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The Tertiary Amino Effect: An Efficient Method for the Synthesis of α-Carbolines

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Abstract: Functionalized annelated α-carbolines have been synthesized from oxindole following a tertiary amino effect reaction strategy.

Key words: α-carboline, oxindole, tertiary amino effect, α-halo aldehyde

α-Carbolines {pyrido[2,3-*b*]indoles} are an important class of naturally occurring compounds of biological importance (Figure 1). Compounds with this ring system possess diverse biological activity such as antitumor,[1] anti-HIV,[2] antiviral,[3] anxiolytic, anti-inflammatory, and CNS-stimulating activity[4] and some of representatives have clinical use as antileukemia drugs.[5] However, the properties which attracted much attention to the α-carbolines are their ability to inhibit CDK-1, CDK-5, and GSK-3 kinases.[6] Finally, some α-carbolines have clinical application for treatment of hypertension.[7]

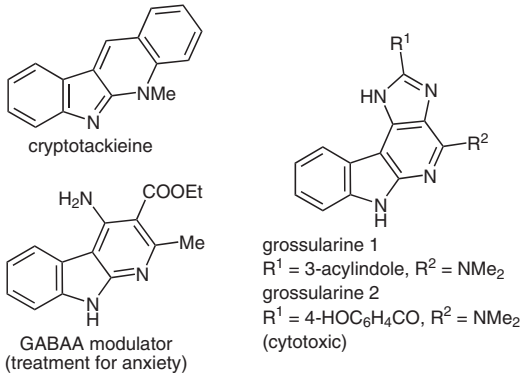

Figure 1

Synthetic approaches to α-carbolines can be classified according to the nature of the starting materials, the bonds formed, and the ring-closing step. Most of the syntheses utilize indoles as appropriate precursors[8] although triazoles have also been used as starting materials in the modified Graebe–Ulmann reaction.[9] The Fischer indole reaction gives partially hydrogenated α-carbolines from 2-piperidone phenylhydrazones or cyclohexanone 2-pyridyl hydrazones.[10] A number of syntheses from other starting materials have also been reported, for example, 2-(1*H*)-pyrazinones, *N*-arylcarbodiimides, and 2-arylaminopyrimidines give α-carbolines via intramolecular hetero Diels–Alder reaction.[11] (*o*-Pivaloylamino)phenyl-*o*′-fluoropyridines have also been reported as starting materials in nucleophilic aryl fluorine displacement reactions.[12] Recently, a modified Graebe–Ullmann reaction has been reported using microwave heating.[13]

α-Cyclization of tertiary amines is a mechanistically intriguing and synthetically useful process, which has not received much attention. Certain tertiary anilines, enamines, and enamine esters undergo such cyclization leading to annelated pyrrolidines. Suschitzky and Meth-Cohn[14] have coined the term 'tertiary amino effect' for such a process which has been further developed by Reinhoudt and Verboom.[15] Following these reports, variants of this reaction have been developed[16] and, in many cases, the benzene ring has been replaced by different heterocycles.[17] A literature survey also revealed a short report describing the synthesis of α-carbolines by exploring the tertiary amino effect as a reaction strategy. However, the workers utilized only cyclic tertiary amino indoles with cyclic β-diketones/β-diamides which afforded spirocyclic fused α-carbolines (only two compounds) in poor yields (4%, 11%) under thermal conditions.[18] In a recent development this intermolecular redox process was carried out at room temperature using Lewis acid catalyst. However, there are some limitations in the reaction.[19]

As part of our continued interest in the synthesis of diverse heterocyclic compounds of biological importance,[20] we report herein an efficient method for the synthesis of functionalized α-carbolines and their annelated derivatives by utilizing the tertiary amino effect as a reaction strategy (Scheme 1).

Oxoindole **1** was taken as starting material in our reaction strategy[21] and, on treatment with Vilsmeier reagent, afforded the key β-haloaldehyde intermediate **2**. The Boc-protected indole **3** underwent nucleophilic substitution at C-2 by diethylamine **4a** to give **5a**. Treatment of the tertiary amine **5a** with nitrile **6a** in the presence of catalytic base afforded the indole derivative **7a** with an olefinic bond at the β-position of the tertiary amine group, which is the requirement for the key reaction step. The final α-cyclization of the tertiary amine **7a** was carried out at 90 °C using DMF as solvent, which afforded the α-carboline **8a**. The product was obtained in 76% yield after purification by column chromatography. The structure of the compound was ascertained from spectroscopic data and

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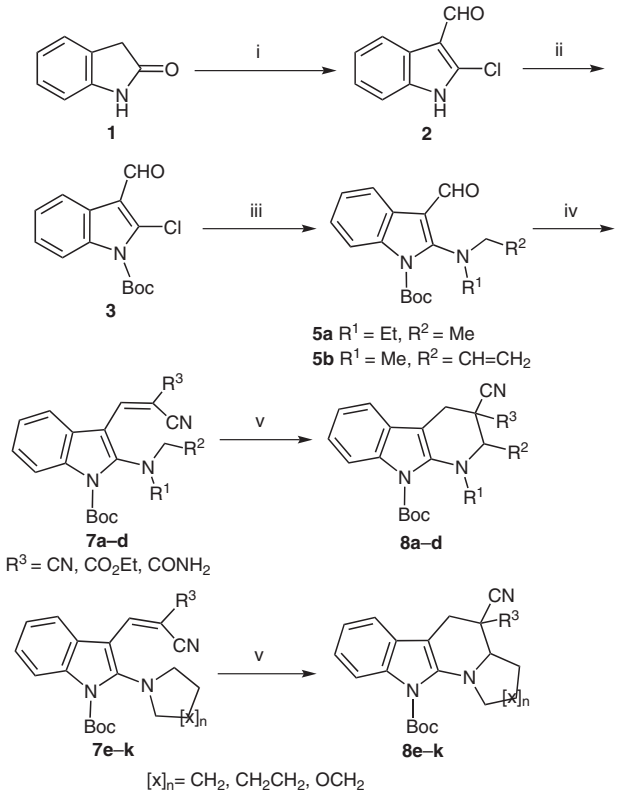
elemental analysis. The ^{1}H NMR spectrum shows the presence of the two typical isolated protons (CH_2) at δ = 4.57 ppm as an apparent singlet. The generality of the reaction was then established by synthesizing a series of compounds **8a**–**d**, by utilizing different secondary amines **4a**,**b** and alkyl nitriles **6a**–**c** in the respective steps, and characterizing them (Table 1).



Scheme 1 *Reaction conditions*: (i) DMF, $POCl_3$; (ii) Boc_2O; (iii) Et_2NH (**4a**) or $HNMe(CH_2CH{=}CH_2)$ (**4b**) or pyrrolidine (**4c**) or piperidine (**4d**) or morpholine (**4e**); (iv) piperidine, $CH_2(CN)_2$ (**6a**) or $CNCH_2CO_2Et$ (**6b**) or $CNCH_2CONH_2$ (**6c**); (v) DMF, 90 °C.

In order to explore the synthetic utility of the process further, we utilized various cyclic amines **4c**–**e** and alkyl nitriles **6a**–**c** in the nucleophilic substitution and Knoevenagel condensation steps, respectively, to obtain the compounds **7e**–**k**. According to expectation, cyclization of the cyclic tertiary amines **7e**–**k** occurred smoothly under identical reaction conditions to give annelated α-carboline derivatives **8e**–**k** in excellent yields (Table 1).

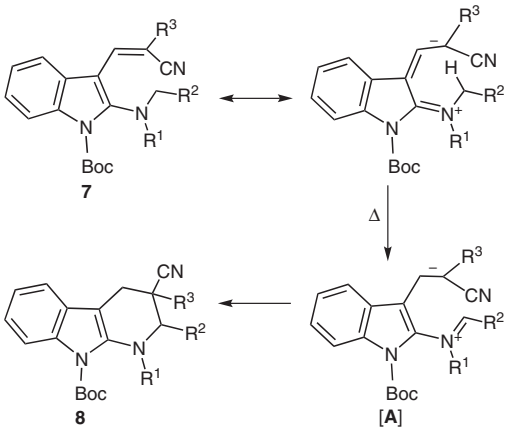
It is very interesting to note that the electrocyclization of compound **7** to **8** also occurred readily in the absence of solvent under thermal conditions. Pyrrolidino- and piperidinoamines were found to be highly reactive; whilst morpholinoamines are comparatively less reactive.

Initially, we studied the reaction without protecting the nitrogen atom of the indole moiety. But nucleophilic substitution by secondary amines did not occur even under very drastic conditions. Simple alkylation was also not effective. However, when the nitrogen atom was protected with an electron-withdrawing group such as Boc, the nucleophilic substitution and the cyclization steps occurred very smoothly to give the desired compounds in excellent yields. This observation is explained by the mechanism and is in contrast to the reported work in which spirocyclic fused α-carbolines were synthesized by utilizing *N*-methyl indoles.[18]

Table 1 Sythesis of α-Carbolines and their Annelated Compounds **8** from Oxindole **1** by Exploring Tertiary Amino Effect Reaction Strategy

Product	R^1	R^2	R^3	$[X]_n$	Time (min)	Yield (%)	Mp (°C)
8a	Et	Me	CN	–	45	76	219–220
8b	Et	Me	COOEt	–	60	75	197–198
8c	Et	Me	$COONH_2$	–	60	70	212–213
8d	Me	$CH_2{=}CH_2$	CN	–	45	80	194–195
8e	–	–	CN	CH_2	45	85	217–218
8f	–	–	COOEt	CH_2	60	78	189–190
8g	–	–	$COONH_2$	CH_2	60	70	214–215
8h	–	–	CN	CH_2CH_2	50	87	223–224
8i	–	–	COOEt	CH_2CH_2	60	76	216–217
8j	–	–	CN	CH_2CH_2	50	83	227–228
8k	–	–	COOEt	OCH_2	60	72	231–232

A plausible mechanism for the cyclization step is outlined in Scheme 2. The compound **7** with an aminodiene system can be envisaged to generate a 1,6-dipole [**A**], via 1,5-hydride shift that subsequently cyclizes to give the product **8**. The adjacent strong electron-withdrawing groups (CN, CO_2Et, $CONH_2$) stabilize the carbanion formed in the reaction process. The electron-withdrawing protecting group at the indole nitrogen enhances the generation of the 1,6-dipole by favoring the delocalization of the exocyclic nitrogen lone pair.



Scheme 2

The *N*-Boc deprotection could be achieved using with standard methods,[22] but the better solubility of the protect-

ed materials helped in the characterization of the compounds (the N-deprotected compounds have very low solubility). In conclusion, we have reported a novel and efficient method for the synthesis of functionalised α-carbolines and their annelated derivatives from oxindole utilizing the 'tertiary amino effect' strategy. Most of the reactions were carried out at room temperature. The eletrocyclization step which is usually carried out at very high temperature could be carried out at moderate temperature by using an electron-withdrawing Boc substituent on the nitrogen atom of the indole. The formation of the products is explained by a proposed mechanism. This reaction which can be further utilized in the synthesis of many other heterocyclic compounds of biological importance is a valuable addition to the chemistry of α-carbolines in particular and heterocyclic compounds as a whole. Further study of the reaction is in progress.

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(21) **Synthesis of 2-Chloro-3-formylindole** (**2**)
To a mixture of anhyd DMF (10 mL) and anhyd $CHCl_3$ (10 mL) was added phosphorous oxychloride (10 mL) over 15 min. To this a solution of oxindole **1** (3.2 g, 24 mmol) and pyridine (5 mL), both in anhyd $CHCl_3$ (25mL), was slowly added. The reaction mixture was kept for 48 h at r.t. and then poured into ice-cold H_2O (100 mL). The solid compound **2** formed was filtered and dried. Yield 2.48 g (80%); mp 167–168 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.38 (m, 2 H), 7.95–7.99 (m, 1 H), 8.15–8.18 (m, 1 H), 9.61 (s, 1 H), 10.10 (s, 1 H).
Synthesis of 1-(*tert*-Butoxycarbonyl)-2-chloro-3-formylindole (**3**)
Equimolar amounts of 2-chloro-3-formylindole (**2**; 10 mmol, 1.79 g) and Boc_2O (10 mmol, 2.18 g) were stirred in the presence of catalytic amount of DMAP (0.12 g) and Et_3N (0.10 g) at 0–5 °C for 1 h using CH_2Cl_2 (15 mL) as solvent.

The solvent was evaporated under reduced pressure, and the solid compound obtained was purified by column chromatography using PE–EtOAc (9:1) as eluent. The product **3** was obtained in 70% yield (1.20 g) as colorless crystals; mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 9 H), 7.26–7.40 (m, 2 H), 8.02–8.06 (m, 1 H), 8.27–8.30 (m, 1 H), 10.29 (s, 1 H).

Synthesis of 1-(*tert*-Butoxycarbonyl)-2-diethylamino-3-formylindole (5a)

Equimolar amounts of **3** (10 mmol 2.79 g), Et_2NH (**4a**; 10 mmol, 0.72 g), and Et_3N (10 mmol, 1.01g) were treated at r.t. for 4 h using CH_2Cl_2 (10 mL) as solvent. The solvent was evaporated under reduced pressure, and the compound **5a** obtained was purified by preparative TLC using PE–EtOAc (8:2) as eluent. The compound was not crystallized and used directly in the next step; yield 1.98 g (71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (t, 6 H), 1.71 (s, 9 H), 3.43 (q, 4 H), 7.22–7.31 (m, 2 H), 7.82–7.85 (m, 1 H), 8.20–8.23 (m, 1 H), 10.16 (s, 1 H). Similarly compounds **5b–e** were synthesized and characterized.

Synthesis of Compound 7a via Knoevenagel Condensation

To equimolar amounts of 1-(*tert*-butoxycarbonyl)-2-diethylamino-3-formylindole (**5a**; 5 mmol, 1.5 g) and malononitrile (**6a**; 5 mmol, 0.33 g) in EtOH (10 mL) was added a catalytic amount of piperidine (1 drop), and the resulting solution was stirred for 30 min. The resultant solid was filtered washed with small amount of EtOH and dried. The bright yellow product **7a** was obtained in pure form. Yield 1.20 g (80%); mp 122–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, 6 H), 1.70 (s, 9 H), 3.43 (q, 4 H), 7.26–7.38 (m, 2 H), 7.74 (s, 1 H), 7.82–7.85 (m, 1 H), 7.96–7.98 (m, 1 H).

Synthesis of α-Carboline 8a from 7a under Thermolytic Conditions

Compound **7a** (2 mmol, 0.73 g) was heated at 80–90 °C for 1 h using DMF (5 mL) as solvent (the conversion was monitored by TLC). The reaction mixture was poured into H_2O and the solid filtered off. The compound was purified by column chromatography using PE–EtOAc (6:4) as eluent to obtain **8a** as a yellow solid; yield 0.62 g (85%); mp 219–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.35 (m, 6 H), 1.70 (s, 9 H), 3.48–3.58 (m, 3 H), 4.57 (s, 2 H), 7.15–7.26 (m, 2 H), 7.61–7.65 (m, 2 H). ^{13}C NMR (75 MHz, DMSO): δ = 13.46, 14.20, 28.42, 39.77, 40.05, 40.33, 47.31, 61.82, 99.22, 110.46, 119.23, 121.34, 121.95, 122.74, 125.45, 135.24, 148.74, 155.37. IR: ν_{max} = 2210, 1736, 1631, 1540. MS: *m/z* = 363 [M$^+$]. Anal. Calcd (%) for $C_{21}H_{23}N_4O_2$: C, 69.42; H, 6.33; N 15.42. Found: C, 69.65; H, 5.98; N, 15.56.

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