



A mild and efficient dehydrogenation of indolines[†]

Ulf Tilstam,* Michael Harre, Thilo Heckrodt and Hilmar Weinmann

Process Research, Schering AG-Berlin, D-13342 Berlin, Germany

Received 10 April 2001; revised 3 May 2001; accepted 8 June 2001

Abstract—A new mild and efficient dehydrogenation of indolines to indoles has been developed. For the dehydrogenation trichloroisocyanuric acid is used in combination with DBU. After work-up with sodium hydrogen sulfite it was possible to obtain indole in an almost quantitative yield. The new method is also suitable for indolines bearing electron withdrawing or electron donating groups. Under the reaction conditions no ring chlorination was observed. © 2001 Elsevier Science Ltd. All rights reserved.

Indole and its myriad of derivatives continue to capture the attention of organic chemists. Several new indole ring syntheses have been developed over the years and this trend is still ongoing.¹

Indoles bearing various substituents on the benzene ring often have potent physiological activities and can be useful intermediates for the synthesis of indole alkaloids. Synthetic interconversion of substituted indoles and the corresponding dihydro derivatives (indolines) is an important process giving access to uncommonly substituted indoles.² The conversion of the indole ring to an indoline ring can easily be accomplished by catalytic hydrogenation or reduction with sodium cyanoborohydride in acetic acid. For the dehydrogenation of indolines to indoles, although studied extensively there has up to now never been an efficient general method. Various methods like oxidations (e.g. with MnO₂, CuCl₂-pyridine, DDQ, chloranil, Co(Salen)/O₂, etc.) or catalytic dehydrogenation over noble metal catalysts (e.g. Pd/C Raney Ni, etc.) at elevated temperature have been used.³ All needing a large excess of reagent, producing large amounts of heavy metal waste and carefully controlled reaction conditions to control overoxidation precludes them from large scale synthesis. The use of a catalytic amount of tetra-*n*-propylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide has also been reported to give indole from indoline in 73%.⁴

Another method for the dehydrogenation of indolines to indoles through an azasulfonium salt utilizing dimethyl sulfide, *tert*-butyl hypochlorite and a base such as sodium ethoxide at low temperature (–65°C) has been reported by Kikugawa et al.⁵ Utilizing this method it was possible to obtain indole from indoline in 74%. Due to the use of dimethyl sulfide and low temperature (–70°C), allowing various other oxidizable groups in the molecule, this method is unsuitable for large scale synthesis. Furthermore *tert*-butyl hypochlorite is not commercially available in bulk quantities anymore.

The dehydrogenation of indolines to indoles has also been reported using *N*-chlorinating agents. The first time by Somei et al.⁶ utilizing *N*-chlorosuccinimide with triethyl amine as base in methylene chloride at room temperature. Under the reported conditions low yields of indole were obtained from indoline (35%) and the obtained products were contaminated with considerable amounts of nuclear chlorinated products. Later Kikugawa et al.⁵ found that the yield of indole is greatly affected by the used solvent and base. After a detailed study it was possible to optimize the yield of indole to 84% and to minimize the amount of chlorinated products through change to *t*-butyl hypochlorite as chlorinating agent, with DBU as base and diethyl ether with some DMF as solvent.

We now report to the best of our knowledge the first use of trichloroisocyanuric acid (TCCA) for the dehydrogenation of indolines to indoles.

Trichloroisocyanuric acid, 1,3,5-trichloro-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione, has become increasingly important as disinfectant being more stable and easier

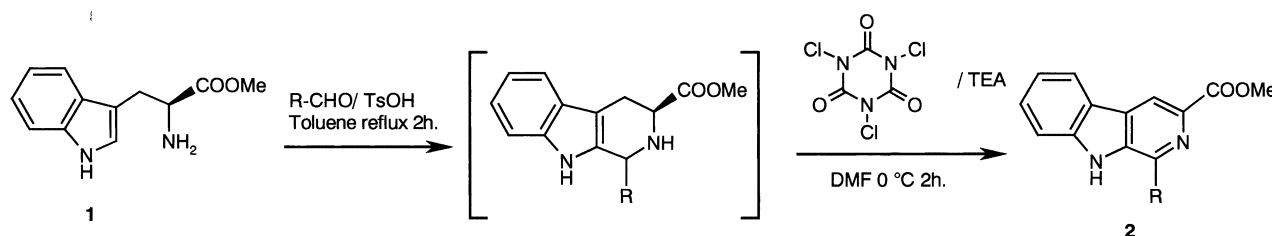
* Corresponding author. Tel.: +49-30-46812074; e-mail: ulf.tilstam@schering.de

[†] Dedicated to Professor Jan Bergman on the occasion of his 60th birthday.

to handle than metal hypochlorites. TCCA is used as disinfectant for swimming pools, cleaning and sterilizing bathrooms and laundry bleach. TCCA is sparingly soluble in water but highly soluble in organic solvents. In comparison, *N*-chlorosuccinimide is sparingly soluble in most organic solvents. TCCA is cheap and easily accessible and, even on a large scale, the high solubility in organic solvents makes it an ideal oxidant for organic synthesis. The waste cyanuric acid is environmentally non-hazardous.⁷

tetrahydro- β -carbolines.¹² TCCA was found to be an extremely efficient *N*-chlorinating agent, and all three chlorine atoms are available for the chlorination. The question about possible nuclear chlorinated derivatives as possible impurities in the product was studied in detail. No chlorinated derivatives were ever detected in the products.

Due to the interesting results obtained with β -carbolines, being aware of the difficulties encountering the



Up to now TCCA has been mainly used in organic synthesis for the chlorination of aromatic nucleus and ketones^{8,9} and for the oxidation of secondary alcohols to ketones with pyridine as base.¹⁰ TCCA has also been used as a co-oxidant in a TEMPO catalyzed oxidation of primary and secondary alcohols.¹¹

We recently published a preliminary study on the use of TCCA and triethyl amine for the dehydrogenation of

dehydrogenation of indolines we decided to adopt our method.

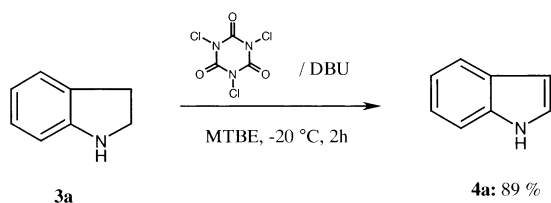
The first attempt to dehydrogenate indoline in DMF at -20°C gave an isolated yield of 58% of indole after chromatographic purification. TLC monitoring of the reaction showed a spot to spot reaction. The reaction was complete after 2 h. A detailed study showed that no 3-chloro-indole was formed under the reaction con-

Table 1. Indoles prepared from indolines using TCCA/ DBU

Entry	Indoline of type 3	Indole of type 4*	Yield
			89 %
			82 %
			81 %
			83 %
			72 %
			76 %

* all physical data were in concordance to literature data.

ditions, reported by previous groups being the major impurity utilizing *N*-chlorosuccinimide or *t*-butyl hypochlorite as oxidant.^{7,8}



The use of DMF as solvent led to a tedious work-up as indole **4a** did not precipitate during work-up.

Due to the high solubility of TCCA in organic solvents it was possible to change to MtB-ether giving a direct phase separation after addition of the sodium hydrogensulfite solution. The amount of oxidant and base for a complete conversion of indoline to indole was found to be a 10% molar excess of TCCA with 2 equiv. of DBU (Table 1). The reaction time in MtB-ether remained the same and utilizing these reaction conditions it was possible to obtain indole in 89% after filtration of the organic phase after work-up through a silica pad and crystallization from petrol ether.

To study the scope of the reaction various electron rich and electron poor indoline derivatives were subjected to the reaction conditions.¹³

All indoline derivatives except the nitro derivatives were found to behave in the same manner as indoline **3a** under the standard reaction conditions. For the nitro substituted indolines the reaction had to be performed at higher temperature (addition of TCCA at 20°C and heating to reflux after completion of the addition). After this reaction some starting material could also be recovered but the reaction conditions were not further optimized especially for these substrates.

To ascertain a good yield of product it was found necessary especially for electron rich derivatives to destroy all remaining oxidants prior to phase separation. The optimal method was found to stir the reaction mixture with the sodium sulfite solution for at least 10 h as the remaining *N*-chloro derivatives from TCCA slowly react with water and release hypochlorous acid which readily oxidize the product. Unfortunately, it was not possible to further reduce the amount of TCCA as the reaction then stopped before completion.

We have shown that the use of trichloroisocyanuric acid TCCA in combination with DBU as base for the dehydrogenation of indolines to indoles is a mild and efficient method for electron rich as well as electron poor derivatives, making it the first general method for this conversion. A detailed study showed that indole was not contaminated with ring chlorinated products being the major obstacle for other reported methods. The reaction was found to be very clean giving the indole derivatives in high yields.

Acknowledgements

The authors gratefully thank the Spectroscopical Department of Schering AG for the measurement of the physical data.

References

- Gribble, G. J. *Chem Soc., Perkin Trans. 1* **2000**, 1045.
- Preobrazhenskaya, M. N. *Russ. Chem. Rev. (Engl. Transl.)* **1967**, 36, 753.
- The Chemistry of Indoles*; Sundberg, R. J., Ed.; Academic Press: New York, 1970.
- Goti, A.; Romani, M. *Tetrahedron Lett.* **1994**, 35, 6567.
- Kawase, M.; Miyake, Y.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1401.
- Somei, M.; Hashiba, K.; Yamada, F.; Maekawa, T.; Kimata, T.; Kaneko, C. *Chem. Lett.* **1978**, 1245.
- Ullman's Encyclopedia of Industrial Chemistry*, 6th ed., 1999; Electronic Release (Chloroamines).
- Manchand, P. S.; Coffen, D. L.; Belica, P. S.; Wong, F.; Wong, H. S.; Berger, L. *Heterocycles* **1994**, 39, 833.
- Hiegel, G. A.; Nalbandy, M. *Synth. Commun.* **1992**, 22, 1589.
- Hiegel, G. A.; Nalbandy, M. *Synth. Commun.* **1992**, 22, 1589.
- Jenny, C. J.; Lohri, B. *Eur. Pat.* 775684, 1997, to Hoffmann La Roche.
- Haffer, G.; Nickisch, K.; Tilstam, U. *Heterocycles* **1998**, 48, 993.
- Typical procedure: Indoline **3a** (6.0 g, 50.4 mmol) was dissolved in 60 ml MtB-ether, and 17.2 ml (2.3 equiv.) of DBU were added. The solution was cooled to -30°C and a solution of 4.55 g TCCA dissolved in a mixture of 75 ml MtB-ether and 25 ml ethyl acetate was added while maintaining the temperature below -20°C . After completion of the addition the mixture was allowed to warm up slowly over 2 h to 0°C . After completion of the reaction, 50 ml of a saturated solution of sodium hydrogen sulfite was added while maintaining the temperature below 9°C . The mixture was stirred overnight at room temperature prior to separation of the phases. The precipitated solid was filtered off and washed with 20 ml of MtB-ether. The phases were separated and the aqueous phase was extracted with 30 ml of MtB-ether. The combined organic phases were washed twice with 50 ml of water. The organic solution was filtered through a pad of silica gel (75 g) and the silica gel pad was subsequently washed with 100 ml of MtB-ether. The combined organic phase was stripped to dryness and the residue was taken up in 100 ml of petroleum ether and 0.25 g of activated charcoal was added. The mixture was heated to reflux, filtered hot and the colorless solution was cooled slowly to -20°C . The obtained crystalline material was filtered off and dried giving 5.25 g of indole **4a** as colorless crystals.