The Vespiary

Main Topics => Publications => Topic started by: psyhare on March 03, 2020, 02:08:47 AM

Title: **Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **psyhare** on **March 03, 2020, 02:08:47 AM**

I would not go into detail of 3,4,5-trimethoxy-ß-nitrostyrene (3,4,5-TMNS) synthesis, but it was prepared as per Shulgin (see PiHKAL #96) except that n-butylamine has been used as catalyst instead of cyclohexylamine. The yield was slighly larger than that reported in PiHKAL.

Crude 3,4,5-TMNS was dissolved in near-boiling methanol (15 mL/g) and left to slowly crystallize in a beaker that was insulated by 2 layers of a thick tin foil. The crystals were washed with ice cold methanol, somewhat dried on filter and and finally dried in a vacuum desiccator over CaCl2 overnight.

Here is the resulting 3,4,5-TMNS ready for synthesis:

(http://i.imgur.com/OXVPxIHm.jpg) (https://imgur.com/OXVPxIH)

A 500 mL, 3-neck round-bottom flask was equipped with an overhead stirrer, reflux condenser and a thermometer. An ice water bath was placed on a lab jack underneath the flask to regulate temperature by immersion in the bath.

The flask was charged with 160 mL ice cold denatured alcohol (min. 94% EtOH), 60 mL water - i.e. 220 mL 70% ethanol (cold).

Strong stirring was turned on and kept over the course of the whole reaction.

8.4 g (0.22 mol) NaBH4 (powdered in a mortar) and left stirring for 30 minutes. Then, 25 g (0.1 mol) 3,4,5-TMNS (powdered in an electric coffee grinder) was added in small portions over the course of 15-30 minutes. TMNS was left to react before each new addition. The canary yellow TMNS slowly turned pale yellow, almost white-ish after each addition:

(http://i.imgur.com/EOPSn9cm.jpg) (https://imgur.com/EOPSn9c)

The temperature was kept between 30-60 °C by lifting the ice water bath as needed. The mixture was left stirring for 30 minutes.

Another 8.4 g (0.22 mol) NaBH4 (powdered in a mortar) was added to the mixture immediately followed by 1.5 g (0.01 mol) CuCl2 dissolved in 3 mL water and added in a several quick additions from a pipette. The rxn mixture immediately turned brown, sizzled and gave off gray fumes that quickly subsidized. There was lots of bubbling and gas evolution.

NOTE: A little more NaBH4 (0.24 mol ?) should probably be used to compensate for the reaction with CuCl2. Additionally, the CuCl2 solution should have been more dilute (10% instead of 50%) when added to the rxn mixture.

There was no need to cool down the reaction and the ice water bath was replaced by a heating mantle. Here is the full-blown NaBH4/CuCl2 reduction:

(http://i.imgur.com/TSSHZNFm.jpg) (https://imgur.com/TSSHZNF)

Once the reaction slowed down a bit, the heating mantle was turned on (low heat) to jump start it again. A care was taken to avoid thermal runaway. Finally, a sweet spot was found where the rxn mixture refluxed steadily (1-2 drops per second).

The mixture was left to reflux for full 60 minutes.

Here is the rxn. mixture right after the reaction is done:

(http://i.imgur.com/2GRezgjm.jpg) (https://imgur.com/2GRezgj)

Note the "copper mirror". For some reason, elemental Cu appeared. Either some copper has been reduced or my CuCl2 contains some unreacted elemental cooper:

(http://i.imgur.com/1Spapfym.jpg) (https://imgur.com/1Spapfy)

The mixture was left to cool down, acidified with 1M sulfuric acid to a pH of 4-4.5. The black copper boride particulates slowly settled on bottom and the brown solution cleared up over the course of several hours:

(http://i.imgur.com/ELfsjhom.jpg) (https://imgur.com/ELfsjho)

The mixture was vacuum-filtered but immediately crystallized in the Buchner funnel (sulfates crashing out?):

(http://i.imgur.com/1sZOQv3m.jpg) (https://imgur.com/1sZOQv3)

This could have been expected... 300 mL hot water was added in total to dissolve the crystalline mass.

The filtered solution was transferred to a 1 L round-bottom flask and further diluted with water to the total volume of about 900 mL:

(http://i.imgur.com/yFUXqksm.jpg) (https://imgur.com/yFUXqks)

The alcohol was distilled off (simple distillation until head temperature shown 100 °C) and a little bit of brown tar crashed out of solution. Here is the rxn mixture after the removal of alcohol:

(http://i.imgur.com/rAvneQsm.jpg) (https://imgur.com/rAvneQs)

The mixture was transfered to a 2 L separatory funnel. The flask was washed with water and DCM to remove any residues, including the brown tar.

The mixture was then washed with 3 x 150 mL DCM. Here is the first and third washing:

(http://i.imgur.com/J3DL8Aim.jpg) (https://imgur.com/J3DL8Ai)

(http://i.imgur.com/UHpGZ1Cm.jpg) (https://imgur.com/UHpGZ1C)

The aqueous layer was basified with 10% NaOH to a pH of 10 and extracted with 3 x 200 mL DCM:

(http://i.imgur.com/EVSRXrRm.jpg) (https://imgur.com/EVSRXrR)

(http://i.imgur.com/5MTKMTxm.jpg) (https://imgur.com/5MTKMTx)

There was only a very minor emulsion:

(http://i.imgur.com/jDAgwQNm.jpg) (https://imgur.com/jDAgwQN)

The pooled DCM extracts were briefly washed with 50 mL water, dried with MgSO4, filtered and transfered to a clean 2 L sep. funnel. 200 mL water with few drops of 0.1% nitrazine yellow indicator was added:

(http://i.imgur.com/M1JpJSPm.jpg) (https://imgur.com/M1JpJSP)

Few drops of 1 M sulfuric acid were added and the funnel swirled for a while. This was repeated until the aqueous layer stayed neutral/acidic even after prolonged swirling and inversions of the funnel.

Unfortunately, the water turned emerald green instead of expected yellow from the indicator, probably due to a presence of copper compoud.

Nevertheless, the pH of the aqueous layer turned out to be fairly neutral:

(http://i.imgur.com/7CRfQ63m.jpg) (https://imgur.com/7CRfQ63)

A small sample of water was taken from the solution and acetone was added, immediately showing precipitation of mescaline sulfate:

(http://i.imgur.com/Up89DGmm.jpg) (https://imgur.com/Up89DGm)

50 mL acetone was added to the beaker and left to crystallize in a freezer.

Here is the beaker containing small mescaline sulfate crystals:

(http://i.imgur.com/vTmMbkAm.jpg) (https://imgur.com/vTmMbkA)

The crystals were filtered and washed with dry, ice cold acetone, yielding 13.2 g of crude product:

(http://i.imgur.com/JwCFEdMm.jpg) (https://imgur.com/JwCFEdM)

The crude product was redissolved in hot water (10 mL/g) and left to crystallize in a fridge:

(http://i.imgur.com/gHcMP5Nm.jpg) (https://imgur.com/gHcMP5N)

After another filtering and washing, 7.6 g of glistening crystals of mescaline sulfate dihydrate were obtained:

(http://i.imgur.com/1V9Nz8ym.jpg) (https://imgur.com/1V9Nz8y)

Unfortunately, crystallization solution was too dilute and maybe more like 5 mL/g water should have been used.

Copious amount of acetone has been added to to the filtrate to crash out more crystals (crude).

Finally, a second extraction with 2 x 200 mL DCM has been done on the basified mother liquor (currently work in progress).

This was just a first trial of mescaline synthesis with NaBH4/CuCl2 reduction. It was a success but there is a huge room for improvement.

Here is the list of possible improvements:

- no need to pre-chill the alcohol, just use the ice water bath
- consider using IPA instead of EtOH, extraction with IPA instead of DCM
- use more NaBH4 (6-7 mol. eq.) instead of 2 mol. eq.
- use pre-made Ni2B or Cu2B catalyst to get rid of water-soluble Cu/Ni compounds and improve yield
- filter, then acidify/dilute (to use smaller filtration flask - mescaline freebase is soluble enough in water)
- boil the water w. backsalted mescaline to remove any residual DCM
- use more acetone to get more xtals in the first batch (100 mL?)
- use less water for re-x (5 mL/g ?)

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **loft** on **March 03, 2020, 05:58:31 AM**

Beautifully written and nice pictures - high quality writeup as always! Thank you for sharing :)

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **mathiasxx94** on **March 03, 2020, 09:55:06 AM**

Great writeup, makes me want to throw away my LAH.
Did you take any m.p, TLC etc. of the crude product, it looks so pure already before the final recrystallization.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **CathCath** on **March 03, 2020, 10:38:01 AM**

Very good write-up, my apreciations , did you use equimolar amaunts of NaBH4 to 3,4,5-TMNS and i never worked with phentylamine sulfates did they all crash out of water in the fridge from a water/acetone solutions? I shoud mention the crystals are unbeliavalbly good for this salt i have never seen sulfate looking like that, very nice job !

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **blade_runner** on **March 03, 2020, 12:24:33 PM**

Nice write up. You haven't noticed any apparent loss in crude yield from using 4.4 molar equivalents of NaBH4 rather than 7.5 molar equivalents as the paper shows, so that's good news.

The pictures of the reaction mixture are interesting. In my friend's lab notes, he writes that the black solids usually break up into small, free flowing flakes and very fine particles after 10-15 minutes of reflux. Maybe this is a consequence of quality of stirring?

Small amounts of shiny copper are visible in his reaction mixture too, usually embedded in his stir bar by the end of the reaction.

My friend has repeated this reaction 3-4 times on a small scale (1 g nitorstyrene) and has never seen a yellow-orange post reaction mixture. His is usually a clear solution made slightly gray by the suspended black particles. I wonder why this is? He also filters the solids from the post-reaction mixture and has never seen that crystallization phenomena you observed, that is very odd. His procedure, which needs work, is to cool to room temperature on a cold water bath then vacuum filter the clear-gray solution to yield a clear filtrate which has only a very slight gray tint.

I see that you are trying to recover more crystals from recrystallization solvent. If you don't get anything even after crashing out with acetone and freezing, maybe strip it all down and take a look at what is recovered. If it's hard and dull white in appearance (not sparkling shards like in your pictures) then it's probably a side product from incomplete reduction, maybe the nitroalkane? These are usually soluble in acetone while the sulfuric acid salts (and hydrochloric acid salts) of mescaline are not.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **psyhare** on **March 03, 2020, 01:23:00 PM**

The stirring was pretty strong during the whole synthesis, so it probably broke up the flakes.

I use PTFE stirrer so it's easy to clean up. I stick to glass and PTFE since CuCl2 si quite corrosive for metals.

The rxn mixture crystallized probably because I've used H2SO4 for the acidification step. I don't like using HCl or AcOH, since they come over easily when distilling off the alcohol - and then it takes more work to recover. I don't know how well AcOH or HCl would work, but probably won't cause crystallization due to higher solubility of mescaline hydrochloride/acetate. Sulfate has pretty low solubility in cold water.

The rxn mixture coloration is very different if I use CuSO4 instead of CuCl2, at least for P2NP. I will try to make copper boride catalyst beforehand to get a cleaner run.

You know, there are so may factors affecting the looks and behaviour of the rxn mixture it's hard to tell...

The second batch of crystals crashed out very nicely from the filtrate - the precipitate is actually crystalline powder. I will just use less water for re-x next time.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Corrosive Joeseph** on **March 03, 2020, 02:29:28 PM**

Quality.... Thank you for the eye candy 8)

/CJ

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **aniracetam** on **March 03, 2020, 04:19:00 PM**

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yeah, that's badass.
I have a pound of Aldrich vanillin (and another 150g gallic acid), just itching to get converted.

what about 3,4,5-trimethoxybenzoic acid? I have 30g of that. that would require LAH, huh?

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **psyhare** on **March 03, 2020, 06:15:21 PM**

Quote from: aniracetam on March 03, 2020, 04:19:00 PM

> I have a pound of Aldrich vanillin (and another 150g gallic acid), just itching to get converted.
>
> what about 3,4,5-trimethoxybenzoic acid? I have 30g of that. that would require LAH, huh?

As for the gallic acid, I plan to decarboxylate it to pyrogallol, methylate to 3,4,5-trimethoxybenzene, then formylate using Blanc chloromethylation followed by Sommelet reaction according to the following patent (they give examples for the 3,4,5-trimethoxybenzene specifically):

Quote

> Mohapatra, Manoj Kumar, et al. "An efficient process for the synthesis of alkoxy substituted benzaldehydes." U.S. Patent Application No. 15/538,012.

As for the 3,4,5-trimethoxybenzoic acid, I believe this can be reduced with LAH to corresponding benzyl alcohol, then either catalytically convert this to aldehyde, or convert to benzyl chloride with excess HCl, take up in toluene, then Sommelet reaction (just adding hexamine to heated stirred solution of 3,4,5-trimethoxybenzyl chloride) and acid hydrolysis of the hexaminium chloride to aldehyde (adding e.g. 50% AcOH).

Finally, as for the vanillin, I have 750 g of food grade vanillin, planning to demethylate first with AlCl3/pyridine, then with Al/Br (AlB3 formed in-situ). Then methoxylate with NaOMe to syringic aldehyde (syringaldehyde) and finally either methylate with MeI or DMC ... OR ethylate with EtI/K2CO3 to escaline.

So many materials, so many possible pathways... :)

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **psyhare** on **March 04, 2020, 01:16:47 AM**

Quote from: aniracetam on March 03, 2020, 04:19:00 PM

> what about 3,4,5-trimethoxybenzoic acid? I have 30g of that. that would require LAH, huh?

It seems you can do without LAH. Many carboxylic acids can be reduced with NaBH4/ZnCl2, NaBH4/ZrCl4, NaBH4-I2 and some other systems:

Quote

> Periasamy, Mariappan, and Muniappan Thirumalaikumar. "Methods of enhancement of reactivity and selectivity of sodium borohydride for applications in organic synthesis." Journal of Organometallic Chemistry 609.1-2 (2000); pp. 139-140

Hmmm... this smells like an OTC route to benzaldehyde from sodium benzoate via benzoic acid :)

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Hooloovoo** on **March 04, 2020, 05:13:35 PM**

Congratulations - beautiful write up. 8)
Bio assay when? ;D

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **carl** on **March 04, 2020, 07:57:47 PM**

Sucks that you got such a low yield, but I am sure you will fix the issues in your workup.
Otherwise a nice piece of work, do you want me to move that to the publication section?

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **psyhare** on **March 04, 2020, 09:34:00 PM**

Quote from: Hooloovoo on March 04, 2020, 05:13:35 PM

> Congratulations - beautiful write up. 8)
> Bio assay when? ;D

Thanks.
Perhaps I will test it this weekend with my GF.

BTW I ran several color tests (Marquis, Mecke, Mandelin, Lieberman, Froehde) and all took the color corresponding to the desired the compound.

Quote from: carl on March 04, 2020, 07:57:47 PM

> Sucks that you got such a low yield, but I am sure you will fix the issues in your workup.
> Otherwise a nice piece of work, do you want me to move that to the publication section?

I still have unprocessed DCM pulls that likely contain some product.

Yeah it will hopefully improve next time.

No need to publish it, but do as you like. I am just trying to reproduce an existing procedure... I will post an update after the 2nd run.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **carl** on **March 05, 2020, 08:24:54 PM**

Honestly, such a procedure that beautiful written up deserves to be in the publication section.
Mainly because of your neat pictures.

You can protest if you don't want that, but otherwise, I decide it belongs there ;)
I mean, almost all the things in the publication section are just reproductions of working procedures, but since we reproduced them and it did work, it is good enough for us to have as an example of how a beautiful and working procedure(and publication) should look like.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **psyhare** on **March 08, 2020, 01:58:53 AM**

Carl, okay please consider it public domain, so whatever you decide to do with it, go ahead :)

Hopefully I will post results of second run next week.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Hooloovoo** on **March 08, 2020, 09:25:33 AM**

It *is* a gorgeous writeup - kudos to you, **psyhare** for freely releasing it upon the world. 8)
No bio assay yet? :-X

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **RoidRage** on **March 08, 2020, 11:35:58 PM**

Thanks for the awesome work!

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **carl** on **March 08, 2020, 11:44:05 PM**

Quote from: Hooloovoo on March 08, 2020, 09:25:33 AM

> No bio assay yet? :-X

Oh come on, that is something you need much time and preparation for! ::)
If you want to read good bioassays about mescaline, check the posts of tregar.
I made mescaline over two years ago and I still haven't tried it yet.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Hooloovoo** on **March 09, 2020, 07:05:27 PM**

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lol, I'd have had some right down me not long after it dried. 8)
You can take the junkie out of the lab, but something something...

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Kasey Jones** on **March 10, 2020, 01:49:57 AM**

Congratulations---fantastic write up!! Thank you!

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Halogen** on **March 11, 2020, 12:14:02 PM**

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great work! 8) 8)

actual question is right there.

Quote from: psyhare on March 03, 2020, 02:08:47 AM

> I would not go into detail of 3,4,5-trimethoxy-ß-nitrostyrene (3,4,5-TMNS)

not 3,4,5-TMNS, but 3,4,5-trimethoxy-benzaldehyde. it's not OTC anywhere and would

be great if someone made write-up about it's synthesis with OTC materials.
swim made 2-hydroxy-5-methoxybenzaldehyde some time ago and learned that methylating those benzaldehydes without *carcinogenic chemical weapon dimethyl sulfate* is really hard!

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **carl** on **March 11, 2020, 12:18:07 PM**

Quote from: Halogen on March 11, 2020, 12:14:02 PM

> actual question is right there.
>
> Quote from: psyhare on March 03, 2020, 02:08:47 AM
>
> > I would not go into detail of 3,4,5-trimethoxy-ß-nitrostyrene (3,4,5-TMNS)
>
> not 3,4,5-TMNS, but 3,4,5-trimethoxy-benzaldehyde. it's not OTC anywhere

Actually we just buy it.
It is cheap.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Halogen** on **March 11, 2020, 12:27:21 PM**

Quote from: carl on March 11, 2020, 12:18:07 PM

> Quote from: Halogen on March 11, 2020, 12:14:02 PM
>
> > actual question is right there.
> >
> > Quote from: psyhare on March 03, 2020, 02:08:47 AM
> >
> > > I would not go into detail of 3,4,5-trimethoxy-ß-nitrostyrene (3,4,5-TMNS)
> >
> > not 3,4,5-TMNS, but 3,4,5-trimethoxy-benzaldehyde. it's not OTC anywhere
>
> Actually we just buy it.
> It is cheap.

I can see that now. thanks! :D

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **loft** on **March 11, 2020, 07:38:44 PM**

Quote from: Halogen on March 11, 2020, 12:14:02 PM

> great work! 8) 8)
>
> actual question is right there.
>
> Quote from: psyhare on March 03, 2020, 02:08:47 AM
>
> > I would not go into detail of 3,4,5-trimethoxy-ß-nitrostyrene (3,4,5-TMNS)
>
> not 3,4,5-TMNS, but 3,4,5-trimethoxy-benzaldehyde. it's not OTC anywhere and would be great if someone made write-up about it's synthesis with OTC materials.
> swim made 2-hydroxy-5-methoxybenzaldehyde some time ago and learned that methylating those benzaldehydes without *carcinogenic chemical weapon dimethyl sulfate* is really hard!

Trimethylphosphate :) Definitely safer than all other alkylation agents!

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **blade_runner** on **March 11, 2020, 10:21:02 PM**

> Quote from: Halogen on March 11, 2020, 12:14:02 PM
>
> great work! 8) 8)
>
> actual question is right there.
>
> > Quote from: psyhare on March 03, 2020, 02:08:47 AM
> >
> > I would not go into detail of 3,4,5-trimethoxy-ß-nitrostyrene (3,4,5-TMNS)
>
> not 3,4,5-TMNS, but 3,4,5-trimethoxy-benzaldehyde. it's not OTC anywhere and would be great if someone made write-up about it's synthesis with OTC materials.
> swim made 2-hydroxy-5-methoxybenzaldehyde some time ago and learned that methylating those benzaldehydes without *carcinogenic chemical weapon dimethyl sulfate* is really hard!

No it's not. https://www.thevespiary.org/talk/index.php?topic=16804.msg54183344#msg54183344

My friend used syringaldehyde as the starting material. His results show it's quite easy and DMF can likely be substituted for DMSO as they are both polar, aprotic solvents.

He's attempting to back track even more and start from vanillin --> 5-iodovanillin (KI/NaOCl) --> syringaldehyde (NaOMe/cat. CuBr). Forming the nitrostyrene from 3,4,5-TMBA is trivial. He plans on putting some more time into understand the Zn/HCl reduction of the nitrostyrene because he is convinced that it does work, it's just very hard to get working. Once this is understood, the entire synthesis from vanillin is very much OTC.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **carl** on **March 11, 2020, 10:34:27 PM**

Also check this writeup: https://www.thevespiary.org/talk/index.php?topic=15090.msg54190464#msg54190464
Notice the higher yield he got.
Your workup seems to include way too much steps.
I haven't done it likewise complex and thus wasteful for 2C-H, but I have the spectra of the final 2C-B made from it and it actually measures at least 98%.

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **blade_runner** on **March 11, 2020, 11:30:41 PM**

> Quote from: carl on March 11, 2020, 10:34:27 PM
>
> Also check this writeup: https://www.thevespiary.org/talk/index.php?topic=15090.msg54190464#msg54190464
> Notice the higher yield he got.
> Your workup seems to include way too much steps.
> I haven't done it likewise complex and thus wasteful for 2C-H, but I have the spectra of the final 2C-B made from it and it actually measures at least 98%.

Yields sound consistent with this https://www.thevespiary.org/talk/index.php?topic=15090.msg54187139#msg54187139

Amines complex with metals so the prevailing idea was to use a better extraction solvent

than IPA and perform a subsequent acid/base workup. But maybe it's just a waste of time. Maybe stirring the crude under boiling acetone and recrystallizing several times would be enough to remove the major impurities (unreacted or partially reduced nitrostyrene, copper, borate salts, etc.)

Title: **Re: Successful Mescaline from 3,4,5-TMNS (Writeup)**
Post by: **Halogen** on **March 12, 2020, 02:11:57 AM**

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loft
carl
blade_runner

well, I didn't expect that kind of attention :D thank you guys very much for those answers!

https://www.youtube.com/watch?v=z0NfI2NeDHI