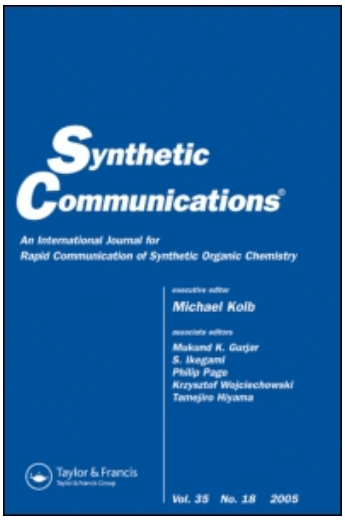


Synthetic Communications

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597304

Iodine-Catalyzed Highly Effective Pictet-Spengler Condensation: An Efficient Synthesis of Tetrahydro--carbolines

Dipak Prajapati [a]; Mukut Gohain [a]
[a] Medicinal Chemistry Division, North East Institute of Science and Technology, Jorhat, Assam, India

Online Publication Date: 01 January 2008

To cite this Article Prajapati, Dipak and Gohain, Mukut(2008)'Iodine-Catalyzed Highly Effective Pictet-Spengler Condensation: An Efficient Synthesis of Tetrahydro--carbolines',Synthetic Communications,38:24,4426 — 4433

To link to this Article: DOI: 10.1080/00397910802369547

URL: http://dx.doi.org/10.1080/00397910802369547

Synthetic Communications®, 38: 4426–4433, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802369547

Taylor & Francis
Taylor & Francis Group

Iodine-Catalyzed Highly Effective Pictet–Spengler Condensation: An Efficient Synthesis of Tetrahydro-β-carbolines

Dipak Prajapati and Mukut Gohain
Medicinal Chemistry Division, North East Institute of Science and Technology, Jorhat, Assam, India

Abstract: Molecular iodine was found to be an efficient catalyst for the two-component Pictet–Spengler condensation of tryptamine with aldehydes, which leads to the formation of tetrahydro-β-carbolines in high yields.

Keywords: Pictet–Spengler condensations, molecular iodine, tetrahydro-β-carbolines

INTRODUCTION

The Pictet–Spengler condensation involving an intramolecular Mannich reaction of β-arylethylamines with carbonyl components is now established as one of the most powerful methods toward the synthesis of tetrahydro-β-carbolines and tetrahydro-isoquinolines.[1,2] The tetrahydro-β-carboline template possesses multiple sites for modification, allowing it to be ideally suited to combinatorial elaboration. The World Drug Index for instance, contains more than 200 listings of this heterocycle, which is usually assembled by the Pictet–Spengler reaction.[3] Combinations of various reactions with Pictet–Spengler condensation in a sequential/tandem fashion has been studied by several research groups.[4,5] Ganesan et al. reported an efficient one-pot synthesis of acylated

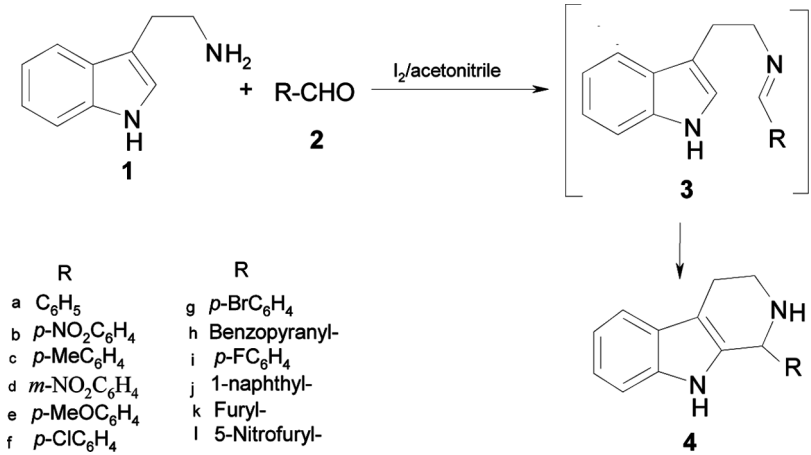
Received March 20, 2008.
Address correspondence to Dipak Prajapati, Medicinal Chemistry Division, Northeast Institute of Science and Technology, Jorhat 785 006, India. E-mail: dr_dprajapati2003@yahoo.co.uk

tetrahydro-β-carboline en route to dimethoxyfumit-remorgin C through acylation of the imine with Fmoc-L-proline and acid chloride.[3,6] Katzenellenbogen recently reported a vinylogous Pictet–Spengler cyclization as the key step to prepare breast tumor imaging agents.[7] It has also been employed as the key reaction in the preparation of β-carboline-3-carboxylic acid esters which are active at the benzodiazepine receptor.[8] Reports appeared in the literature describing β-carboline synthesis on solid support using strong acidic conditions.[9] However, protic acid–catalyzed Pictet–Spengler reactions of tryptamine often feature harsher conditions and poor yields.[10] In a very recent finding, Muller et al. investigated a four-component coupling–amination–aza-annulation–Pictet–Spengler (CAAPS) sequence of acid chloride, terminal alkynes, tryptamine derivatives, and acryloyl chloride, which provides one-pot access to tetrahydro-β-carbolines in moderate to good yields.[11]

In recent years, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations.[12] In continuation of our studies on carbon–carbon bond-formation reactions,[13] we show that molecular iodine is an efficient catalyst for the synthesis of 1,2,3,4-tetrahydro-β-carbolines via Pictet–Spengler condensation.

RESULTS AND DISCUSSION

When tryptamine **1** was treated with an equimolar amount of aldehyde **2** in the presence of a catalytic amount of molecular iodine (1 mol%) in acetonitrile and stirred at ambient temperature, after completion, the corresponding tetrahydro-β-carboline **4b** was obtained (Scheme 1). Complete conversion was observed with 0.5 mol% and thus optimized. All the products thus obtained were characterized by spectral analyses (IR, NMR, MS) and finally by comparison with literature data. Among many solvents utilized, acetonitrile was found to be the best. The reaction also proceeded smoothly under solvent-free conditions to afford the corresponding tetrahydro-β-carbolines, although the yield was comparatively less (83%). To demonstrate the generality of this reaction, we next studied the scope of this reaction under the optimized conditions (acetonitrile, 1 mol% iodine, rt), and the results are summarized in Table 1. But with furfural and 5-nitrofurfural, the reaction did not yield any tetrahydro-β-carbolines, rather corresponding imines **3k** and **3l** were isolated in 70–72% yields (Table 1). An attempt to cyclize these imines by increasing the reaction time and temperature (5 h, reflux) or use of excess of catalyst (20 or 30 mol%) also failed, and decomposition of starting materials occurred. In conclusion, we have developed a mild and efficient route



Scheme 1. Iodine-catalyzed synthesis of tetrahydro-β-carbolines.

for the synthesis of 1,2,3,4-tetrahydro-β-carbolines utilizing molecular iodine as a new catalyst via Pictet–Spengler condensation.

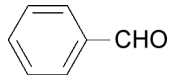
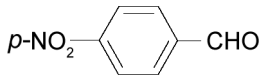
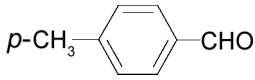
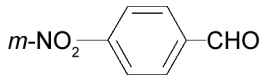
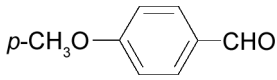
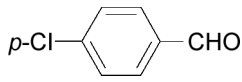
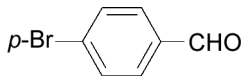
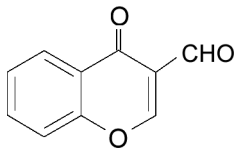
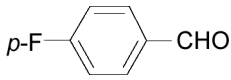
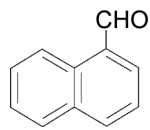
EXPERIMENTAL

Melting points were determined by using a Buchi melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 240 °C analyzer using KBr disks. ^{1}H NMR spectra were recorded on 90-MHz spectrometers, and chemical shift values were recorded in δ units (ppm) relative to Me_4Si as internal standard. The 100-MHz NMR spectra are recorded with tetramethylsilane (TMS) as internal standard (by RSIC, Shillong). Mass spectra were recorded in an AEIMS-30 spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyser. Silica gel G (E-Merck, India) was used for thin-layer chromatography (TLC).

Iodine-Catalyzed Pictet–Spengler Condensation at Room Temperature

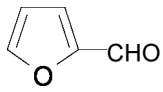
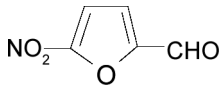
A mixture of tryptamine (0.16 g, 1 mmol) and *p*-nitrobenzaldehyde (0.152 g, 1 mmol) was added to a 50-ml round-bottomed flask containing a catalytic amount of molecular iodine (0.025 g) in acetonitrile (15 ml). The resulting mixture was then stirred at room temperature for 4.5 h. After completion of the reaction (monitored by TLC), acetonitrile was

Table 1. Molecular iodine-catalyzed Pictet–Spengler reaction and synthesis of tetrahydro-β-carbolines

Entry	Carbonyl compounds, **2**	Products	Reaction time (h)	Yield[a] (%)
1		**4a**	3.5	90[14]
2		**4b**	4.5	92
3		**4c**	4.0	89
4		**4d**	4.0	86
5		**4e**	4.0	88
6		**4f**	4.0	87
7		**4g**	4.5	88
8		**4h**	4.5	80
9		**4i**	4.5	85
10		**4j**	4.5	83

(*Continued*)

Table 1. Continued

Entry	Carbonyl compounds, **2**	Products	Reaction time (h)	Yield[a] (%)
11		**3k**	5.0	70
12		**3l**	5.0	72

[a]All the yields refere to isolated pure compounds.

distilled off and 5% $Na_2S_2O_7$ solution was added. The product was extracted with ethylacetate (3×20 ml) and then dried over anhydrous Na_2SO_4 overnight, which upon evaporation and to column chromatography (1:6 hexane–ethylacetate) gave 1-(*p*-nitrophenyl)-1,2,3,4-tetrahydro-β-carboline, **4b**, mp 170–171°C in 92% yield. Similarly other substituted carbonyl compounds and tryptamine were reacted together with molecular iodine, and the results are summarized in Table 1. All the compounds obtained were characterized fully by spectral analysis (IR, ^{1}H NMR, and MS) and finally by comparison with authentic samples.

Data

1-(*p*-Nitrophenyl)-1,2,3,4-tetrahydro-β-carboline (**4b**)

Mp 170–171 °C. IR (KBr): $\nu_{max} = 3310$, 3415, 1515 cm^{-1}; ^{1}H NMR: δ 2.68–2.90 (m, 2H), 3.10 (m, 1H), 3.22 (m, 1H), 5.32 (s, 1H), 6.90–7.25 (m, 4H), 7.48 (d, 2H), 7.82 (br, 1H), 8.06 (d, 2H); MS: m/z = 293 (M +). Anal. calcd. for $C_{17}H_{15}N_3O_2$: C, 69.63; H, 5.12; N, 14.33%. Found: C, 69.74; H, 5.01; N, 14.41%.

1-(*p*-Tolyl)-1,2,3,4-tetrahydro-β-carboline (**4c**)

Mp 192–193 °C. IR (KBr): $\nu_{max} = 3315$, 3400 cm^{-1}; ^{1}H NMR: δ 2.20 (s, 3H), 2.54–2.76 (m, 2H), 3.18 (m, 1H), 3.32 (m, 1H), 5.40 (s, 1H), 7.05–7.35 (m, 4H), 7.52 (d, 2H), 7.90 (br, 1H), 8.13 (d, 2H); MS: m/z = 262 (M +). Anal. calcd. for $C_{18}H_{18}N_2$: C, 82.44; H, 6.87; N, 10.69%. Found: C, 82.53; H, 6.75; N, 10.76%.

1-(*m*-Nitrophenyl)-1,2,3,4-tetrahydro-β-carboline (**4d**)

Mp 143–145 °C. IR (KBr): $\nu_{max} = 3310,\ 1525\,cm^{-1}$; ^1H NMR: δ 2.70–2.94 (m, 2H), 3.06 (m, 2H), 5.30 (s, 1H), 7.02–7.22 (m, 2H), 7.34 (d, 1H), 7.58 (d, 1H), 7.72 (t, 1H), 7.82 (d, 1H), 8.12 (s, 1H), 8.25 (d, 1H); MS: m/z = 293 (M +). Anal. calcd. for $C_{17}H_{15}N_3O_2$: C, 69.67; H, 5.16; N, 14.35%. Found: C, 69.59; H, 5.07; N, 14,47%.

1-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-β-carboline (**4e**)

Mp 205–206 °C. IR (KBr): $\nu_{max} = 3330,\ 3420\,cm^{-1}$; ^1H NMR: δ 2.62–2.85 (m, 2H), 3.08 (m, 1H), 3.32 (m, 1H), 3.86 (s, 3H), 5.40 (s, 1H), 6.90–7.32 (m, 4H), 7.52 (d, 2H), 7.92 (br, 1H), 8.10 (d, 2H); MS: m/z = 278 (M +). Anal. calcd. for $C_{18}H_{18}N_2O$: C, 77.70; H, 6.47; N, 10.07%. Found: C, 77.61; H, 6.58; N, 10.16%.

1-(*p*-Chlorophenyl)-1,2,3,4-tetrahydro-β-carboline (**4f**)

Mp 207–208 °C. IR (KBr): $\nu_{max} = 3210\,cm^{-1}$; ^1H NMR: δ 2.66–3.00 (m, 2H), 3.05 (m, 1H), 3.32 (m, 1H), 5.12 (s, 1H), 6.95–7.15 (m, 2H), 7.20–7.34 (m, 2H), 7.40–7.54 (m, 4H), 7.72 (br, 1H), 7.92 (m, 1H); MS: m/z = 282 (M +). Anal. calcd. for $C_{17}H_{15}N_2Cl$: C, 72.34; H, 5.32; N, 9.93%. Found: C, 72.42; H, 5.25; N, 9.82%.

1-(*p*-Bromophenyl)-1,2,3,4-tetrahydro-β-carboline (**4g**)

Mp 215–216 °C. IR (KBr): $\nu_{max} = 3190\,cm^{-1}$; ^1H NMR: δ 2.72–2.98 (m, 2H), 3.10 (m, 1H), 3.28 (m, 1H), 5.20 (s, 1H), 7.02–7.16 (m, 2H), 7.22 (m, 2H), 7.30–744 (m, 4H), 7.78 (br, 1H), 7.94 (m, 1H); MS: m/z = 327 (M +). Anal. calcd. for $C_{17}H_{15}N_2Br$: C, 62.39; H, 4.59; N, 8.56%. Found: C, 62.46; H, 4.48; N, 8.63%.

1-(Benzopyranyl)-1,2,3,4-tetrahydro-β-carboline (**4h**)

Mp 190–191 °C. IR (KBr): $\nu_{max} = 3250\,cm^{-1}$; ^1H NMR: δ 2.46–2.76 (m, 2H), 3.00 (m, 1H), 3.16 (m, 1H), 5.24 (s, 1H), 6.90–7.25 (m, 4H), 7.35–7.56 (m, 4H), 7.82 (br, 1H), 8.06 (s, 1H); MS: m/z = 316 (M+). Anal. calcd. for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86%. Found: C, 75.88; H, 5.15; N, 8.77%.

1-(*p*-Flurophenyl)-1,2,3,4-tetrahydro-β-carboline (**4i**)

Mp 139–140 °C. IR (KBr): $\nu_{max} = 3160\,cm^{-1}$; ^1H NMR: δ 2.74–3.02 (m, 2H), 3.10 (m, 1H), 3.32 (m, 1H), 5.22 (s, 1H), 6.98–7.12 (m, 2H), 7.20 (m, 2H), 7.34–7.45 (m, 4H), 7.56 (br, 1H), 7.74 (m, 1H); MS: m/z = 266 (M +). Anal. calcd. for $C_{17}H_{15}N_2F$: C, 76.69; H, 5.64; N, 10.52%. Found: C, 76.79; H, 5.59; N, 10.61%.

1-(Napthyl)-1,2,3,4-tetrahydro-β-carboline (**4j**)

IR (KBr): $\nu_{max} = 3210\,cm^{-1}$; ^1H NMR: δ 2.68–2.90 (m, 2H), 3.10 (m, 1H), 3.22 (m, 1H), 5.32 (s, 1H), 6.90–7.25 (m, 4H), 7.45–7.88 (m, 8H); MS: m/z = 298 (M +). Anal. calcd. for $C_{21}H_{18}N_2$: C, 84.56; H, 6.04; N, 9.40%. Found: C, 84.65; H, 6.11; N, 9.52%.

ACKNOWLEDGMENTS

We thank the Department of Science and Technology (DST), New Delhi, for financial support and the director, Northeast Institute of Science and Technology (NEIST), Jorhat, for his keen interest and constant encouragement.

REFERENCES

1. (a) Cox, E. D.; Cook, J. M. The Pictet–Spengler condensation: A new direction for an old reaction. *Chem. Rev.* **1995**, *95*, 1797–1842; (b) Beke, G.; Szabo, L. F.; Podanyi, B. Investigation of Pictet–Spengler type reactions of secologanin with histamine and its benzyl derivative. *J. Nat. Prod.* **2002**, *65*, 649–655.
2. For recent applications of P–S reaction in natural product and unnatural product synthesis, see Zhou, H.; Liao, H.; Cook, J. M. Regiospecific, enantiospecific total synthesis of the 12-alkoxy-substituted indole alkaloids, (+)-12-methoxy-Na-methylvellosimine, (+)-12-methoxyaffinisine, and (−)-fuchsiaefoline. *Org. Lett.* **2004**, *6*, 249–252.
3. Srinivasan, N.; Ganesan, A. Highly efficient Lewis acid–catalysed Pictet–Spengler reactions discovered by parallel screening. *J. Chem. Soc., Chem Commun.* **2003**, 916–917.
4. Dondas, H. A.; Duraisingham, J.; Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Thornton-Pett, M.; Sridharan, V.; Suganthan, S. Sequential 1,3-dipolar cycloaddition Pictet–Spengler reactions: A versatile tactical combination. *Tetrahedron* **2000**, *56*, 4063–4070.
5. Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Sridharan, V.; Suganthan, S.; Thornton-Pett, M.; Zhang, J. Pictet–Spengler/palladium

catalyzed allenylation and carbonylation processes. *Tetrahedron* **2000**, *56*, 6585–6594.
6. Wang, H.; Ganesan, A. Concise synthesis of the cell cycle inhibitor demethoxyfumitremorgin C. *Tetrahedron Lett.* **1997**, *38*, 4327–4328.
7. Cesati, R. R.; Katzenellenbogen, J. A. Preparation of hexahydrobenzo-[f]isoquinolines using a vinylogous Pictet–Spengler cyclization. *Org. Lett.* **2000**, *2*, 3635–3538.
8. Allen, M. S.; Hagen, T. J.; Trudell, M. L.; Codding, P. W.; Skolnick, P.; Cook, J. M. Synthesis of novel 3-substituted β-carbolines as benzodiazepine receptor ligands: Probing the benzodiazepine receptor pharmacophore. *J. Med. Chem.* **1988**, *31*, 1854–1861.
9. Wu, C.-Y.; Sun, C.-M. Parallel synthesis of 1,2,3,4-tetrahydro-β-carbolines using microwave irradiation. *Synlett.* **2002**, 1709–1711.
10. Grigg, R.; Gunaratne, H. Q. N.; McNaghten, E. Observations on the Pictet–Spengler synthesis of 1,2,3,4-tetrahydro-β-carbolines. *J. Chem. Soc., Perkin Trans. 1* **1983**, 185–187.
11. Karpov, A. S.; Oeser, T.; Muller, T. J. J. A novel one poy four component access to tetrahydro-β-carbolines by a coupling–amination–aza-annulation–Pictet–Spengler sequence (CAAPS). *J. Chem. Soc., Chem. Commun.* **2004**, 1502–1503.
12. Phukan, P. Iodine as a very powerful catalyst for three-component synthesis of protected homoallylic amines. *J. Org. Chem.* **2004**, *69*, 4005–4006.
13. (a) Prajapati, D.; Laskar, D. D.; Gogoi, B. J.; Devi, G. Indium-mediated propargylation of imines and imine oxides in aqueous media: Propargylation of C = N- centres. *Tetrahedron Lett.* **2003**, *44*, 6755–6757; (b) Prajapati, D.; Gohain, M. Recent advances in the application of supercritical fluids for carbon–carbon bond formation in organic synthesis. *Tetrahedron* **2004**, *60*, 815–833, and references cited therein.
14. Narayanan, K.; Schindler, L.; Cook, J. M. Carboxyl-mediated Pictet–Spengler reaction: Direct synthesis of 1,2,3,4,-tetrahydro-β-carbolines from tryaptamine-2-carboxylic acids. *J. Org. Chem.* **1991**, *56*, 359–365.