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

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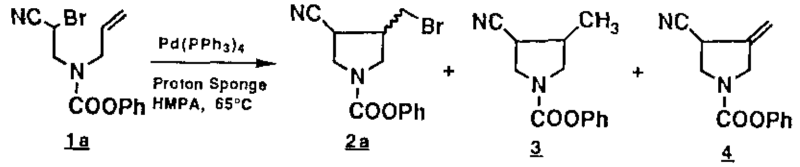
Abstract——α-Halonitriles and α-haloesters reacted with internal olefin in the presence of KI to give cyclized products in good yields via radical intermediate. α-Iodonitrile 1b afforded 2b and 2b' merely upon heating.

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 $Pd(PPh_3)_4$ 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 $Pd(PPh_3)_4$ (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]



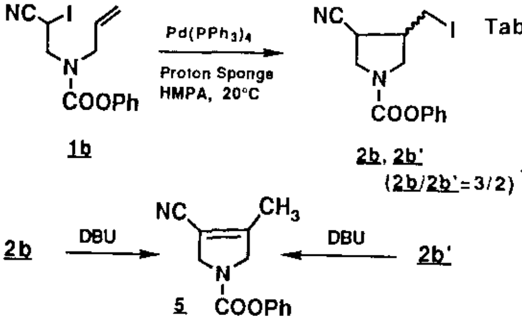
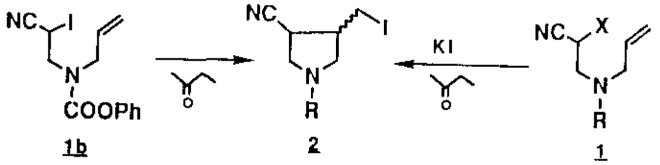


Table 1 Cyclization of α-iodonitrile 1b with $Pd(PPh_3)_4$

Run	Catalyst (mol. eq.)	2b,2b'	recovered 1
1	$Pd(PPh_3)_4$(0.1)	67 %	-
2	$Pd(PPh_3)_4$-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 $Pd(PPh_3)_4$(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 followes.



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

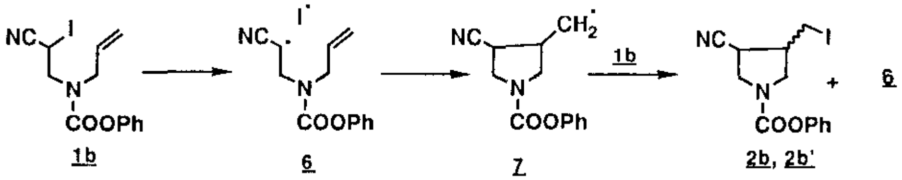
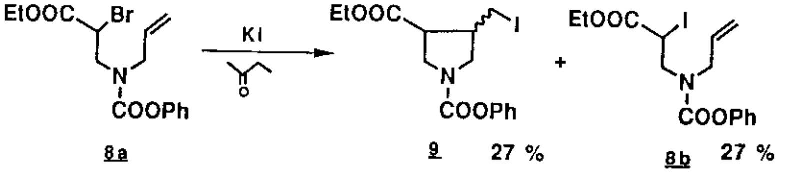


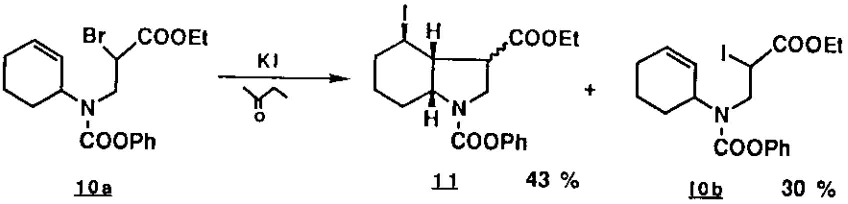
Table 3 Cyclization of α-halonitrile 1 with KI in 2-butanone

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-Bu_3SnH/AIBN, AIBN or distannane. In regards these points, it may be significunt that present reactions proceed through merely upon heating or in the presence of KI.

REFERENCES AND NOTES

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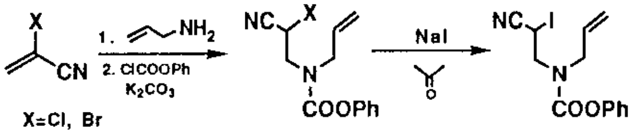
2. α-Bromonitrile 1a was prepared from 2-bromoacrylonitrile by treatment with allylamine in the presence of K_2CO_3 followed by protection of nitrogen with ClCOOPh(56 % yield from 2-bromoacrylonitrile). α-Chloronitrile 1c was prepared in a similar manner from 2-chloroacrylonitrile(41 % yield). α-Iodonitrile 1b was prepared from α-bromonitrile 1a by treatment with NaI in acetone at room temperature overnight(56 % yield).



1a, X=Br
1c, X=Cl

1b

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 ^{13}C-nmr spectral datum of compounds 2b or 2b' shows a pair of each signal at room temperature in $CDCl_3$ or in DMSO-d_6 because of its rotamer of C-N bond of carbamate.
5. Dehalogenation of 2b and 2b' with $NaBH_4$ in DMSO afforded 12b and 12b'. ^{13}C-Nmr spectra of 12b and 12b' in DMSO-d_6 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.

12b

12b'

6. The stereochemistry of compound 11 was decided by comparison with the spectral data[1e] of the authentic sample .
7. a) B. Giese, *"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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