A New Route to α-Carbolines Based on 6π-Electrocyclization of Indole-3-alkenyl Oximes

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ABSTRACT

Indoles are converted into α-carbolines in four steps by acylation at C-3, Boc-protection, olefination of the resulting 3-indolyl aldehydes or ketones to give N-Boc-3-indolyl alkenyl oxime O-methyl ethers, which upon heating to 240 °C under microwave irradiation undergo loss of the Boc-group, and 6π-electrocyclization to α-carbolines, following aromatization by loss of methanol (11 examples, 30–90% yield).

In contrast to β-carbolines that are widely represented among natural products and synthetic bioactive compounds,1–3 α-carbolines (pyrido[2,3-b]indoles) are considerably less well investigated.4,5 Nevertheless there are some important examples such as the naturally occurring anticancer compounds grossularine-1 and -26 and the neuronal cell protective agent mescengricin (Figure 1).10 In the medicinal chemistry arena, α-carbolines such as the GABA modulator,11 and the inhibitor of microsomal triglyceride transport protein implitapide,12,13 have also been widely studied.

As a consequence, routes for the construction of the α-carboline nucleus are of interest, but unlike their β-carboline counterparts that are almost invariably prepared from tryptophan or tryptamine derivatives, there is no main synthetic access to the isomeric α-carbolines. Thus, α-carbolines have been obtained from 2-aminoindoles,14 by a variation of the Graebe Ullmann synthesis of

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carbazoles,\(^{17}\) by intramolecular Diels–Alder reaction of pyrazinones,\(^{18}\) from palladium-catalyzed reactions of anilines with 2,3-dihalopyridines,\(^{19,20}\) by cyclization of 2-isocyanato-indoles,\(^{6–8}\) and of iminyl radicals.\(^{21–24}\)

However, we were attracted by the possibility of developing a more general route based on a 6π-electrocyclic process, and we now report our initial results.

The projected precursors to α-carbolines were the 3-indolyl alkenyl oxime ethers 1, accessible from 3-acylindoles 2 (Scheme 1). 3-Acylindoles are readily available by exploiting the natural reactivity of indoles to undergo facile acylation at the 3-position. The participation of oxime ethers in 6π-electrocyclic processes is known from the work of Hibino,\(^{25}\) and the possible intermediacy of imines related to 1 has been implicated in other work\(^{23}\) and in a biomimetic synthesis of grossularine-1.\(^{9}\)

The precursors to the desired oxime ethers were 3-acylindoles 2 and phosphonates 3. The phosphonates were prepared by reaction of the corresponding carbonyl compound with O-methyl hydroxylamine, with the aldoxime precursor being prepared by acid hydrolysis of the commercially available diethyl (2,2-diethoxy)ethylphosphonate. The subsequent Horner–Wadsworth–Emmons reaction with N-Boc-protected 3-indolyl aldehydes or ketones gave the required alkenyl oxime ethers 4 generally as mixtures of E/Z-alkene isomers that could be readily separated and characterized, apart from alkene 4g which was formed as the E-alkene.

In general only one oxime isomer was observed which, on the basis of the chemical shift of the oxime RCH=NOMe proton in the \(^1\)H NMR spectrum, suggested that

Figure 1. Structures of naturally occurring and bioactive α-carbolines.

Figure 2. X-ray crystal structure of (E)-3-(1-methyl-1H-indol-3-yl)-propenal (Z)-methyl oxime.

Scheme 1. Projected Route to α-Carbolines by 6π-Electrocyclization of 3-Indoly Alkenyl Oxime Ethers

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the oximes have the \((Z)\)-geometry. In the case of oxime 4a, removal of the Boc-protecting group gave the crystalline \(E\)-alkene-\(Z\)-oxime (Figure 2), confirming the \(Z\)-stereochemistry of the oxime double bond. The olefination reaction was then extended to indole-3-carbaldehydes bearing chloro- and alkoxy-groups, and indolyl ketones with methyl or ester groups (Table 1).

Assumed that it would be cleaved under the high temperature conditions. In the event, heating 4a, as a mixture of geometric isomers, to 180°C in 1,2-dichlorobenzene gave a mixture of the desired \(\alpha\)-carboline 5a (12%) plus the Boc-deprotected starting material. Increasing the temperature to 240°C under microwave irradiation delivered the \(\alpha\)-carboline 5a in 73% yield. We assume that the reaction involves initial thermal removal of the Boc-group to give the NH indole in which isomerization of the alkene into the \(cis\)-isomer required for electrocyclization is facilitated. In support of this, prior removal of the Boc-group in 4a under hydrolytic conditions (82%) gave the corresponding NH indole that cyclized to \(\alpha\)-carboline 5a (54%) upon heating to 240°C. It would appear that the NH is essential for cyclization since the corresponding \(N\)-methyl compound does not give 9-methyl-\(\alpha\)-carboline under the same conditions. Electrocyclization of the indolyl alkenyl oxime ethers 4b–4k, starting with either \((Z)\)- or \((E)\)-alkene isomers, proceeded similarly to give a range of \(\alpha\)-carboline 5 in 30–90% yield (Table 1). The structures of the carbolines 5f and 5h were confirmed by X-ray crystallography (Figure 3).

In conclusion, we have developed a new general route to \(\alpha\)-carbolines that proceeds in just four steps from indoles.

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Supporting Information Available. All experimental procedures, copies of \(^1\)H and \(^{13}\)C NMR spectra, and cif files for X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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**Table 1. Preparation of Indolyl Alkenyl Oxime Ethers 4 [Indoles, Phosphonates, 3a, \(R^2 = H\); 3b, \(R^2 = Me\)] and Their Conversion into \(\alpha\)-Carbolines 5 by \(6\pi\)-Electrocyclization**

| Entry | \(R^2\) | \(R^4\) | \(R^3\) | Entry | \(R^2\) | \(R^4\) | \(R^3\) | \(E\) Yield% | \(Z\) Yield% | Entry | \(R^2\) | \(R^4\) | \(R^3\) | Yield% |
|-------|--------|--------|--------|-------|--------|--------|--------|----------|----------|-------|--------|--------|--------|--------|
| 1     | H      | H      | a      | 1     | H      | H      | a      | 46        | 38       | 1      | H      | a      | 73     |
| 2     | 5-OMe | H      | a      | 2     | H      | b      | 37     | 25        | 6-OMe    | 36     |
| 3     | 6-OMe | H      | a      | 3     | H      | c      | 38     | 60        | 7-OMe    | 30     |
| 4     | 5-Cl   | H      | a      | 4     | H      | d      | 49     | 42        | 6-Cl     | 55     |
| 5     | H      | H      | b      | 5     | H      | e      | 11     | 22        | H        | 90     |
| 6     | 6-OMe | H      | b      | 6     | H      | f      | 28     | 62        | 7-OMe    | 77     |
| 7     | 5-OMe | H      | b      | 7     | H      | g      | 34     | --        | 6-OMe    | 41     |
| 8     | H      | CO\(_2\)Me | a    | 8     | H      | h      | 38     | 49        | H        | 52     |
| 9     | H      | Me     | a      | 9     | H      | i      | 49     | 16\(\alpha\) | H        | 62     |
| 10    | H      | Me     | b      | 10    | Me     | j      | 45     | 23        | H        | 65     |
| 11    | H      | CO\(_2\)Me | b    | 11    | Me     | k      | 52     | 29        | H        | 51     |

\(^a\)Indole numbering. \(^b\)\(\alpha\)-Carboline numbering. \(^c\)Mixture of oxime geometric isomers.