Communications to the Editor

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A NEW METHOD FOR THE PREPARATION OF 3,4-DIHYDRO-β-CARBOLINES

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N-Alkylthiocarbonyl tryptophan (1a-f) and tryptamine (1g-j) derivatives can be converted into the corresponding 3,4-dihydro-β-carbolines (3) under mild and non-acidic conditions by use of alkylating reagents.

KEYWORDS —— 3,4-dihydro-β-carbolines; methyl 1-substituted-3,4-dihydro-β-carboline-3-carboxylates; the Bischler-Napieralski reaction; N-thiocarbonyl tryptophan; alkylthioiminium salt; cyclodesulfurization

For the preparation of 3,4-dihydro-β-carboline (3,4-dihydro-9H-pyrido[3,4-b]indole) nucleus,[1] the Bischler-Napieralski reaction has been widely used. However, the reaction usually involves the treatment of an amide with phosphorus oxychloride or phosphorus pentoxide at an elevated temperature and a tedious work-up for purification. Under these rather drastic conditions, N-acetyltryptophan and its ester analogs yield 1-methyl-β-carboline (harman) instead of 1-methyl-3,4-dihydro-β-carboline-3-carboxylic acid derivatives, owing to the accompanying decarboxylation and aromatization.[2] Several improved methods using polyphosphate ester,[3] mercuric chloride,[4] and trifluoroacetic acid-acetyl chloride[5] under milder conditions have been reported recently.

In this communication, we also report another practical method for the preparation of 3,4-dihydro-β-carbolines (3) from thiocarbonyl derivatives (1a-j) under mild and non-acidic conditions as illustrated in the Chart.

Thiocarbonyl derivatives (1a-j) were readily prepared by the reaction of the corresponding amides with Lawesson's reagent.[6] Treatment of 1 with methyl iodide or benzyl bromides (R^3X) in an appropriate solvent gave a thioiminium salt (2) as an intermediate, which, at room temperature or in the refluxing solvent, spontaneously cyclized and released methanethiol or phenylmethanethiols to yield the corresponding salt of 3.

Following are typical procedures:

i) Preparation of 3a (1a → 3a) ----- A solution of 1a (5.52g, 20mmol) and methyl iodide (5.5ml) in acetone (55ml) was stirred for 24 h at room temperature under an argon atmosphere with protection from light. The acetone solution was concentrated under reduced pressure. The resulting precipitates were collected by filtration and recrystallized from methanol to give 6.66g (90%) of 3a,[7] mp 214-216°C (decomp.).

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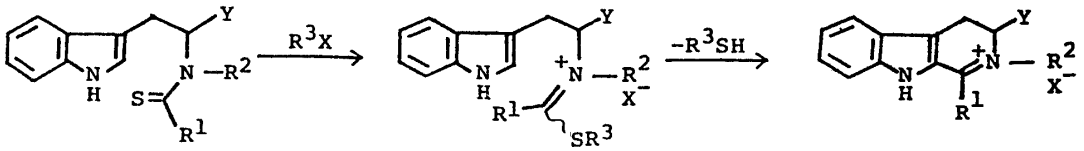

1 2 3

a) $R^1=CH_3$ $R^2=H$ $Y=CO_2CH_3$
b) $R^1=C_6H_5$ $R^2=H$ $Y=CO_2CH_3$
c) $R^1=C_6H_{11}$ $R^2=H$ $Y=CO_2CH_3$
d) $R^1=C(CH_3)_3$ $R^2=H$ $Y=CO_2CH_3$
e) $R^1=CH_3$ $R^2=CH_2C_6H_5$ $Y=CO_2CH_3$
f) $R^1+R^2=(CH_2)_3$ $Y=CO_2CH_3$
g) $R^1=Y=H$ $R^2=CH_3$
h) $R^1=Y=H$ $R^2=C_6H_5$
i) $R^1=Y=H$ $R^2=C_6H_{11}$
j) $R^1=CH_3$ $R^2=CH_2C_6H_5$ $Y=H$

Chart

ii) Preparation of 3f (1f → 2f → 3f) ----- A solution of 1f (3.02g, 10mmol) and methyl iodide (3ml) in acetone (30ml) was stirred for 15 h at room temperature. Removal of the solvent and excess methyl iodide gave a methylthioiminium salt (2f) (4.4g)[8,9] as an oil. This oil was dissolved again in acetone (30ml) and refluxed for 60 h. After cooling, the precipitated crystals were collected and recrystallized from 2-propanol to give 3.40g (86%) of 3f,[10] mp 169-170°C (decomp.).

The other examples are shown in the Table. It is noteworthy that the use of p-nitrobenzyl bromide in place of methyl iodide remarkably improved the yields of 3i and 3j (entry 12 and 15).

The following results are suggestive for mechanistic consideration. Treatment of 1g with excess methyl iodide at room temperature gave the methylthioiminium salt, 2g, as stable crystals (mp 145-147°C)[11] in 91% yield. This isolated crystalline salt (2g) was, in turn, heated at reflux in acetonitrile to give the cyclized product, 3g, in 91% yield. Similarly, 1j gave 2j (74% yield, mp 151-153°C)[11] at room temperature, which was converted into 3j (55% yield, mp 263-264°C) by refluxing in acetonitrile. Considering these results, stoichiometrically an equivalent mole of methyl iodide is required for the conversion of 1 into 2, and the cyclization to 3 proceeds spontaneously, accompanied by the release of methanethiol.[12]

The similar cyclization of optically active alkylthiocarbonyl tryptophan derivatives (1) to 3 without racemization, and the reduction of 3 to methyl 1-substituted 1,2,3,4-tetrahydro-β-carboline-3-carboxylate[13] are under studying.

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Table. The Cyclization of 1 with Alkyl Halides

Entry	1	Alkyl Halide[a]	Reaction Conditions			Yield of 3 (%)[b]
			Solvent	Temp.	Time (h)	
1	a[c]	CH_3I	CH_3COCH_3	r.t	24	90
2	a	$C_6H_5CH_2Br$	CH_2Cl_2	refl	24	82
3	b	CH_3I	CH_2Cl_2	refl	24	83
4	c	CH_3I	CH_3CN	50°C	24	80
5	d	CH_3I	CH_3CN	50°C	60	52
6	e	CH_3I	CH_2Cl_2	refl	24	62
7	f	CH_3I	CH_3COCH_3	refl	60	86
8	g	CH_3I	CH_3CN	refl	24	83
9	h	CH_3I	CH_3CN	refl	24	72
10	i	CH_3I	CH_3CN	refl	24	28[d]
11	i	$C_6H_5CH_2Br$	CH_3CN	refl	48	70
12	i	$P\text{-}NO_2C_6H_4CH_2Br$	CH_3CN	refl	15	90
13	j	CH_3I	CH_3CN	refl	5	43
14	j	$C_6H_5CH_2Br$	CH_3CN	refl	4	56
15	j	$P\text{-}NO_2C_6H_4CH_2Br$	CH_3CN	refl	2	76

a) 4-5 equiv. molar amounts of methyl iodide or 1.5 equiv. molar amounts of benzyl bromides were used.

b) All products gave satisfactory spectroscopic and analytical data.

c) Compound 1a also cyclized to 3a (X=Cl) by use of the following reagents: C_6H_5COCl (83%); CH_3COCl (72%); $ClCO_2C_2H_5$ (38%); $C_6H_5CH_2Cl$ (16%).

d) Isolated as free base.

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6) $(P\text{-}CH_3O\text{-}C_6H_4)_2P_2S_4$, [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]
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7) 3a: IR (nujol) 3250, 1730, 1620, 1550 cm^{-1}; NMR (d_6-DMSO) δ: 2.85 (s, 3H), 3.65 (d, 2H), 3.75 (s, 3H), 5.25 (t, 1H), 7.0-8.0 (m, 4H), 12.40 (br s, 1H).

8) 2f: IR (nujol) 3480-3240, 1750, 1570 cm^{-1}; NMR ($CDCl_3$) δ: 2.0-2.6 (m, 2H), 2.75 (s, 3H), 3.3-3.8 (m, 4H), 3.80 (s, 3H), 4.20 (quasi t, 2H), 5.00 (t, 1H), 7.0-7.8 (m, 5H), 9.70 (br.s, 1H).

9) Reduction of 2f with $NaBH_4$ gave methyl 3-(3-indolyl)-2-pyrrolidinopropionate in 84% yield.

10) 3f: IR (nujol) 3080, 1750, 1620, 1580 cm^{-1}; NMR ($CDCl_3$) δ: 1.9-2.7 (m, 2H); 3.5-4.0 (m, 4H); 3.75 (s, 3H); 4.0-4.7 (m, 2H); 5.30 (br, 1H); 6.9-7.8 (m, 4H); 11.95 (br s, 1H).

11) Satisfactory analytical and spectroscopic data (IR, NMR) were obtained for 2g and 2j.

12) In the synthesis of 3a using benzyl bromide (entry 2), phenylmethanethiol was isolated with more than 75% yield from the mother liquor.

13) Treatment of (S)-(+)-methylthiocarbonyl tryptophan methyl ester ((S)-1a) with methyl iodide gave (S)-3a in 90% yield ($[\alpha]_D^{20}$+221°), which was reduced to metnyl (1S, 3S)-(-)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate ((S)-4a) in 90% yield. (S)-4a·HCl; mp 253-255°C (decomp.), $[\alpha]_D^{20}$-83.2°.

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