SYNTHESIS OF DMT (AND ANALOGS) FROM TRYPTAMINE

HTML by Rhodium

(KrZ's Voice:)

TRYPTOPHAN TO TRYPTAMINE

Tryptophan (454g) was suspended in tetralin (1150 ml) containing acetone (12.9 g) and the mixture was heated to reflux for 12 hours with vigorous stirring until no more carbon dioxide was evolved and the reaction mixture became clear. The solvent was removed under vacuum, and the residue was distilled under reduced pressure to give a yellow crystalline solid.

TRYPTAMINE TO N,N-DIMETHYLTRYPTAMINE (DMT)

Next, 30g of formaldehyde and 120g Tryptamine were disolved in 1800ml of MeOH, to this was slowly added dropwise 50g of $NaCNBH_3$ disolved in 550ml MeOH. Then 14g Glacial Acetic Acid was added dropwise with stirring. The mixture was then stirred for 60 hours. The majority of the MeOH was distilled off (2000 ml collected) to the distillation flask was added 1L of 5% Aq. Ammonia which was extracted with 3x250ml of DCM. The DCM was washed with a salt solution (not saturated but still pretty strong) then the DCM separated and dried with a large portion of anhydrous $MgSO_4$. The DCM was distilled off at atmospheric pressure and then the distillation was continued under vacuum (~1 torr now) until the dimethyltryptamine was collected. Which was recrystalized from boiling hexane with a few mls of Ethyl Acetate added. This afforded 48.8g of DMT, a 35% yield.

> ***Note by Rhodium:*** *The reason for the low yield should be a too low amount of formaldehyde added to the reaction mixture. At least two moles of formaldehyde per mole of tryptamine is needed for complete conversion to DMT.*

DMT; HIGHER YIELD VARIATION

Tryptamine hydrochloride (10 g, 62.4 mmol) and sodium cyanoborohydride (6.28 g, 100 mmol) in a mixture of methanol (400 mL) and glacial acetic acid (11.76 g, 196 mmol) were cooled to 0°C in an ice bath over a steady stream of nitrogen. A solution of 4.20 g formaldehyde (140 mmol, 11.05 mL of 38% aq. CH_2O) in 125 mL of Methanol was added dropwise to the solution over a period of one hour with mild stirring. The flask was stoppered, the reaction allowed to return to room temperature slowly, and allowed to proceed for the next 60 hours. Upon completion the pH was adjusted to 8.0 by the dropwise addition of an aqueous solution of sodium bicarbonate. The mixture was then extracted 4x with 50 mL of ethyl acetate. The combined extracts were washed once with 250mL of brine and dried over $MgSO_4$ (15g) for 15 minutes. The $MgSO_4$ was washed clean with another 75 mL of ethyl acetate. The solvent was reduced to 100 mL on the rotary evaporator. The hot solution was added to a 200mL beaker and covered with plastic wrap which was sealed on with a rubber band. Upon cooling in the freezer overnight, the precipitated DMT was removed by filtration, and dried in the dessicator.

Overall yield: 7.88g, 45 mmol, 67%. The mp is solid, right around 64-67°C.

REMOVAL OF N-METHYLTRYPTAMINE AND TRYPTAMINE FROM DMT

If you're worried about NMT/T contaminating your product just do the workup this way;

Basify the aq. reaction mix to 13-14 with NaOH. Extract repeatedly with DCM. Rotovap off the DCM and add Petroleum Ether, heat to a boil and decant the Pet. Ether from any undissolved material. Cool the Pet. Ether in the freezer and collect any precipitated solids. This will remove any unreacted tryptamine. To remove NMT you can react

this mixture with acetic anhydride and seperate. I know that's quite a hassle but it's a good way to cover all the bases as far as purity is concerned.

(Thoughtcrime23's Voice:)

This is my first post here. But I've been following this procedure a little and am quite pleased to see this dug up from possible permanent deletion. The journal ref. for KrZ's method is as follows:

> **EXPERIMENTAL**
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> **General Procedure for the preparation of N,N-Dimethyltryptamines**[1]
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> To a cooled (-2°C) and stirred solution of a substituted amine (7.0 mmol), $NaCNBH_3$ (14.0 mmol), and glacial acetic acid (35.0 mmol) in MeOH, a soln of CH_2O (38% w/v aq. sol.) in MeOH was added dropwise over 17 min. After 20 min of stirring at 0°C and 2.5 h at room temp, saturated aqueous K_2CO_3 was added and the MeOH was removed under vacuum. The residue was diluted with H_2O and the product was extracted with EtOAc twice, washed with satd NaCl twice, dried, and concentrated. Yield of substituted DMT = 83%.

It is ironic that this is actually quite similar to another proposed DMT synthesis[3] back at DMT world that was also "lost and forgotten" with the only major difference being the catalyst $NaBH_4$ vs. the more selective $NaCNBH_3$. I recall it actually being discarded, without much trial, as producing quarternary tryptamines (β-carbolines) rather than the desired N,N-dimethyl because of a certain mechanism in the reaction (Pictet-Spengler?).

> ***Note by Rhodium:*** *The Pictet-Spengler side-reaction occurs whenever a reductive amination of Tryptamine is performed under acidic conditions (such as HCOOH/HCHO methylation), the reason sodium borohydride usually is disfavored is because it is powerful enough to reduce the formaldehyde to methanol before it has any chance to react with the tryptamine (unless suitable measures are taken to prevent this from happening).*

However, to my knowledge when our revolutionary bee KrZ first posted the procedure of this thread's topic, Rhodium somewhat concluded that the combo of a gentler catalyst AND the use of GAA to regulate the pH of the reaction that quarternary product formation would be reduced and/or eliminated!! WOW!

I feel that if KrZ's method is what it seems to be, that this could be potentially the most accessible hypothetical route to DMT thus present so far. Sodium Cyanoborohydride, albeit be no means OTC, is less hazadous than LAH or Red-Al (not to mention its varied applications in other realms), and everthing else in the process's second half (from Tryptamine to DMT) *can* be had in some relative OTC form, save Ethyl Acetate. I've always dreamed of open the Pandora's box of dimethyltryptamine accessability via revolutionary synthesis, and I have to be cautious in my enthusiasm so as to remain rational and wary of hard evidence.

(Rhodium's Voice)

KrZ's synthesis in particular is not optimized, he runs the reaction for a far longer time than necessary, and in the first procedure he posted he used far too little formaldehyde for the reaction to go to completion. Try the procedure below instead (it is a DMT-specific version of the above procedure), if you don't have any silica gel for chromatography, then you can try repeated recrystallization instead to purify the product, either from hexane (petroleum ether), ethyl acetate (EtOAc) or a mixture of both, but assuredly, if the product is flashed through a short silica gel column, it crystallizes *so* much easier.

Another crystallization tip of possible merit, gleaned from a forensic paper where a busted large-scale chemist told of his methods: *A kilogram of DMT [freebase] dissolved in 2L ether would [crystallize] when added to 8L hexane. Rhomboid crystals would spontaneously form in the [resulting solution].*

If you would have tryptamine hydrochloride at hand instead of the freebase, you can use the general procedure given

for the alkylation of 5-Cyanotryptamine given below. It uses one equivalent of sodium methoxide to deprotonate the hydrochloride salt to the freebase, only forming NaCl and methanol as byproduct (which is used as the solvent anyway). It is identical in all other aspects, beside the fact that they use 4 equivalents of HOAc instead of 5, but I don't think that has any big significance.

DMT by reductive methylation of Tryptamine with 37% Formaldehyde and $NaBH_3CN$ in Methanol[1]

Tryptamine (1.12g, 7 mmol), Sodium Cyanoborohydride (0.88g, 14 mmol) and Glacial Acetic Acid (2ml, 35 mmol) was dissolved in 110ml Methanol at 0°C, and a solution of 37% Formaldehyde (1.4 mL, 18.5 mmol) in 15ml Methanol was added dropwise over 20 min, and the resulting solution was allowed to stir for 20 min at 0°C and 2.5h at room temp. The methanol was evaporated under reduced pressure, and 80ml 25% aqueous potassium carbonate was added and the solution extracted with 2x125ml EtOAc, the extracts washed with 2x40ml brine, dried over $MgSO_4$and the solvent evaporated under reduced pressure to give an amber oil, which was purified by flash chromatography on 30g silica gel (using a gradient of EtOAc:MeOH) to give an oil, which was crystallized from boiling hexane to give N,N-Dimethyltryptamine as colorless waxy crystals, weighing 0.9g (69%).

5-Cyano-DMT from 5-Cyano-Tryptamine[4]

0.121g (0.545 mmol) 5-Cyanotryptamine HCl was dissolved in 25ml methanol, and with good stirring 0.1ml 30% methanolic sodium methoxide (1 eq) was added, followed by 0.125ml HOAc (2.18 mmol, 4 eq) and 68mg (1.09 mmol, 2 eq) $NaBH_3CN$. Next 0.103ml 38% aqueous formaldehyde (1.36 mmol, 2.5 eq) in 10ml methanol was added over 30 minutes. The solution was allowed to stir for 3.5h at room temperature, and 25ml 4M NaOH was added and the methanol evaporated off under vacuum. The residue was extracted with 3x25ml Et_2O, the organic extracts washed with 2x20ml brine, dried over MgSO4 and the solvent evaporated to give 5-Cyano-DMT in 75% yield.

(Lilienthal's Voice)

Voilà, here are the PTC-killer-reactions for (di-)methylation of tryptamines:

These one-pot reactions utilize only cheap and (more or less) non-toxic chemicals (no carcinogenic and expensive methyl iodide!). Because of the aprotic, non acidic reaction and work-up conditions no cyclization to β-carbolines should occur. The yields after purification are good to excellent (phenylethylamine: 72%, diisopropylamine: 92%, holafébrine: 85%).

EXPERIMENTAL

USING *IN SITU* PREPARED ZINC BOROHYDRIDE[2]

A mixture of primary amine *[i.e. tryptamine]* (5 mmol) or secondary amine (10 mmol), $ZnCl_2$ (20 mmol) and paraformaldehyde (20 mmol) in 25 ml CH_2Cl_2 was stirred at RT for 1h under dry atmosphere. $NaBH_4$ 20 mmol was then added and the resulting mixture was stirred for 9 h (secondary amines) or 12h (primary amines). The reaction mixture was then quenched by addition of aqueous ammonia (40 ml, 2 N), stirred for 10 min. and the organic layer was separated. The aqueous part was extracted with CH_2Cl_2(1x25 ml) and the combined organic extracts were concentrated *in vacuo* after drying over anhydrous Na_2CO_3. The product from primary amines were purified by distillation, crystallization or flash chromatography. The secondary amines afforded the pure tertiary amines without any chromatographic separation.

USING FORMALDEHYDE/SODIUM BOROHYDRIDE[3]

Formalin (35%, 35 mmol) was added with stirring to a solution of *holafébrine* (primary amine) 3 mmol in methanol (10 ml) and the solution was refluxed for 30 min. After cooling, 400 mg $NaBH_4$ was added slowly.

After 1 h the reaction was evaporated and the mixture was extracted with CH_2Cl_2. Evaporation yields 85% *iréhine* (*dimethyl-holafébrine*).

(Hexane's Voice:)

Guess what? I'm tripping on DET right now. Weird stuff. Anyway, to make a short story long, I'm currently in the midst of a synthesis of DET. Unfortunatley, I am currently deprived of Beilstein Crossfire and have been forced to consult the hardback version (Yes, life is difficult). All I could find for 15 or 20 3-(2-Diethylaminoethyl) indole analouges was the same sorry-ass loser method with diethylamine-$LiAlH_4$ and the occasional amide reduction.

I know Shulgin used a sterically hinder non-nucleophilic base, Hünig's base (EthylDiisopropylamine). It's a good method, unfortunatly, my copy of Tihkal is over 6000 km away right now (on another continent) and I haven't been able to consult it. All I could remember is that there was Ethyldiisopropylamine as the base, tryptamine, and an ethyl halide (which I think was the iodide).

In my reaction, I used 2 equiv of DIPEA, 1 equiv of tryptamine and 2 equiv of ethyl iodide. As solvent I used acetonitrile (alkylations are always fastest in polar solvents). I then let it stir at room temp for 12 hours. (BTW, tryptamine isn't very soluble in this stuff.)

After work-up, I got about 60%, which is not too bad, but it was contaminated with monoethyl tryptamine and a small amount of tryptamine. On TLC, it ran just barely faster than DMT (CH_2Cl_2:EtOH:NH_4OH, 40:8:1), which is exactly what I would expect. 60% is ok, but if I don't want an oil for product, I'll have to run a column, which would suck a great deal.

REFERENCES

1. Jose L. Castro, *et. al.*, **J. Med. Chem. 37(19), 3023-3032 (1994)**
2. Sukanta Bhattacharyya, **Synth. Comm. 25, 2061 (1995)**
3. B. L. Sondengam, **Tet. Lett. 3, 261 (1973)**
4. M. G. N. Russell *et. al.* **J. Med. Chem. 44, 3881-3895 (2001)**