Journal of the Korean Chemical Society
2001, *Vol. 45, No. 6*
Printed in the Republic of Korea

단 신

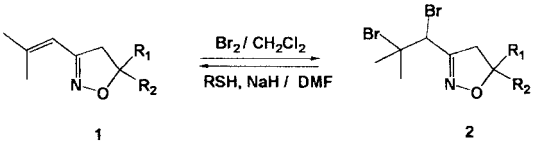
3-(1,2-디브로모-2-메틸프로필)-1,2-이속사졸린들의 나트륨 티올레이트들에 의한 탈브롬화 반응을 통한 3-(2-메틸-1-프로페닐)-1,2-이속사졸린들로의 변환반응

金亨哲 · 趙修演 · 田憧柱 · 金亨來
한국화학연구원 화학물질연구부
(2001. 9. 3 접수)

Debromination of 3-(1,2-Dibromo-2-methylpropyl)-1,2-isoxazolines to 3-(2-Methyl-1-propenyl)-1,2-isoxazolines by Sodium Thiolates

Hyoung Cheul Kim, Su Yeon Jo, Dong Ju Jeon, and Hyoung Rae Kim*
Bioorganic Science Division, Korea Research Institute of Chemical Technology, Daejeon 305-600, Korea
(Received September 3, 2001)

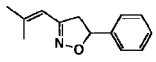
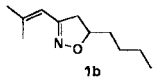
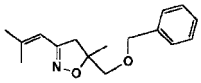
Debromination of *vic*-dibromides to olefins was one of the basic conversion in organic chemistry, which reaction could be achieved by various metals.[1] metal complexes,[2] and some reducing agents.[3] In case of α,β-dibromo carbonyl compounds, sodium thiolates[4] were also applied for the debrominarion of them to α,β-unsaturated carbonyl compounds. Here we report a specific examples of the debrominations of 3-(1,2-dibromo-2-methylpropyl)-1,2-isoxazolines 2 which are fairly stable against various nucleophiles. 1,3-Dipolar cycloaddition reaction of 2-methyl-1-propenonitrile oxide with appropriate olefins afforded the corresponding 3-(2-methyl-1-propenyl)-1,2-isoxazolines **1** in good yields.[5] which were converted to corresponding **2** by treatment of bromine in dichloromethane quantitatively. No reaction occurred when these dibromides **2** was subjected with various nucleophiles such as ethylamine, benzylamine, and sodium azide. Instead, treatment of sodium thiolate with **2** in DMF at 25 °C resulted in **1** in quantitative yield (*Scheme* 1). Debromination of **2** proceeded smoothly by both alkyl and aryl thiolates. The typical examples were summarized in *Table* 1. For the good stability of **2** against nucleophile and easy conversion to **1**. this



1 2

Scheme 1.

Table 1. Bromination of 3-(2-methyl-1-propenyl)-1,2-isoxazolines 1 and debromination of 3-(1,2-dibromo-2-methylpropyl)-1,2-isoxazolines 2

Entry	1	2(%)[1]	RSH	1(%)[1]
1	 1a	96		97
2				94
3			C_2H_5SH	95
4	 1b	99		98
5				96
6	 1c	95		98
7				93

[1]Isolated yields.

bromination-debromination reaction can be applied as a protection method on modification of side chain in isoxazoline ring system.

EXPERIMENTALS

3-(2-Methylpropenyl)-5-phenyl-1,2-isoxazoline (1a). To a solution of 2-methyl-1-propenohydroximoyl chloride (3.11 g, 23 mmol) in dichloromethane (50 mL) was added triethylamine (4.46 g, 34 mmol) and styrene (4.46 g, 46 mmol). After being stirred for 2 h, the reaction mixture was poured into cold water, extracted with dichloromethane (50 mL × 2) and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/10) to give **1a** (4.1 g, 87%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H), 1.96 (s, 3H), 3.09 (dd, 1H, *J*=7.9, 16.6 Hz), 3.58 (dd, 1H, *J*=10.8, 16.6 Hz), 5.59 (dd, 1H, *J*=7.9, 10.8 Hz), 5.59 (s, 1H), 7.35 (s, 5H).

MS m/z (relative intensity) 201 (M^+, 67), 184 (24), 168 (24), 143 (17), 128 (17), 115 (12), 104 (100), 91 (35), 77 (29), 65 (12), 41 (34).

HRMS: Calcd for $C_{13}H_{15}NO$, 201.1153, found 201.1153.

5-Butyl-3-(2-methylpropenyl)-1,2-isoxazoline (1b). To a solution of 2-methyl-1-propenohydroximoyl chloride (4 g, 30 mmol) in dichloromethane (60 mL) was added triethylamine (5.8 g, 45 mmol) and 1-heptene (5.16 g, 60 mmol). After being stirred for 2 h, the reaction mixture was poured into cold water, extracted with dichloromethane (50 mL × 2) and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/10) to give **1b** (4.31 g, 76%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, *J*=6.6 Hz), 1.29~1.48 (m, 4H), 1.52-1.90 (m, 2H), 1.88 (s, 3H), 1.94 (s, 3H), 2.75 (dd, 1H, *J*=8.1, 16.3 Hz), 3.16 (dd, 1H, *J*=10.0, 16.3 Hz), 4.46~4.62 (m, 1H), 5.91 (s, 1H).

MS m/z (relative intensity) 181 (M^+, 100), 166 (7), 124 (74), 106 (14), 94 (36), 70 (15), 55 (59), 41 (41).

HRMS: Calcd for $C_{11}H_{19}NO$ 181.1466, found 181.1460.

5-Benzyloxymethyl-5-methyl-3-(2-methylpropenyl)-1,2-isoxazoline (1c). To a solution of 2-methyl-1-propenohydroximoyl chloride (1.26 g, 9.5 mmol) in dichloromethane (30 mL) was added triethylamine (1.72 mL, 12.3 mmol) and 2-methyl-2-propene-1-ol (2.4 mL, 28.5 mmol). After being stirred for 1 h, the reaction mixture was poured into cold water, extracted with dichloromethane (30 mL × 2) and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/7) to give [5-methyl-3-(2-methylpropenyl)-4,5-dihydro-5-isoxazolyl]methanol (1.36 g, 85%) as a colorless oil. To a solution of [5-methyl-3-(2-methylpropenyl)-4,5-dihydro-5-isoxazolyl]methanol (0.5 g, 2.95 mmol) in DMF (20 mL) was added NaH (0.236 g, 5.9 mmol, 60% Aldrich) and the reaction mixture was stirred for 30 min. Benzyl bromide (0.525 mL, 4.42 mmol) was added and the mixture was stirred for 2 h at 25 °C. It was cooled and poured into cold water and extracted with EtOAc. The organic phase was washed with water, 1 N HCl solution, brine and dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/5) to give **1c** (0.656 g, 81%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.87 (s, 3H), 1.92 (s, 3H), 2.80 (d, 1H, *J*=16.4 Hz) 3.24 (d, 1H, *J*=16.4 Hz), 3.47 (qAB, 2H, *J*=10.0, 12.8 Hz), 4.60 (qAB, 2H, *J*=13.7, 14.5 Hz), 5.90 (s, 1H), 7.25~7.38 (m, 5H).

MS m/z (relative intensity) 259 (M^+, 4), 214 (6), 178 (3), 138 (39), 95 (51), 90 (100), 79 (8), 55 (13), 59 (23), 43 (26).

HRMS: Calcd for $C_{16}H_{21}NO_2$ 259.1579, found 259.1572.

3-(1,2-Dibromo-2-methylpropyl)-5-phenyl-1,2-isoxazoline (2a). To a solution of **1a** (1 g, 4.97 mmol) in dichloromethane (15 mL) was added bromine (0.793 mL, 9.94 mmol) at 25 °C and the mixture was stirred for 1 h at that temperature. It was cooled with ice-bath and 1.0 M aqueous $NaHSO_3$

solution (20 mL) was poured into reaction mixture and extracted with EtOAc The organic layer was washed with water, brine and dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/15) to give a diasteromeric mixture of **2a** (1.73 g, 96%) as a pale brown oil.

^{1}H NMR ($CDCl_3$) δ 1.93 (s, 3/2H), 1.95 (s, 3/2H), 1.97 (s, 3/2H), 1.99 (s, 3/2H), 3.20~3.29 (m, 1H), 3.31~3.81 (m, 1H), 5.20 (s, 1H), 5.60~5.71 (m, 1H), 7.35~7.43 (m, 5H).

MS m/z (relative intensity) 363 (M^-+2, 1), 360 (M^--1, 1), 280 (51), 201 (16), 182 (8), 168 (13), 158 (8), 127 (26), 104 (87), 84 (100), 77 (27), 55 (11), 41(25).

HRMS: Calcd for $C_{13}H_{15}NOBr_2$ 358.9520, found 358.9520.

Same procedure was applied for the preparation of **2b** and **2c**.

5-Butyl-3-(1,2-dibromo-2-methylpropyl)-1,2-isoxazoline (2b). a diastereomeric mixture as pale brown oil (99%). ^{1}H NMR ($CDCl_3$) 0.91 (t, 3H, J= 5.8 Hz), 1.31~1.47 (m, 4H), 1.48~1.72 (m, 2H), 1.93 (s, 3H), 1.97 (s, 3H), 2.82~2.97 (m, 1H), 3.21~3.39 (m, 1H), 4.61~4.72 (m, 1H), 5.10 (s, 1/2H), 5.12 (s, 1/2H).

MS m/z (relative intensity) 342 (M^-+1, 1), 341 (M^-, 6), 262 (100), 181 (67), 124 (51), 98 (16), 84 (37), 79 (11), 55 (46), 41 (37).

HRMS: Calcd for $C_{11}H_{19}NOBr_2$ 338.9833, found 338.9823.

5-Benzyloxymethyl-3-(1,2-dibromo-2-methylpropyl)-5-methyl-1,2-isoxazoline (2c). a diastereomeric mixture as pale brown oil (95%). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3/2H), 1.47 (s, 3/2H), 1.86 (s, 3/2H), 1.92 (s, 3/2H), 1.94 (s, 3/2H), 1.96 (s, 3/2H), 2.86 (d, 1/2H, J=7.7 Hz) 2.94 (d, 1/2H, J=7.5 Hz) 3.31-3.58 (m, 3H), 4.60 (qAB, 2H, J=9.2, 9.9 Hz), 5.07 (s, 1/2H), 5.09 (s, 1/2H), 7.24~7.35 (m, 5H).

MS m/z (relative intensity) 420 (M^-+1, 6), 388 (7), 338 (11), 298 (100), 258 (51), 228 (10), 216 (11), 204 (8), 177 (27), 163 (19), 107 (12), 91 (100), 79 (27), 55 (30), 43 (60).

HRMS: Calcd for $C_{16}H_{21}NO_2Br_2$ 416.9913, found 416.9910.

Debromination of 2a by sodium thiophenolate. To a solution thiophenol (0.304 mL, 2.76 mmol) in DMF (20 mL) was added NaH (0.11 g, 2.76 mmol, 60% Aldrich) and the reaction mixture was stirred for 30 min. 3-(1,2-Dibromo-2-methylpropyl)-5-phenyl-1,2-isoxazoline (**2a**) (0.5 g, 1.38 mmol) in DMF (5 mL) was added and the mixture was stirred for 2 h at 25 °C. The reaction mixture poured into cold water and extracted with EtOAc The organic phase was washed with water, 1 N HCl solution, brine and dried over anhydrous $MgSO_4$, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1/13) to give **1a** (0.269 g, 97%) as a pale yellow oil.

Debrominarions with various thiolates were summarized in *Table* 1.

REFERENCES

1. (a) Sato, F.; Akiyama, T.; Iida, K.; Sato, M. *Synthesis* **1982**, 1025. (b) Ames, D. E.; Bowman, R. E. *J. Chem. Soc.* **1951**, 1079. (c) Wilson, C. L. *J. Chem. Soc.* **1945**, 48. (d) Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1982**, *47*, 876. (e) Wang, L.; Zhang, Y. *Tetrahedron* **1999**, *55*, 10695. (f) Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett.* **1996**, *37*, 9313. (g) Ranu, B. C.; Guchhait, S. K.; Sarkar, A. *Chem. Commun.* **1998**, *19*, 2113.
2. (a) Momose, D. I.; Iguchi, K.; Sugiyama, T.; Yamada, Y. *Chem. Pharm. Bull.* **1984**, *32*, 1840. (b) Butcher, T. S.; Zhou, F.; Detty, M. R. *J. Org. Chem.* **1998**, *63*, 169. (c) Takaguchi, Y.; Hosokawa, A.; Yanada, S.; Motoyoshiya, J.; Aoyama, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, *19*, 3147. (d) Huang, X.; Hou, Y. Q. *Synth. Commun.* **1988**, *18*, 2201. (e) Engman, L. *Tetrahedron Lett.* **1982**, *23*, 3601. (f) De Moura Campos, M.; Petragnani, N.; Thome, C. *Tetrahedron Lett.* **1960**, *15*, 5. (g) Willner, I.; Tsfania, T.; Eichen, Y. *J. Org. Chem.* **1990**, *55*, 2656. (h) Sarmah, P.; Sarma, B. K.; Barua, N. C. *Indian J. Chem. Sect. B* **1997**, *36*, 528. (i) Malanga, C.; Aronica, L. A. *Tetrahedron Lett.* **1995**, *36*, 9189. (j) Sarma, J. C.; Borbaruah, M.; Sharma, R. P. *Tetrahedron Lett.* **1985**, *26*, 4657. (k) Inaba, S.; Matsumoto, H.; Rieke R. D. *J. Org. Chem.* **1984**, *49*, 2093. (l) Davies, S. G.; Thomas, S. E. *Synthesis* **1984**, 1027.
3. (a) Oriyama, T.; Mukaiyama, T. *Chem. Lett.* **1984**, 2069. (b) Khurana, J. M.; Sehgal, A. *Synth. Commun.* **1996**, *26*, 3791. (c) Landini, D.; Quici, S.; Rolla, F. *Synthesis* **1975**, 397. (d) Smith, L. I.; Holum, J. R. *J.*

Am. Chem. Soc. **1956**, *78*, 3417. (e) King, J. F.; Albutt, A. D.; Pews, R. G. *Can. J. Chem.* **1968**, *46*, 805.
4. (a) Hamed, E. A. *J. Indian Chem. Soc.* **1996**, *73*, 693. (b) Weygand, F.; Peine, H. G. *Rev. Chem. Acad. Repub. Pop. Romn.* **1962**, *7*, 1379 (*Chem. Abstr.* 61, 4208d).
5. Isager, P.; Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1990**, *44*, 806.