Tetrahedron Letters 57 (2016) 5348–5350

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Sequential Heck–Heck reactions for the dibenz[*a*,*f*]indolizine skeleton: synthetic application to decumbenine B

Bok-Jin Lee, Gil-Pyo Hong, Guncheol Kim *

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

ARTICLE INFO

Article history:
Received 12 September 2016
Revised 8 October 2016
Accepted 18 October 2016
Available online 18 October 2016

Keywords:
Decumbenine B
Benzamidoacrylate
Heck reaction
Dibenzindolizine

ABSTRACT

Cyclization of benzamidoacrylate intermediates has been applied for the synthesis of dibenz[*a*,*f*]indolizine skeleton. Heck reaction for the 5-membered ring first and the following Heck reaction provided the 6-membered ring next. For the synthetic application properly arranged diiodo-aromatic intermediate has been prepared and subjected to the sequential Heck reactions, and the following decarboxylation provided the known precursor of decumbenine B.

Polycyclic alkaloids frequently encountered in natural products have shown numerous physiological activities.[1] Especially, nitrogen fused bicyclic medium rings arranged with aromatic moieties around have attracted many synthetic chemists' attention because of skeletal as well as biological attraction.[2,3] As an extension of our interests on the synthesis of the natural alkaloid products containing medium sized ring,[4] we designed to explore sequential cyclization reactions using Heck reactions for the construction of dibenzo 6/5-membered ring system (Scheme 1). And we wanted to apply this approach for the synthesis of 3-arylisoquinoline alkaloid, decumbenine B (Fig. 1). This alkaloid has been isolated from plant tubers of *Coridalis decumbens* Pers,[5] which has been used in Chinese folk herbal medicine for the treatment of hypertension, hemiplegia, rheumatoid arthritis, and sciatic neuralgia. And it has been synthesized only by a few groups.[6]

We have used benzamidoacrylate precursors for alkaloid synthesis,[4d] and we want to construct dibenz[*a*,*f*]indolizine skeleton through consecutive cyclization reactions from intermediate **3**: Heck reaction for 5-membered ring first and the same Heck reaction for 6-membered ring next. Compound **3** would be prepared by aza-Michael reaction of amide **2**.[4d] The bicyclic ring skeleton could be formed by differentiating reactivity in the cyclization steps (Scheme 1).

For the sequential cyclization, we have prepared amidoacrylate intermediate **6** from the corresponding aromatic halides through conventional acid and amine coupling condition using EDCI, and the following aza-Michael reaction with ethyl propiolate under Cs_2CO_3 in DMF in good yields (85% in 2 steps) (Scheme 2).

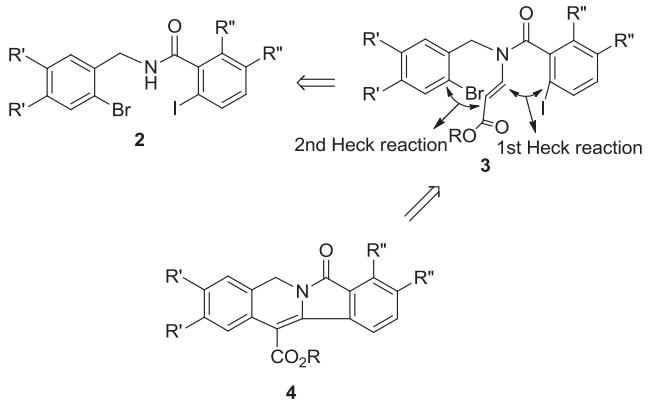
We hoped that the 2-iodobenzene moiety should undergo Pd-oxidative insertion faster at the early stage of the process and the 5-membered ring would be formed favorably via Heck reaction.[4d] In order to confirm the desired cyclization and find the optimum condition, we have treated **6** with a palladium reagent under conventional conditions (Table 1). All the conditions described in Table 1 provided only a single isomer **7**.[7] Amine base such as trimethylamine or diisopropylethylamine (DIEA) provided less yields (Entries 1 & 2) than inorganic bases such as Cs_2CO_3, $NaHCO_3$, or Na_2CO_3 (Entries 3–7), and the addition of additive could reduce the reaction time only (Entries 4 and 5). The optimum condition has been found to be using $Pd(OAc)_2$ and $NaHCO_3$ in DMF, yielding 79% of **7** (Entry 5). Dibromo-derivative of **6** provided the same product in less yield under similar conditions along with 5% of an undesired isomer having exchanged 5, 6 membered rings at the core. On the other hand, the corresponding diiodo-derivative of **6** provided **7** as a single product in similar yields.

The scope of this reaction has been investigated under the optimized condition found. The desired products have been formed as a single isomer in various scopes of yields (Table 2). The effect of position or electronic characters of substituents in each aromatic ring on yields could not be explained distinctively (*cf.* **4d**, **4f**, **4h**). However, electron withdrawing chlorine or nitro group has afforded lower yield than the corresponding hydrogen or methoxy group (*cf.* **4a**, **4c**, **4i**, **4j**).

Although sequential Heck reactions for bi-cyclization have been attempted rarely,[8] we consider this route would suggest a practical

* Corresponding author. Tel.: +82 42 821 5475; fax: +82 42 821 8896.
E-mail address: guncheol@cnu.ac.kr (G. Kim).

http://dx.doi.org/10.1016/j.tetlet.2016.10.064
0040-4039/



Scheme 1.

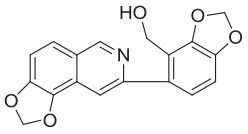
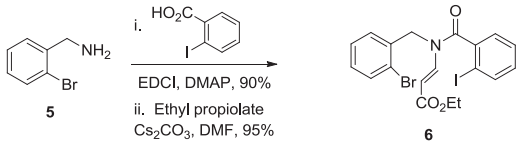
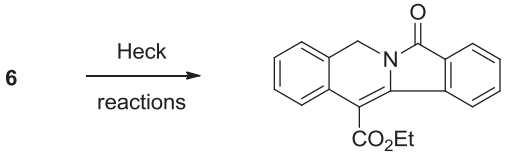


Figure 1.



Scheme 2.

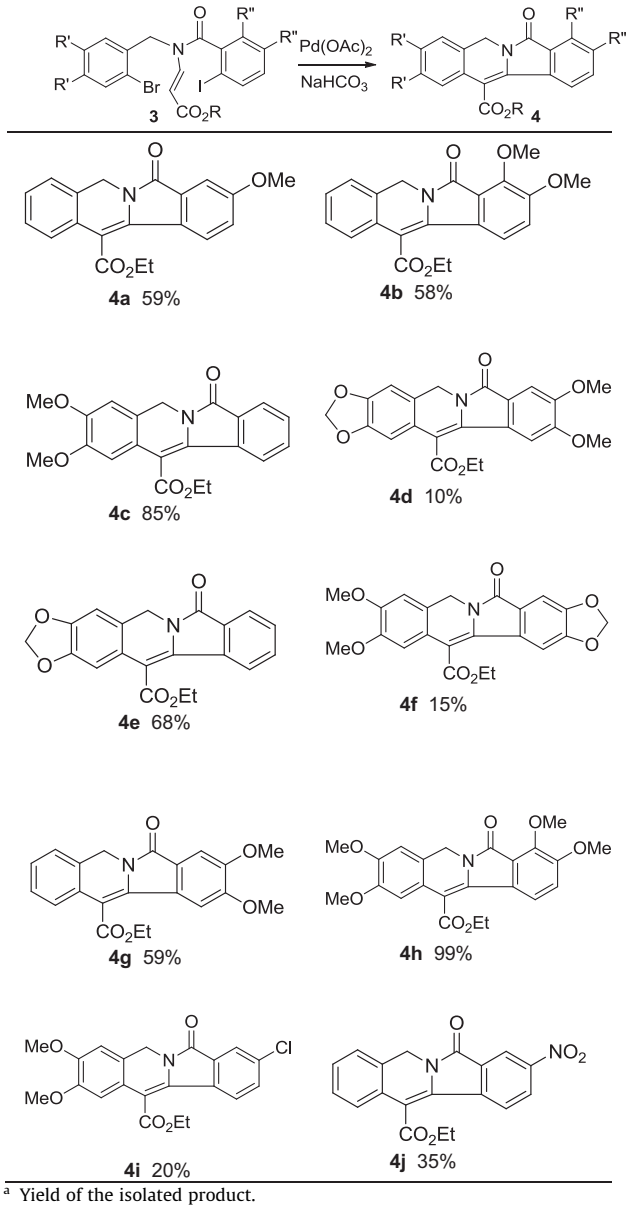
Table 1
Heck reaction conditions for the cyclization of **6**



Entry	Pd (0.1 equiv)	Conditions[a]	Yield[b] (%)
1	$Pd(OAc)_2$	Et_3N, TBAC, 24 h	53
2	$Pd(OAc)_2$	DIEA, TBAC, 24 h	26
3	$Pd(OAc)_2$	Cs_2CO_3, TBAC, 2 h	61
4	$Pd(OAc)_2$	$NaHCO_3$, TBAC, 2 h	72
5	$Pd(OAc)_2$	$NaHCO_3$, 5 h	79
6	$Pd(OAc)_2$	Na_2CO_3, 5 h	66
7	$Pd(PPh_3)_2Cl_2$	$NaHCO_3$, TBAC, 6 h	64

[a] 110 °C in DMF, base (2 equiv).
[b] Isolated yield of **7**.

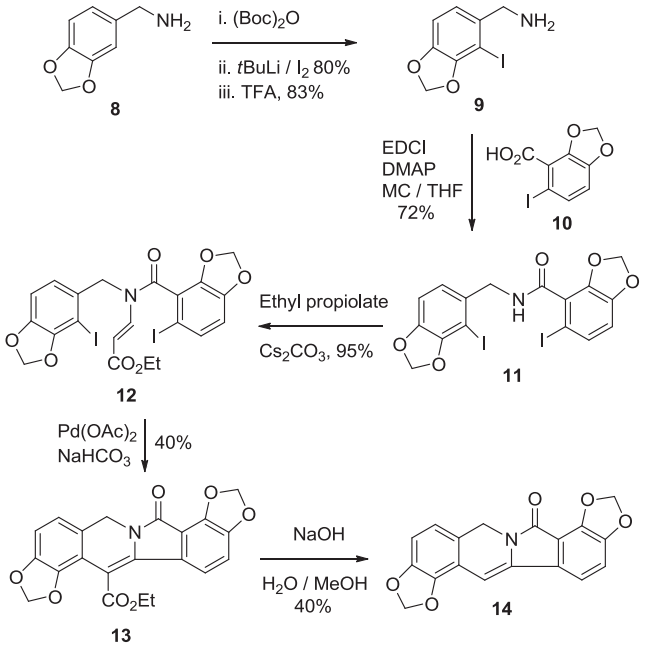
Table 2
Substrate scopes for the cyclization[a]



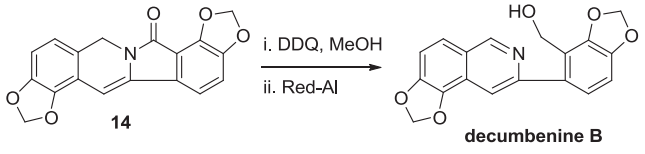
[a] Yield of the isolated product.

way to dibenz[*a*,*f*]indolizine skeleton and could be applied to a natural product, decumbenine B. Dibenz[*a*,*f*]indolizine intermediate **14** has been a known precursor to the natural alkaloid,[6c] so we first tried to prepare intermediate **13** from the corresponding intermediate **3**. And a process including decarboxylation would convert **13** to **14**. The required bromo-derivative of **9**, however, was too unstable to be prepared. So we replaced it with iodobenzylamine compound **9** which could be prepared from **8** through protection of amine with Boc, deprotonation with *t*-BuLi at ortho-position followed by iodination, and deprotection with TFA.[9] Diiodo amide **11** could be prepared in 72% yield by a coupling reaction of **9** with compound **10**, which was prepared by oxidation of the corresponding known aldehyde with $AgNO_3$ and 10% NaOH in MeCN.[10] The amidoacrylate **12** has been prepared from **11** with ethyl propiolate. Bicyclization under $Pd(OAc)_2$ and $NaHCO_3$ provided desired **13** in 40% yield, and hydrolysis followed by concurrent decarboxylation afforded the known precursor **14** in 40% yield (Scheme 3).[11]

As conversion of **14** to decumbenine B could be repeated as described in reference (Scheme 4),[6c] we could perform a formal synthesis of decumbenine B. In summary, we have developed a practical way to dibenz[*a*,*f*]indolizine skeleton via double Heck reactions, and the scope including synthesis of a natural alkaloid has been suggested.



Scheme 3.



Scheme 4.

Acknowledgment

This work was supported by Research Fund of Chungnam National University.

References and notes

1. (a) Cordell, G. A. In *The Alkaloids: Chemistry and Pharmacology*; Academic Press: San Diego, 1998; Vol. 50, (b) Weinstock, J.; Hieble, J. P.; Wilson, J. W. *Drugs Future* **1985**, *10*, 645–651; (c) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414–2421.
2. (a) Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 39–42; (b) Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599–602.
3. (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491–1499; (b) Padwa, A.; Beall, L. S.; Eidel; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414–2421; (c) Yoda, H.; Nakahama, A.; Koketsu, T.; Takabe, K. *Tetrahedron Lett.* **2002**, *43*, 4667–4669; (d) Kim, G.; Kim, J. H.; Kim, W.; Kim, Y. A. *Tetrahedron Lett.* **2003**, *44*, 8207–8209; (e) Yoda, H.; Inoue, K.; Ujihara, Y.; Mase, N.; Takebe, K. *Tetrahedron Lett.* **2003**, *44*, 9057–9060; (f) Koseki, Y.; Katsura, S.; Kusano, S.; Sakata, H.; Sato, H.; Monzene, Y.; Nagasaka, T. *Heterocycles* **2003**, *59*, 527–540; (g) Sahakitpichan, P.; Ruchirawat, S. *Tetrahedron* **2004**, *60*, 4169–4172; (h) Honda, T.; Sakamaki, Y. *Tetrahedron Lett.* **2005**, *46*, 6823–6825; (i) Tomasevich, L. L.; Kennedy, N. M.; Zitelli, S. M.; Hull, R. T., II; Gillen, C. R.; Lam, S. K.; Baker, N. J.; Rohanna, J. C.; Conley, J. M.; Guerra, M. L.; Starr, M. L.; Sever, J. B.; Carroll, P. J.; Leonard, M. S. *Tetrahedron Lett.* **2007**, *48*, 599–602; (j) Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 1849–1853; (k) Kim, G.; Lee, K. Y.; Yoo, C.-H. *Synth. Commun.* **2008**, *38*, 3251–3259; (l) Fuwa, H.; Sasaki, M. *Heterocycles* **2008**, *76*, 521–539; (m) Onozaki, Y.; Kurono, N.; Senboku, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2009**, *74*, 5486–5495; (n) Piko, B. E.; Keegan, A. L.; Leonard, M. S. *Tetrahedron Lett.* **2011**, *52*, 1981–1982.
4. (a) Kim, G.; Jung, P.; Tuan, L. A. *Tetrahedron Lett.* **2008**, *49*, 2391–2392; (b) Oh, K. R.; Kim, G. *Bull. Korean Chem. Soc.* **2012**, *33*, 3933–3934; (c) Kim, H. D.; Kim, G. *Tetrahedron Lett.* **2013**, *54*, 1765–1767; (d) Seo; Seong, -Y.; Kim, G. *Tetrahedron Lett.* **2015**, *56*, 3835–3837; (e) Kim, H.; Kim, G. *Bull. Korean Chem. Soc.* **2002**, *67*, 1743–1744.
5. Zhang, J.; Zhu, D.; Hong, S. *Phytochemistry* **1995**, *39*, 435–437.
6. (a) Xu, X.-Y.; Qin, G.-W.; Xu, R.-S.; Zhu, X.-Z. *Tetrahedron* **1998**, *54*, 14179–14188; (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86–94; (c) Wada, Y.; Nishida, N.; Kurono, N.; Ohkuma, T.; Orito, K. *Eur. J. Org. Chem.* **2007**, 4320–4327.
7. Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) 1.47 (t, 3H, J = 7.2 Hz), 4.58 (q, 2H, J = 7.2 Hz), 5.11 (s, 2H), 7.27 (t, 1H, J = 5.8 Hz), 7.30–7.56 (m, 3H), 7.56–7.64 (m, 2H), 7.76 (dd, 1H,, J = 7.1, 1.5 Hz), 7.93 (ddd, 1H,, J = 7.1, 1.5, 0.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 14.10, 42.71, 62.34, 104.32, 123.04, 126.26, 126.63, 127.73, 128.82, 128.93, 130.23, 131.80, 133.20, 133.95, 134.20, 135.20, 140.90, 164.61, 167.58, EIMS 305.11 (M^+). When the reaction was quenched earlier, less than 2 hr, starting material **6** and isomers of mono-cyclized product by single Heck reaction were detected. However, all the intermediates were converted to the desired product under longer reaction time. None of dehalogenated product without cyclization has been detected.
8. García, A.; Rodírques, D.; Castedo, L.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2001**, *42*, 1903–1905.
9. Mattson, R. J.; Sloan, C. P.; Lockhart, C. C.; Catt, J. D.; Gao, Q.; Huang, S. *J. Org. Chem.* **1999**, *64*, 8004–8007.
10. Bogucki, D. E.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 588–593.
11. Spectral data of the compound obtained were identical to those of the known.[6c]