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Note

Pictet-Spengler Reaction Using Ion-Exchange Resin as a Catalyst and Support for 'Catch and Release' Purification

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The Pictet-Spengler reaction between tryptamine and aldehydes was catalyzed by Dowex 50W-X4 acidic ion-exchange resin. The products were obtained from the resin in high purity by 'catch and release' without the need for separate chromatographic purification.

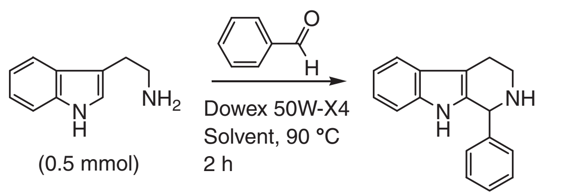
Key words: Pictet-Spengler reaction; ion-exchange resin; parallel synthesis; alkaloid; catch and release

The Pictet-Spengler reaction is a major means for heterocyclic synthesis that is used by organic chemists and also in nature for alkaloid biosynthesis. An acidic catalyst activates the imine intermediate before cyclization to the tetrahydroisoquinoline or tetrahydro-β-carboline in this reaction.[1–4)] However, classic Lewis acids usually have high reactivity, and hence promote such a secondary reaction as the polymerization of indoles or phenols. We therefore attempted to discover an acidic catalyst that was much milder and more effective.

The isolation of products is often a tiresome and time-consuming procedure in organic synthesis, and various techniques have therefore been developed to achieve a high throughput.[5–8)] For example, we have previously found basic ion-exchange resins to be suitable dual-purpose reagents that can act as catalysts and aid purification in carbanion-mediated cyclization.[9–11)] We report in this paper that the acidic ion-exchange resin, Dowex 50W-X4, is similarly powerful as an acidic catalyst for the Pictet-Spengler reaction as well as a polymer support for 'catch and release' purification of heterocyclic products. A Nautilus 2400 automated synthesizer was used to examine various combinations of amines and aldehydes, and their reactivity was surveyed with our protocol.

We first investigated the effects of the solvent and reagent stoichiometry by using the Pictet-Spengler reaction of tryptamine and benzaldehyde as a model case. All reactions were performed at 90 °C for 2 h with the Nautilus 2400 automated synthesizer. The excess reagents were removed after 2 h by simply rinsing with $CHCl_3$. The product on the Dowex resin was then treated with a solution of 10% triethylamine (TEA) in $CHCl_3$ to release the compound from the resin. Both the tryptamine starting material and the product are basic amines, so they may not be separable by this strategy. Instead, we used an excess amount of aldehyde to drive the Pictet-Spengler reaction to completion and minimize the amount of remaining tryptamine.

Table 1. Pictet-Spengler Reactions Promoted by Dowex 50W-X4 Resin



Entry	Aldehyde (eq.)	Catalyst (g)	Solvent (5 mL)	Yield[a)] (%)
1	5	1	DMF	18
2	5	3	DMF	34
3	5	5	DMF	23
4	5	3	H_2O	14
5	5	3	Toluene	40
6	5	3	BuOH	11
7	5	3	HFIP[b)]	18
8	5	3	DCE	39
9	1	3	DCE	16
10	1.5	3	DCE	16
11	3	3	DCE	32
12	10	3	DCE	26
13	5	3	DCE-HFIP[b)] (1:1)	22

[a)]The product did not need purification by silica-gel column chromatography, because no by-product was detected by 1H-NMR and TLC for each reaction.
[b)]1,1,1,3,3,3-hexafluoropropan-2-ol

Among the ion-exchange resins investigated, Dowex 50W-X4 gave the best results for the Pictet-Spengler reaction. Such other ion-exchange resins as Dowex 2-X8, Diaion WK10, and Amberlyst 15Dry did not undergo the Pictet-Spengler reaction. The effects of loading the Dowex 50W-X4 catalyst on the yield of the product (Table 1, entries 1–3) suggested that 3 g gave the best results. Screening of various solvents showed that 1,2-dichloroethane (DCE) was suitable for the Pictet-Spengler reaction (Table 1, entries 4–8). The importance of using excess aldehyde is shown by entry 9, where 1 or 1.5 equivalents gave a very poor yield of

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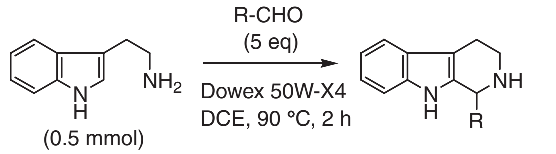
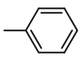
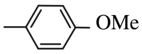
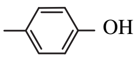
Abbreviations: DCE, 1,2-dichloroethane; DMF, *N*,*N*-dimethylformamide; NAADP, nicotinic acid adenine dinucleotide phosphate; TEA, triethylamine; TLC, thin-layer chromatography

Table 2. Pictet-Spengler Reaction with Various Aldehydes Using Dowex 50W-X4



Entry	Aldehyde R–CHO (5 eq)	Yield[a)] (%)
1	R=H	12
2	R=CH_3	28
3	R=C_2H_5	22
4	R=C_5H_{11}	20
5	R= 	39
6	R= 	25
7	R= 	43

[a)]The product did not need purification by silica-gel column chromatography, because no by-product was detected by 1H-NMR and TLC for each reaction.

mainly unreacted starting materials by thin-layer chromatography (TLC; entries 9 and 10). On the other hand, there were many by-products in the case of 10 equivalents of aldehyde (entry 12). A fairly high yield was obtained when the temperature was 90 °C, the reaction time was 2 h, and the amount of catalyst was 3 g. More importantly, the purity of the resulting compound was very high and further chromatography was not required, because no by-product was detected by 1H-NMR and TLC for each reaction.[12)]

Our method was then applied to various aldehydes in order to synthesize a library of tetrahydro-β-carboline compounds. For example, Ned-19, which was synthesized from a tryptophan derivative in five steps, was a potent cell-permeable NAADP receptor antagonist.[13,14)] The reaction with aromatic aldehydes had a higher yield than could be achieved by aliphatic aldehydes that were vulnerable to other pathways due to enolization and higher reactivity (Table 2, entries 5–7).

In conclusion, we demonstrated that the acidic ion-exchange resin, Dowex 50W-X4, catalyzed the Pictet-Spengler reaction of tryptamine with various aldehydes in DCE. The resin also efficiently sequestered the desired product to facilitate purification by 'catch and release.' We believe that the Pictet-Spengler reaction using Dowex 50W-X4 will be widely applicable for synthesis and provide products without the need for separate chromatographic purification.

References and Notes

1) Pictet A and Spengler T, *Ber.*, **44**, 2030–2036 (1911).
2) Whaley WM and Govindachari TR, *Org. React.*, **6**, 74–150 (1951).
3) Cox ED and Cook JM, *Chem. Rev.*, **95**, 1797–1842 (1995), and references therein.
4) Saito A, Numaguchi J, and Hanazawa Y, *Tetrahedron Lett.*, **48**, 835–839 (2007), and references therein.
5) Curran DP, *Angew. Chem. Int. Ed.*, **37**, 1174–1196 (1998).
6) Yoshida J and Itami K, *Chem. Rev.*, **102**, 3693–3716 (2002), and references therein.
7) Mothana S, Chahal N, Vanneste S, and Hall DG, *J. Comb. Chem.*, **9**, 193–196 (2007), and references therein.
8) Kim CB, Cho CH, Kim CK, and Park K, *J. Comb. Chem.*, **9**, 1157–1163 (2007), and references therein.
9) Kulkarni BA and Ganesan A, *Angew. Chem. Int. Ed.*, **36**, 2454–2455 (1997).
10) Kulkarni BA and Ganesan A, *Chem. Commun.*, 785–786 (1998).
11) Kulkarni BA and Ganesan A, *Tetrahedron Lett.*, **40**, 5637–5638 (1999).
12) General Procedure for Pictet-Spengler Reactions using Automated Synthesizer Nautilus 2400: The case of 1-phenyl-1,2,3,4-tetrahydro-β-carboline; To a mixture of tryptamine (80 mg, 0.5 mmol) and benzaldehyde (0.255 mL, 2.5 mmol) in 1,2-dichloroethane (5 mL) was added Dowex 50W-X4 (3.0 g). The resulting mixture was heated and mixed at 90 °C in the Nautilus 2400 (Argonaut). The reaction mixture was filtered and the supernatant discarded and the resin then washed sequentially with $CHCl_3$ (30 mL, 3 times). The resin was treated with 10% TEA of $CHCl_3$ (30 mL, 3 times) to effect product release, and the combined solution evaporated to give the desired compound. 1-Phenyl-1,2,3,4-tetrahydro-β-carboline: 1H-NMR (300 MHz, $CDCl_3$) δ 1.88 (br s, 1H), 2.78–2.86 (m, 1H), 2.88–2.99 (m, 1H), 3.14 (ddd, 1H, $J = 12.0$, 9.0, 5.1 Hz), 3.38 (ddd, 1H, 12.0, 5.1, 3.9 Hz), 5.17 (s, 1H), 7.11–7.15 (m, 2H), 7.18–7.23 (m, 1H), 7.29–7.36 (m, 5H), 7.53–7.57 (m, 2H). ESI-MS calcd for $C_{17}H_{16}N_2$ 248.1 $[M]^+$, found 249.1 $[M+H]^+$.
13) Naylor E, Arredouani A, Vasudevan SR, Lewis AM, Parkesh R, Mizote A, Rosen D, Thomas JM, Izumi M, Ganesan A, Galione A, and Churchill GC, *Nat. Chem. Biol.*, **4**, 220–226 (2009).
14) Rosen D, Lewis AM, Mizote A, Thomas JM, Aley PK, Vasudevan SR, Parkesh R, Galione A, Izumi M, Ganesan A, and Churchill GC, *J. Biol. Chem.*, **284**, 34930–34934 (2009).