Tetrahedron Letters 53 (2012) 5027–5029

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of indolo[2,3-*a*]quinolizine and hexahydro-1*H*-indolizino[8,7-*b*]indole derivatives by cascade condensation, cyclization, and Pictet–Spengler reaction: an application to the synthesis of (±)-harmicine

Chakrapani Sanaboina [a,b], Samaresh Jana [a,*], Sridhar Chidara [a], Balaram Patro [a], Gajendrasinh Balvantsinh Raolji [a], Laxminarayana Eppakayala [b]

[a] *Medicinal Chemistry Laboratory, GVK Biosciences Private Limited, IDA Nacharam, Hyderabad 500076, Andhra Pradesh, India*
[b] *Department of Chemistry, Sreenidhi Institute of Science and Technology (Autonomous), Ghatkesar, Hyderabad 501301, Andhra Pradesh, India*

ARTICLE INFO

Article history:
Received 24 May 2012
Revised 9 July 2012
Accepted 11 July 2012
Available online 15 July 2012

Keywords:
Cascade reaction
Pictet–Spengler reaction
Indole alkaloid
Harmicine

ABSTRACT

Synthesis of indole alkaloid related compounds using Schiff base formation, intramolecular cyclization (or N-alkylation), and Pictet–Spengler reaction as a cascade one pot condensation has been reported. The cascade chemistry has been applied to the synthesis of (±)-harmicine as a key step.

Cascade reactions are important in synthetic organic chemistry due to their well recognized advantages: atom-economy, economy of time, labor, resource management, and low waste generation. In addition, the most important benefit is construction of complex moieties starting with simple materials. The undeniable benefits of cascade reactions are so prominent that organic chemists are inclined to apply the cascade-type chemistry for the synthesis of natural products and related compounds.[1]

Utilizing the cascade reaction methodology, we wish to report herein the synthesis of different nitrogen-containing heterocyclic moieties, for example, indolizino[8,7-*b*]indole and indolo[2,3-*a*]quinolizine. Because of the widespread occurrence in nature and diverse medicinal properties, these moieties are important to organic and medicinal chemists and biologists.[2] The above-mentioned moieties are found as a core structure in many indole alkaloids as for example harmicine,[3] deplancheine,[4] and arborescidine A[5] (Fig 1). So development of a simple and efficient strategy for the construction of these motifs is of interest. Recently Saha et al. from our laboratory reported[6] the synthesis of indole alkaloid (±)-harmicine using cyclopropylimine rearrangement. In this communication, we describe a cascade reaction strategy to improve the method for the synthesis of different types of indole alkaloid-related moieties along with (±)-harmicine.

The cascade-type chemistry in this work involves three consecutive steps depicted in Scheme 1. Condensation of indole amine **4** with halo aldehyde **5** affords the intermediate imine **A**, which generates iminium ion **B** by intramolecular cyclization (or N-alkylation) reaction in the second step, and finally Pictet–Spengler (P–S) reaction of the iminium ion produces the desired product **6**.

We first evaluated our methodology using tryptamine **4a** and halo aldehyde **5a** (Fig. 2) as starting materials. We found that, after mixing **4a** and **5a** in acetonitrile at room temperature, intermediate **A** (R=R^3=H, R^1=R^2=CH_3, n = 2) was formed, as well as intermediate **B** (R=R^3=H, R^1=R^2=CH_3, n = 2). The expected compound **6a** (Table 1, entry 1) was not detected after stirring the reaction mixture for 12 h at the same temperature, whereas we ascertained formation of iminium ion **B**, which was characterized by mass spectroscopy and ^{1}H NMR data (see Supplementary data). So it was understandable that condensation and intramolecular N-alkylation reactions were completed at room temperature but

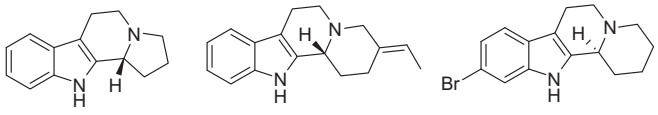
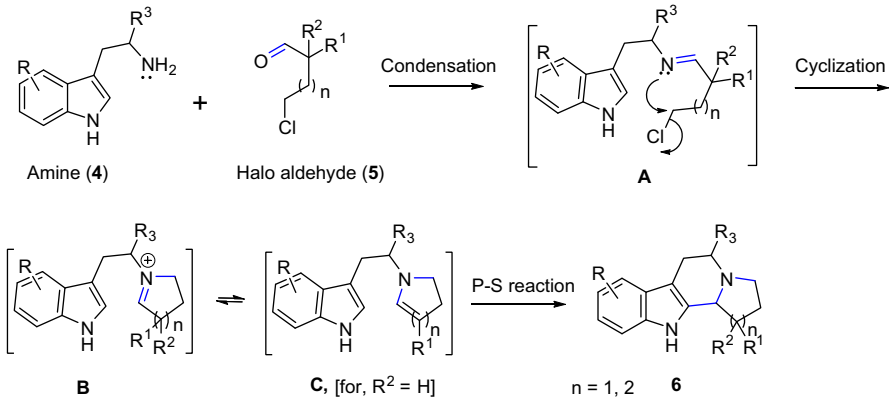


Figure 1. Indole alkaloids.

* Corresponding author. Tel.: +91 40 66281166; fax: +91 40 66281505.
E-mail address: samaresh.jana@gvkbio.com (S. Jana).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.044



Scheme 1. Steps of cascade reaction.

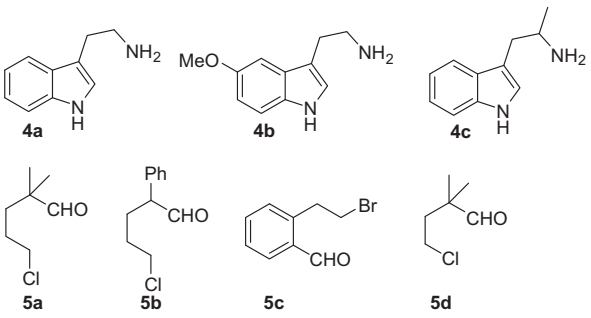


Figure 2. Indole amines and halo aldehydes used.

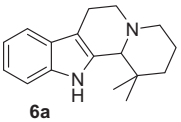
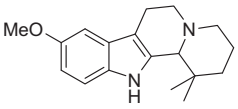
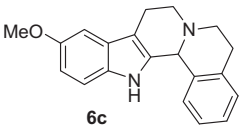
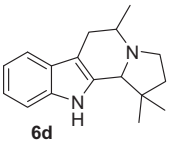
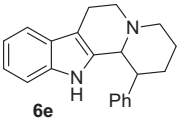
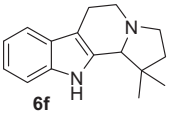
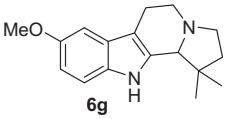
Pictet–Spengler reaction did not occur at that temperature. We have optimized the reaction conditions[7] using various solvents and changing the temperature. We found that if we mix amine **4a** and halo aldehyde **5a** in acetonitrile in the presence of trifluoroacetic acid and heat at 90 °C for 12 h, we obtain good yields of the desired product **6a** (Scheme 2, Table 1, entry 1). Following the same experimental protocol, we have synthesized the structural analogues **6b**–**6g** (Scheme 2, Table 1, entries 2–7) using the commercially available indole amines **4a**–**4c** and halo aldehydes **5a**–**5d** (Fig. 2). All the results of the reactions are summarized in Table 1.

We have studied the key reaction using halo aldehydes; no other leaving group (like OTs, OMs) in place of halide was used for our chemistry. The various halo aldehydes used were synthesized from commercially available starting materials following known method.[8] It was observed that α,α-disubstituted halo aldehydes (**5a, 5c, 5d**, Fig. 2) gave improved yields compared to the α-monosubstituted aldehyde (**5b**). This observation can be explained on the basis of stability of the iminium ion **B** (Scheme 1). An enolizable proton in the iminium ion enhances its stability by the formation of enamine and hence reduces its reactivity. On the other hand, disubstitutions at α-position of the aldehyde enhances the reactivity of the iminium ion by disrupting the enolization process.

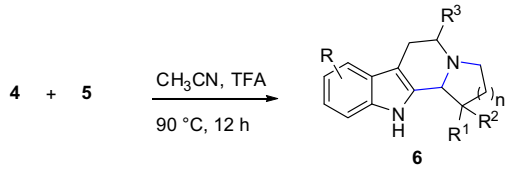
As an extension of this cascade-type chemistry, we turned our attention to the synthesis of harmicine **1** (Fig. 1), a structural indolizino[8,7-*b*] motif. This indole alkaloid was isolated in 1998 from the leaf extracts of *Kopsia griffithii*, and it was found to exhibit antileishmania activity.[3]

During the last eight years, harmicine has been one of the attractive targets in synthetic organic chemistry.[6,9] To apply our approach we required 4-chlorobutyraldehyde **5e** (Scheme 3). We have used freshly prepared compound **5e**, which was made by reducing ethyl 4-chlorobutyrate with diisobutylaluminium hydride (DIBAL-H).[10] In the optimum reaction conditions[11] (±)-harmicine was isolated in 48% yield. There is a report[12] of the reaction between tryptamine (as hydrochloride salt) and 4-chlorobutyraldehyde for the synthesis of 1-(γ-chloropropyl) 1,2,3,4-β-carbolines in excellent yield. But to our knowledge, synthesis of harmicine is not reported in the literature applying this

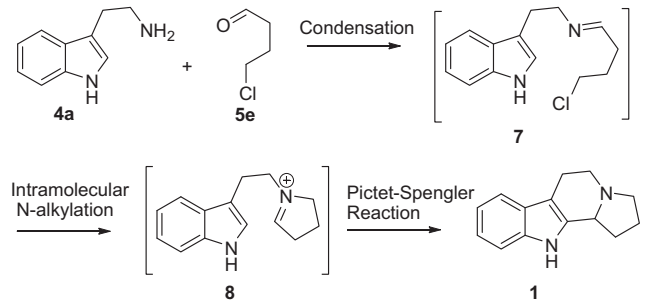
Table 1
Products **6** synthesized by reacting **4** and **5**

Entry	Substrates	Product	Yield[a] (%)
1	**4a**,**5a**	 **6a**	58
2	**4b**,**5a**	 **6b**	45
3	**4b**,**5c**	 **6c**	70
4	**4c**,**5d**	 **6d**	47[b]
5	**4a**,**5b**	 **6e**	43[c]
6	**4a**,**5d**	 **6f**	52
7	**4b**,**5d**	 **6g**	50

[a] Yield refers to isolated materials.
[b] dr = 25:1.
[c] dr = 2:1.2.



Scheme 2. Synthesis of heterofused indoles **6**.



Scheme 3. Synthesis of harmicine. Reagents and conditions: CH_3CN, TFA, 90 °C, 12 h, 48%.

cascade-type methodology. Thus, we are pleased to report the one-step synthesis of (±)-harmicine in good yields using the commercially available tryptamine **4a** and 4-chlorobutyraldehyde **5e**.

In summary, we have described a cascade reaction methodology for the synthesis of indole alkaloid related compounds in an efficient way. The synthesis of (±)-harmicine has been accomplished in a shortest route applying this cascade-type chemistry as a key step. Syntheses of other indole alkaloids are in progress in our laboratory recently and will be reported in due course.

Acknowledgments

We are grateful to GVK BioSciences Private Limited, India for financial and analytical support during this program. C.S. thanks JNTU, Hyderabad, India for continuous encouragement.

Supplementary data

Supplementary data (experimental procedures and characterization data of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.044.

References and notes

1. For application of cascade reaction in total synthesis of natural products see (a) Stearman, C. J.; Wilson, M.; Padwa, A. *J. Org. Chem.* **2009**, *74*, 3491; (b) England, D. B.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 2792; (c) Flick, A. C.; Caballero, Maria José A.; Padwa, A. *Org. Lett.* **1871**, *2008*, 10; (d) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279; (e) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341; (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134; (g) Nicolaou, K. C.; Lister, T.; Denton, R. M.; Gelin, C. F. *Tetrahedron* **2008**, *64*, 4736; (h) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183; (i) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167; (j) Xiong, Z.; Busch, R.; Corey, E. J. *Org. Lett.* **2010**, *12*, 1512; (k) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360; (l) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515.
2. (a) Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455; (b) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000**, *17*, 349; (c) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, *15*, 327; (d)*The Alkaloids*; Saxon, J. E., Cordell, G. A., Eds.; Academic Press: New York, 1998. Vol. 50 and 51.
3. Kam, T. S.; Sim, K. M. *Phytochemistry* **1998**, *47*, 145.
4. (a) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357; (b) Da Silva, W. A.; Rodrigues, M. T., Jr.; Shankaraiah, N.; Ferreira, R. B.; Andrade, Carlos K. Z.; Pilli, R. A.; Santos, L. S. *Org. Lett.* **2009**, *11*, 3238; (c) Takasu, K.; Nishida, N.; Tomimura, A.; Ihara, M. *J. Org. Chem.* **2005**, *70*, 3957.
5. (a) Chbani, M.; Païs, M.; Delauneux, J. M.; Debitus, C. *J. Nat. Prod.* **1993**, *56*, 99; (b) Santos, L. S.; Pilli, R. A.; Rawal, V. H. *J. Org. Chem.* **2004**, *69*, 1283.
6. Saha, S.; Reddy, V. R.; Patro, B. *Tetrahedron Lett.* **2011**, *52*, 4014.
7. Reaction conditions: **4** (1 equiv), **5** (1.5 equiv), TFA (1 equiv), CH_3CN, 90 °C, 12 h.
8. For the synthesis of **5a**, **5c** and **5d** see (a) Coldham, I.; Jana, S.; Watson, L.; Pilgram, C. D. *Tetrahedron Lett.* **2008**, *49*, 5408; (b) Coldham, I.; Jana, S.; Watson, L.; Martin, N. G. *Org. Biomol. Chem.* **2009**, *7*, 1674. Compound **5b** was prepared as reported for the preparation of **5a**..
9. For synthesis of harmicine see (a) Knolker, H. J.; Agarwal, S. *Synlett* **2004**, 1767; (b) Allin, S. M.; Gaskell, S. N.; Elsegood, M. R. J.; Martin, W. P. *Tetrahedron Lett.* **2007**, *48*, 5669; (c) Szawkało, J.; Czarnocki, S. J.; Zawadzka, A.; Szawkało, J.; Czarnocki, S. J.; Zawadzka, A.; Maurin, J. K.; Czarnockia, Z.; Drabowicz, J. *Tetrahedron Assym.* **2007**, *18*, 406; (d) Gonzalez-Gomez, A.; Domınguez, G.; Perez-Castells, J. *Tetrahedron* **2009**, *65*, 3378; (e) King, F. D. *J. Heterocycl. Chem.* **2007**, *44*, 1459; (f) Chiou, W. H.; Lin, G. H.; Hsu, C. C.; Chaterpaul, S. J.; Ojima, I. *Org. Lett.* **2009**, *11*, 2659; (g) Dasilva, W. A.; Rodrigues, M., Jr; TShankaraiah, N.; Ferreira, R. B.; Andrade, C. K. Z.; Pilli, R. A.; Santos, L. S. *Org. Lett.* **2009**, *11*, 3238; (h) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404; (i) Huang, D.; Xu, F.; Lin, X.; Wang, Y. *Chem.-A Eur. Journal* **2012**, *18*, 3148; (j) Singh, V.; Hutait, S.; Batra, S. *Eur. J. Org. Chem.* **2010**, *3*, 684.
10. Witiak, D. T.; Tomita, K.; Patch, R. J.; Enna, S. J. *J. Med. Chem.* **1981**, *24*, 788.
11. *Experimental procedure for synthesis of (±)-harmicine (**1**)*: Tryptamine **4a** (250 mg, 1.56 mmol) and 4-chloro butyraldehyde **5e** (825 mg, 7.81 mmol) in acetonitrile (5 mL) were stirred at room temperature under inert atmosphere. After 10 min, trifluoro acetic acid (0.11 mL, 1.56 mmol) was added slowly, and stirring was continued for 10 min at room temperature. Then reaction mixture was heated at 90 °C for 12 h, cooled to room temperature, diluted with CH_2Cl_2 (20 mL), washed sequentially with 10% sodium bicarbonate solution (2 × 5 mL), water (5 mL) and brine (2 × 5 mL) and dried over Na_2SO_4. The organic solution was evaporated under reduced pressure and the resultant crude mass was purified by flash chromatography ($MeOH/CH_2Cl_2$ 2:98 to $MeOH/CH_2Cl_2$ 1:9) to obtain a pure material **1** (160 mg, 48%) as light yellow solid. Mp 170–172 °C [lit.[6] 171–174 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ 1.80–1.95 (m, 3H), 2.25–2.33 (m, 1H), 2.60–2.70 (m, 1H), 2.82–3.00 (m, 3H), 3.04–3.10 (m, 1H), 3.30–3.33 (m, 1H), 4.23 (br s, 1H), 7.07–7.15 (m, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 23.4, 29.4, 45.9, 49.3, 56.9, 107.8, 110.7, 118.1, 119.3, 121.4, 127.3, 135.4, 136.0; HRMS calcd for $C_{14}H_{17}N_2$: 213.1313, found: 213.1378. Spectral data are in agreement to those reported in literature.[9g]
12. Kropp, R. U.S. Patent 4565870, 1986.