Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8207–8209

TETRAHEDRON LETTERS

Intramolecular Heck reaction of methylenephthalimidine derivatives: a simple route to lennoxamine and chilenine

Guncheol Kim,* Jin Hee Kim, Won-jeong Kim and Yeon Ah Kim

Department of Chemistry, College of Natural Sciences, Chungnam National University, Daejon 305-764, Republic of Korea

Received 27 August 2003; revised 9 September 2003; accepted 11 September 2003

Abstract—A new concise route to the key intermediate for isoindolobenazepine alkaloids, lennoxamine and chilenine, was developed using amine and keto-ester condensation followed by Heck reaction.

Isoindolobenazepine alkaloids lennoxamine **1** and chilenine **2**, isolated from the plants of the Chilean Berberis species, are a new class of alkaloids belonging to the aporhoedane series.[1] Although these alkaloids do not have important biological activities, their unique structural feature, five- and seven-membered rings fused with aromatic moiety has drawn the synthetic interest of many groups.[2] The formation of isoindolobenazepine ring has been accomplished mainly by various cyclization reactions including trans-annulation. Several ring expansion reactions have been also applied successfully.[2f] Herein we report an alternative simple route to the known key intermediate **3**[2e,j] for the two products via intramolecular Heck reaction (Fig. 1).

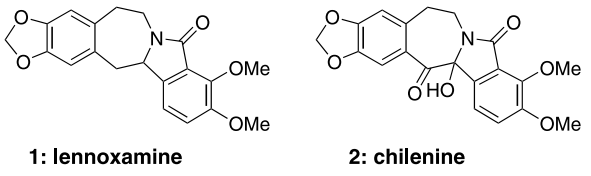
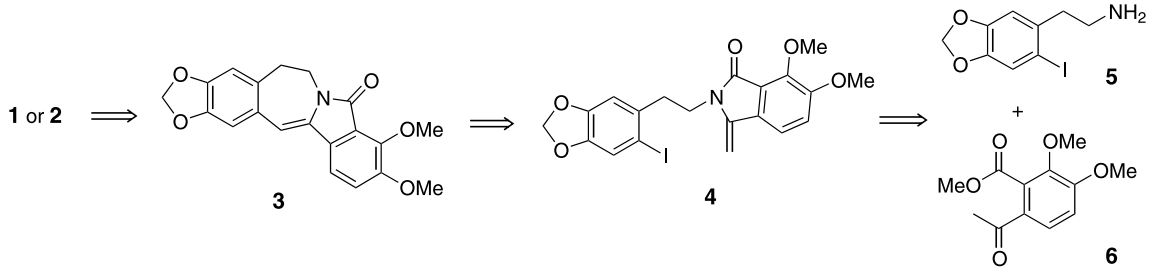


Figure 1.

In the application of Heck reaction for the benzazepine alkaloids, we considered that intermediate **3** could be prepared by the reaction from the precursor **4**, which would be readily obtained by the one-pot condensation reaction of two compounds,[3] 2-iodoarylamine **5** and aryl keto-ester **6** (Scheme 1).

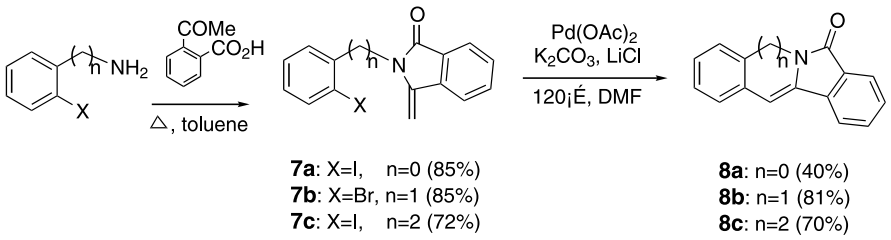
Preliminary experiments for cyclization have been carried out on the simple molecules employing a conventional Heck type reaction condition, $Pd(OAc)_2$ in DMF containing K_2CO_3 and LiCl. Methylenephthalimidine precursors **7**, which have been prepared by reaction of 2-acetylbenzoic acid with the corresponding 2-haloarylamines in good yields, were heated in DMF containing the reagents at 120°C for 12–16 h. Tetracyclic amides **8** with 5–7-membered rings were made in moderate to satisfactory yields, respectively (Scheme 2).



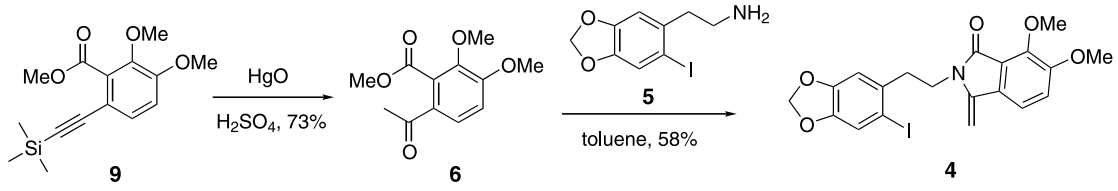
Scheme 1.

Keywords: Heck reaction; lennoxamine; chilenine; methylenephthalimide.
* Corresponding author. Tel.: 082-42-821-5475; fax: 082-42-823-1360; e-mail: guncheol@cnu.ac.kr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.069

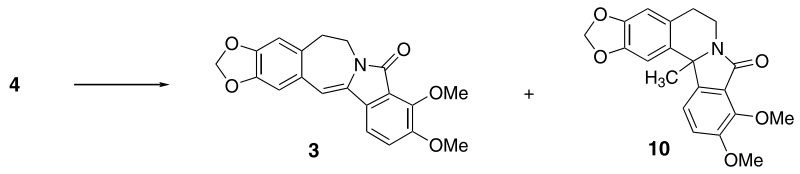


Scheme 2.



Scheme 3.

Table 1. Heck reaction conditions for the cyclization of **3**



Entry	$Pd(OAc)_2$ (equiv.)	Conditions	Yield[a] (%) of	
			3	**10**
1	0.1	nBu_4NCl (1 equiv.), $NaHCO_3$ (2.5 equiv.), DMF, 110°C, 16 h	50	
2	0.1	nBu_4NCl (1 equiv.), $NaHCO_3$ (2.5 equiv.), 3A MS, CH_3CN, reflux, 16 h	28	
3	0.1	nBu_4NCl (2 equiv.), KOAc (5.5 equiv.), 3A MS, DMF, 110°C, 18 h	34	
4	0.1	nBu_4NCl (2 equiv.), KOAc (5.5 equiv.), DMF, 110°C, 18 h	54	
5	0.1	PPh_3 (0.2 equiv.), Et_3N (2 equiv.), CH_3CN, reflux, 18.5 h		47
6	0.12	Et_3N (3 equiv.), DMF, 110°C, 120 h		34

[a] Isolated yield.

With these results, we were prompted to pursue the synthesis of **3**. Compound **9** was prepared readily by slight modification of the known procedure,[4] and hydration of **9** under HgO/H_2SO_4 provided **6** in 73% yield. The intermediate **5** was prepared as reported from the commercialized 3,4-methylenedioxyphenethylamine.[5] The condensation reaction of **5** and **6** under refluxing toluene provided 58% yield of **4** (Scheme 3).

Finally, cyclization of **4** to **3** was attempted under the same condition used above. However, the desired compound **3** was obtained in only 10% yield with a few unidentified by-products. In order to obtain the optimum yield of **3**, we used several conditions reported for the Heck type cyclization[6] as shown in Table 1. The use of nBu_4NCl in the reaction mixture was found to be critical for the endo-type cyclization to provide **3**[7] with recovered starting material. The yields were from 28 to 54% (entries 1–4). Other conditions without the reagent yielded only **10**[8] in 34 or 47% yield (entries 5 and 6).

In summary, we developed a new concise route to the key intermediate for isoindolobenazepine alkaloids using amine and keto-ester condensation followed by Heck reaction.

Acknowledgements

This work was supported by grant (R01-2000-000-00048-0) from the Basic Research Program of Korea Science and Engineering Foundation, and we appreciate Center for Research Facility, CNU for the permission of using NMR spectrometer.

References

1. (a) Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett*. **1984**, *25*, 599–602; (b) Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M.; Urzua,

A.; Fajardo, V. *Tetrahedron* **1984**, *40*, 3957–3962; (c) Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett*. **1982**, *23*, 39–42.

2. (a) Fuchs, J. R.; Funk, R. L. *Org. Lett*. **2001**, *3*, 3923–3925; (b) Yoda, H.; Nakahama, A.; Koketsu, T.; Takabe, K. *Tetrahedron Lett*. **2002**, *43*, 4667–4669; (c) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem*. **2001**, *66*, 2414–2421; (d) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491–1499; (e) Ruchirawat, S.; Sahakitpichan, P. *Tetrahedron Lett*. **2000**, *41*, 8007–8010; (f) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett*. **1999**, *40*, 2169–2172; (g) Rodriguez, G.; Castedo, L.; Dominguez, D.; Saa, C. *Tetrahedron Lett*. **1998**, *39*, 6551–6554; (h) Ishibashi, H.; Kawanami, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 817–821; (i) Rodriguez, G.; Cid, M. M.; Saa, C.; Castedo, L.; Dominguez, D. *J. Org. Chem*. **1996**, *61*, 2780–2782; (j) Ishibashi, H.; Kawanami, H.; Iriyama, H.; Ikeda, M. *Tetrahedron Lett*. **1995**, *36*, 6733–6734 and references cited therein.
3. Katritzky, A. R.; He, H.-Y.; Jiang, R. *Tetrahedron Lett*. **2002**, *43*, 2831–2833.
4. Koseki, Y.; Nagasaka, T. *Chem. Pharm. Bull*. **1995**, *43*, 1604–1606.
5. Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc*. **1999**, *121*, 10264–10269.
6. (a) Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447–455; (b) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc*. **1995**, *117*, 7834–7835; (c) Gibson, S. E.; Middleton, R. J. *J. Chem. Soc., Chem. Commun*. **1995**, 1743–1744.
7. Spectral data of **3** (^{1}H and ^{13}C NMR, mp, and mass) were identical to the reported in Ref. 2e.
8. Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) 1.75 (s, 3H), 2.67 (dd, 1H, $J=4.4$ Hz and 16.4 Hz), 3.01 (m, 1H), 3.28 (dt, 1H $J=13.2$ Hz and 4.4 Hz), 3.88 (s, 3H), 4.06 (s, 3H), 4.54 (dd, 1H $J=5.2$ Hz and 13.2 Hz), 5.86 (d, 1H, $J=1.6$ Hz), 5.93 (d, 1H, $J=1.6$ Hz), 6.54 (s, 1H), 7.11 (s, 1H), 7.13 (d, 1H, $J=8.4$ Hz), 7.46 (d, 1H, $J=8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 29.16, 29.52, 34.90, 56.65, 62.37, 62.52, 100.95, 105.82, 108.89, 116.36, 117.16, 123.42, 126.69, 132.50, 144.00, 146.19, 146.31, 146.86, 152.43, 165.39. EIMS 353 (M^+, 10), 338 (M^+-CH_3, 100).