

ATOM TRANSFER CYCLIZATION OF α -HALONITRILE AND α -HALOCARBONYL COMPOUNDS

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Abstract— α -Halonitriles and α -haloesters reacted with internal olefin in the presence of KI to give cyclized products in good yields via radical intermediate. α -Iodonitrile **1b** afforded **2b** and **2b'** merely upon heating.

We have already found that alkyl halides such as α -haloamides, α -haloesters and α -haloketones could oxidatively add to the low-valent metal complex to give σ -alkylmetal complexes, which reacted with internal olefinic bond to afford various heterocycles.¹ It was expected that α -halonitrile should react with internal double bond in the presence of palladium catalyst to afford a cyclized product. In this paper, we want to report a cyclization of α -halonitrile having internal double bond in the presence of palladium catalyst or KI or in the absence of catalyst. Thus, when α -bromonitrile **1a**² was treated with $\text{Pd}(\text{PPh}_3)_4$ in the presence of proton sponge[1,8-bis(dimethylamino)-naphthalene] in HMPA at 65 °C for 3.5 h, five membered cyclized products **2a**, **3** and **4** were obtained in 18 %, 20 % and 6 % yields, respectively. Any six membered product was not detected. α -Iodonitrile **1b** was treated with $\text{Pd}(\text{PPh}_3)_4$ (10 mol %) in HMPA in the presence of proton sponge at room temperature to give cyclized products **2b** and **2b'** in 67 % yield(**2b**:**2b'**=3:2).³

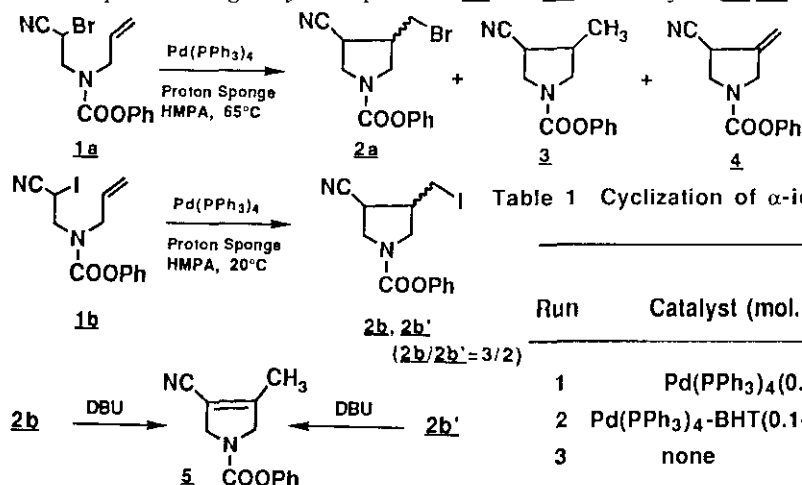
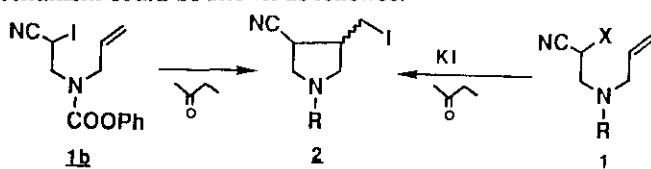


Table 1 Cyclization of α -iodonitrile **1b** with $\text{Pd}(\text{PPh}_3)_4$

Run	Catalyst (mol. eq.)	recovered	
		2b, 2b'	1
1	$\text{Pd}(\text{PPh}_3)_4$ (0.1)	67 %	-
2	$\text{Pd}(\text{PPh}_3)_4$ -BHT (0.1-0.1)	81	-
3	none	12	53 %

On the ^{13}C -nmr spectra of these compounds, the chemical shift of the iodomethyl group of the former product **2b** in DMSO- d_6 at 100°C appeared at δ 1.72, but that of the latter one **2b'** was observed at δ 4.67.⁴ These results suggest that the former product **2b** has cis substituents because the chemical shift of the iodomethyl group of **2b** on ^{13}C -nmr spectrum should appear at the higher field due to the steric compression of cis substituents. Compounds **2b** and **2b'** were treated with DBU in DMSO to give the same elimination product **5** in 88 % and 82 % yields, respectively. To survey whether this reaction proceeds via radical intermediate or σ -alkylmetal complex, α -iodonitrile **1b** was treated with $\text{Pd}(\text{PPh}_3)_4$ (10 mol %) in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT, 10 mol %) as radical scavenger to afford cyclized product in good yield (Table 1, Run 2), which results indicate that this reaction would have passed through σ -alkylmetal complex. However, it was very surprising that this reaction proceeded without palladium catalyst though the yield was low (Table 1, Run 3). In view of these interesting results, the cyclization of α -halonitrile under thermal conditions was investigated. It is noteworthy that α -iodonitrile **1b** on refluxing in 2-butanone for 2 h afforded the cyclized products **2b** and **2b'** in high yield (82 %, **2b**:**2b'**=1:1) (Table 2, Run 1). This reaction would proceed via radical **6** derived from the carbon-halogen bond cleavage of **1b** under thermal conditions because the reaction was depressed by radical scavenger such as 4,4'-thio-bis(6-*t*-butyl-*m*-cresol) (TBMP) or 2,6-di-*t*-butyl-4-methylphenol (BHT) (Table 2, Runs 2 and 3). A possible reaction mechanism could be shown as follows.



- a** X=Br R=COOPh
b X=I R=COOPh
c X=Cl R=COOPh
d X=Cl R=COOEt
e X=Cl R=Ts

Table 2 Cyclization of α -iodonitrile **1b** in 2-butanone

Run	Additive	Yield of 2 (2b / 2b')	Recovered 1
1	-	82 % (1/1)	7 %
2	TBMP	32 (1/1)	40
3	BHT	9 (1/2)	77

Possible Reaction Mechanism

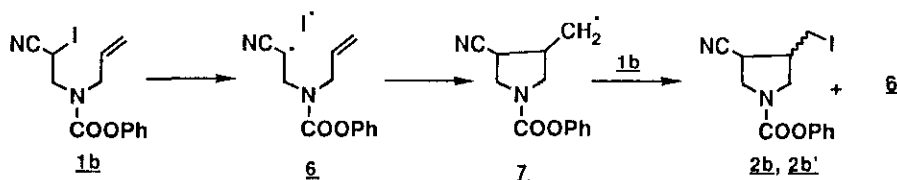
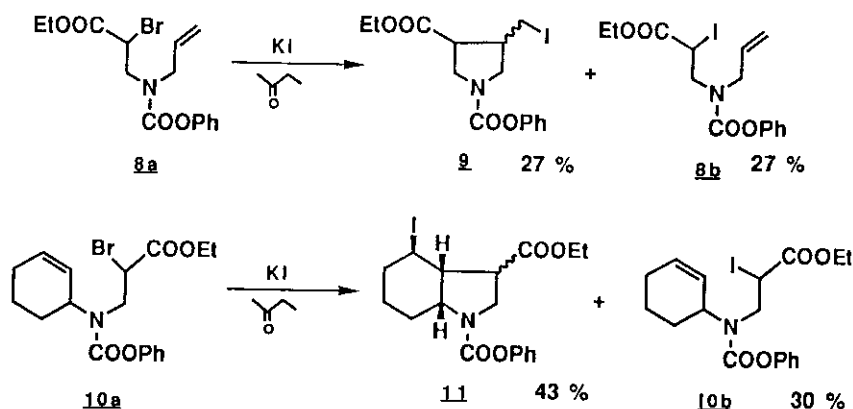


Table 3 Cyclization of α -halonitrile **1** with KI in 2-butanone

Run	R	X	Temp.	Time	Yield of 2 (cis/trans)	Recovered 1
1	COOPh	Cl	80°C	2 h	28% (1.2/1)	47 %
2	COOEt	Cl	80	2 h	10 (1/1)	61
3	Ts	Cl	80	2 h	2 (1/1)	70
4	COOPh	Cl	80	1 day	60 (3/2)	40
5	COOPh	Cl	rt	1 day	0	100
6	COOPh	Br	80	1 day	85 (1.2/1)	0

This cyclization also occurred on conversion of α -chloronitrile to α -iodonitrile by treatment with KI. When α -chloronitrile **1c** was refluxed with KI in 2-butanone for 2 h, the cyclized products **2b** and **2b'** were obtained in 15 % and 13 % yields (Table 3, Run 1), respectively. The yield was improved when the solution of **1c** and KI in 2-butanone was refluxed overnight (Run 4). None of the cyclized product was obtained at room temperature and α -bromonitrile **1a** gave a good result. (Runs 5 and 6). The substituents on the amide nitrogen affected this cyclization (Runs 1-3). Since the recovered starting material has original halogen, the cyclization of α -chloronitrile with KI should occur after conversion of α -chloronitrile to α -iodonitrile (Runs 1-5).

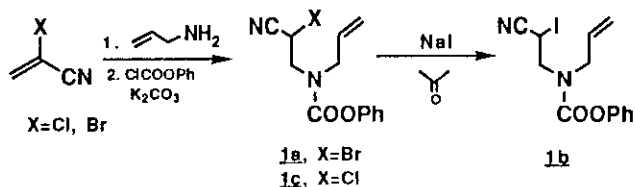
Similar reaction occurred when various α -bromocarbonyl compounds were treated with KI. α -Bromoester **8a** was refluxed with KI in 2-butanone for 2 h to afford a cyclized product **9** and α -iodoester **8b** in the yields of 27 % and 27 %, respectively. Similar treatment of compound **10a** afforded the bicyclic compound **11** (43 % yield)⁶ along with **10b** (30 % yield). In these cases, α -iodoesters **8b** and **10b** were obtained.



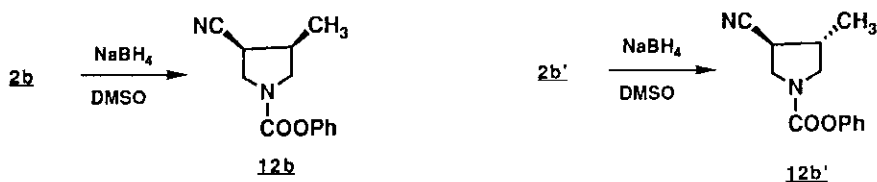
The atom transfer reaction of C-X bond across a double bond is accepted to be a fundamental reaction of organic free radicals.⁷ They requires the initiator such as n-Bu₃SnH/AIBN, AIBN or distannane. In regards these points, it may be significant that present reactions proceed through merely upon heating or in the presence of KI.

REFERENCES AND NOTES

1. a) M. Mori, I. Oda, and Y. Ban, *Tetrahedron Lett.*, 1982, **23**, 5315. b) M. Mori, N. Kanda, I. Oda, and Y. Ban, *Tetrahedron*, 1985, **41**, 5465. c) M. Mori, Y. Kubo, and Y. Ban, *Tetrahedron Lett.*, **26**, 1985, 1519. d) M. Mori, N. Kanda, and Y. Ban, *J. Chem. Soc., Chem. Comm.*, 1986, 1375. e) M. Mori, Y. Kubo, and Y. Ban, *Tetrahedron*, **44**, 1988, 4321.
2. α -Bromonitrile **1a** was prepared from 2-bromoacrylonitrile by treatment with allylamine in the presence of K₂CO₃ followed by protection of nitrogen with ClCOOPh (56 % yield from 2-bromoacrylonitrile). α -Chloronitrile **1c** was prepared in a similar manner from 2-chloroacrylonitrile (41 % yield). α -Iodonitrile **1b** was prepared from α -bromonitrile **1a** by treatment with NaI in acetone at room temperature overnight (56 % yield).



3. Separation of cyclized products **2b** and **2b'** was performed by preparative thin layer chromatography on silica gel (hexane:ethyl acetate=3:1). The structures of these compounds **2b** and **2b'** were confirmed by pure products **2b** and **2b'**, and the ratio was calculated by nmr.
4. Each ¹³C-nmr spectral datum of compounds **2b** or **2b'** shows a pair of each signal at room temperature in CDCl₃ or in DMSO-d₆ because of its rotamer of C-N bond of carbamate.
5. Dehalogenation of **2b** and **2b'** with NaBH₄ in DMSO afforded **12b** and **12b'**. ¹³C-Nmr spectra of **12b** and **12b'** in DMSO-d₆ at 100°C showed that the methyl signals of these compounds were appeared at δ 13.6 and δ 14.9 ppm, respectively. These results also suggested that the former compound **12a** has cis substituents and that of the latter compound has trans substituents.



6. The stereochemistry of compound **11** was decided by comparison with the spectral data^{1c} of the authentic sample.
7. a) B. Glese, *"Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds"*, Pergamon Press, 1986. b) D. P. Curran and C. Chang, *J. Org. Chem.*, 1989, **54**, 3840.

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