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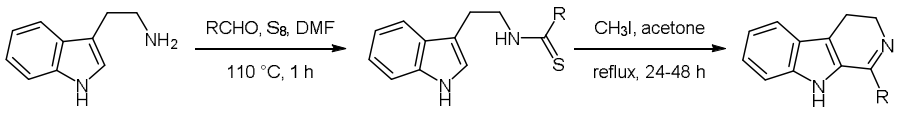
GRAPHICAL ABSTRACT



Efficient synthesis of N_b-thioacyltryptamine derivatives by a three-component Willgerodt–Kindler reaction, and their transformation to 1-substituted-3,4-dihydro-β-carbolines

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ABSTRACT

A practical and efficient synthesis of N_b-thioacyltryptamines has been developed *via* the three-component reaction of tryptamine, various aldehydes and elemental sulfur. The products were obtained in moderate to excellent yields and proved to be valuable intermediates for the syntheses of 3,4-dihydro-β-carbolines, a compound family of biological significance.

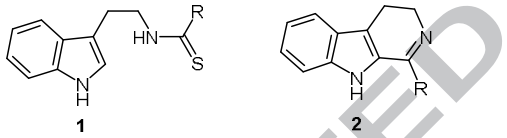
KEYWORDS

Willgerodt–Kindler reaction; Three-component reaction; Tryptamine; Thioamides; β-Carbolines

INTRODUCTION

Thioamides are an important functional group in organic and medicinal chemistry.[1,2] In particular, compounds bearing a thioamide moiety have been reported as useful intermediates in the synthesis of natural products[3] and other biologically active heterocycles.[4–7] Thioamides are structural analogues of carboxamides, however, they possess different chemical behaviour.[2,8] Recently, the physical and biological properties of peptide derivatives containing thioamide functional groups have been extensively studied.[9–12] Finally, thioamide containing chiral compounds have been utilised as catalysts in asymmetric acylation.[13,14] Due to the great interest in thioamides, various methodologies for their preparation have been described in the literature.[15–19]

In continuation of our efforts to develop synthetic methods that can be applied to the field of indole chemistry,[20–22] we herein describe a simple and efficient procedure for the preparation of various *N*-[2-(1*H*-indol-3-yl)ethyl]carbothioamides (N_b-thioacyltryptamines, **1**) *via* the one-pot, three component reaction of tryptamine, an aldehyde and sulphur, as well as their transformation into 1-substituted-3,4-dihydro-β-carboline derivatives (**2**, Scheme 1).

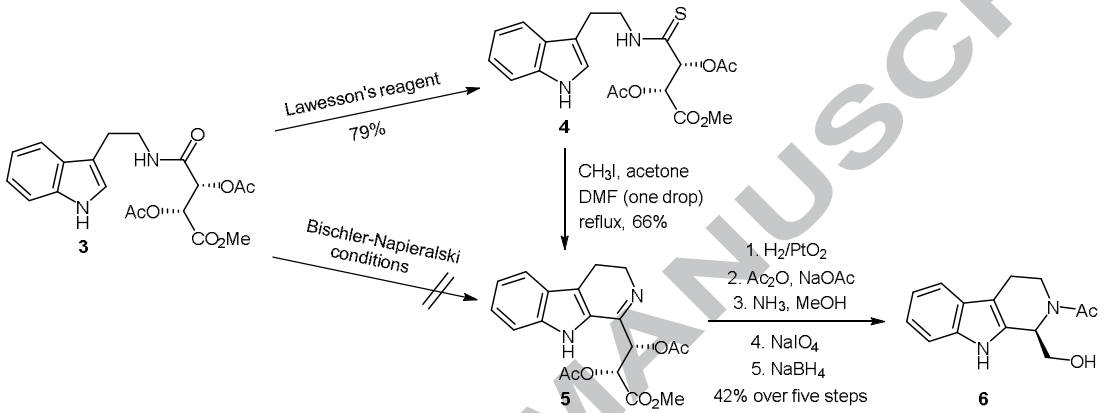


Scheme 1

β-Carbolines, incorporating a tricyclic pyrido[3,4-*b*]indole scaffold, form a prominent group of alkaloids[23–25] which along with their reduced dihydro- and tetrahydro-β-carboline analogues are found in various plants, mammals and marine invertebrates.[26–28] Both simple and complex β-carboline derivatives possess a broad spectrum of biological and pharmacological activities including antimicrobial,[29] antimalarial,[30] antithrombotic,[31] parasiticidal,[32] anti-HIV,[33] anti-Alzheimer,[34] and antifungal effects.[35]

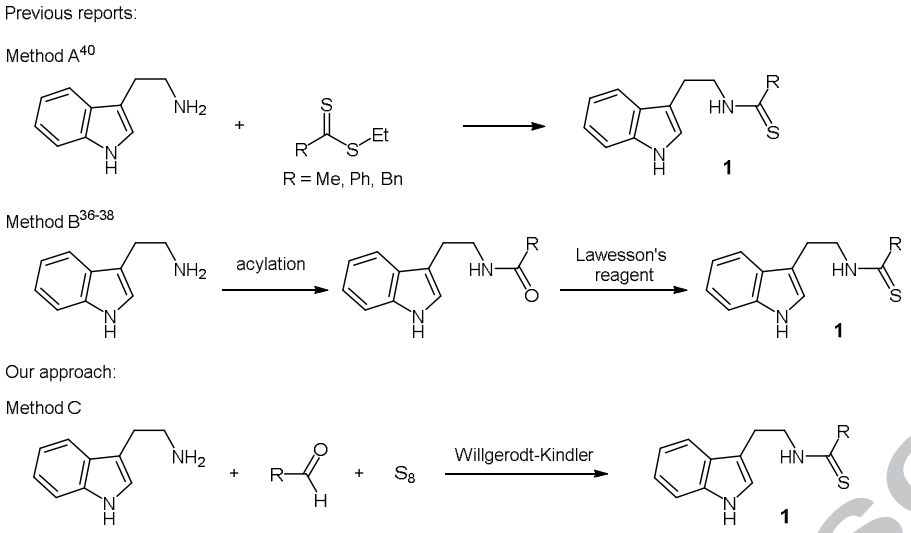
While the widely used Bischler–Napieralski ring closure reaction of N_b-acyltryptamines leading to 3,4-dihydro-β-carbolines (**2**) typically requires harsh conditions, the reaction starting from the thio analogue **1** proceeds under mild, non-acidic conditions by heating in the presence of an alkylating reagent (e.g. MeI, BnBr, allyl bromide).[36–38] This permits the

synthesis of β-carbolines with substituents that are sensitive to the reagents used in the Bischler–Napieralski cyclisation. For example, Czarnocki and co-workers reported the enantioselective synthesis of (1*R*)-1-(hydroxymethyl)-2-acetyl-1,2,3,4-tetrahydro-β-carboline (**6**) in 98% ee utilising L-(+)-tartaric acid, as a cheap, natural source of chirality, for the reduction of 3,4-dihydro-β-carboline derivative **5** (Scheme 2). Notably, attempted ring closure of amide **3** to directly give compound **5** under typical Bischler–Napieralski conditions was unsuccessful.[39]



Scheme 2

The key cyclisation intermediate, N_b-thioacyltryptamines (**1**) can be synthesised by two methods. Yamada and co-workers prepared the required thioamides by the reaction of tryptamine and the ethyl esters of dithiocarboxylic acids[40] (Method A, Scheme 3). The drawback of this method is the limited access and high price of dithioesters. The second approach is a two-step process comprising of the acylation of tryptamine and subsequent thionation using Lawesson's reagent, a thionation agent of low atom efficiency[36–38] (Method B, Scheme 3).

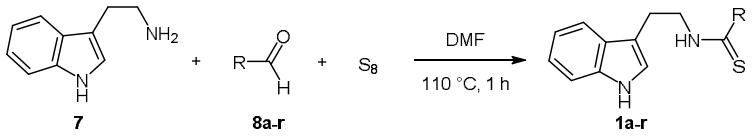


Scheme 3

We decided to apply the Willgerodt–Kindler reaction, which involves the reaction of an amine, aldehyde and elemental sulfur, to give the corresponding N_b-thioacyltryptamines (Method C, Scheme 3). Willgerodt described the synthesis of terminal amides or the ammonium salt of the corresponding carboxylic acids from ketones and aqueous ammonium polysulfide.[41] Originally, the reaction was limited to alkyl aryl ketones, however, this was later extended to aliphatic ketones, aldehydes and acetals.[42] Kindler reported a modification of the Willgerodt procedure using elemental sulfur and dry amines instead of aqueous ammonium polysulfide.[43] This preparation of thioamides is generally referred to as the Willgerodt–Kindler reaction.[19,44] Although, several accounts report the transformation of related phenylethyl amines into the corresponding thioacylphenethylamines,[45–48] to the best of our knowledge, the Willgerodt–Kindler reaction has not been applied to the preparation of this family of compounds.

RESULTS AND DISCUSSION

Initially, a mixture of tryptamine (**7**), benzaldehyde (**8a**) and elemental sulfur were treated under the standard conditions for the Willgerodt–Kindler reaction, using dimethylformamide as the solvent at 110 °C (Scheme 4).[49–51]



Scheme 4

Table 1. The synthesis of N_b-thioacyltryptamine derivatives (**1a**–**r**)

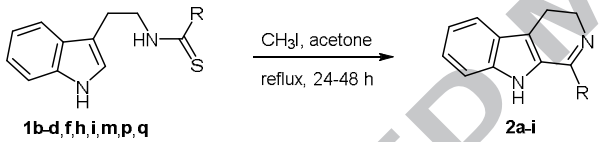
Entry	R	Product	Yield (%)
1	C_6H_5	**1a**	94
2	4-BrC_6H_4	**1b**	60
3	4-$O_2NC_6H_4$	**1c**	67
4	4-$F_3CC_6H_4$	**1d**	90
5	4-$[(HO)_2B]C_6H_4$	**1e**	73
6	4-$PhOC_6H_4$	**1f**	79
7	3-FC_6H_4	**1g**	87
8	3-$PhOC_6H_4$	**1h**	90
9	3-NCC_6H_4	**1i**	73
10	3,5-$(MeO)_2C_6H_3$	**1j**	66
11	*i*-Bu	**1k**	57
12	furan-2-yl	**1l**	83
13	thiophen-2-yl	**1m**	93
14	pyridin-3-yl	**1n**	95
15	indol-3-yl	**1o**	59[a]
16	5-Cl-benzothiophen-2-yl	**1p**	82
17	naphthalen-2-yl	**1q**	83
18	9*H*-fluoren-2-yl	**1r**	35

[a] Reaction time was 4 h.

The reaction proceeded smoothly and resulted in the formation of the desired product **1a** within 1 h in 94% yield (Table 1, entry 1). Next, we turned our attention to the investigation of the scope and limitations of this reaction using a series of aldehydes (Table 1). Thioamides **1b**–**j** starting from *meta*- or *para*-, mono- or disubstituted benzaldehydes **8b**–**j** were obtained in variable yields (60–90%, entries 2–10). Various functional groups on the aromatic ring were well tolerated under the examined reaction conditions. The reaction was also investigated using an aliphatic aldehyde, isovaleraldehyde (**8k**), giving the corresponding thioamide (**1k**) in 57% yield (entry 11). Various heterocyclic carbaldehydes (**8l**–**p**) were applied to the synthesis of thioacyltryptamines and the reaction proceeded efficiently with

furfural (**8l**), thiophene-2-carbaldehyde (**8m**), nicotinaldehyde (**8n**), and 5-chloro-1-benzothiophene-2-carbaldehyde (**8p**) (entries 12–14 and 16). However, the reaction of indole-3-carbaldehyde (**8o**) took four times longer and the yield of the product (**8o**) was only 59% (entry 15). Finally, the Willgerodt–Kindler reaction was investigated with naphthalene-2-carbaldehyde (**8q**) and 9*H*-fluorene-2-carbaldehyde (**8r**) giving the corresponding products (**1q** and **1r**) in 83% and 35% yields, respectively (entries 17, 18). The low yield and by-products observed in the latter reaction might be explained by the steric hindrance of the bulky aldehyde **8r** and the facile formation of fluorene-type radical species resulting from radical side reactions.

After the successful preparation of thioamides **1**, the ring closure reaction of representative thioamides (**1b–d**,**f**,**h**,**i**,**m**,**p**,**q**) was studied (Scheme 5). The corresponding 1-substituted-3,4-dihydro-β-carboline derivatives (**2a–i**) were synthesized in reasonable to good yields (61–90%) according to literature procedure[36,39] using 5 equiv. of CH_3I in boiling acetone (Table 2).



Scheme 5

Table 2. The synthesis of 1-substituted-3,4-dihydro-β-carboline derivatives (**2a–i**)

Entry	R	Starting material	Product	Yield (%)
1	4-BrC_6H_4	**1b**	**2a**	75
2	4-$O_2NC_6H_4$	**1c**	**2b**	89
3	4-$F_3CC_6H_4$	**1d**	**2c**	78
4	4-$PhOC_6H_4$	**1f**	**2d**	72
5	3-$PhOC_6H_4$	**1h**	**2e**	68
6	3-NCC_6H_4	**1i**	**2f**	70
7	thiophen-2-yl	**1m**	**2g**	90
8	5-Cl-benzothiophen-2-yl	**1p**	**2h**	61
9	naphthalen-2-yl	**1q**	**2i**	67

All N_b-thioacyltryptamine derivatives (**1a**–**r**) and 1-substituted-3,4-dihydro-β-carbolines (**2a**–**i**) were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and HRMS. Products **1a**[40] and **2a**[52] have previously been described and fully characterized, compounds **2b**,[53] **2c**,[54] and **2i**[55] are known but poorly characterized, while compounds **1b**–**r**, **2d**–**h** are novel.

In summary, we have described a simple and efficient method for the preparation of N_b-thioacyltryptamine derivatives using a three-component reaction of the corresponding aldehyde, tryptamine and elemental sulfur. The advantages of this procedure are the one-step approach, short reaction times, good yields, inexpensive starting materials and the wide variety of aldehydes that can be used. In addition, a representative set of N_b-thioacyltryptamines were transformed to the appropriate 1-substituted-3,4-dihydro-β-carboline derivatives.

Supporting information

Preparation and characterization of the title compounds. This material is available free of charge *via* the internet.

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