AlCl$_3$/ICl-Mediated iodo-carbocyclization of α-iodo cycloalkanones: a new entry to spirocyclic ketones

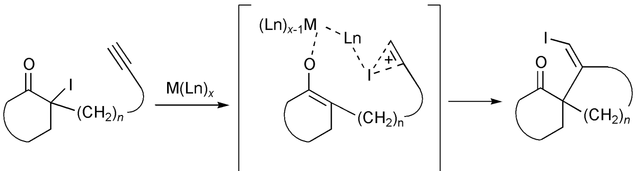
Chin-Kang Sha,* Fong-Cheng Lee and Hsien-Hsun Lin

Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan, ROC. E-mail: cksha@mx.nthu.edu.tw

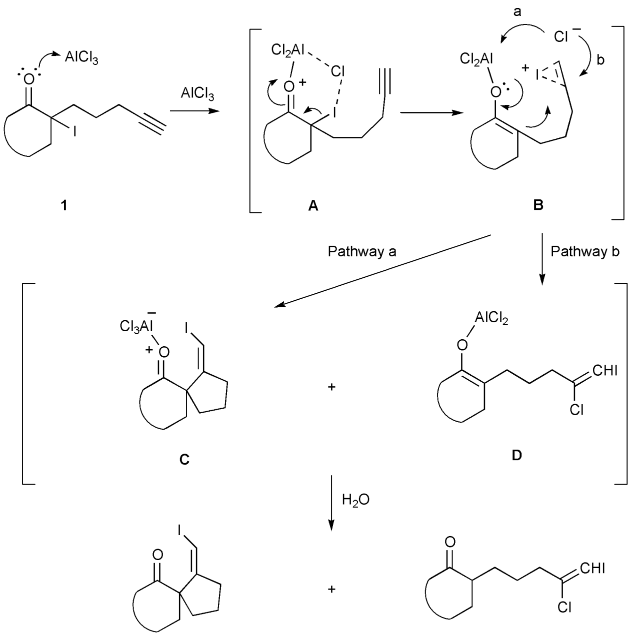
Received (in Cambridge, UK) 9th October 2000, Accepted 20th November 2000
First published as an Advance Article on the web 11th December 2000

Treatment of α-iodo cycloalkanones bearing an acetylenic side chain with AlCl$_3$/ICl afforded spirocyclic ketones in good yields.

Spirocyclic systems are core skeletons of several important natural products, such as gloiosiphone A[1] and ginkgolide B.[2] They also constitute the main frameworks of spirocyclic chiral auxiliaries having a C_2 axis of symmetry.[3] During our work on radical cyclization of α-iodo ketones,[4] we became interested in developing a general method for synthesis of spirocyclic ketones from α-iodo ketones. We envisaged that iodo-carbocyclization of α-iodo ketones, as depicted in Scheme 1, could be exploited for annulation of five- and six-membered rings. Generation of enolate from α-iodo ketone **1** with simultaneous transfer of I^+ to the acetylenic moiety might be effected with a Lewis acid, $M(Ln)_x$, to give intermediate **2**. Subsequent cyclization of the intermediate **2** would afford spirocyclic ketone **3**. In the past decade, free-radical atom-transfer cyclization of iodo substrates mediated with hexabutylditin[5] or other reagents[6] has emerged as a routine method. Ionic iodo-carbocyclization of iodo malonates[7] and ionic seleno-carbocyclization of seleno ketones[8] have also been described. In this communication, we report results obtained from our investigation of iodo-carbocyclization of α-iodo ketones.



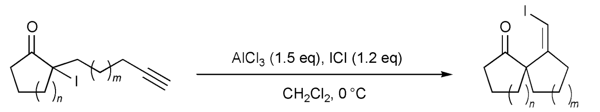
Scheme 1

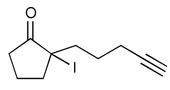
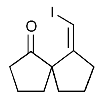
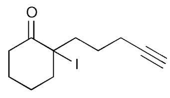
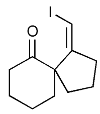
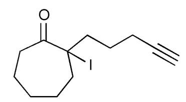
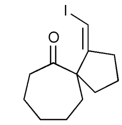
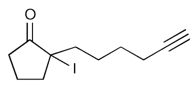
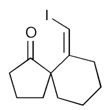
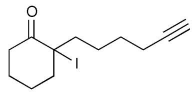
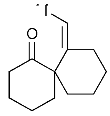
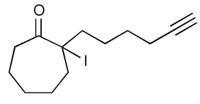
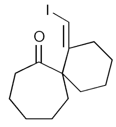


Scheme 2

We first sought appropriate Lewis acids that could effect formation of an enolate from α-iodo ketones. Many Lewis acids including $TiCl_4$, BCl_3, $AlMe_3$, Me_2AlCl, $SnCl_4$, $MgBr_2$ and $AlCl_3$ were examined. We found that $AlCl_3$, Me_2AlCl and $TiCl_4$ effect the desired transformation of **1** to **3** in dichloromethane, although in low yield (10–20%). A plausible mechanism is proposed for the reaction using $AlCl_3$ as catalyst, Scheme 2. $AlCl_3$ reacts with α-iodo ketone to generate an aluminium

Table 1 Ionic iodo-carbocyclization of α-Iodo cycloalkanones



Entry	α-Iodo Cycloalkanone	Reaction Time	Product[a]	Yield (%)
1	 **5**	45 min	 **11**	83
2	 **6**	50 min	 **12**	81
3	 **7**	40 min	 **13**	70
4	 **8**	30 min		94
5	 **9**	60 min	 **15**	74
6	 **10**	60 min	 **16**	77

[a] The stereochemistry of the vinyliodide moiety in each product was tentatively assigned as *Z*.

enolate[9] and ICl. The acetylenic moiety on the side chain then complexes with ICl to give intermediate **B**. Cyclization of **B** (pathway a) would afford $AlCl_3$-complex **C**. In principle, $AlCl_3$ is catalytic and gets regenerated at this stage. Because it would complex with the product, one equiv. of $AlCl_3$ is needed. Upon aqueous work-up, complex **C** is hydrolyzed to spiro ketone **3**. According to this mechanism, ICl is generated in the first step and participates in the subsequent cyclization. Therefore, we felt that addition of ICl from an external source might facilitate cyclization. Indeed, we found that treatment of iodo ketones **5–10**[10] with a mixture of $AlCl_3$ (1.5 equiv.) and ICl (1.2 equiv.) in dichloromethane at 0 °C afforded spirocyclic products **11–16** in good yield.[11] The results are summarized in Table 1. Products **11–16** are all obtained as a single geometric isomer and are tentatively assigned to be *Z* isomers.[12] Presumably, the conformation of intermediate **B**, as depicted in Scheme 2, favors the formation of the exclusive *Z* isomers. Annulation of both five-membered rings (entries 1–3) and six-membered rings (entries 4–6) is achieved. In entries 1–3, by-product **4** is formed in trace amount (< 5%) from direct addition of Cl^- to the iodonium moiety, pathway b in Scheme 2.[13] Since addition of an external source of ICl significantly enhances the yield of the carbocyclization process, an alternative mechanism involving enolate formation with simultaneous complexation of ICl to the acetylene unit is also possible.

In conclusion, we have demonstrated that an ionic iodo-carbocyclization of α-iodo cycloalkanones can be effected with Lewis acid, $AlCl_3$. Addition of ICl greatly enhances yields of spirocyclic ketones. In comparison with free-radical atom-transfer cyclization, the present method has two distinct advantages: (i) as tin reagents are not used, tedious separation of products from tin residues is avoided; (ii) whereas free-radical atom-transfer cyclization is only useful for synthesis of the five-membered ring, this method allows annulation of both five- and six-membered rings. Applications of this reaction for total synthesis of natural products are under investigation in our laboratory.

We thank the National Science Council of the Republic of China for financial support.

Notes and references

1 J. L. Chen, M. F. Moghaddam and W. H. Gerwick, *J. Nat. Prod.*, 1993, **56**, 1205.

2 N. Sakabe, S. Takada and K. Okabe, *J. Chem. Soc., Chem. Commun.*, 1967, 259; K. Okabe, K. Yamada, S. Yamamura and S. Takada, *J. Chem. Soc. C*, 1967, 2201; K. Nakanishi, *Pure Appl. Chem.*, 1967, **14**, 89.

3 A. S. C. Chen, C.-C. Lin, J. Sun, W. Hu, Z. Li, W. Pan, A. Mi, Y. Jiang, T.-M. Huang, T.-K. Yang, J.-H. Chen, Y. Wang and G.-H. Lee, *Tetrahedron: Asymmetry*, 1995, **6**, 2953; H. Suemune, K. Maeda, K. Kato and K. Sakai, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3441; R. Brunner and H. Gerlach, *Tetrahedron: Asymmetry*, 1994, **5**, 1613; J. A. Nieman, M. Parvez and B. A. Keay, *Tetrahedron: Asymmetry*, 1993, **4**, 1973.

4 C.-K. Sha, T.-S. Jean and D.-C. Wang, *Tetrahedron Lett.*, 1990, **31**, 3745; C.-K. Sha, R.-T. Chiu, C.-F. Yang, N.-T. Yao, W.-H. Tseng, F.-L. Liao and S.-L. Wang, *J. Am. Chem. Soc.*, 1997, **119**, 4130; C.-K. Sha, K. C. Santhosh and S.-H. Lih, *J. Org. Chem.*, 1998, **63**, 2699; C.-K. Sha and W.-Y. Ho, *J. Chem. Soc., Chem. Commun.*, 1998, 2709; C.-K. Sha, F.-K. Lee and C.-J. Chang, *J. Am. Chem. Soc.*, 1999, **121**, 9875.

5 D. P. Curran and D. Kim, *Tetrahedron Lett.*, 1986, **27**, 5821; D. P. Curran, *Synthesis*, 1988, 417; D. P. Curran and C. Chang, *J. Org. Chem.*, 1989, **54**, 3140; D. P. Curran, M.-H. Chen and D. Kim, *J. Am. Chem. Soc.*, 1989, **111**, 6265; D. P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746.

6 I. Marek and A. Chakraborty, *J. Chem. Soc., Chem. Commun.*, 1999, 2375; I. Marek, *J. Chem. Soc., Perkin Trans. 1*, 1999, 535; K. Oshima, H. Yorimitsu, T. Nakamura and H. Shinokubo, *J. Org. Chem.*, 1998, **63**, 8604; D. P. Curran and C.-T. Chang, *Tetrahedron Lett.*, 1990, **31**, 933.

7 T. Taguchi, O. Kitagawa and T. Inoue, *Tetrahedron Lett.*, 1992, **33**, 2167; T. Taguchi, O. Kitagawa, T. Inoue and K. Hirano, *J. Org. Chem.*, 1993, **58**, 3106; T. Taguchi, O. Kitagawa and T. Inoue, *Tetrahedron Lett.*, 1994, **35**, 1059; T. Taguchi, T. Inoue, O. Kitagawa, S. Kurumizawa and O. Ochiai, *Tetrahedron Lett.*, 1995, **36**, 1479; T. Taguchi, O. Kitagawa, T. Suzuki, T. Inoue and Y. Watanabe, *J. Org. Chem.*, 1998, **63**, 9470; T. Taguchi, O. Kitagawa, T. Suzuki and H. Fujiwara, *Tetrahedron Lett.*, 1999, **40**, 2549; O. Kitagawa, H. Fujiwara, T. Suzuki, T. Taguchi and M. Shiro, *J. Org. Chem.*, 2000, **65**, 6819.

8 T. Toru, S. Kawai and Y. Ueno, *Synlett*, 1996, 539.

9 For the generation of aluminium enolate from α-bromo carbonyl compounds, see: S. Matsubara, N. Tsuboniwa, Y. Morizawa, K. Oshima and H. Zozaki, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3242.

10 Iodo ketones **5–10** were prepared from the corresponding ketones according to our method: C.-K. Sha, J.-J. Young and T.-S. Jean, *J. Org. Chem.*, 1987, **52**, 3919. The required starting ketones were prepared by Yamashita's procedure: T. Mino, S. Masuda, M. Nishio and M. Yamashita, *J. Org. Chem.*, 1997, **62**, 2633.

11 A representative procedure for iodo-carbocyclization: to a solution of compound **5** (200 mg, 0.72 mmol) in CH_2Cl_2 (7.2 mL) was added $AlCl_3$ (150 mg, 1.08 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min, during which the color turned orange red. A solution of ICl in CH_2Cl_2 (1 M, 0.87 mL, 0.87 mmol) was added dropwise at 0 °C. The color became dark brown. The reaction mixture was stirred at 0 °C for 45 min and then quenched with H_2O (20 mL), saturated $Na_2S_2O_3$ solution (10 mL) and saturated $NaHCO_3$ solution (10 mL). The mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Concentration and silica gel column chromatography (hexane–EtOAc, 50 : 1) gave product **11** (160 mg, 83%) as a pale yellow liquid. δ_H(300 MHz; $CDCl_3$) 6.32 (s, 1H), 2.70−2.60 (m, 1H), 2.60−2.34 (m, 1H), 2.34−1.86 (m, 6H), 1.77−1.59 (m, 1H), 1,59−1.15 (m, 3H); δ_C(75 MHz; $CDCl_3$) 211.2, 137.0, 73.4, 55.9, 40.7, 38.0, 34.4, 25.3, 19.5 (two carbons); IR (neat) 3069, 2953, 1732, 1602; MS (EI): *m/z* 277 (M + H^+), 214 (13), 185 (52), 149 (31), 127 (47), 97 (45), 84 (100), 79 (34), 41 (55); HRMS (EI): Calc. for $C_{10}H_{14}IO$ (M + H^+) 277.0090. Found 277.0087.

12 For purposes of comparison, *E* isomers of **11** and **13** were prepared from compounds **5** and **7** according to the photolytic hexabutylditin method (ref. 5). ^{1}H NMR spectra of **11** and **13** were found to be different from those of *E* isomers. Therefore, all products **11–16** are tentatively assigned to be *Z* isomers.

13 When the reactions of entries 1 and 2 were performed at −78 °C, products **11** and **12** were both obtained along with some by-product **4**, in ratios of 1 : 0.9 and 1 : 0.8 respectively.