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The synthesis of 1,1-disubstituted tetrahydro-β-carbolines induced by iodine

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Abstract—A mild access to 1,1-disubstituted tetrahydro-β-carbolines is described. Tryptamine is subjected to Pictet–Spengler cyclization with various ketones using iodine.

The β-carboline moiety is the core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities.[1–5] Tetrahydro-β-carbolines are conformationally constrained tryptamine analogues, and are of considerable interest due to their diverse pharmacological properties.

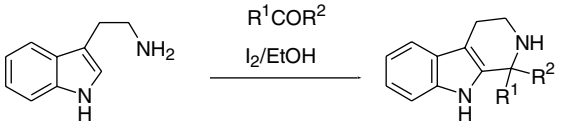
A search of the World Drug Index revealed 222 citations on these compounds in a number of therapeutic areas.[6]

Since its discovery, the Pictet–Spengler reaction[7] has been extensively studied and is used in areas such as the preparation of new heterocycles for combinatorial applications. The Pictet–Spengler reaction is an acid-catalyzed intramolecular cyclization of an intermediate imine formed by condensation with a carbonyl compound. Most examples of Pictet–Spengler reactions are with aldehydes or activated ketones such as 1,2-dicarbonyl compounds. Simple ketones are much less reactive at room temperature (typical reaction time in days) or are sluggish under reflux, whilst some aryl ketones do not react at all. This low reactivity may be attributed firstly to slow imine formation and then to a sterically sensitive, if not totally prohibited, cyclization of the resulting imine to produce a congested tetrasubstituted tetrahydro-β-carboline or tetrahydroisoquinoline. Only a few ketones have shown satisfactory results.[8]

A number of recent approaches for the preparation of 1,1-disubstituted tetrahydro-β-carbolines have been reported, including microwave-accelerated,[9] polymer-bound[10] and using titanium isopropoxide.[11] However, there is still a need to develop a cost effective, safe and environmentally friendly method. Our method provides an easy access to 1,1-disubstituted tetrahydro-β-carbolines and is depicted in Scheme 1.

In recent years, I_2 has been used extensively as a reagent due to its inherent low toxicity, electrophilicity and ease of handling.[12] We have developed an iodine-induced Pictet–Spengler reaction yielding 1,1-disubstituted tetrahydro-β-carbolines as the only products.

The results presented in Table 1 clearly show that all the studied ketones participated in Pictet–Spengler reactions with tryptamine in short reaction times affording good yields of products.



Scheme 1. General scheme for the Pictet–Spengler reaction induced by iodine.

Keywords: Pictet–Spengler cyclization; 1,1-Disubstituted tetrahydro-β-carbolines; Iodine; Ketones and tryptamine.
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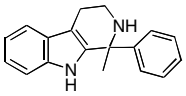
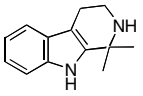
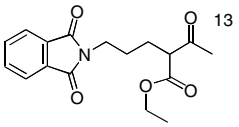
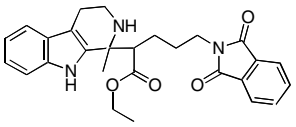
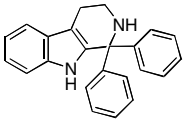
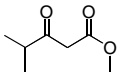
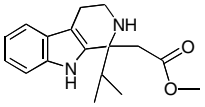
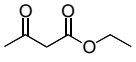
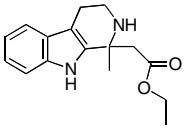
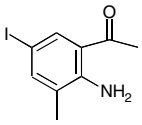
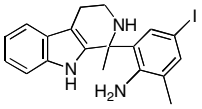
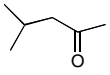
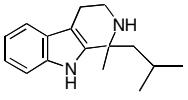
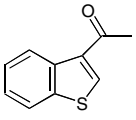
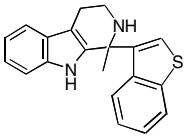
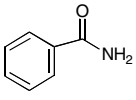
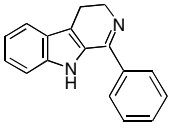
Table 1. Pictet–Spengler cyclization induced by iodine

Entry	Ketone	Product	Yield (%)	Reaction time (h)
1	$PhCOCH_3$	 **1**	47	5
2	CH_3COCH_3	 **2**	56	11
3[a]		 **3**	67	12
4	PhCOPh	 **4**	71[b]	8
5		 **5**	66	7
6		 **6**	72	8
7		 **7**	77	9
8		 **8**	64	8
9		 **9**	78	8
10		 **10**	44	11

[a] See Ref. 13 for the synthesis of the starting ketone.
[b] The same reaction run without iodine as a catalyst led to no conversion.

Tryptamine was reacted with various ketones and a catalytic amount of iodine in ethanol to produce 1,1-disubstituted tetrahydro-β-carbolines in short reaction times at room temperature.[14] The optimized conditions were subsequently applied to several other ketones (Table 1).

When compared to other methods for the synthesis of 1,1-disubstituted tetrahydro-β-carbolines, the iodine-induced reaction tolerates the sensitive indole unit well.

In summary, we have developed a novel, simple and one-pot synthesis of 1,1-disubstituted tetrahydro-β-carbolines and the use of these products for natural product synthesis will be reported in due course.

Acknowledgements

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14. *Synthesis of 1,1-disubstituted tetrahydro-β-carbolines* (**1**–**10**); *General procedure:* Tryptamine (200 mg, 125 mmol) was dissolved in ethanol (10 ml) and ketone (1 equiv) was added to the reaction mixture. Next, a catalytic amount of iodine (0.001 equiv) was added to the reaction mixture. The reaction was maintained at room temperature for 3–12 h and the progress monitored by TLC. After completion, the solvent was evaporated and the product purified by column chromatography using silica gel (230–400 mesh), eluting with 10% ethyl acetate and petroleum ether to yield the products in good to moderate yields (44–78%). For previously known compounds, ^{1}H NMR and mass spectral data were consistent with those reported in the literature. For new compounds ^{1}H NMR, mass and elemental analysis data are provided.
Ethyl 5-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl)-2-(1-methyl-1,2,3,4-tetrahydro-carbolin-1-yl)-pentanoate **3**: Yield 67%. Yellow solid; mp 237–239 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (d, ArH, $J = 3.34$ Hz), 7.70 (d, ArH, $J = 7.4$ Hz), 4.04 (q, 2H, $J = 7.4$ Hz), 3.70 (t, 3H, $J = 7$ Hz), 3.50 (t, 3H, $J = 7.4$ Hz), 1.86 (m, 2H), 1.69 (m, 2H), 1.37 (s, 3H), 1.2 (m, 1H), 0.9 (m, 2H); Anal. Calcd for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14. Found: C, 70.77; H, 6.20; N, 9.27. MS (CI) 460 (M+1).
1,1-Diphenyl-1,2,3,4-tetrahydro-β-carboline **4**: Yield 71%. Light brown solid; mp 163–165 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.62 (d, ArH, $J = 7.8$ Hz), 7.47 (d, ArH, $J = 11.8$ Hz), 3.75 (t, 3H, $J = 7.4$ Hz), 3.13 (t, 3H, $J = 7.8$ Hz); Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.27; H, 6.32; N, 8.54. MS (CI) 325 (M+1).
Methyl 2-(1-isopropyl-1,2,3,4-tetrahydro-β-carbolin-1-yl) acetate **5**: Yield 66%. Light yellow solid; mp 173–176 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.80 (s, 1H), δ 8.07 (s, 1H), 7.59 (d, ArH, $J = 7.2$ Hz), 7.38 (d, ArH, $J = 7.2$ Hz), 3.73 (s, 3H), 3.63 (t, 2H, $J = 21.6$ Hz), 3.08 (t, 2H, $J = 7.4$ Hz), 2.57 (m, 1H), 1.07 (d, 6H, $J = 7.8$ Hz); Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.22; H, 7.62; N, 9.67. MS (CI) 287 (M+1).
Ethyl 2-(1-methyl-1,2,3,4,-tetrahydro-β-carbolin-1-yl) acetate **6**: Yield 72%. Brown solid; mp 227–229 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.65 (s, 1H), δ 8.43 (s, 1H), 7.57 (d, ArH, $J = 7.2$ Hz), 7.26 (m, ArH), 4.17 (m, 2H), 3.73 (t, 3H, $J = 7$ Hz), 3.44 (t, 2H, $J = 7.8$ Hz), 2.99 (d, 1H, $J = 7.2$ Hz), 1.82 (s, 2H), 1.27 (t, 3H, $J = 11.2$ Hz), 1.07 (d, 3H, $J = 12.8$ Hz), Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.02; H, 7.32; N, 10.42. MS (CI) 273 (M+1).