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Development Summary towards a Manufacturable Process for R 83842 [(*S*)-6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole]†

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Abstract:

A scalable process to produce enantiomeric R 83842, (*S*)-6-[(4-chlorophenyl) (1*H*-1,2,4-triazol-1-yl)methyl]-1-methyl-1*H*-benzotriazole, is developed and described as a lecture* transcript. Cheap and safe reagents have been used. A typical procedure for oxidative destruction of aqueous cyanide waste, and stability data on *N*-acetyl hydrazine are provided. Special focus is on cost analysis as an important tool in developing performant synthetic methods. The method consists of preparing a chiral monosubstituted hydrazine which is ring closed to the chiral 1-alkylated 1,2,4-triazole title compound.

I. Racemic R 83842

At first, racemic R 83842 ((±)-(**1**) was selected as a highly selective aromatase inhibitor.[1] An important element in that decision was that nor by synthesis nor by chromatography, both enantiomers could be obtained in sufficient quantity to investigate and differentiate them. During the development however, we were forced to a racemic switch. Racemic R 83842 is discussed first. The discovery route is summarized in schemes 1−5. Suitable 4-nitro benzoic acid derivatives **11** were not commercially available in larger quantities. Hence, it was prepared as in Scheme 3.

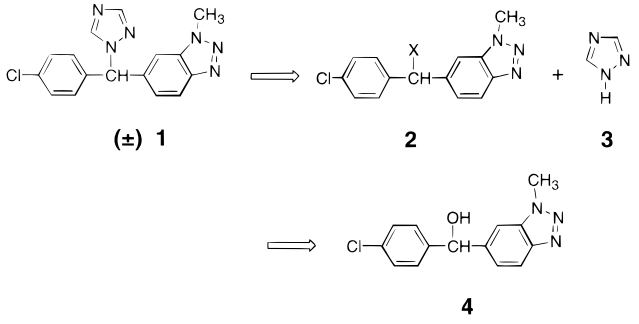
As shown in schemes 3−5, the discovery route is fully linear, comprises 10 synthetic steps and a chromatographic step to remove the isomeric by-product **15**. The overall yield is about 6% which is very high. The average yield per step is 72%. However, some steps raise a concern for the plant like the usage of MnO_2 (abrasive and jeopardising cleaning), $KMnO_4$ (same as MnO_2), $LiAlH_4$, NaH, dimethylsulphate, and a 4:1 ratio of (±)-**1** and **15** in the final step. The chromatographic yield to isolate **1** is very high, but a crystallisation to achieve the removal of **15** will significantly reduce the overall yield.

We managed to solve most of the problems by synthesising (±)-**1** as indicated in Schemes 6 and 7.

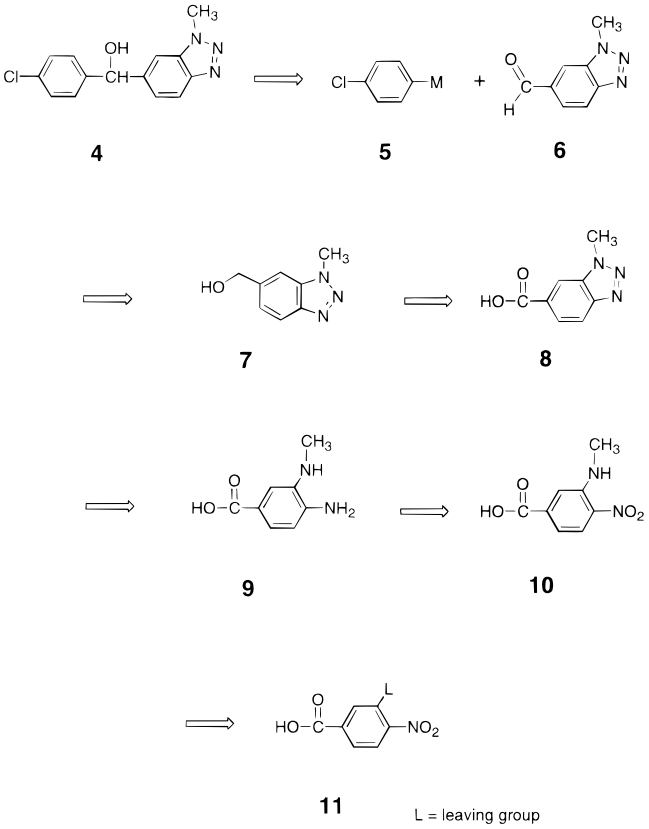
The starting materials are abundantly available and very cheap. Key steps are the regioselective amination with methylamine, the phase-transfer catalysed arylation of 4-chlorophenyl acetonitrile (**18**), and subsequent air oxidation giving **20**.

The benzhydrylic alcohol **4** is obtained in six steps, avoiding the inconvenient reagents mentioned earlier. The regioselective alkylation of 1,2,4-triazole (**3**) is achieved by

Scheme 1



Scheme 2



† Lecture given at the 14th SCI Process Development Symposium in Manchester, and at the 1st International Conference on Organic Process Research and Development in San Francisco.

(1) Raeymaekers, A.; Freyne, E.; Van Gelder, J.; Venet, M. (Janssen Pharmaceutica). Eur. Pat. B-O 293,978, 1987.

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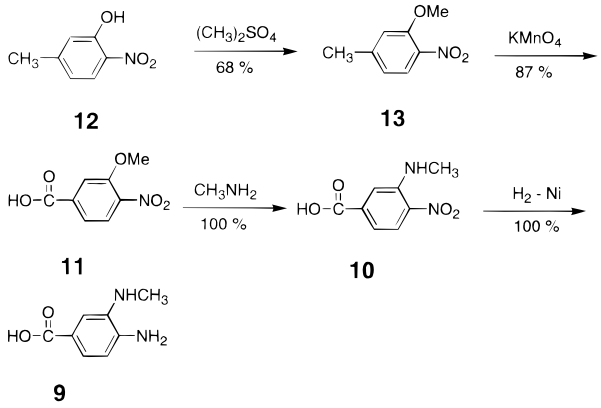
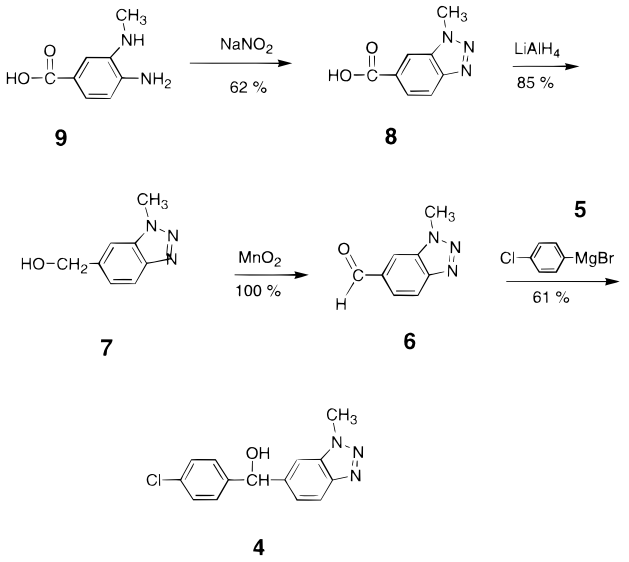
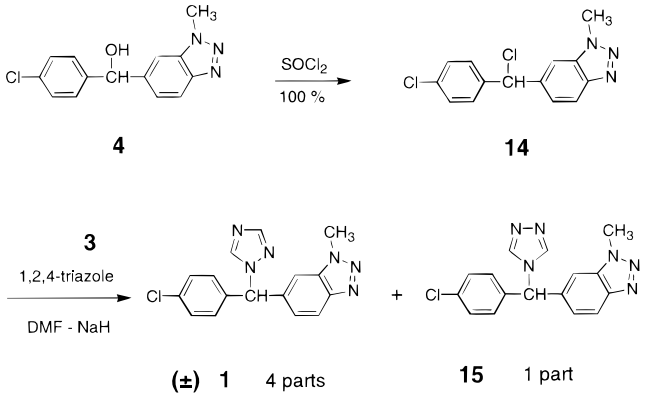
Scheme 3



Scheme 4



Scheme 5

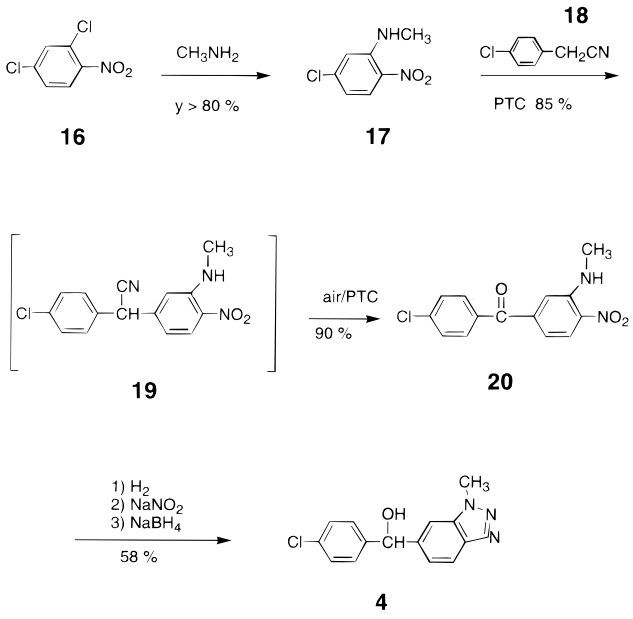


alkylating 4-aminotriazole (**21**) and by deamination, a proven methodology[2] (Scheme 7).

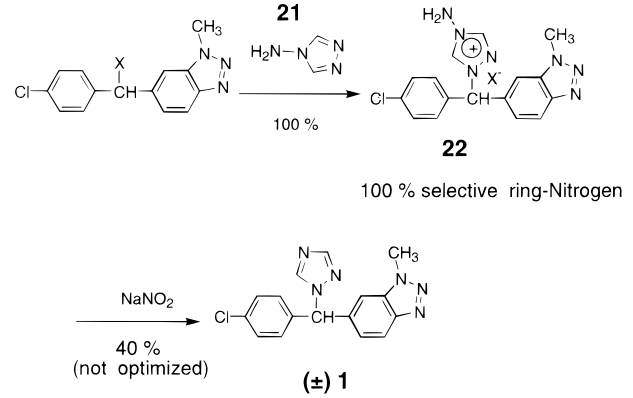
In the meantime some enantiomeric R 83842 was obtained in a very laborious way, intensively using chromatography. The (*S*)-enantiomer proved superior to the (*R*)-enantiomer, and thus we decided for a racemic switch. Before dealing with the racemic switch, a few interesting notes on the chemistry are outlined in Schemes 6 and 7.

(2) Scriven, E.; Astleford, B. A.; Goe, G. L.; Keay, J. G. *J. Org. Chem.* **1989**, *54 (3)*, 731.

Scheme 6



Scheme 7

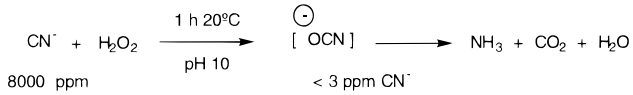


The air oxidation of benzhydrylcyanides to benzophenones was studied by A. Donetti.[3] For diphenylacetonitrile in DMSO, the oxidation appears to almost exclusively follow pathway A, producing mainly cyanate as a by-product (Scheme 8).

We found the air oxidation to proceed smoothly in DMA using *N*-benzyl triethylammonium chloride as a phase-transfer catalyst and by bubbling air through the reaction mixture.

Surprisingly for nitrile **19**, in DMA and using a phase-transfer catalyst, we found pathway B dominating. Next to only 9.5% of cyanate, 90.5% of cyanide was formed.

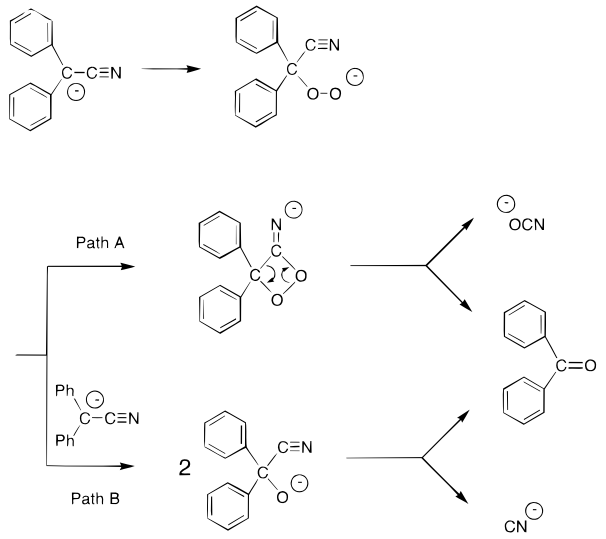
As a consequence, the aqueous cyanide waste needed further processing, that is, oxidation, to reduce the cyanide content below 3 ppm before sending it to the waste water plant.



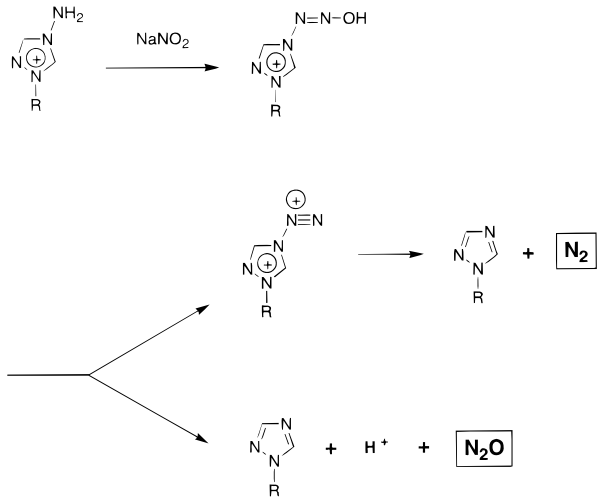
The oxidation is complete within 1 h at room temperature, but **the decomposition of the cyanate formed is much**

(3) Donetti, A.; Boniardi, O. *Synthesis* **1980**, 1009.

Scheme 8



Scheme 9



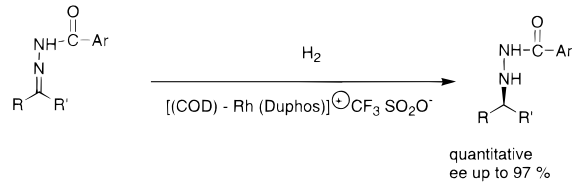
slower, as we found out incidently. The aqueous solution was stored in a closed drum. We should have controlled the decomposition of cyanate before charging in the drums and should have had pressure relief in place, as a **drum ruptured overnight**.

Another example showing the importance of addressing the total reaction equation is the deamination of **22**. One might expect N_2 to be formed as a by-product, but to our surprise, N_2O is also formed. We should have known, as Fischer already published this in 1877.[4] We confirmed it qualitatively, but M. De Rosa[5] quantified the amount of nitrous oxide to be 35% of theory for 1,1-diphenylhydrazine (Scheme 9). This is more than just nice to know, especially in the plant.

II. Enantiomeric (*S*)-R 83842 ((−)-1)

Racemic R 83842 ((±)-(**1**) is a very weak base. The pK_a of triazole is 2.3 and for benzimidazole the pK_a is 1.6, which made it hard to establish a resolution method using chiral

Scheme 10

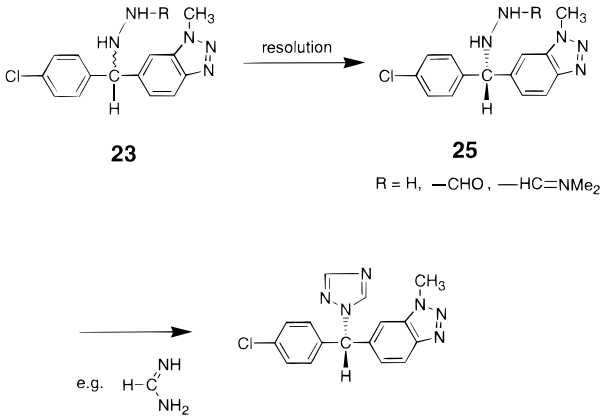


e.g. R = Ph, R' = Me, Et

R = COOR, R' = Ph

not for R = Ar_1, R' = Ar_2

Scheme 11



acids. Chiral chromatography is a practical way for kilogram quantities, less practical for larger scale. 1,2,4-Triazoles can be manufactured from hydrazine derivatives by ring closure with, for example, formamide,[6] formamidine,[7] and 1,3,5-triazine.[8] Preliminary experiments showed little loss in optical purity if chiral hydrazines were used in the ring closure. Fine-tuning of the reaction conditions gave adequate control of the optical purity. Enantioselective reduction of hydrazones is a known route for chiral hydrazines,[9] but unfortunately it is unsuccessful for hydrazones of benzophenones (Scheme 10).

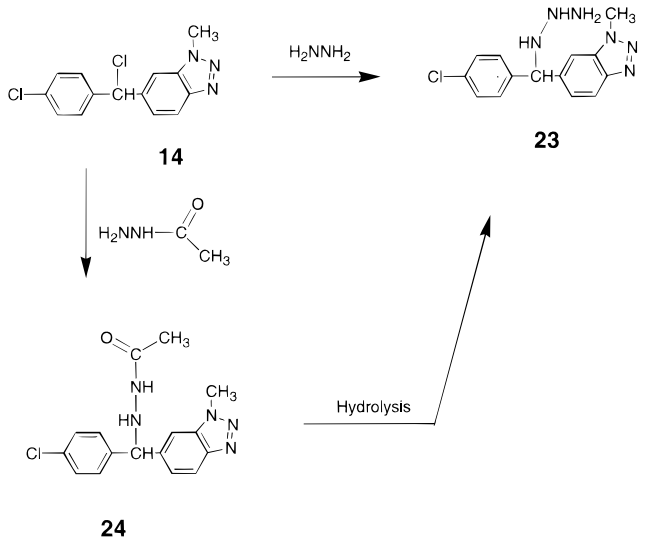
Therefore, we set off screening for resolutions of hydrazine derivatives suitable for ring closure to the desired 1,2,4-triazole **1** (Scheme 11).

We found the monosubstituted hydrazine **23** (R═H) the most suitable for both the resolution and ring closure.[10] Hydrazine derivative **23** can be obtained either by direct alkylation of **14** on aqueous hydrazine, or on mono-acetylhydrazine and subsequent hydrolysis (Scheme 12).

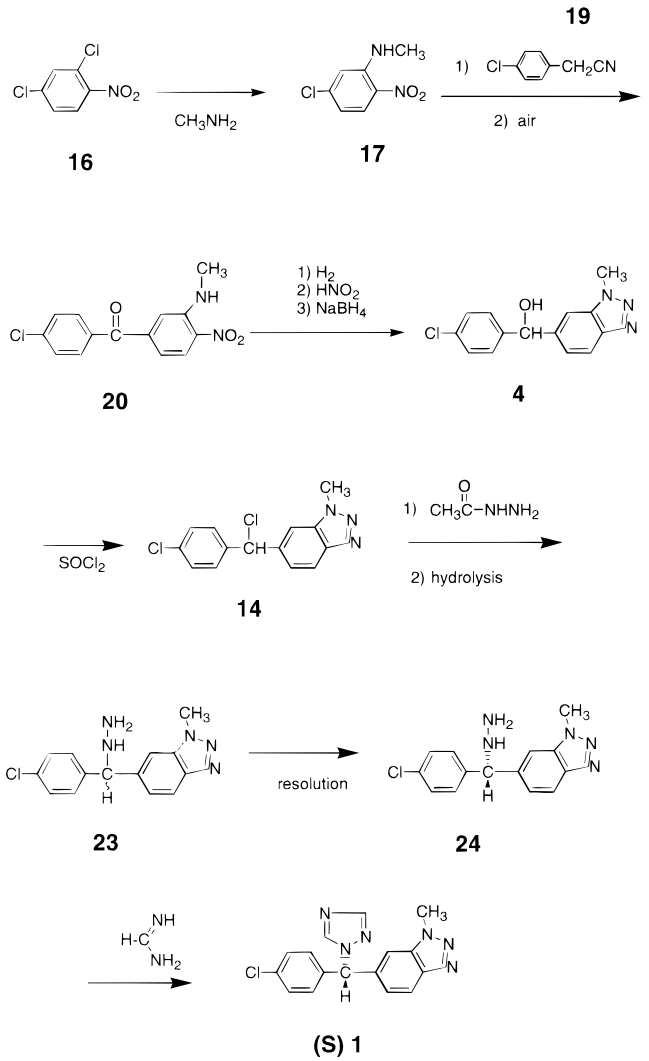
For safety reasons, we do not want to handle hydrazine in our plants. As mono-acetyl hydrazine is a very cheap solid, we accepted the extra step going over **24**. Note, however, that mono-acetyl hydrazine is hygroscopic and should be stored cold for not too long a period of time, as it rearranges slowly on standing, giving di-acetylhydrazine and hydrazine.

(4) Fischer, E. J. *Liebigs Ann. Chem.* **1877**, *170*, 158.
(5) De Rosa, M.; Haberfield, P. *J. Org. Chem.* **1981**, *46*, 2639.
(6) Petree, H. (Ciba-Geigy). U.S. Patent 79-92 257,791,107, 1981.
(7) Huang, Y. *Zhongguo Yiyao Gongye Zazhi* **1990**, *21 (10)*, 466.
(8) Grundmann, C.; Rätz, R. *J. Org. Chem.* **1956**, *21*, 1037.
(9) Burk, M.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.
(10) Willemsens, B.; Verstappen, W.; Copmans, A.; Vandendriessche, A.; De Knaep, A.; Venet, M. (Janssen Pharmaceutica). Eur. Pat. A-O 668,861, 1992.

Scheme 12



Scheme 13



Scheme 13 gives a summary of the optimised synthesis of (***S***)-**1**. It is an 11-step linear synthesis using cheap and safe reagents that was scaled up and validated successfully.

During development, cost analysis is a standard tool used to achieve optimal economics. Not only raw materials and reagents, but also solvents used and waste produced are considered, as well as operations.

Table 1

full cost	%
1. labour	65.5
2. equipment	8.9
3. THF	3.6
4. DMA	2.8
5. NRS[a] low Cl	2.5
6. NRS high Cl	2.3
7. Pt 5% on carbon	2.3
8. HBr acetic acid solution	2.3
9. formamidine acetate	2.2.

[a] NRS = non recoverable solvent.

Table 2

raw material cost	%
solvent + solvent waste	50.8
first building block	8.6
total building blocks	26.6
miscellaneous (additives, cats, packaging, inorganics, ...)	14.0

Table 1 shows that indeed we succeeded in using very cheap reagents, as the first building block (formamidine) is only in position 9 of the full cost breakdown, contributing only 2.2%. The major cost is labour accounting for two/thirds of the costs. It is clear where our focus for further cost reduction should be.

Solvents often surprise many beginning development chemists, and solvent waste, even more.

Isn't it surprising that simple solvents such as THF and DMA take position 3 and 4?

Low chlorine-containing solvent waste (<5% chlorine) and higher are in position 5 and 6!

The raw material cost breakdown is even more striking (Table 2). Solvents and solvent waste make up half of it, almost double the total cost of all building blocks. Note also that aids (miscellaneous) account for half of the cost of building blocks. Clearly, cost analysis during development is critical.

And there is more to a good synthetic method than the number of steps and the simplicity of the reagents. Process engineering, solvent recycling and recovery, mastering waste, and safety assessment of reactions, reagents, and intermediates are equally important elements for chemical development.

Experimental Section

1. Oxidative Destruction of Cyanide in Aqueous Waste. Typical Procedure. The pH of 500 mL of aqueous cyanide solution (8100 ppm or 0.156 mol of cyanide) is adjusted to 10.5 by adding sulphuric acid. At 50 °C is added dropwise over 1 h, 1 equiv of H_2O_2 (15 g, 35.4 wt %), and the pH is kept between 9.5 and 10.5. At higher pH (>11) the reaction slows down, and some H_2O_2 may decompose. Typically, the oxidation is done within 1 h. Cyanide concentration should

have dropped <3 ppm; if not, some additional H_2O_2 is added.

***DO NOT* store the resulting solution in a closed system, as pressure may build up** as a result of cyanate decomposition. Always check the compatibility of all constituents of the aqueous cyanide solution with H_2O_2.

2. Stability of *N*-Acetyl Hydrazine. *N*-acetylhydrazine was found to be very hygroscopic and prone to decomposition giving *N*,*N*′-di-acetylhydrazine along with hydrazine. The decomposition is relatively fast at room temperature. After a few months already, the solid material has turned into a semi-liquid mass, with product concentrations going <80%. At 4 °C, however, in a triple polyethylene bag with a desiccant present, the product is reasonably stable (no decomposition after 3 months). *N*-acetylhydrazine HCl was found to be stable at room temperature (no change after 4 months).

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