DOI 10.5012/bkcs.2011.32.2.735

Pd-Catalyzed Bicylization to the Mitosene Skeleton

Hyeyoung Pyeon, Sung Hwan Pyo, Jeong Keun Ahn,† and Guncheol Kim*

Department of Chemistry, College of Natural Science, Chungnam National University, Daejon 305-764, Korea
**E-mail: guncheol@cnu.ac.kr*
†Department of Microbiology, Chungnam National University, Daejon 305-764, Korea
Received November 30, 2010, Accepted December 20, 2010

Key Words: Mitomycin, Mitosene, Bicyclization, Pyrrolo-[1,2-*a*]indole

The mitomycin family have attracted much attention due to their intricate ring structures and potent antitumoral and antibacterial activities (Figure 1).[1] The mechanistic studies of these antitumor agents have been carried out intensively over years since their discovery.[2] Bioreduction of the quinone system initiates the activation of mitomycins leading to the eventual covalent DNA linking which is responsible for their antitumor activity.[3] Several total syntheses as well as various synthetic approaches have been described.[4] Most of synthetic approaches are concerned for the effective construction of the pyrrolo-[1,2-*a*]indole ring system by radical cyclizations, carbenoid insertion, nitrone cyclization, RCM metathesis reaction, or intramolecular cyclizations. In these approaches, the ring system has been mostly constructed by stepwise ring addition manner. For a more efficient way, Iwasawa group recently reported the sequential cyclization method for the construction of the mitosene skeleton through transition metal carbene complex in 2006.[5]

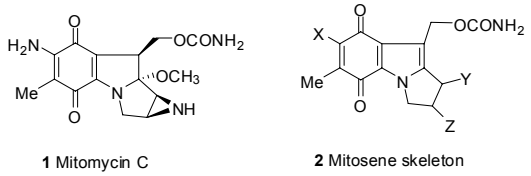
As for the rapid formation of the mitosene bicyclic system *via* sequential process, initially we tried the indole formation reaction of 2-bromoaniline with iodopentyne **3** under palladium catalysis followed by S_N2 reaction or *vice versa* (Scheme 1). However, the various known conditions for the indole synthesis did not afford the desired product at all, mostly decomposition was detected.

Although numerous reactions have been studied for the formation of the indole structure using palladium,[6] no example for the bicyclization using alkyne moieties toward the pyrrolo-[1,2-*a*]indole ring has been shown, though only one example using allenes has been published.[7] So, we decided to investigate the intramolecular cyclization of compound **5** which was prepared through the coupling reaction of 2-bromoaniline and **3** in 50% yield. Firstly, in order to find the optimum condition for the cyclization, we screened the palladium source, solvent, and base (Table 1). Although the Pd-catalyzed reaction afforded the desired cyclization slowly, the yields were mostly moderate. The best condition was found to be using $Pd(PPh_3)_4$ in DMF with LiCl and K_2CO_3 in a sealed tube, yielding **4** in 58% yield (Entry 6). The reaction mechanism would be a general sequence of indole formation, oxidative addition of Pd(0) to aromatic bromide followed by nucleophilic addition of nitrogen to alkyne and the concurrent bromide displacement, and the final reductive palladium(II) elimination.

When we applied the optimum reaction condition to the substituted substrates **6**, the cyclization afforded the desired products **7** in 20 to 52% yields in the case of aromatic substituents on alkyne (Table 2, Entry a to d). The ester moiety provided the best yield, 80% (Table 2, Entry e).

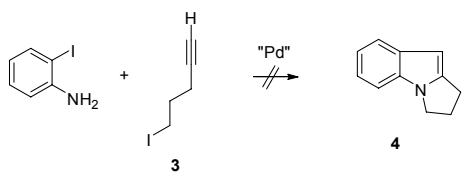
With the result in hand, we wanted to reinvestigate the initial intermolecular bicyclization reaction with 2-bromoaniline and compound **8** (Scheme 2). The condition applied to reactions in Table 2 provided the desired compound **7e**, however at most 10% yield. The double bond of **7e** has not been selectively reduced successfully under various hydrogenation conditions. Instead, the reduction with lithium aluminium hydride provided the known compound **9**[8] in 40% yield.

In summary, we have shown an efficient way of constructing



1 Mitomycin C **2** Mitosene skeleton

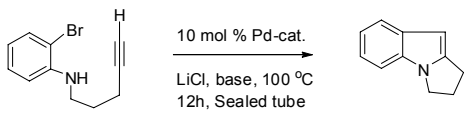
Figure 1. Structures of mitomycin C and mitosene skeleton.



3 **4**

Scheme 1. Preliminary study *via* intermolecular bicyclization

Table 1. Study of intramolecular bicyclization of compound **5** using Pd

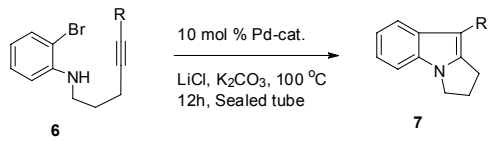


5 **4**

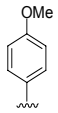
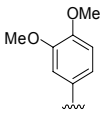
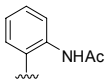
Entry	Cat	Solvent	Base	Yield (%)
1	$Pd(OAc)_2$	THF	K_2CO_3	15
2	$Pd(OAc)_2$	DMF	Cs_2CO_3	13
3	$Pd(OAc)_2$[a]	DMF	K_2CO_3	23
4	$Pd(dba)_2$	DMF	K_2CO_3	16
5	$Pd(PPh_3)_4$	DMF	Cs_2CO_3	27
6	$Pd(PPh_3)_4$	DMF	K_2CO_3	58

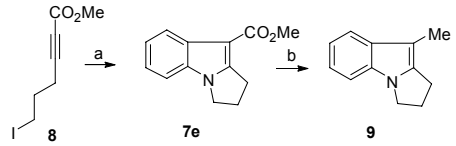
[a]Ligand: PPh_3

Table 2. Bicyclization of **6** under the optimized condition



6 7

Entry	R	Yield (%)
a		20
b		20
c		30
d		52
e		80



8 7e 9

Scheme 2. Reagents: (a) 2-Bromoaniline, $Pd(Ph_3)_4$, K_2CO_3, DMF; (b) $LiAlH_4$, THF, 40%

the mitosene skeleton *via* bicylization manner. The intramolecular reaction afforded moderate yields, however, the intermolecular reaction was successful only in the case of **7e** formation, yielding 10%. Further study of functionalization and application of the skeleton is under way.

Experimental Section

General Procedure for 7. A solution of compound **6** (0.42 mmol) in DMF (5 mL) containing LiCl (0.42 mmol), K_2CO_3 (2.09 mmol), $Pd(PPh_3)_4$ (0.04 mmol) was heated at 100 °C for 12 h in a sealed tube. After dilution with water (20 mL) the reaction mixture was extracted with diethyl ether (30 mL × 3). The organic layer was washed with water, sat'd $NaHCO_3$ solution, and brine and dried over $MgSO_4$. Crude products obtained by concentration under reduced pressure was purified by silica-gel column chromatography (hexane:EtOAc = 9:1) to afford compound **7**.

7a: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.66 (2H, *t*, *J* = 7.2 Hz), 3.18 (2H, *t*, *J* = 7.4 Hz), 3.90-3.94 (6H, *m*), 4.12 (2H, *t*, *J* = 7.0 Hz), 6.95-6.98 (1H, *m*), 7.13-7.17 (4H, *m*), 7.25-7.28 (1H, *m*), 7.83-7.85 (1H, *m*); MS (EI) *m*/*z* 233 (M^+).

7b: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.66 (2H, *t*, *J* = 7.2 Hz), 3.17 (2H, *t*, *J* = 7.4 Hz), 3.86 (3H, *s*), 4.13 (2H, *t*, *J* = 7.0 Hz), 6.99-7.01 (2H, *m*), 7.12-7.17 (2H, *m*), 7.26 (1H, *m*), 7.53-7.56 (2H, *m*), 7.82-7.83 (1H, *m*); MS (EI) *m*/*z* 263 (M^+).

7c: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.66 (2H, *t*, *J* = 7.2 Hz), 3.20 (2H, *t*, *J* = 7.4 Hz), 4.12 (2H, *t*, *J* = 7.0 Hz), 7.14-7.29 (4H, *m*), 7.41-7.46 (2H, *m*), 7.62-7.64 (2H, *m*), 7.64-7.90 (1H, *m*); MS (EI) *m*/*z* 293 (M^+).

7d: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.60 (3H, *s*), 2.67 (2H, *t*, *J* = 7.2 Hz), 3.21 (2H, *t*, *J* = 7.6 Hz), 4.13 (2H, *t*, *J* = 7.0 Hz), 7.14-7.30 (4H, *m*), 7.42-7.46 (2H, *m*), 7.62-7.64 (2H, *m*), 7.86-7.90 (1H, *m*); MS (EI) *m*/*z* 290 (M^+).

7e: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.60 (2H, *m*), 3.24 (2H, *t*, *J* = 7.2 Hz), 3.88 (3H, *s*), 4.04 (2H, *t*, *J* = 7.6 Hz), 7.24-7.17 (3H, *m*), 8.09 (1H, *d*, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.9, 152.8, 132.6, 130.9, 121.6, 121.5, 121.3, 109.8, 99.0, 50.6, 44.4, 26.5, 26.0; (MS (EI) *m*/*z* 215 (M^+).

Acknowledgments. This work was supported by the Korea Research Foundation Grant funded by Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2008-313-C00461), and we appreciate Center for Research Facilities, CNU for the permission to NMR.

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