A MILD AND EFFICIENT DEHYDROGENATION METHOD FOR 3-CARBOXY-1,2,3,4-TETRAHYDRO-β-CARBOLINES

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Abstract - A new mild and efficient method for the dehydrogenation of 3-carboxytetrahydro-ß-carbolines using trichloroisocyanuric acid (TCCA) / triethylamine (TEA) has been developed.

INTRODUCTION

β-Carbolines are widely distributed in nature and new ones are constantly being reported.[1] There is a lot of interest in the synthesis and reactivity of β-carbolines, owing to the wide range of biological activity found among members of this class of compound. Even some relatively simple β-carbolines for instance Schering´s anxiolytic (**2**) possess significant biological activity. [2]

A mild method for the aromatization of the tetrahydro-β-carboline (**1**) was required for studying the preparation of **2**. Scrutiny of the literature showed numerous methods[1] demanding carefully controlled conditions and some of which were not generally applicable. Many groups have looked for better methods for the dehydrogenation using reagents including DDQ,[3-5] photooxidation,[6] activated MnO_2,[7,8] SeO_2[9-12] and $Ph_2Se(OCOCF_3)_2$,[13] none of them suitable for large-scale production, so a new one had to be sought.

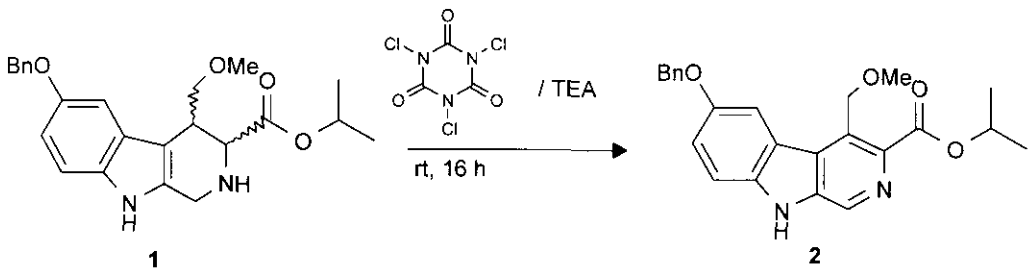
RESULT AND DISCUSSION

The dehydrogenation of indolines to indoles using NCS/ TEA in methylene chloride was reported by Somei *et al.*[14] Later Kikugawa *et al.*[15] found that *tert*-butyl hypochlorite with DBU in methylene chloride gave a higher yield and a better quality. This method was previously adopted by us[16] for the dehydrogenation of lysergic acid derivatives as well as for the aromatization of tetrahydro-β-carbolines on laboratory scale.

A major drawback of this method is to be seen in the reports of explosions occurring with *tert*-butyl hypochlorite which excludes this reagent from large scale production.[17] To avoid having to produce our own *tert*-butyl hypochlorite it was decided to search for an alternative method. A second hurdle for an optimal procedure is the instability of the trans isomer of (**1**) as well as the sensitivity of the side chain as regards cleavage. Condensation and dehydrogenation are the two most crucial steps in

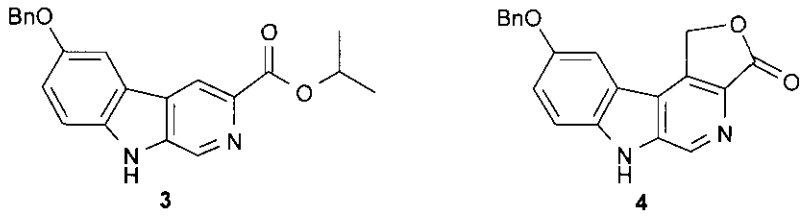
the synthesis of **2** and are done preferably as a one pot reaction. Other *N*-chlorinating or *N*-brominating reagents, *e.g.* NBS, NCS, thionyl chloride, sulphuryl chloride as well as trichloroisocyanuric acid (TCCA), were selected as alternatives and combined with various tertiary amines for comparison with *tert*-butyl hypochlorite / TEA. Iodine was also selected as numerous studies[18-20] have shown the applicability of iodine / potassium acetate for the aromatization of tetrahydro-isoquinoline derivatives.

We now report that the best conditions for the dehydrogenation of **1** in our study are TCCA / TEA at room temperature giving the β-carboline (**2**) in high yield and excellent quality. Due to the ease of handling of TCCA the reaction conditions were optimized and scaled up to full production plant scale.[21] TCCA is a stable chlorinating solid, easy to handle and normally used for bleaching textiles. Under the reaction conditions described no nuclear chlorinated products were observed even on large scale.



1 **2**

None of the other methods were as high yielding and selective as TCCA /TEA. $SOCl_2$/TEA[22] for instance caused a high degree of degradation of the methoxymethyl side chain during the aromatization yielding the compound (**3**) as the main product of the reaction.



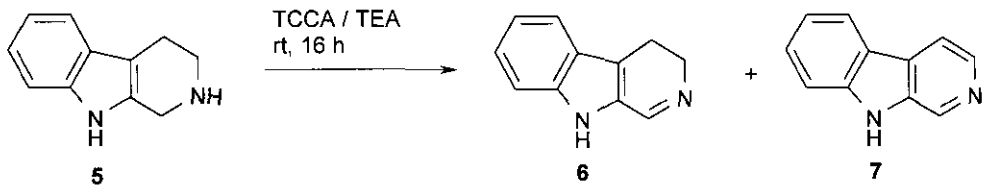
3 **4**

When the free acid was subjected to the same reaction conditions the yield of the lactone (**4**) was almost as large.

NCS/ TEA in methylene chloride facilitated clean oxidation of the tetrahydro ring-system, but the crude product was contaminated with up to 25 molar % of succinimide which was not removable except with preparative HPLC, which excluded the reaction for large scale production.

Iodine / KOAc on this system was not as selective as tetrahydroquinolines, and produced an appreciable amount of the corresponding dihydro derivative.

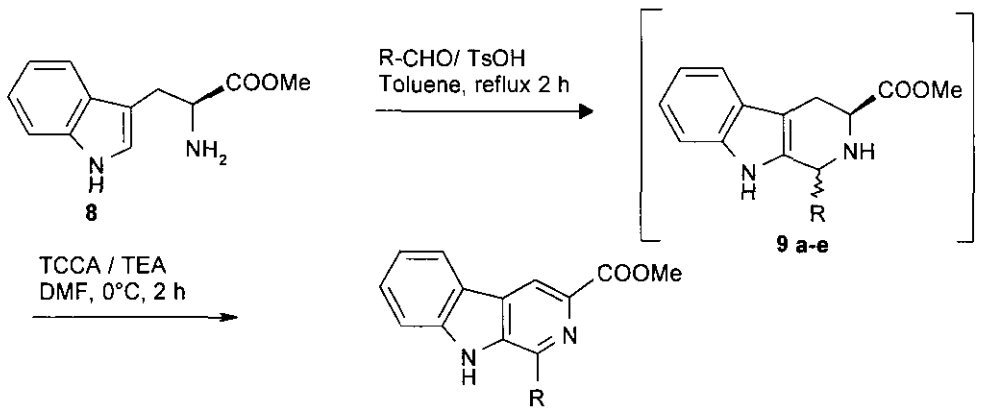
To determine the scope of the new method the simple tryptamine derivative (**5**) was examined first. In this case the dihydroderivative (**6**) was the main product, although accompanied by the desired β-carboline (**7**) as well as the starting material (**5**), probably due to disproportionation of the dihydro-β-carboline (**6**).[1] This persistence of tryptamine derivatives towards oxidation is known from the *literature*. [1]



5 **6** **7**

We then turned our attention to tryptophan derivatives, as many studies on the synthesis of various β -carbolines have been performed with tryptophan esters or derivatives thereof.[1] To show the applicability of the method we chose three simple aldehydes; formaldehyde, acetaldehyde and benzaldehyde. We also decided to apply the method to the preparation of two naturally occurring β-carbolines, flazin[23] and nitramarine. [24]

L-Tryptophan methyl ester (**8**) was condensed with the corresponding aldehydes and the crude tetrahydro-β-carbolines (**9a-e**) were directly dehydrogenated with TCCA/TEA to afford the various 1-substituted 3-carbomethoxy-β-carbolines (**10a-e**) in excellent yield. Simple recrystallisation of the crude product from methanol gave an analytically pure sample.



8 **9 a-e** **10 a-e**

The details are shown in Table 1.

Table 1.

Compd	R	Yield*	Physical data
10a	H	91 %	mp (MeOH) 246-247 °C (decomp) lit., [25] 248 °C (decomp); ^{1}H-NMR (DMSO d_6) 3.92 (s, 3H), 7.32 (t, 1H, J = 8 Hz), 7.61 (t, 1H, J = 8 Hz), 7.68 (d, 1H, J = 8 Hz), 8.43 (d, 1H, J = 8 Hz), 8.93 (s, 1H), 8.98 (s, 1H), 12.08 (s, 1H, NH).
10b	Me	83 %	mp (MeOH) 249-250 °C lit., [26] 246-48 °C; ^{1}H-NMR (DMSO d_6) 2.83 (s, 3H), 3.91 (s, 3H), 7.30 (t, 1H, J = 8Hz), 7.59 (t, 1H, J = 8Hz), 7.67 (d, 1H, J = 8 Hz), 8.35 (d, 1H, J = 8 Hz), 8.77 (s, 1H), 12.03 (s, 1H, NH).
10c	Ph	89 %	mp (MeOH) 256-258 °C (decomp), lit.,[12] 257-60 °C(decomp); ^{1}H-NMR (DMSO d_6) 4.0 (s,3H), 7.35 (t, 1H, J = 8Hz), 7.55-7.75 (m, 5H), 8.05 (d, 2H, J = 8Hz), 8.43 (d, 1H, J = 8 Hz), 8.94 (s 1H), 11.95 (s, 1H).
10d	2-(5´-Acetoxymethyl)-furanyl	87 %	mp (MeOH) 153-154 °C, lit.,[23] 154-156 °C; ^{1}H-NMR ($CDCl_3$) 2.20 (3H,s), 4.06 (3H,s), 5.25 (s, 2H), 6.65 (d,1H, J=3.5 Hz), 7.32 (d,1H, J=3.5 Hz), 7.38 (d,1H, J= 8 Hz), 7.61 (t,1H, J= 8 Hz), 7.75 (d,1H, J= 8 Hz), 8.19 (d,1H, J= 8 Hz), 8.81 (s, 1H), 10.28 (br s, 1H NH).
10e#	2-Quinolinyl	81.5 %	mp 195-197 °C (decomp); Anal. Calcd for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89; Found C, 75.09; H, 4.18; N, 12.06; ^{1}H-NMR (DMSO d_6) 4.01 (s, 3H), 7.37 (t, 1H, J = 8 Hz), 7.67-7.74 (m, 2H), 7.90-7.96 (m, 1H), 8.06-8.10 (m, 2H), 8.51 (d, 1H, J = 9 Hz), 8.62 (d, 1H, J = 9 Hz), 8.79 (d, 1H, J = 9 Hz), 8.87 (d, 1H, J = 9 Hz), 9.09 (s, 1H), 12.37 (s, 1H, NH).

* The yield is based on L-tryptophan methyl ester.
# The Pictet-Spengler cyclization was in this case completed after 15 min.

The derivative (**10d**) has previously been reported by Gessner *et al.*[22] as the final intermediate in the synthesis of flazin. The aromatization was reported to proceed with Pt/C catalyst in the presence of oxygen in refluxing toluene to form the intermediate (**10d**). The derivative (**10d**) gave flazin after hydrolysis. Using our procedure high quality (**10d**) was obtained with a yield of 87 %. All spectroscopic data on **10d** were in accordance with those reported by Gessner *et al.*[22]
The corresponding ethyl ester of **10e** was reported by Hibino *et al.*[23] to yield nitramarine in a quantitative yield through hydrolysis of the ester and decarboxylation in quinoline. The aromatization of **9e** to **10e** was performed with Pd/C in refluxing xylene affording the ethyl ester with a yield of 63 %. Using our procedure high quality (**10e**) was obtained with a yield of 81.5 %.

CONCLUSION

A new efficient method for the dehydrogenation of tetrahydro-3-carboxy-ß-carbolines has been developed. The TCCA / TEA method previously not known for the dehydrogenation of saturated nitrogen heterocycles has been found to afford excellent yield of 3-carboxy-β-carbolines under very

mild reaction conditions, contrary to the offen harsh reaction conditions of methods described in the literature.

EXPERIMENTAL

All reactions were carried out in a nitrogen atmosphere using standard techniques for the exclusion of air. TLC was performed on Merck Aluminum foil 60 F 254. MS spectra were recorded on a Micromass AutoSpec EQ Massspectrometer. ^{1}H- (300 MHz) NMR spectra were recorded in DMSO d_6 or in $CDCl_3$using TMS as internal standard.

General procedure for the synthesis of 10a-e:

10 Mmol aldehyde and a catalytic amount (*ca.* 10 mg) of TsOH are added to a solution of 10 mmol tryptophan methyl ester in 50 mL of toluene and the resulting mixture is refluxed for 2 h under inert atmosphere. After completion of the reaction the mixture is cooled and stripped to dryness. The residue is taken up in 20 mL of DMF and neutralized with TEA. 4.5 mL of TEA is then added to the solution and the mixture is cooled to -20 °C. Subsequently 10 mmol TCCA dissolved in 10 mL of DMF are slowly added keeping the temperature below -10 °C. After the addition is completed the mixture is allowed to slowly warm up to 0 °C and stirred for 2 h at this temperature to complete the reaction. The resulting product is precipitated from ice water, filtered, washed with water and dried. For analytical purpose a sample is recrystallized from methanol.

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