Tetrahedron 69 (2013) 2193–2198

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 5-(7′-indolyl)oxazoles and 2,5-di-(7′-indolyl)oxazoles

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ARTICLE INFO

Article history:
Received 30 October 2012
Received in revised form 7 December 2012
Accepted 21 December 2012
Available online 11 January 2013

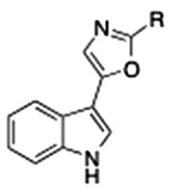
Keywords:
Bis-indoles
Oxazoles
7-Aminoacetylindoles
Indoles

ABSTRACT

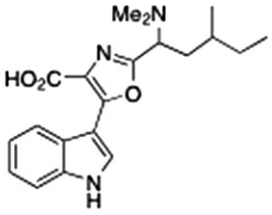
The synthesis of 7-aminoacetylindoles was achieved via the hydrogenation of 7-acylcyanides, which were produced through the oxidation of indole-7-cyanohydrin silylether intermediates. 7-Oxotryptamines were subsequently converted into 5-(7′-indolyl)oxazoles by reaction with acetic anhydride followed by phosphoryl chloride, and to 2,5-di-(7′-indolyl)oxazoles by reaction with 7-trichloroacetylindoles followed by phosphoryl chloride.

1. Introduction

Indole-related natural products bearing the oxazole moiety are an important class of heterocyclic scaffolds as they are naturally occurring and known to display diverse biological activity. To date, however, the structural variations offered in these systems are confined to those with 5,3′-linkages. For example, the naturally occurring 5-(3′-indolyl)oxazoles, such as the dipeptide derivative almazole C,[1] the extracellular alkaloid pimprinine **1**,[2,3] which possesses antiepileptic effects and its analogues WS-30581 A and B, which show inhibitory effects of platelet aggregation.[4] The labradorins, such as labradorin 1 **2** are other 2-substituted-5-(3′-indolyl) oxazoles, which display inhibitory activity against various human cancer cells,[5] while martefragin A **3** has been reported to be a strong inhibitor of lipid peroxidation.[6]



1 R = Me
2 R = CH_2CHMe_2



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In view of the interesting biological activities exhibited by indole linked oxazoles, we were interested in the development of novel 5-(7′-indolyl)oxazoles and 2,5-di(7′-indolyl)oxazoles.

Many synthetic approaches have been reported for the synthesis of indole linked oxazoles. Some of these protocols involve rhodium catalysed reactions of diazoacetylindoles with nitriles,[7] aza-Wittig reactions of iminophosphoranes derived from 3-azidoacetyl-1-methylindole with isocyanates[8] and the conversion of 3-acetylindole into 5-(3′-indolyl)oxazoles using metal free [hydroxyl(2,4-dinitrobenzenesulfonyloxy)iodo]benzene.[9] Alternatively, the indole ring can be derived from a 5-acylmethylene-substituted-oxazole using the Fischer synthetic sequence.[10] Recently, the synthetic preparation of indolyloxazoles has been facilitated by the use of oxotryptamine via cyclodehydration of acylaminoketones.[5,6,11–13]

3-Aminoacetylindole is most typically synthesised from the corresponding 3-acylcyanide via hydrogenation using Pd/C in acetic acid. In turn, the substrate indolyl-3-carbonyl nitrile can be prepared via treatment of the readily available indole 3-acid chloride with copper (I) cyanide.[14] Another efficient synthesis of the acylcyanide can be achieved via the cyanohydrin silylether intermediate, which is prepared through the heating of indole-3-carbaldehyde with trimethylsilylcyanide (TMSCN) under reflux in acetonitrile. Oxidation of the silyl cyanohydrin intermediate with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane at room temperature then affords the corresponding indole carbonyl nitrile.[15] It has been previously reported that 4,6-dimethoxyindoles can react with oxalyl chloride to yield 7-glyoxyloyl chlorides and some derived acids, esters or amides in 20–74% yields.[16] In contrast, indole-7-carbaldehydes can be prepared in 70–100% yields via

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0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.12.084

Vilsmeier formylation.[17] We therefore followed this latter approach for the synthesis of 7-aminoacetylindoles followed by their use as precursors for the preparation of 5-(7′-indolyl)oxazoles and 2,5-di(7′-indolyl)oxazoles.

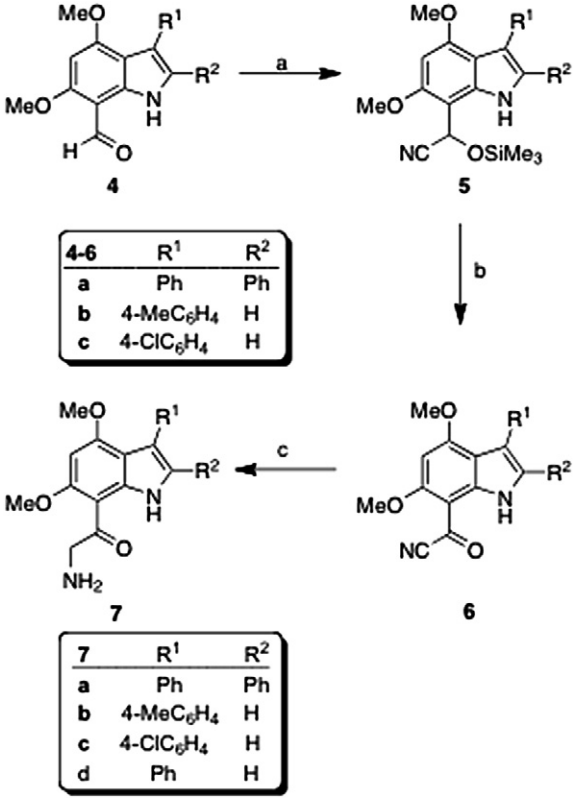
2. Results and discussion

2.1. Synthesis of 7-aminoacetylindoles

The synthesis of 7-acylcyanides **6a**–**c** was successfully accomplished over two consecutive steps as illustrated in Scheme 1. The first step involved the treatment of 7-formylindoles **4a**–**c** with TMSCN in acetonitrile at reflux to afford the 7-cyanohydrin silylether intermediates **5a**–**c** in good yields. The stability of these 7-indolyl silylethers at room temperature was found to be very high in comparison to the 3-indolyl silylethers.

The ^{1}H NMR spectrum of compound **5c**, for example, displayed the trimethylsilyl protons at δ 0.2, the CH proton at 6.19 and the H5 proton at 6.26. This assignment was confirmed by both HSQC and HSBC analysis. The ^{13}C NMR spectrum indicated the presence of the trimethylsilyl groups and the nitrile groups with carbon resonances at δ 0.58 and 119.2, respectively. Also, the nitrile absorption band was seen at 3428 cm^{-1} in the infrared spectrum.

The compounds **5a**–**c** were subsequently oxidised with DDQ in dioxane at room temperature to the corresponding 7-acylcyanides **6a**–**c**. Although a single product was isolated from the reaction mixture, the residue was subjected to column chromatography in order to eliminate baseline impurities. The orange products were obtained in 80–90% yields. The ensuing step was hydrogenation of the 7-acylcyanides to the 7-aminoacetylindoles as shown in Scheme 1. Accordingly, 7-acylcyanides **6a**–**c** were stirred under hydrogen in the presence of 10% Pd/C in a mixture of ethyl acetate and acetic acid (2:3) for 20 h to afford 7-aminoacetylindoles **7a**–**c** in 65–91% yields.



4-6	R^1	R^2
a	Ph	Ph
b	4-MeC$_6$H$_4$	H
c	4-ClC$_6$H$_4$	H

7	R^1	R^2
a	Ph	Ph
b	4-MeC$_6$H$_4$	H
c	4-ClC$_6$H$_4$	H
d	Ph	H

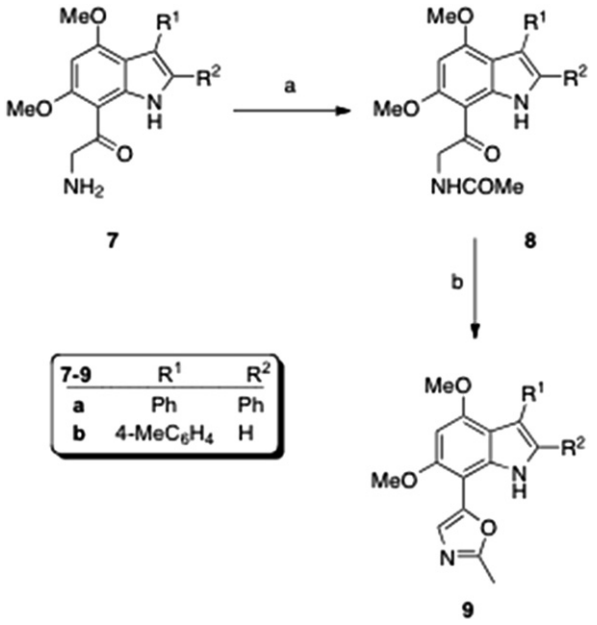
Scheme 1. Reagents and conditions: (a) TMSCN, CH_3CN, reflux, overnight (64–78%); (b) DDQ, dioxane, rt (80–90%); (c) H_2, 10% Pd/C, EtOAc/AcOH, rt (only **7a**,**b** 77–91% as HCl and HOAc salts, respectively).

Interestingly, the ^{1}H NMR spectrum of the anticipated compound **7c** demonstrated resonances for two H5 protons at δ 6.5 and two indole NHs at 11.58 and 11.63. Two carbonyl resonances at 190.0 and 190.1 were observed in the ^{13}C NMR spectrum, indicating a mixture of halogenated and dehalogenated 7-aminoacetylindoles **7c** and **d**, respectively. The formation of this mixture was further confirmed by a high-resolution mass spectrum, which showed two molecular ions at 345.0998 $(M+H)^+$ and 311.1389 $(M+H)^+$ corresponding to oxotryptamines **7c** and **d**, respectively. Attempts to separate the mixture failed because of the high polarity of the compounds, which remained on the baseline during attempted thin layer chromatography.

2.2. Synthesis of 5-(7′-indolyl)oxazoles

It was of interest to use a monomeric model for the preparation of 7-oxazole substituted indoles before extending the chemistry to bis-indole systems. Therefore, the synthetic study began with the acylation of readily available 7-oxotryptamines **7a**, **b** with acetic anhydride at 0–10 °C for 4 h to produce the corresponding ketoamides **8a**, **b** in 72% and 71% yield, respectively.

The next step involved the treatment of indoles **8a**, **b** with excess phosphoryl chloride at reflux in ethyl acetate for 2 h. This process afforded the 7-methyloxazoles **9a**, **b** in 79% and 51% yield, respectively (Scheme 2).



7-9	R^1	R^2
a	Ph	Ph
b	4-MeC$_6$H$_4$	H

Scheme 2. Reagents and conditions: (a) $(CH_3CO)_2$, 0–10 °C, 4 h (71–72%); (b) $POCl_3$, EtOAc, reflux, 2 h (51–79%).

2.3. Synthesis of 2,5-di(7-indolyl)oxazoles

With the successful execution of the monomeric model in hand, preparation of related bis-indole systems was examined. The successful preparation of 7,7′-bis-oxazoles **12a**, **b** was achieved with a convenient two-step process as shown in Scheme 3. The first step involved heating 7-aminoacetylindoles **7a**, **b** with 7-trichloroacetylindoles **10a**, **b** at reflux overnight in the presence of triethylamine in acetonitrile to afford the unsymmetrical 7,7′-amide linked bis-indoles **11a**, **b** in 61% and 55% yield, respectively.

The new amide functionality was clearly evident in the ^{1}H NMR and ^{13}C NMR spectra of compound **11a**, with the appearance of an amide NH proton as a triplet at δ 9.33 (J 8.5 Hz) and the carbonyl