine
NaOH (pellets)
$NaNO_2$
KOH (pellets)
$Pd(OAc)_2$
*tert*-Butyl 3-butenoate

[3] For formation of diazomethane from Diazald® see: www.sigmaaldrich.com, Technical Bulletin AL-180 Diazald® and Diazomethane Generators.
For an example of palladium catalyzed cyclopropanation of an alkene with diazomethane see: Bristol-Myers Squibb Company, Patent: WO2005/46712 A1.

## 4. Special equipment to be used in the experiment.

Macro Diazald Kit® (Sigma Aldrich) with Clear-Seal Joints®

## 5. The essence and futures of the synthesis described.

Formation and handling of diazomethane, which was used for the synthesis of an unfunctionalized cyclopropan, was disclosed. Diazomethane is an extremely toxic, carcinogenic, and explosive gas that can only be handled safely under controlled manners in an ethereal solution.[3]

## 6. Special synthetic methods.

Handling of diazomethane can be challenging as it is a volatile (bp. -23 $^{o}$C), toxic, carcinogenic, and explosive compound. To overcome the toxicity of the compound, extreme care must be taken to ensure exposure to the compound is avoided during the synthesis. As gasses can be difficult to contain, all work must be done in a proper functioning fume hood and gloves and long sleeved lab coats should be worn at all time to minimalize the area of bare skin that could potentially come into contact with the gas in case of a leak.
The explosive nature of the diazomethane calls for the usage of special Clear-Seal Joints® glassware, that lacks the standard ground joints and has been treated to ensure the glassware is free of sharp edges as rough surfaces have been proven to be initiators of detonations.[4] Great care must be taken to ensure that the diazomethane is contained in an ethereal solution of low concentration, as neat and supersaturated solutions of diazomethane are known to be unstable. This makes the distillation of the diazomethane a subtle process that demands thoughtfulness from the chemist.
As rough surfaces are know to initiate detonations, adding ethereal solutions of diazomethane into heterogeneous mixtures should be avoided, especially if a crystalline precipitate is presence.

[4] Boer, T. J. D, Backer, H. J. *Organic Synthesis, Collective Vol. IV*, Rabjohn, N., Ed., John Wiley & Sons: New York, **1963**, p 250.

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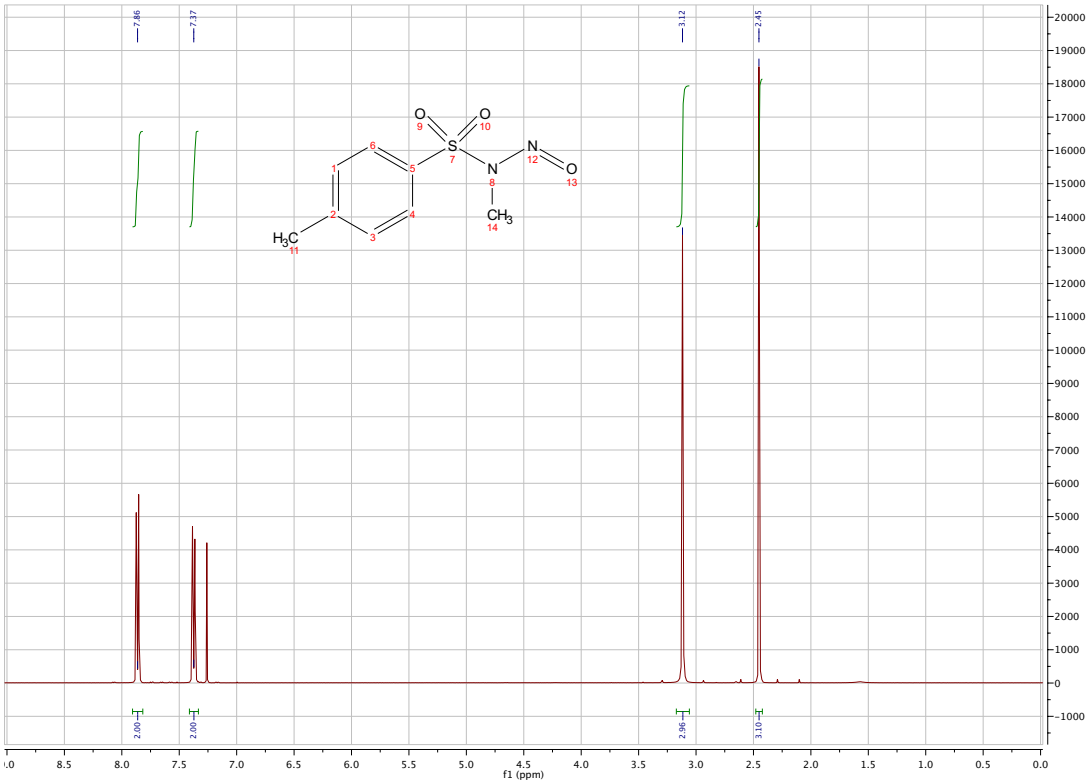
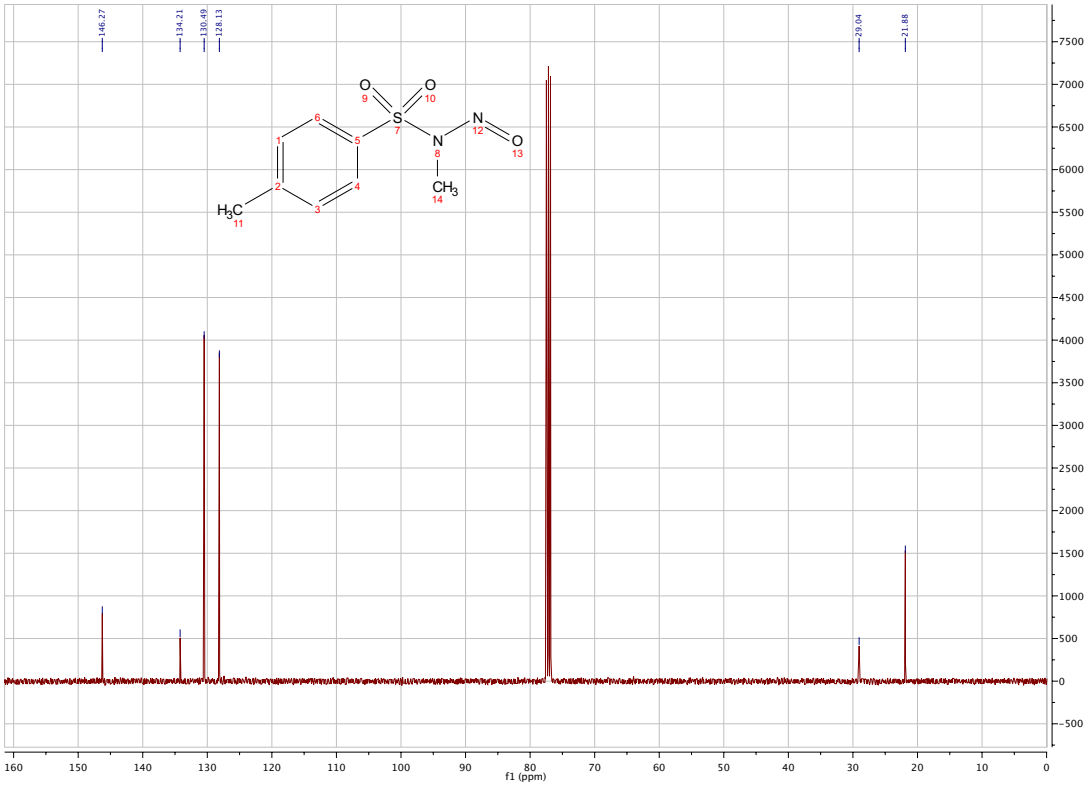
# 7. Spectra.



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