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Dicobalt Octacarbonyl Promoted Rearrangement of 4-Isoxazolines to Acylaziridines: Dramatic Rate Acceleration with Very High Substrate Tolerance

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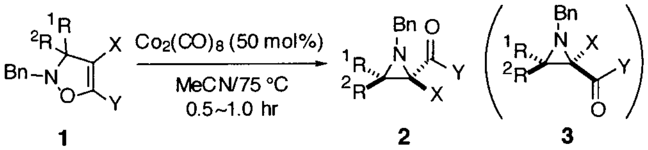
ABSTRACT



Dicobalt octacarbonyl [Co$_2$(CO)$_8$] in acetonitrile at 75 °C triggers the cleavage of the N–O bond of 4-isoxazolines (1) to bring about the valence rearrangement to 2-acylaziridines (2). The isoxazolines were stable at 75 °C in the absence of the cobalt complex.

The potential of 4-isoxazolines (**1**) as synthons for 2-acylaziridines (**2**) through thermal valence rearrangements was pointed out by Baldwin in 1969.[1] However, this reaction has not developed into a practical synthetic method because of the severe limitations of the rearrangement.[2] On the other hand aziridines have been playing an important role as precursors for diverse cyclic or acyclic nitrogen compounds.[3] The significance of aziridines in organic synthesis has been stimulating research to develop a number of synthetic methods,[4] although the substrate limitation problem has also been addressed.

This situation directed our attention to the previous work of Baldwin[1] when we thought about almost free availability of 4-isoxazolines through [3 + 2] cycloaddition reactions between nitrones and alkynes[2a] or more promising addition−cyclization processes between nitrones and metal acetylides.[5]

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(1) Baldwin, J. E.; Pudussery, R. G.; Qureshi, A. K.; Sklarz, B. *J. Am. Chem. Soc.* **1968**, *90*, 5325−5326.

(2) (a) Freeman, J. P. *Chem. Rev.* **1983**, *83*, 241−261. (b) For *N*-methoxy-4-isoxazoline to *N*-methoxyaziridine transformation, see: Grëe, R.; Carrie, R. *J. Am. Chem. Soc.* **1977**, *99*, 6667−6672. (c) Shim, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798−5800. (d) For isoxazolidinone to aziridine transformation, see: Chidichimo, G.; Gum, G.; Lelj, F.; Uccella, N. *J. Am. Chem. Soc.* **1980**, *102*, 1372−1377. The rearrangement took place, in general, when a substituent on the nitrogen atom was a phenyl, *tert*-butyl, or methoxy group except for the case in which X or Y was an electron-withdrawing group.

(3) For reviews on reactions of aziridines, see: (a) Mitunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, Chapter 1.3. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.9. (c) Thompson, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 4.1. (d) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 8.1. (e) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619.

(4) For leading references for aziridine synthesis, see: (a) Kemp, J. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 7, Chapter 3.5. (b) Reference 3e. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (d) Wulff, W. D.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518−4521. (e) Hada, K.; Watanabe, T.; Isobe, T.; Ishikawa, T. *J. Am. Chem. Soc.* **2001**, *123*, 7705−7706. (f) Dauban, P.; Saniélie, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707−7708.

(5) Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331−2333.

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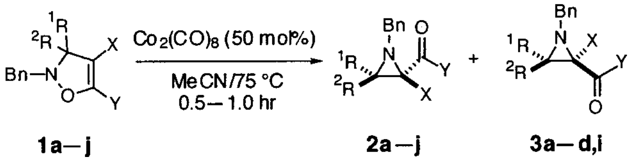
Thus, we made extensive efforts to accelerate the valence rearrangement of **1** to the aziridines.

It is well-known that $Mo(CO)_6$ can cleave a N−O bond.[6] However, heating a solution of **1h**, for example, in aqueous acetonitrile in the presence of $Mo(CO)_6$ under reflux afforded not the aziridine but the acylsilane derivative.[7] We also tried dicobalt octacarbonyl $[Co_2(CO)_8]$ in vain. However, it was found that $Co_2(CO)_8$ in *anhydrous acetonitrile* (or propionitrile) provides a practical solution to this longstanding problem. Established synthetic procedure is as follows: to a solution of **1** in CH_3CN (20 mL/1 mmol of **1**) was added powdered $Co_2(CO)_8$ (50 mol %) at ambient temperature under stirring, and the resulting mixture was immediately heated at 75 °C for 0.5−1 h under nitrogen atmosphere until the disappearance of **1** on TLC.[8] Then, the mixture was kept in contact with air for a few hours to facilitate the decomposition of the cobalt complex through oxidation to form precipitates, which were removed by filtration. The filter cake was rinsed with ethyl acetate. The combined organic solutions were dried and concentrated to give an oil, which was purified by column chromatography (silica gel). The diastereoisomers, if any, were able to be separated, and the stereochemistry was determined by means of both NOE and *J*-values. In Table 1 are summarized the results of the rearrangement of isoxazolines **1a**−**j**[9] to predominantly 2-acylaziridines **2a**−**j**. The following three representative cases illustrate how 4-isoxazolines **1f**, **1h**, and **1j**, were formed from benzalacetone, 2-methylpropanal, and isoxazolidinone, respectively, and converted to the corresponding arizidino ketones **2f**, **2h**, and **2j** (Scheme 1).

Table 1. $Co_2(CO)_8$-Promoted Rearrangements of 4-Isoxazolines **1** to Isomeric 2-Acylaziridines **2** and **3**[a]

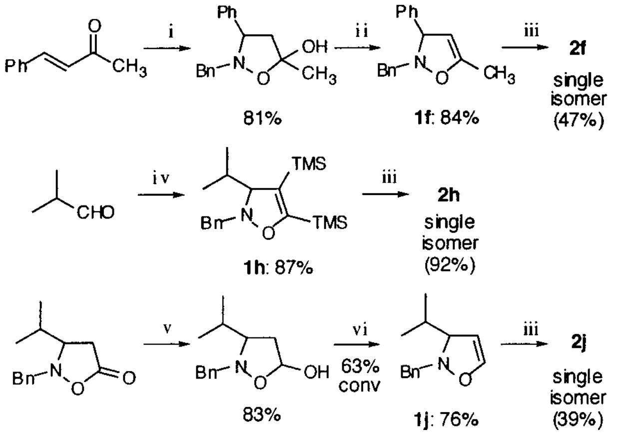


1a−**j** **2a**−**j** **3a**−**d,i**

entry	1					yield, %[b] (**2**: **3**)
		R^1	R^2	X	Y	
1	**1a**	isopropyl	H	H	Ph	51 (4:1)
2	**1b**	Ph	H	H	Ph	61 (2.8:1)[c]
3	**1c**	4-MeOPh	H	H	Ph	75 (2.3:1)
4	**1d**	heptyl	H	H	Ph	86 (2.5:1)
5	**1e**	CH_3	CH_3	H	Ph	66[d]
6	**1f**	Ph	H	H	CH_3	47[d,e]
7	**1g**	Ph	H	$SiMe_3$	$SiMe_3$	56[f]
8	**1h**	isopropyl	H	$SiMe_3$	$SiMe_3$	92[f]
9	**1i**	isopropyl	H	H	butyl	67 (17:1)
10	**1j**	isopropy	H	H	H	39[d]

[a] Neither 4-isoxazolines nor cobalt complex was recovered. Structures were determined by ^1H and ^{13}C NMR spectroscopy including NOE and two-dimensional correlation techniques. [b] Isomers, separated by flash column chromatography (silica gel). Yields are for combined products. No other identifiable products were isolated. [c] Padwa, A.; Hamilton, L. *Tetrahedron Lett.* **1967**, *20*, 1861−1864. [d] Isomeric aziridines **3** not detected. [e] Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801−1812. [f] Single diastereomer; relative configurations, not determined.

Scheme 1[a]



[a] (i) BnNHOH/THF/rt, 6 h; (ii) $MsCl/Et_3N$/THF/0 °C, 0.5 h; (iii) see Table 1; (iv) (1) BnNHOH/THF/rt, 2 h, (2) TMSCCTMS (5 equiv)/100 °C, 4 h; (v) DIBALH/PhMe/−78 °C, 0.5 h; (vi) MsCl/Et_3N/THF/0 °C → rt, 1 h.

It should be noted that **1a**−**j** was recovered unchanged when solutions in acetonitrile, DMF, DMSO, THF, or toluene were heated at 75 °C for 26 h without $Co_2(CO)_8$, and these solvents other than acetonitrile were totally ineffective even if used with $Co_2(CO)_8$.

It turned out that the rearrangement proceeded with exclusive diastereoselectivity when a stereogenic center existed in the substituent on the nitrogen atom, such as **1k** prepared from optically pure isoxazolidinone **4**[10] to give aziridino ketone **2k** as a single isomer (Scheme 2).[11] The fully substituted 4-isoxazoline **1l**, obtained through 1,3-dipolar cycloaddition between nitrone-**A** and methyl 3-phenylpropiolate followed by reduction and protection, afforded 2,2-disubstituted aziridine **2l** in an excellent yield with a high diastereomeric ratio (10:1). Furthermore, the rearrangement of diastereomerically pure 4-isoxazoline **1m**, prepared likewise employing (*S*)-lactate-based nitrone-**B**, afforded **2m**, which is otherwise difficult to access, albeit in low yield.[12]

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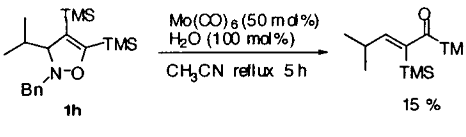
(6) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401−1406.

(7)



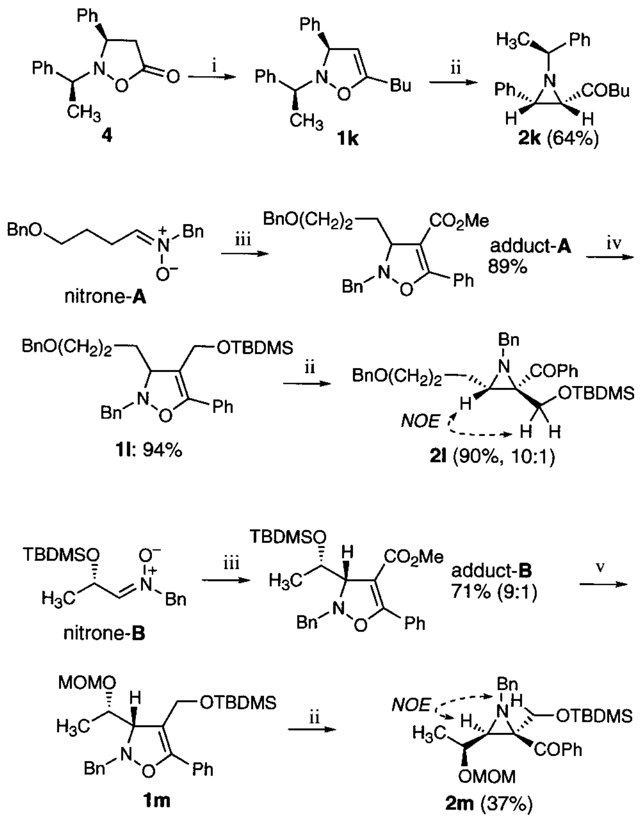
(8) No reaction occurred below 70 °C.

(9) Synthetic procedures of **1** are provided in Supporting Information.

(10) For the preparation of **4**, see: Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1995**, 1171−1173.

(11) This process opens a general strategy for the synthesis of chiral aziridines from chiral isoxazolidinones. For the asymmetric synthesis of isoxazolidinones, see: (a) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. *Synlett* **1998**, 1291−1293. (b) Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *2*, 3393−3396 and references therein.

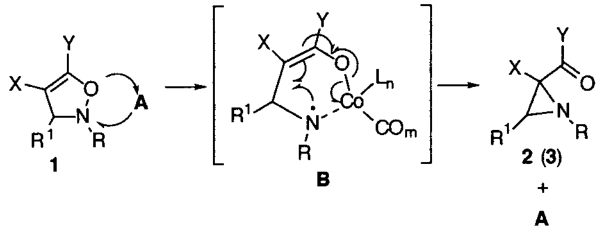
Scheme 2[a]



[a] (i) (1) BuLi/THF, (2) MsCl, Et_3N/THF; (ii) $Co_2(CO)_8$/acetonitrile, 75 °C, 0.5 h; (iii) $PhCCCO_2Me/PhCH_3$/75 °C, 2 h; (iv) LAH/THF/rt, 1 h; (v) (1) LAH/THF/rt, 1 h/separation of diastereoisomers (81%), (2) TBDMSCl/ imidazole/THF/0 °C → rt, 2.5 h (46%), (3) DIPEA/MOMCl/THF/40 °C, 24 h (73%).

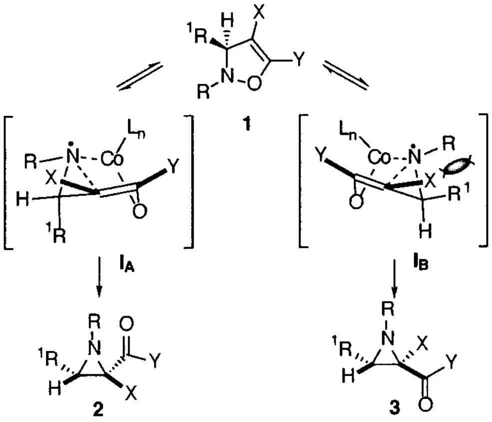
When **1** was added to a solution of $Co_2(CO)_8$ in acetonitrile that had been standing at room temperature for 5 min or more, no rearrangements occurred at all.[13] Thus, it is important to use an active species (**A**, Scheme 2) as soon as it is generated. The complete consumption of substrates **1** required 50 mol % of $Co_2(CO)_8$, which probably means that one $Co_2(CO)_8$ molecule can generate two of the active species. Therefore, although the elucidation of this active species must await future study, it might be a cobalt radical species.[14,15] If this is the case, the cobalt radical could promote the fragmentation of the N−O bond[6,16] probably as shown in Scheme 3. We can expect that **A** might initiate the valence rearrangement of **1** through a series of reactions involving one-electron reduction to trigger N−O bond cleavage, generation of intermediate **B**, and final one-electron oxidation to complete the formation of aziridino ketones **2** (or **3**).

Scheme 3



The selective formation of aziridines **2** can be explained on this basis by assuming the preferential formation of chelated aza-radical intermediates I_A over I_B. The electron reorganization from I_A or I_B may lead to 2-acylaziridines **2** or the isomers **3** (Scheme 4).

Scheme 4



In conclusion, we have developed the valence rearrangement of 4-isoxazolines to 2-acylaziridines promoted by Co_2-

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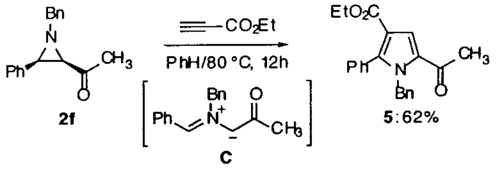
(12) The generation of azomethine ylide intermediates from **2** or **3** under the given conditions might be responsible for the low yield of **2** (or **3**) (entries 1, 6, and 10 in Table 1 and **2m** in Scheme 1). In fact a solution of **2f** in benzene at 80 °C for 12 h in the presence of ethyl propiolate afforded substituted pyrrole **5** apparently through regioselective [1,3]-dipolar cycloaddition of azomethine ylide (**C**) followed by oxidation.



For azomethine ylide formation, see: (a) Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A.; McPhail, A. T. *J. Org. Chem.* **1985**, *50*, 4114−4119. (b) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 3238−3246 and references therein. See also: (c) L.-Calle, E.; Eberbach, W. *J. Chem. Soc., Chem. Commun.* **1994**, 301−302.

(13) Evolution of CO was observed on mixing $Co_2(CO)_8$ with acetonitrile. When the evolution of CO ceased, the mixture turned out to be useless for the rearrangement. Therefore, the cobalt complex should be added to a solution of **1** in acetonitrile.

(14) For the mechanism of the thermal rearrangement of **1** with an *N*-aryl or *N*-methoxy substituent to 2-acylaziridines, three possibilities have been proposed involving concerted, zwitterionic, or biradical processes. See ref 2.

(15) For radical generation from $Co_2(CO)_8$, see: (a) Absi-Halabi, M.; Atwood, J. D.; Forbus, N. P.; Brown, T. L. *J. Am. Chem. Soc.* **1980**, *102*, 6248−6254. See also: (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp 266−267 and (c) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609−2612. However, we cannot completely rule out an anionic mechanism because cobalt carbonyl anion $[Co(CO)_4]^-$ can be generated from $Co_2(CO)_8$ on treatment with a weak base. See: Hinterding, K.; Jacobsen, E. N. *J. Org. Chem.* **1999**, *64*, 2164−2165.

$(CO)_8$ in acetonitrile with very high substrate tolerance, which occurs under mild conditions and, in some cases, is diastereoselective. We have also proposed the role of $Co_2(CO)_8$ in the rearrangement of this class, which in general may provide a concept for activating heteroatom bonds.

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Supporting Information Available: Synthesis and spectroscopic data for **1a−m**, **2a−m**, and **5** and copies of ^{1}H and ^{13}C NMR spectra of **2a−m**.nts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For other examples of the rearrangement involving N−O bond cleavage processes, see: (a) Hutchins, C. W.; Coates, R. M. *J. Org. Chem*. **1979**, *44*, 4742−4744. (b) Padwa, A.; Wong, G. S. K. *J. Org. Chem*. **1986**, *51*, 3125−3133.