Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5041-5044, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01012-X

Pictet-Spengler Reaction On Solid Support.

Lihu Yang* and Liangqin Guo

Modular Synthesis, Department of Medicinal Chemistry, Merck Research Laboratories,
PO Box 2000, Rahway, NJ 07065

Abstract: Merrifield resin-bound tryptophan undergoes Pictet-Spengler reaction with aldehydes at ambient temperature to give tetrahydro-β-carbolines in excellent yield and purity after cleavage.

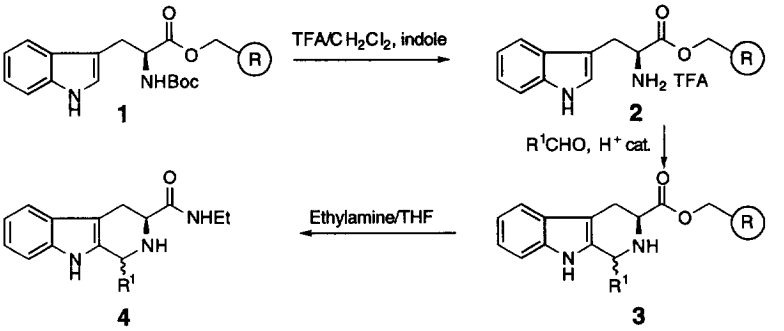
Solid-phase synthesis is widely used for the rapid synthesis of oligomers and more recently for small organic molecules.[1] The development of new chemistry and the extension of known solution chemistry to resin-supported substrates is being actively pursued in industry and academia for the synthesis of structurally diverse small molecule combinatorial libraries. Several classes of heterocyclic compounds including tetrahydrofurans,[2] hydantoins,[3] benzodiazepines,[4] piperazinediones,[5] thiazolidinones,[6] pyrrolidines,[7] and beta-lactams [8] have been synthesized on solid supports. In this communication, we report that the Pictet-Spengler cyclization [9] of tryptophan and aldehydes to form 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles (tetrahydro-β-carbolines) using polymer-bound tryptophan at ambient temperature under acidic conditions.[10]

We were initially intrigued by the potential of applying the Pictet-Spengler cyclization on solid support, since it has been used extensively for the synthesis of indole alkaloids and isoquinoline alkaloids. The reaction should be suitable for the construction of combinatorial libraries since diversity can be achieved through the derivatization of the indole NH and the amine NH in addition to the aldehydes. Additional substitutions can be realized by using bromo or hydroxy-substituted tryptophan followed by palladium-mediated cross-coupling[11] or Mitsunobu[12] reactions respectively.

The Pictet-Spengler reaction was traditionally carried out in a protic solvent with acid catalysts.[13] We sought to avoid such conditions because most ungrafted resins do not swell in protic solvents, and the acidic conditions would exclude the use of the acid-cleavable linkers which are most commonly used in solid-phase synthesis. We initially investigated the Pictet-Spengler reaction under neutral conditions in an aprotic solvent such as benzene or toluene[14] using the commercially available Fmoc-Trp-Wang resin. After removal of Fmoc, the resin was incubated with benzaldehyde (10 equivalents) in toluene. The reaction was very slow at ambient temperature.[15] Running the reaction at 80°C overnight effected cyclization to give the desired product with modest purity (80%) after acidic cleavage (TFA-H_2O). In addition to the inconvenience of heating, many aldehydes are not soluble in toluene. We therefore abandoned this approach.

We next turned our attention to the acid promoted Pictet-Spengler reaction, since it has been reported that the reaction proceeds smoothly in aprotic solvents at ambient temperature under acidic conditions (TFA/CH_2Cl_2).[16] Removal of the Boc group from commercially available Boc-Trp-Merrifield resin[17] under the normal acidic conditions (TFA/CH_2Cl_2 1:1) caused a significant amount of t-butyl alkylation to the indole. Inclusion of indole or thioanisole in the reaction mixture suppresses this side reaction.[18]

Scheme 1



We initially investigated the effect of TFA concentration on the cyclization. A series of experiments were conducted with TFA concentrations of 0, 1, 5, 10, 20, 50% in dichloromethane. Excess benzaldehyde (10 equiv.) was used to facilitate intermediate imine formation. Cleavage of the product from the resin was readily achieved with ethylamine (70% ethylamine in water and THF (1:1), room temperature, 8 hours), providing the ethyl amide. We chose ethylamine for its low boiling point, since it can be removed by evaporation. Other small primary amines also worked well. All of the TFA containing reactions were effective in the cyclization, although lower acid concentrations required longer reaction times. In each case, the ethyl amide was obtained in >90% purity. When the reaction was exposed to air for a prolonged time, a nonpolar fluorescent product was observed via TLC and HPLC. The compound is apparently the fully aromatized β-carboline.[19] In the cases with ≥10% TFA, the reaction was complete within a few hours. Furthermore, polar aldehydes tend to be more soluble with increased TFA content. Therefore, 10% TFA in methylene chloride was chosen as the standard procedure for subsequent experiments.

Table I illustrates the results obtained by this method with a variety of aldehydes. As can be seen from the table, with the exception of 4-nitro substitution, substitution of the benzene ring has little effect on the product purity or yield. Aliphatic aldehydes gave somewhat lower purity and will be optimized in the future. The results with bromobenzaldehydes and 4-formylphenylboronic acid are especially encouraging since additional diversity could be introduced by the Suzuki reaction.

In summary, the Pictet-Spengler reaction on solid support for the preparation of tetrahydro-β-carbolines at room temperature with a high degree of purity has been developed. A variety of substituted (from electron-deficient to electron-rich) aryl aldehydes as well as aliphatic aldehydes are viable substrates. The ready availability of aldehydes from commercial sources allows the preparation of large heterocyclic compound libraries. Moreover, the method allows the

incorporation of halides and boronic acid in the molecule for further molecular diversity development. Finally, the procedure may be easily adapted to other acid stable resins with base or photo-labile linkers.

Table I

Entry	R^1-	HPLC purity[20]	Rt (min.)*	MS (M+1)	Yield¥
1	Ph-	94%	13.79, 14.15	320	98%
2	4-MeO-Ph-	92%	14.81, 15.09	350	99%
3	3-MeO-Ph-	94%	14.86, 15.20	350	100%
4	2-MeO-Ph-	93%	15.19, 15.52	350	99%
5	4-NO_2-Ph-	<20%	-	-	-
6	3-NO_2-Ph-	89%	14.84, 15.27	365	97%
7	2-NO_2-Ph-	96%	14.38,14.78	365	97%
8	4-Py-	81%	8.00, 8.14	321	97%
9	3-Py-	87%	8.16#	321	100%
10	2-Py-	89%	11.41,11.68	321	100%
11	4-Ph-Ph-	82%	19.97#	396	100%
12	4-AcNH-Ph-	84%	11.83, 12.10	377	97%
13	4-Cl-Ph-	90%	16.25, 16.58	354	97%
14	3-Cl-Ph-	86%	16.01, 16.35	354	98%
15	2-Cl-Ph-	88%	14.92#	354	91%
16	4-Br-Ph-	89%	16.74, 17.01	400	95%
17	3-Br-Ph-	91%	16.61, 16.86	400	94%
18	2-Br-Ph-	82%	15.26, 15.35	400	96%
19	4-$B(OH)_2$-Ph-	85%	11.55, 11.82	364	92%
20	$PhCH_2$-	65%	15.46, 15.62	334	96%
21	$PhCH_2CH_2$-	79%	17.65#	348	94%
22	Cyclohexyl-	68%	15.99#	326	92%
23	i-Bu-	80%	11.97, 12.15	286	91%

*: The two peak ratios are generally 2/1 to 0.5/1. #: no diastereomeric resolution was observed under these HPLC conditions. ¥: Crude chemical yields.

A typical procedure for the cyclization is as follows. To a suspension of the resin **2** (100 mg; 0.6 mmol/g resin) in 10% TFA/CH_2Cl_2 (2 mL) with indole (2 mg, optional) was added benzaldehyde (60 μL). After shaking at room temperature overnight, the resin was washed successively with CH_2Cl_2 (2 mL, three times), 5% DIEA/CH_2Cl_2 (2 mL, twice), 20% MeOH/CH_2Cl_2 (2 mL, three times), CH_2Cl_2 (2 mL, 3 times), THF (2 mL, 4 times). The product was cleaved from the resin by shaking with a mixture of THF (1 mL) and ethylamine (70% in water, 1 mL) overnight. The resin was removed by filtration and was washed with MeOH/THF (1:1, 2 mL, 3 times), The filtrate and washings were concentrated to provide the product **4** (entry 1 in Table I) as a slightly yellow solid (19 mg, 100%).

Acknowledgment: We would like to thank Dr. A. Patchett, Dr. G. Berger, Dr. K. Chapman and the Merck combinatorial group for helpful discussions, and thank Ms. A. Bernick for performing mass spectral analysis.

References:

1 (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A. and Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A. and Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (c) Terret, N., Gardner, M., Gordon, D. W. Kobylecki, R. J., Steele, J., *Tetrahedron*, **1995**, *51*, 8135. (d) Borman, S. *Chemical and Engineering News*, **1996**, *74*, 7, 29

2 Beebe, X., Schore, N. E., Kurth, M. J., *J. Am. Chem. Soc.*, **1992**, *114*, 10061.

3 DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.;Cody, D. M. R., Pavia, M. R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909.

4 Plunkett, M. J. and Ellman, J. A. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4708.

5 Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47-50.

6 Holmes, C. P.; Chinn, J. P.; Look, G. C; Gordon, E. M.; Gallop, M. A. *J. Org. Chem.* **1995**, *60*, 7328

7 Murph, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029.

8 Ruhland, B., Bhandari, A. Gordon, E. M., Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.

9 Pictet, A. and Spengler, T. *Chem. Ber.* **1911**, *44*, 2030;

10 During the preparation of the manuscript, a report of Pictet-Spengler reaction on solid support in the presence of molecular sieves at elevated temperature appeared. Kaljuste, K.; Unden, A., *Tetrahedron Lett.* **1995**, *36*, 9211.

11 (a) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177; (b) Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613. (c) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171.

12 Rano, T. A., Chapman, K. T., *Tetrahedron Lett.*, **1995**, *36*, 3789.

13 Whaley, W.; Govindochari, T. *Org. React.*, **1951**, *6*, 141.

14 (a). Soerenes, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; Dipierro, M.; Cook, J. M.; *J. Org. Chem.* **1979**, *44*, 535.(b) Zhang, L. H.; Cook, J. M. *Heterocycles*, **1983**, *27*, 1357.

15 Monitoring the progress of the solid phase reaction by acidic cleavage (TFA/CH_2Cl_2) is precluded, since the cyclization may occur rapidly under the cleavage conditions and give a false positive results. A parallel solution reaction of tryptophan benzyl ester and benzaldehyde under similar conditions gave the intermediate imine as the major product and unreacted starting material after 1 day.

16 Massiot, G. and Mulamba, T. *J. Chem. Soc. Chem. Commun.* **1983**, 1147.

17 Boc-L-Trp-Merrifield resin was purchased from Bachem Bioscience Inc. with loading capacity of 0.61 mmol/g. To increase the utility of this reaction in combinatorial chemistry, other substituted tryptophans were tested with equally good results. Generally, the substituted tryptophans were first converted to the N-Boc derivative followed by attaching to the Merrifield resin under standard conditions.

18 A small amount of resin was cleaved as described later at this step to check purity.

19 The structure was confirmed by oxidation of the tetrahydro-β-carboline with DDQ on solid support followed by cleavage. Details will be reported in due course.

20 Analysis was performed using a Zorbax RX-C8 (250x4.6 mm, 5 μm) column eluting with a linear gradient of 20-80% acetonitrile in water containing 0.1% TFA as buffer over 30 minutes at 1 mL/min, the HPLC is equipped with PDA detector and the results are plotted at 220 nm with band width of 8 nm.

(*Received in USA* 8 *April* 1996; *revised* 21 *May* 1996; *accepted* 22 *May* 1996)