ORGANIC LETTERS

2000
Vol. 2, No. 23
3635−3638

Preparation of Hexahydrobenzo[*f*]isoquinolines Using a Vinylogous Pictet–Spengler Cyclization

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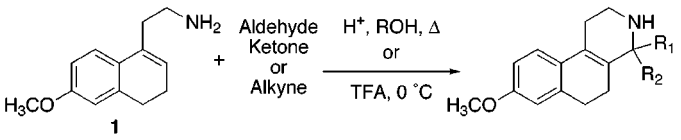
Received August 31, 2000

ABSTRACT



A vinylogous Pictet–Spengler cyclization has been carried out using activated aldehydes, ketones, and alkynes to prepare a variety of substituted hexahydrobenzo[*f*]isoquinolines. A unique set of conditions was utilized to effect efficient cyclization with acid-sensitive electrophiles.

The Pictet−Spengler cyclization has been extensively studied since its discovery in 1911.[1] Over the years, the reaction has been applied in the context of several heterocyclic syntheses,[2] and it continues to be a significant focus of research. Early applications of the Pictet−Spengler reaction were for the preparation of complex heterocycles such as aza-steroids[3] and morphine alkaloids.[4] However, most of the current literature is focused on the development of diastereo- and enatioselective variants of the Pictet−Spengler reaction, especially for preparing substituted tetrahydroisoquinolines[5] and tetrahydro-β-carbolines.[6] Recent mechanistic investigations have provided some insight into the stereochemical course of tetrahydro-β-carboline formation.[7]

For some time, we have been interested in the synthesis of receptor-targeted breast tumor imaging agents, which integrate metallic radionuclides, for use in single photon emission computed tomography (SPECT) and positron emission tomography (PET).[8] We have recently designed a novel series of compounds that possess steroidal backbones (Figure 1). Our approach to the ligands for these complexes evolved around the use of a vinylogous Pictet−Spengler reaction[9] in a manner similar to that used previously for the preparation of a variety of 13-aza-steroids.[10] In the course of our studies, we surveyed several electrophiles (aldehydes, ketones, and alkynes) and examined different reaction conditions.

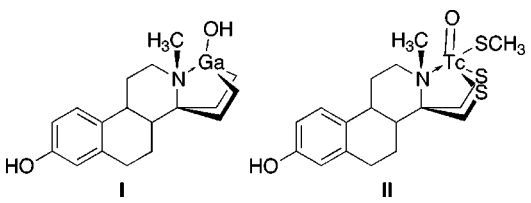


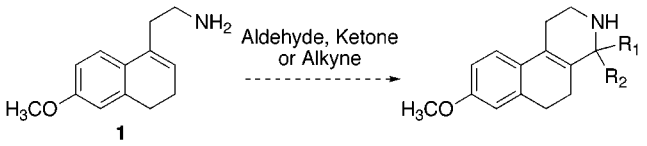
Figure 1. Receptor-targeted breast tumor imaging agents that possess steroidal backbones.

(1) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.
(2) (a) Bailey, P. D.; Morgan, K. M. *Chem. Commun.* **1996**, 1479. (b) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (c) Hino, T.; Nakagawa, M. *Heterocycles* **1997**, *46*, 673.
(3) (a) Dijkink, J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 935. (b) Kano, S.; Yuasa, Y. *Heterocycles* **1983**, *20*, 857. (c) Schleigh, W. R.; Catala, A.; Popp, F. D. *J. Chem. Soc.* **1965**, 379. (d) Zunnebeld, W. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1717.
(4) Douglas, J. L.; Meunier, J. *Can. J. Chem.* **1975**, *53*, 3681.
(5) (a) Czarnocke, A.; Arazby, Z. *Heterocycles* **1999**, *44*, 2871. (b) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903.
(6) (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *50*, 1033. (c) Waldmann, H.; Schmidt, G. *Tetrahedron* **1994**, *50*, 11865.

10.1021/ol006533u CCC: $19.00
Published on Web 10/21/2000

A generic diagram of the vinylogous Pictet−Spengler reaction that we proposed to study for preparing the 13-aza-steroid analogues is depicted in Scheme 1. The dihydronaphthylamine (**1**) has been reported in the literature and can be prepared in a number of ways.[11] For our purposes, we found that homologation of 6-methoxy-1-tetralone via a Horner−Emmons reaction with diethyl cyanomethylphosphonate,[12] followed by Lewis acid mediated reduction ($LiAlH_4/AlCl_3$), worked well. By this method, we were able to obtain the $\Delta^{8(9)}$ isomer (steroid numbering) exclusively in 70% overall yield after recrystallization of the corresponding hydrochloride salt.

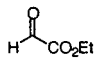
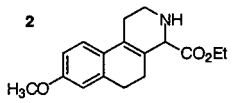
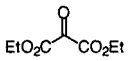
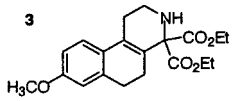
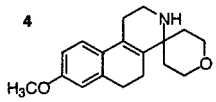
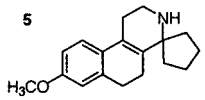
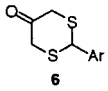
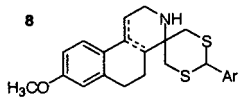
Scheme 1



In our initial investigation of this reaction, we utilized a traditional Pictet−Spengler synthetic protocol of heating the dihydronaphthylamine hydrochloride (**1**·HCl) and the carbonyl compound in an alcoholic solvent. We found that although propionaldehyde cyclized readily, acetone did not. In other cases, the products were isolated as mixtures of the $\Delta^{8(9)}$ and $\Delta^{9(11)}$ olefin isomers (steroid numbering), and only upon extended heating, or in those cases where there was additional functionalization, were we able to obtain products consisting only of the $\Delta^{8(9)}$ isomer (see below). If butanol rather than methanol was used as the solvent, reaction times were shortened and product yields improved.[13]

Despite these complications, we were pleased to find that the cyclization worked very well with more electrophilic aldehydes and with cyclic ketones. The details of these investigations are given in Table 1. Ethyl glyoxylate and diethyl ketomalonate both reacted smoothly with **1** in 24 h to yield the corresponding hexahydrobenzo[*f*]isoquinolines in 84% and 97% yield, respectively, as single olefin isomers. Preparation of the spiro-fused compounds **4** and **5** using tetrahydro-4*H*-pyran-4-one and cyclopentanone, respectively, required longer reaction times (72 h). These extended reaction times were needed not to improve reaction yield but rather to isomerize the intermediate mixture of isomers exclusively to the $\Delta^{8(9)}$ isomer.

Table 1. Cyclization with Aldehydes and Ketones

Carbonyl[a]	Time[b] (h)	Product[c]	Yield (%)
	24	 **2**	84
	24	 **3**	97
	72	 **4**	88
	72	 **5**	54
 **6**	72	 **8**	51

[a] Ar = *p*-$OCH_3C_6H_4$. [b] Time at reflux in butanol. [c] Compound **8** exists as a 9:1 mixture of olefin isomers.

The preparation of cyclic ketone **8** deserves some additional comment. In our approach to target molecule **II** we desired to synthesize a compound that bore a dithiol functionality of suitable orientation to form a tripartite chelate (S,N,S) for technetium in a [3 + 1] fashion. However, when we attempted to cyclize an acyclic version of ketone **6** (specifically, thioacetic acid *S*-(3-acetylsulfanyl-2-oxo-propyl) ester (**7**)), we were unable to obtain any of the tricyclic product. Hence, we decided to try ketone **6**, which could be readily prepared in two steps from 4-methoxybenzaldehyde and ethyl 2-mercaptoacetate, according to a literature method.[14] We were pleased that compound **6** indeed underwent smooth cyclization under conditions similar to those described above for compound **4**. However, despite an extended reaction time, we could only obtain compound **8** as a 9:1 mixture of isomers favoring the desired $\Delta^{8(9)}$ isomer.

Robust substrates were needed to withstand cyclization under the rather harsh conditions described above. In fact,

(7) (a) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennet, D. W.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 44. (b) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164. (c) Soerens, 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. (d) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403. (e) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119. (f) Kawate, T.; Nakagawa, M.; Ogata, K.; Hino, T. *Heterocycles* **1992**, *33*, 801. (g) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089 and references cited therein.

(8) (a) Chi, D. Y.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 7045. (b) Chi, D. Y.; O'Neil, J. P.; Anderson, C. J.; Welch, M. J.; Katzenellenbogen, J. A. *J. Med. Chem.* **1994**, *37*, 928. (c) Hom, R. K.; Katzenellenbogen, J. A. *Nucl. Med. Biol.* **1997**, *24*, 485. (d) Skaddan, M. B.; Katzenellenbogen, J. A. *Bioconjugate Chem.* **1999**, *10*, 119. (e) Skaddan, M. B.; Wust, F. R.; Katzenellenbogen, J. A. *J. Org. Chem.* **1999**, *64*, 8108.

(9) If one considers that a *p*-methoxystyrene is a trienol system and that reactions of enols with imines are termed Mannich reactions, then the reaction described in this report could be considered a vinylogous Mannich reaction. However, this term is currently employed by Martin to illustrate the nucleophilic addition of 2-trialkylsiloxy furans to cyclic iminium ions; cf. Martin, S. F. et al. *J. Am. Chem. Soc.* **1996**, *118*, 3299 and Martin, S. F. et al. *J. Am. Chem. Soc.* **1999**, *121*, 6990. It should also be noted that Overman has described a related intramolecular Mannich reaction; cf. Loegers, M. et al. *J. Am. Chem. Soc.* **1995**, *117*, 9139 and references cited therein.

(10) Refer to ref 3b−d.

(11) Refer to ref 4.

(12) Geier, M.; Hesse, M. *Synthesis* **1990**, 56.

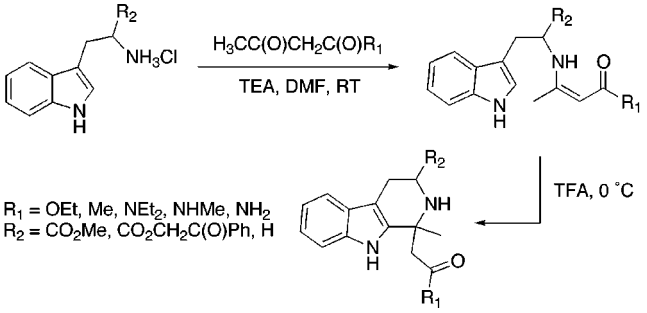
(13) Similar temperature affects have been observed in the Pictet−Spengler reaction of tryptamines carried out in nonacidic, aprotic media; cf. ref 7c.

(14) Luettrinhaus, A. *Justus. Liebigs Ann. Chem.* **1963**, *661*, 84.

several attempts to achieve cyclization using activated ketones under these conditions were unsuccessful. Specifically, when we attempted the reaction with either a β-ketoester or β-keto-γ-lactone, these substrates were degraded during the reaction. Therefore, we sought to develop a milder protocol for use with these acid-sensitive functionalities.

We were aware of previous work in the tetrahydro-β-carboline literature, which showed that indeed esters, ketones, and amides with a β-carbonyl functionality could be cyclized by acid catalysts (Scheme 2).[15] The two-step protocol

Scheme 2. Two-Step Synthesis of Tetrahydro-β-carbolines

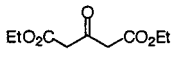
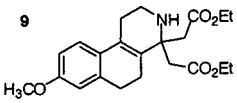
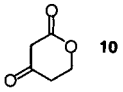
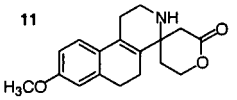
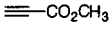
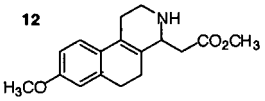
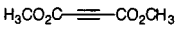
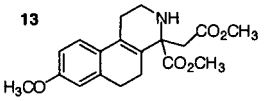


reported in this work consisted of initial enamine formation at room temperature, followed by treatment with acid at low temperature. With this excellent precedent in hand, we proceeded to submit the substrates we desired to the conditions described above. The results of these studies are summarized in Table 2.

When a solution of **1**·HCl and triethylamine in DMF is treated with diethyl 1,3-acetonedicarboxylate at room temperature for 12 h, the desired enamine could be isolated as a single isomer. Although we did not rigorously determine the geometry of the intermediate enamine for compounds **9**, **12**, and **13** (see below), we believe that it is *Z*, on the basis of earlier reports.[16] In this geometry, the enamino ester system would be stabilized via intramolecular hydrogen bonding, and there is evidence for such an interaction by the extreme downfield shift of the amine proton in the NMR (δ 8.58, 7.83, and 8.09, respectively). In contrast, in the case of the intermediate enamine resulting from reaction with dihydropyran-2,4-dione,[17] the cyclic geometry aminodihydropyran requires that the geometry of the enamine be *E*, which is supported by the upfield location (δ 4.56) of the hydrogen atom.

The cyclization of these enamines was effected by treatment of the *neat* oils with excess trifluoroacetic acid at 0 °C for 30 min.[18] The yields of these compounds are given in Table 2. We were gratified to find that, in contrast to the

Table 2. Cyclization with Activated Ketones and Alkynes[a]

Ketone or Alkyne	Time (h)	Product[b]	Yield (%)
	24	 **9**	84(92)
 **10**	24	 **11**	27(72)
	120	 **12**	24(54)
	24	 **13**	35(60)

[a] The reactions shown in this table were performed using a two-step protocol similar to that shown in Scheme 2. The enamine intermediates were used directly in the subsequent cyclization step, but could be isolated by column chromatography if desired. [b] The time refers to the duration with which enamine formation was allowed to occur. A reaction time of 30 minutes was used for all subsequent cyclizations; neat TFA, 0 °C. [c] Yields are combined for the two-step process. Yields in parentheses are for the enamine formation.

results of the one-step protocol reported above, under these milder two-step conditions, the desired $\Delta^{8(9)}$ isomer was produced exclusively. We also found that anhydrous TFA was required for this procedure, because small amounts of water in the reagent caused extensive hydrolysis of the enamines during the cyclization. Unlike what happened in our earlier attempts, we observed no ring opening of the lactone during the formation of the spiro compound (**11**) by the two-step procedure.

Amines are known to undergo conjugate addition with activated alkynes to yield the corresponding enamines.[19] In fact, the use of alkynes in the Pictet−Spengler reaction has been previously documented in the synthesis of several tetrahydro-β-carbolines.[20] Upon the basis of these precedents, we reasoned that the alkynes methyl propiolate and dimethyl acetylenedicarboxylate (DMAD) would be suitable substrates for the vinylogous Pictet−Spengler reaction. In the case of methyl propiolate, we found enamine formation to be exceedingly slow. In fact, reasonable yields of the conjugate product were only obtained after 120 h at room temperature. The enamine was isolated as a mixture of *Z*:*E* isomers in a 3:1 ratio, determined by integration of the signals of the vinyl hydrogen atoms. Although the yield was modest, this enamine underwent smooth cyclization upon treatment with TFA to afford the hexahydrobenzo[*f*]isoquinoline (**12**) in 24% overall yield. As expected, conjugate addition with the more

(15) Kirkpatrick, A.; Maclaren, J. A. *Aust. J. Chem.* **1983**, *36*, 833.
(16) (a) Barillier, D.; Strobel, M. P.; Morin, L.; Paquer, D. *Tetrahedron* **1983**, *39*, 767. (b) Kozerski, L.; Kawecki, R.; Hansen, P. E. *Magn. Reson. Chem.* **1994**, *32*, 517.
(17) D'Angelo, J.; Gomez-Pardo, D. *Tetrahedron Lett.* **1991**, *32*, 3063.
(18) TFA is known to cause C(1)−N(2) bond cleavage in methoxy-substituted tetrahydro-β-carbolines through a carbocation-mediated mechanism; cf. ref 7a and Reedy, S. M.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 5413.
(19) Henin, J.; Vercauteren, J.; Mangenot, C.; Henin, B.; Nuzillard, J. M.; Guilhem, J. *Tetrahedron* **1999**, *55*, 9817.
(20) (a) Bailey, P. D.; Hollinshead, S. P.; Dauter, Z. *J. Chem. Soc., Chem. Commun.* **1985**, *21*, 1507. (b) Vercauteren, J.; Lavaud, C.; Levy, J.; Massiot, G.; Fac. Pharm, R. F. *J. Org. Chem.* **1984**, *49*, 2278.

reactive DMAD was complete after only 24 h. The enamine product was of single configuration, and when submitted to the cyclization conditions, provided the desired tricyclic product (**13**) in 35% overall yield.

The results of this brief investigation of a vinylogous Pictet−Spengler reaction have been encouraging. Not unexpectedly, both aldehydes and ketones can be cyclized using standard Pictet−Spengler conditions with relative ease, and we found that high yields are obtained only when cyclic substrates are used. The harsh conditions required to cyclize unactivated ketones were not suitable for more acid-sensitive substrates, but a milder, two-step protocol was developed for these cases. Suitable enamine cyclization precursors could be prepared by condensation with activated ketones or by conjugate addition with activated alkynes. The vast Pictet−Spengler cyclization literature provides for further extension of this reaction through a rational choice of electrophiles.

Acknowledgment. We are grateful for support of this research through grants from the Department of the Army (DAMD17-97-1-7292), National Cancer Institute DHHS (PHS 5 T32 CA09067), and the Department of Energy (DE FG02 86ER60401).

Supporting Information Available: Complete experimental procedures and spectral data for compounds **1**−**9** and **11**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org

OL006533U