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Water as an efficient medium for the synthesis of tetrahydro-β-carbolines via Pictet–Spengler reactions☆

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Abstract—A mild and efficient protocol for the Pictet–Spengler reaction in water using an acid catalyst has been described. The condensation of tryptophan, tryptamine, and N_b-benzyl tryptophan with different aldehydes having both electron-withdrawing and -donating substituents in the presence of a catalytic amount of TFA in water furnished tetrahydro-β-carbolines in good isolated yields. A salient feature of the water mediated Pictet–Spengler reaction was the general trend observed during the condensation of Trp-OMe and aryl/aliphatic aldehydes furnishing diastereomeric mixtures with a preference for the cis-isomer.
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The Pictet–Spengler reaction[1] is a widely used method for C–C bond formation.[2] In general, it is a two-step method and involves acid catalyzed condensation of an aliphatic amine attached to a sufficiently reactive aromatic nucleus with aldehydes. It is now established as a method of choice for the construction of tetrahydro-β-carboline (THBC) and -isoquinoline frameworks; however, the current literature mostly relates to the synthesis of THBC. The latter is found abundantly in the plant and animal kingdom, and many exhibit potent biological activities.[3] 1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acids, generally found in foods, arise from the condensation of L-tryptophan and aldehydes.[4] Research in the last two decades has described the occurrence of tetrahydro-β-carbolines and β-carbolines in biological tissues and fluids,[5] in fruit- and meat-derived products such as juices, jams[6] and sausages.[7] These compounds are readily produced, as a result of a reaction between tryptophan and/or tryptamine and aldehydes, during the production, processing and storage of food products.[8] It has been argued that dietary sources provide tetrahydro-β-carbolines that may subsequently accumulate in biological tissues and fluids.

Natural products with a β-carboline nucleus possess widespread and potent biological activities. The reported effects of this class of compounds comprise antineoplastic (tubulin binding),[9,10] anticonvulsive, hypnotic and anxiolytic (benzodiazepine receptor ligands),[11,12] antiviral,[3a] antimicrobial[5] as well as topoisomerase-II inhibition,[13] inhibition of cGMP-dependent processes,[14] and antiplasmodial activity.[15,16] The increasing popularity of the Pictet–Spengler reaction has been fueled by the ubiquitous nature of nitrogen-containing compounds in drugs and natural products.[17]

In this context, several groups have studied the detailed mechanistic aspects of this reaction and have developed a number of diastereo- and enantioselective methods for the Pictet–Spengler cyclization.[18,19] However, despite the diverse synthetic routes in both protic and aprotic solvents reported so far for this reaction, the strategy has not been investigated in water. The use of water as a medium for this extensively used C–C bond forming reaction would greatly contribute to the development of an environmentally friendly process since it is cheap, readily available, and nontoxic. Indeed, industry prefers to use water as a solvent rather than toxic organic solvents and in recent years, water has been demonstrated as an ideal medium for many organic transformations even if starting materials and products appear to be insoluble.[20] Many organic reactions such as Claisen rearrangement, aldol condensation, benzoin condensation, and Diels–Alder cycloaddition exhibit rate enhancement in water.[21] Recently, a comprehensive

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review on C–C bond formation in aqueous conditions has been published.[22] The significant enhancement in the rate of the reaction in water has been attributed to hydrophobic packing,[23] solvent polarity,[24] hydration,[25] and hydrogen bonding.[26]

In this Letter we describe a mild, convenient, and simple procedure for the condensation of an amine and an aldehyde to give tetrahydro-β-carbolines in water in the presence of an acid catalyst. The studies are part of our ongoing program[27] for the development of new variants/applications of Pictet–Spengler reactions.

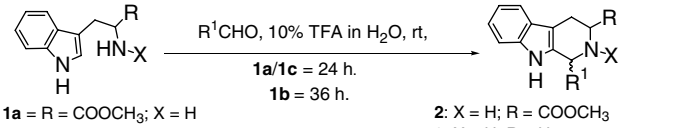
Initially, the two-component Pictet–Spengler reaction of freshly distilled benzaldehyde (0.45 mmol) and tryptophan methyl ester (0.45 mmol) was examined in water (7.5 mL) at room temperature in the presence of a series of acid catalysts, traditionally used under Pictet–Spengler protocols. We were pleased to see that the Pictet–Spengler reactions in 10% TFA–water, proceeded smoothly and afforded the desired compound in 82% isolated yield (HPLC revealed a mixture of two diastereomers) at room temperature (Table 1).[28] Reduction in the concentration of TFA from 10 to 5 or 2% produced cyclized products in diminished yields. *endo* Cyclization in the presence of 10% AcOH at rt furnished the desired compound in only 23% yield. The use of other acid/Lewis acid catalysts traditionally used under Pictet–Spengler protocols such as *p*-TsOH and $Yb(OTf)_3$ at rt or complete absence of acid catalyst failed to produce *endo* cyclized products. No attempt was made to carry out the reaction at elevated temperatures as racemization has been reported under heating.[29]

For characterization of the crude cyclized product **2a**, we initially isolated the Pictet–Spengler product as a mixture of diastereomers to determine the yields and cis:trans ratios. This was followed by the separation of the cis and trans diastereomers by column chromatography and characterization using HPLC, MS, and NMR. The assignments of the stereochemistry were based on NOESY, HMBC, and by ^{13}C NMR[30] experiments developed by Cox and Cook.[2c]

After successfully optimizing the reaction conditions in water, we conducted a broader investigation of this reaction utilizing various amine substrates and aldehydes. The results of the Pictet–Spengler reaction of tryptophan methyl ester (**1a**; L-Trp-OMe), tryptamine (**1b**) and N_b-benzyl-L-tryptophan methyl ester (**1c**) with different aldehydes are summarized in Table 1.

In 10% TFA–water, aryl aldehydes having either electron-withdrawing or -donating groups underwent Pictet–Spengler reaction with Trp-OMe to furnish **2a–g** in good yields. This is unlike the traditional Pictet–Spengler protocol involving aprotic solvents wherein aldehydes bearing electron-donating substituents failed to undergo cyclization and furnished imines as the only product. This was attributed to the decrease in the reactivity of the iminium ion intermediate derived from aldehydes bearing the electron-donating group,[31] which in

Table 1.



1a = R = $COOCH_3$; X = H
1b = R = H; X = H
1c = R = $COOCH_3$; X = $CH_2C_6H_5$

2: X = H; R = $COOCH_3$
3: X = H; R = H
4: X = $CH_2C_6H_5$; R = $COOCH_3$

Entry	Amine	R^1	Product[a]	Yield[b] (%)	Cis:trans[c]
1	**1a**	4-NO_2–C_6H_4	**2a**	83	75:25
2	**1a**	C_6H_5	**2b**	82	70:30
3	**1a**	4-CH_3–C_6H_4	**2c**	75	83:17
4	**1a**	2-HO–C_6H_4	**2d**	68	90:10
5	**1a**	4-$(CH_3)_2N$–C_6H_4	**2e**	72	60:40[d]
6	**1a**	4-Br–C_6H_4	**2f**	77	80:20
7	**1a**	4-CH_3O–C_6H_4	**2g**	79	55:45
8	**1a**	CH_3–CH_2–	**2h**	65	70:30[d]
9	**1a**	$C_6H_5CH_2$	**2i**	68	75:25[d]
10	**1b**	4-NO_2–C_6H_4	**3a**	72	—
11	**1b**	C_6H_5	**3b**	75	—
12	**1b**	4-CH_3–C_6H_4	**3c**	64	—
13	**1b**	2-HO–C_6H_4	**3d**	61	—
14	**1b**	4-$(CH_3)_2N$–C_6H_4	**3e**	45	—
15	**1c**	4-NO_2–C_6H_4	**4a**	73	(0:100)
16	**1c**	C_6H_5	**4b**	77	(0:100)
17	**1c**	4-CH_3O–C_6H_4	**4g**	61	(0:100)

[a] Compound **2** = diastereomeric mixture, **3** = enantiomeric mixture, **4** = trans-isomer.
[b] Yields are quoted for the pure isolated cis/trans mixture of diastereoisomers.
[c] As determined by integration of the ^1H NMR spectrum (±3%). The stereochemistry of the diastereomers was determined by ^{13}C NMR spectroscopy using the method of Cox and Cook[2c] and Bailey et al.[29]
[d] Diastereomers not separated.

Table 2. Comparative profile of the Pictet–Spengler reaction of aldehydes having electron-donating groups with amines under three different protocols (A, B, and C)

Amine	Aldehydes	Product	Yield (%) under different protocols[a]		
			A	B	C
1a	4-Dimethylaminobenzaldehyde	**2e**	72	38	NR
1a	Salicylaldehyde	**2d**	68	42	NR
1b	4-Dimethylaminobenzaldehyde	**3e**	45	22	NR
1b	Salicylaldehyde	**3d**	61	19	NR

[a] Protocol A: 10% TFA in water, rt; protocol B: 10% TFA in DCM, rt; protocol C: 10 mol % *p*-TsOH in toluene, reflux.; NR = no reaction.

turn prevented the formation of tetrahydro-β-carbolines. We further established this fact experimentally by examining the Pictet–Spengler reaction of the aryl aldehydes having electron-donating groups (salicylaldehyde and 4-dimethylaminobenzaldehyde) with **1a** in 10% TFA–water, 10% TFA–dichloromethane and 10 mol % *p*-TsOH in toluene at reflux (Table 2).

Condensation of Trp-OMe with salicylaldehyde in aprotic medium and in dichloromethane furnished cyclized products in 0% and 42% yields, respectively, while the same reaction in water furnished the Pictet–Spengler product in 68% isolated yield. Similarly, condensation of 4-dimethylaminobenzaldehyde with **1a** in toluene again failed to produce the cyclized product, whereas dichloromethane and water furnished *endo* cyclized products in 22% (Table 2) and 72% yields, respectively. Thus, water, probably due to its unique abilities such as hydrogen bonding and high dielectric constant appears to be a more efficient medium than toluene or dichloromethane in promoting *endo* cyclization of aldimines derived from Trp-OMe and aldehydes with different electronic environments. Further, it is interesting to note that using our protocol at room temperature, condensation of **1a** with different aldehydes furnished the cis 1, 3-disubstituted tetrahydro-β-carboline as the major isomer, whereas reports in the literature for the same set of reactions in aprotic and protic media depict no general trend in the diastereoselectivity.[2c,32] The Pictet–Spengler product **2d** derived from **1a** and salicylaldehyde exhibited the best cis selectivity (9:1).

Encouraged by our results with Trp-OMe, we extended our protocol to tryptamine (**1b**), which is known to be a less reactive substrate than Trp-OMe, toward Pictet–Spengler reaction. Interestingly, using our protocol, tryptamine successfully underwent *endo* cyclization in water in good yields, when condensed with 4-nitrobenzaldehyde, benzaldehyde, 4-methylbenzaldehyde, salicylaldehyde, and 4-dimethylamino benzaldehyde (Table 1, entries 10–14). Our findings are in contrast to the reaction in aprotic solvents where tryptamine furnished only Schiff's bases when condensed with benzaldehyde/salicylaldehdye/4-dimethylaminobenzaldehyde and failed to undergo *endo* cyclization due to the poor electrophilicity of the resulting imines.[2c] Similarly, in 10% TFA–dichloromethane, reaction of 4-dimethyl aminobenzaldehyde and salicylaldehyde with tryptamine furnished the *endo* cyclized product in only 22% and 19% yields, respectively (Table 2). However, in 10% TFA–water, the yield for the same set of reactions was 45% and 61%, respectively (Table 2). It is thus apparent that in 10% TFA–water, the electrophilicity (a driving force for *endo* cyclization) of the aldiminium ions derived from aryl aldehydes, irrespective of their electronic environment, appears to be enhanced, a phenomenon, which is neither observed in 10% TFA–dichloromethane nor in *p*-TsOH–toluene.

To enhance further the scope of our strategy, we examined the reaction of N_b-benzyl-L-Trp-OMe (**1c**) with three different aryl aldehydes: 4-nitrobenzaldehyde, 4-anisidine, and benzaldehyde in water. The utility of the substrate **1c** has been demonstrated, (1) in enhancing the electrophilicity of the iminium ion derived from aldehydes having an electron-donating substitutent (salicylaldehyde), which in turn favors cyclization and, (2) in the diastereoselective synthesis of the trans-isomer of the 1,2,3-trisubstituted tetrahydro-β-carbolines.[2c,28] In 10% TFA–water, the Pictet–Spengler products (**4a**, **4b**, and **4g)** derived from **1c** were obtained in good isolated yields (Table 1, entries 15, 16, and 17) and, as expected, were obtained as a single trans-isomer. Their structural identity was established using the ^{13}C chemical shift of the *N*-benzylic carbon as described earlier by Bailey et al.[29] and accordingly, the δ value for the benzylic carbon for compound **4b** matched with the reported value for the trans-isomer. Aliphatic aldehydes: propanaldehyde (Table 1, entry 8) and phenylacetaldehyde dimethylacetal (Table 1, entry 9) underwent *endo* cyclization with **1a** in good yields and high cis selectivity; however, the ketones completely failed to undergo *endo* cyclization in water.

In conclusion, we have developed a mild and efficient protocol for the synthesis of tetrahydro-β-carbolines via Pictet–Spengler reaction in water. With judicious choice of tryptophan derivative (**1a** or **1c**) good yields and high cis or trans selectivity for the Pictet–Spengler products can be obtained in water. Another interesting feature of our studies was that aryl aldehydes bearing either electron-withdrawing or -donating groups successfully underwent the Pictet–Spengler reaction with equal ease. Finally, our Pictet–Spengler strategy in water might be an attractive starting point for the synthesis of indole alkaloids by avoiding the use of toxic solvents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.112.

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28. *Representative Procedure*: To a 10% solution of TFA in water (7.5 mL), tryptophan methyl ester (2.0 mmol) and aldehyde (2.0 mmol) were added at rt. The mixture was

further stirred at ambient temperature and the progress of the reaction was monitored by TLC. Upon completion of the reaction, 5% aqueous $NaHCO_3$ was added to quench the acid in the reaction mixture. The product was extracted using ethyl acetate (50 mL) and the organic layer was washed with water (2×10 mL), brine solution (1×10 mL) and finally dried over anhydrous Na_2SO_4. It was then evaporated in vacuo to afford a residue and purified by column chromatography to give **2**. Purification of the crude reaction mixture was carried out by flash column chromatography to afford a cis/trans mixture of diastereoisomers. Care was taken to avoid separation of the isomers, to ensure that NMR would give accurate values for the cis:trans ratios. Finally, the mixture was again subjected to column chromatography on silica gel (200–400 mesh) using hexane/EtOAc (5:1) as eluent to separate both the isomers and their stereochemistry was assigned using the methods of Cox and Cook[2c] and Bailey et al.[29]

Compound **2d**: cis-isomer, white solid; yield 59%; mp: 162–164 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.51 (2H, m), 7.31–7.26 (2H, m), 7.21–7.12 (3H, m), 6.98–6.93 (1H, m), 6.86 (1H, d, $J = 7.7$ Hz), 5.37 (1H, s), 3.98–3.96 (1H, m), 3.89 (3H, s), 3.54–3.30 (1H, m), 3.14–2.98 (1H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 172.14, 157.69, 136.50, 132.39, 130.27, 128.50, 127.14, 123.45, 122.32, 119.93, 119.61, 118.45, 118.01, 111.24, 107.92, 58.92, 56.63, 52.76, 24.94, IR (KBr) 3397, 3334, 2941, 2849, 1741, 1594 cm^{-1}; MS (ES$^+$) m/z: 323.1 (M+H)$^+$. Anal. Calcd for $C_{19}H_{18}N_2O_3$ C, 70.79; H, 5.63; N, 8.69%. Found: C, 70.59; H, 5.53; N, 8.89%.

Compound **2c**: cis-isomer: white solid; yield 61%; mp: 142–144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (1H, dd, $J = 5.5$, 3.0 Hz), 7.46 (1H, br s), 7.30–7.28 (2H, m), 7.21–7.11 (5H, m), 5.23 (1H, s), 4.00 (1H, dd, $J = 11.1$, 4.2 Hz), 3.83 (3H, s), 3.28–3.21 (1H, m), 3.07–2.98 (1H, m), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 173.39, 138.52, 137.83, 136.25, 135.04, 129.74, 128.67, 127.26, 122.01, 119.71, 118.32, 111.07, 108.90, 58.47, 57.05, 52.38, 25.87, 21.33; IR (KBr) 3344, 2941, 2845, 1717, 1593 cm^{-1}; MS (ES$^+$) m/z: 321.1 (M+H)$^+$, HRMS (EI$^+$) $C_{20}H_{20}N_2O_2$ m/z calcd 320.1525 for [M]$^+$ found 320.1527; trans-isomer: Yield 11%; white solid; mp: 174–176 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (1H, br s), 7.59–7.56 (1H, m), 7.26–7.24 (2H, m), 7.20–7.11 (5H, m), 5.34 (1H, s), 4.00 (1H, t, $J = 6.1$ Hz), 3.74 (3H, s), 3.33–3.26 (1H, m), 3.18–3.11 (1H, m), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.28, 139.14, 138.03, 136.30, 133.56, 129.52, 128.48, 127.12, 122.01, 119.59, 118.34, 111.07, 108.80, 54.79, 52.55, 52.25, 24.85, 21.25; IR (KBr) 3287, 2949, 2843, 1744, 1595 cm^{-1}; MS (ES$^+$) m/z 321.1 (M+H).

Compound **3b**: grey solid; yield 75%; mp: 160–161 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64 (1H, br s), 7.57 (1H, dd, $J = 5.5$, 2.9 Hz), 7.38–7.32 (5H, m), 7.25–7.22 (1H, m), 7.19–7.11 (2H, m), 5.18 (1H, s), 3.43–3.36 (1H, m), 3.20–3.11 (1H, m), 3.00–2.82 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 141.86, 136.03, 134.48, 128.90, 128.68, 128.30, 127.43, 121.78, 119.43, 118.30, 110.99, 110.23, 58.09, 42.77, 22.57, IR (KBr) 3406, 2925, 2846, 1594 cm^{-1}; MS (ES$^+$) m/z: 271.1 (M+Na)$^+$.

Compound **4b**: yellow solid; yield 77%; mp: 218–220 °C [Bailey et al. *Heterocycles* **1987**, *26*, 389; mp: 221–223 °C]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.47 (3H, m, $J = 8.6$, 2.2 Hz), 7.36 (1H, s), 7.33–7.16 (8H, m), 7.22–7.10 (1H, m), 7.10–7.07 (2H, m), 5.46 (1H, s), 3.94 (1H, t, $J = 4.59$ Hz), 3.87 (2H, d, $J = 5.58$ Hz), 3.62 (3H, s), 3.21 (2H, d, $J = 1.17$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.76, 142.34, 139.59, 136.65, 135.10, 129.08, 128.90, 128.72, 128.51, 128.23, 127.26, 127.17, 121.76, 119.45, 118.38, 111.00, 106.49, 61.01, 56.21, 54.51, 51.55, 24.60; IR (KBr) 3338, 2925, 2843, 1721 cm^{-1}; MS (ES$^+$) m/z: 397 (M+H). Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07%. Found: C, 78.66; H, 6.34; N, 6.88%.

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