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SPIROCYCLIZATION OF SIX-MEMBERED CYCLIC *N*-ACYLIMINIUM IONS WITH A CONJUGATED DIENE

Hideki Abe,[1] Yoshinori Muramatsu,[2] Kazuhiro Watanabe,[1] Sakae Aoyagi,[2]* Chihiro Kibayashi,[2] and Tadashi Katoh[1]*

[1]Department of Chemical Pharmaceutical Science, Tohoku Pharmacuetical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan (e-mail: katoh@tohoku-pharm.ac.jp), [2]School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Dedicated to the memory of Professor John Daly, scientist emeritus of the National Institutes of Health

Abstract – Intramolecular spirocyclization of six-membered cyclic *N*-acyliminium ions with a tethered conjugated diene has been studied. The reaction of an *N*-acyliminium ion bearing an endocyclic amide carbonyl group led to spirocyclization to give a 1-azaspiro[5.5]undecane compound.

INTRODUCTION

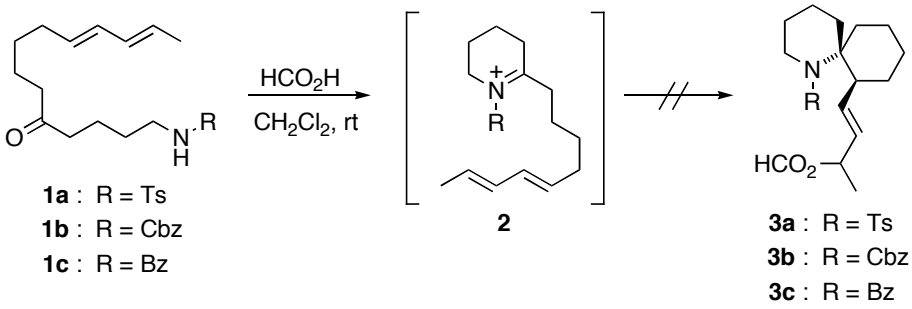
N-Acyliminium ions are among the most important species employed in the synthesis of nitrogen-containing natural products. A wide variety of reactions between *N*-acyliminium ions and nucleophiles have been developed to date, and have found widespread use in the total synthesis of bioactive natural products,[1] in which many species such as olefins, allylsilanes, and aromatic rings act as π-nucleophiles in inter- or intramolecular reactions involving spirocyclizations.[2-9] We recently reported a total synthesis of tricyclic marine alkaloids by *N*-acyliminium ion–conjugated diene spirocyclization.[10] The key spirocyclization reaction proved to be a highly efficient method for rapid construction of the 1-azaspirocyclic substructure of the tricyclic alkaloids. In this previous report, we described that spirocyclization of five-membered cyclic *N*-acyliminium ions having exocyclic amide carbonyl groups proceeded smoothly to afford 1-azaspiro[4.5]decanes. However, attempts to obtain the spirocyclization product *via* a six-membered *N*-acyliminium ion by treating an *N*-Boc-amide ketone with acids was

unsuccessful. In this case, tetrahydropyridine was obtained as a single product through cleavage of the Boc group followed by intramolecular dehydrocondensation of the resulting amino ketone, instead of the formation of the desired spirocompound.[11]

Herein, we report the extension of the spirocyclization reaction to six-membered cyclic *N*-acyliminium ions bearing endocyclic amide carbonyl groups with a tethered conjugated diene to afford 1-azaspiro[5.5]undecane compounds.

RESULTS AND DISCUSSION

With the previous results in mind, we investigated the possibility of forming the 1-azaspiro[5.5]undecane compounds via spirocyclization of six-membered *N*-acyliminium ions. These were expected to be formed from *N*-tosyl-, *N*-benzyloxycarbonyl-, and *N*-benzoyl-amide ketones **1a**, **1b**, and **1c** which would be stable under acidic conditions (Scheme 1). Unfortunately, all attempts at spirocyclization of the amide ketones **1a**, **1b**, and **1c** by treatment with formic acid gave complex mixtures of products, and the corresponding desired spirocompounds **3a**, **3b**, and **3c** were not detected.



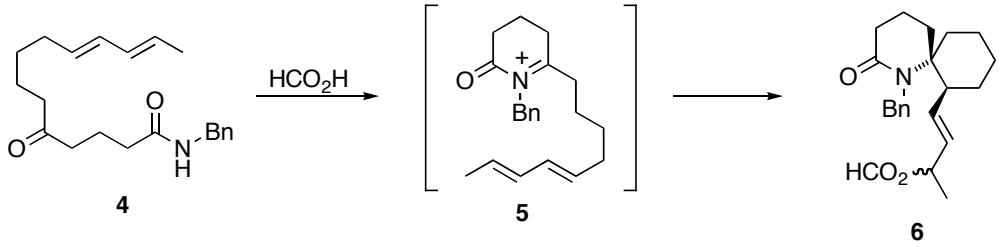
Scheme 1. Spirocyclization of amide ketones via exocyclic *N*-acyliminium ions [a]

These results suggested that the six-membered cyclic iminium ions with exocyclic amide carbonyl groups were less reactive toward electrophilic addition reactions than the five-membered analogues that led to spirocyclization to afford 1-azaspiro[4.5]decane derivatives in our previous report.[10a] These observations are consistent with a recent report by Eberlin and co-workers[12] on the electrophilic reactivity of a series of cyclic *N*-acyliminium ions, which shows that the LUMO energy of five-membered cyclic *N*-acyliminium ions with exocyclic amide carbonyl groups is lower than that of the six-membered analogues. In addition, they also reported that cyclic iminium ions with endocyclic amide carbonyl groups were more reactive than those with exocyclic amide carbonyl groups.

We therefore investigated the spirocyclization of the six-membered cyclic iminium ion bearing an endocyclic carbonyl group (Table 1). Thus, *N*-benzylamide ketone **4** was treated with formic acid in CH_2Cl_2 at 0 °C for 24 h. No product was observed under these conditions (Table 1, entry 1). However,

when the reaction was carried out at rt spirocyclization occurred to afford the desired spirocompound **6** in 30% yield after 18 h and in 47% yield after 72 h (entries 2 and 3). Increasing the reaction temperature shortened the reaction time from 72 h to 24 h, albeit with only a moderate 43% yield (entry 4). Using CH_3CN or THF as the solvent resulted in lower yields (entries 5 and 6). The best result was achieved by treatment only with formic acid without solvent at rt, giving **6** in 59% yield (entry 7).

Table 1. Spirocyclization of *N*-benzylamide ketone **4** via endocyclic *N*-acyliminium ion **5** [a]



4 **5** **6**

entry	solvent	temp.	time (h)	yield (%) [b]	
				6	recovered **4**
1	CH_2Cl_2	0 °C	24	n.d.[c]	81
2	CH_2Cl_2	rt	18	30	18
3	CH_2Cl_2	rt	72	47	10
4	CH_2Cl_2	reflux	24	43	9
5	MeCN	rt	24	20	42
6	THF	rt	24	n.d.	87
7	none	rt	24	59	n.d.

[a] All reactions were performed at a substrate concentration of 0.05 M in the appropriate solvent containing formic acid in a 1 : 1 ratio. [b] Isolated yield. [c] N.D. = None determind.

In conclusion, we have demonstrated the spirocyclization of a six-membered cyclic iminium ion bearing an endocyclic carbonyl group with a conjugated diene. The reaction proceeded at rt to give the 1-azaspiro[5.5]undecane compound, which is expected to be useful in the synthesis of natural products.

EXPERIMENTAL

Formic acid (2 mL) was added to *N*-benzylamide ketone **4** (34.4 mg, 0.105 mmol) at 0 °C, then the reaction mixture was stirred for 24 h at rt. After cooling to 0 °C, the mixture was basified with 28% aqueous ammonia, and extracted with Et_2O. The combined organic layers were washed with brine, dried

($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$–Et_2O, 1:1) to give (2*E*)-3-(1-benzyl-2-oxo-1-azaspiro[5.5]dec-7-yl)-1-methyl-2-propenyl formate **6** (22.0 mg, 59%) as a pale yellow oil. IR (neat): 1719, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 and 1.28 (total 3H in 1.1:1 ratio, d, *J* = 6.2 Hz, each), 1.32–1.43 (2H, m), 1.53–1.77 (9H, m), 1.94–1.98 (1H, m), 2.21–2.58 (3H, m), 4.42 and 4.50 (total 1H in 1.1:1 ratio, 1/2ABq, *J* = 15.9 Hz, each), 4.89 and 4.94 (total 1H in 1.1:1 ratio, 1/2ABq, *J* = 15.9 Hz, each), 5.28–5.42 (2H, m), 5.56 and 5.60 (total 1H in 1.1:1 ratio, dd, *J* = 5.6, 5.2 Hz, and dd, *J* = 5.5, 5.0 Hz, respectively), 7.16–7.29 (5H, m), 7.988 and 7.993 (total 1H in 1.1:1 ratio, s, each); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.9, 20.4 and 20.2 (1C in 1.1:1 ratio), 22.6, 25.0, 26.1 and 26.2 (1C in 1.1:1 ratio), 27.0 and 27.1 (1C in 1.1:1 ratio), 33.2 and 33.3 (1C in 1.1:1 ratio), 35.2 and 35.4 (1C in 1.1:1 ratio), 44.3, 44.8 and 45.1 (1C in 1.1:1 ratio), 63.59 and 63.62 (1C in 1.1:1 ratio), 71.3 and 70.7 (1C in 1.1:1 ratio), 126.5, 126.9 and 126.8 (1C in 1.1:1 ratio), 128.3 (3C), 130.4 and 130.6 (1C in 1.1:1 ratio), 132.9 and 132.6 (1C in 1.1:1 ratio), 139.5, 160.37 and 160.44 (1C in 1.1:1 ratio), 172.8; HRMS (EI) calcd for $C_{22}H_{30}NO_3$ ($[M + H]^+$) 356.2226, found 356.2228. Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.50; H, 8.24; N, 3.95. Found: C, 74.57; H, 8.42; N, 3.89.

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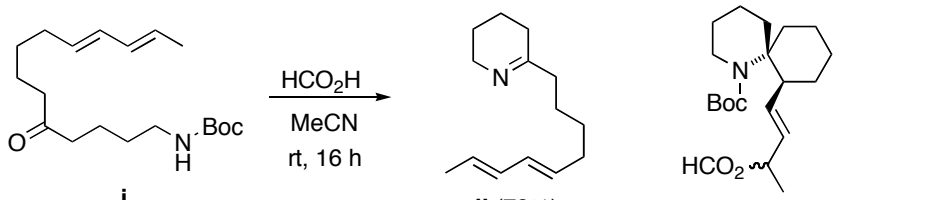
REFERENCES

1. (a) W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367; (b) W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, 2000, **56**, 3817; (c) B. E. Maryanoff, H.-C. Zhang, J. H. Coheu, I. J. Turchi, and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431.
2. (a) H. E. Schoemaker and W. N. Speckamp, *Tetrahedron Lett.*, 1978, 1515; (b) H. E. Schoemaker and W. N. Speckamp, *Tetrahedron Lett.*, 1978, 4841; (c) H. E. Schoemaker and W. N. Speckamp, *Tetrahedron*, 1980, **36**, 1515.
3. (a) D. A. Evans and E. W. Thomas, *Tetrahedron Lett.*, 1979, 411; (b) D. A. Evans and R. E. Cherpeck, *J. Am. Chem. Soc.*, 1982, **104**, 3695.
4. W. H. Whaley and T. R. Govindachari, *Org. React.*, Wiley: New York, 1951, pp 151.
5. E. Langkopf and D. Schinzer, *Chem. Rev.*, 1995, **95**, 1375.
6. C. Y. Hong, N. Kado, and L. E. Overman, *J. Am. Chem. Soc.*, 1993, **115**, 11028.
7. A. R. Ofial and H. Mayr, *J. Org. Chem.*, 1996, **61**, 5823.
8. (a) F. Pin, S. Comesse, B. Garrigues, S. Marchalín, and A. Daïch, *J. Org. Chem.*, 2007, **72**, 1181;

(b) M. Amat, M. M. M. Santos, A. M. Gómez, D. Jokic, E. Molins, and J. Bosch, *Org. Lett.*, 2007, **9**, 2907; (c) S. Gao, Y. Q. Tu, X. Hu, S. Wang, R. Hua, Y. Jiang, Y. Zhao, X. Fan, and S. Zhang, *Org. Lett.*, 2006, **8**, 2373.

9. (a) M. A. Brodney and A. Padwa, *Tetrahedron Lett.*, 1997, **38**, 6153; (b) A. Padwa and M. A. Brodney, *ARKIVOC*, 2002, 35; (c) H. Abe, K. Takaya, K. Watanabe, S. Aoyagi, C. Kibayashi, and T. Katoh, *Heterocycles*, 2007, **74**, 205.
10. (a) H. Abe, S. Aoyagi, and C. Kibayashi, *J. Am. Chem. Soc.*, 2005, **127**, 1473; (b) H. Abe, S. Aoyagi, and C. Kibayashi, *Angew. Chem., Int. Ed.*, 2002, **41**, 3017.
11. When *N*-Boc-amide ketone **i** was treated with formic acid in MeCN, tetrahydropyridine derivative **ii** was obtained in 79% yield instead of the desired spirocompound **iii**.



i **ii** (79%) **iii** (not detected)

12. M. G. M. D'Oca, L. A. B. Moraes, R. A. Pilli, and M. N. Eberlin, *J. Org. Chem.*, 2001, **66**, 3854.