Tetrahedron Letters, Vol. 34, No. 32, pp. 5117-5120, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

The Reaction of Nitrile Oxide with Organometallic Compounds

Jae Nyoung Kim, Hyoung Rae Kim, and Eung K. Ryu*

Korea Research Institute of Chemical Technology.
Daedeog-Danji, Daejeon 305-606, Korea

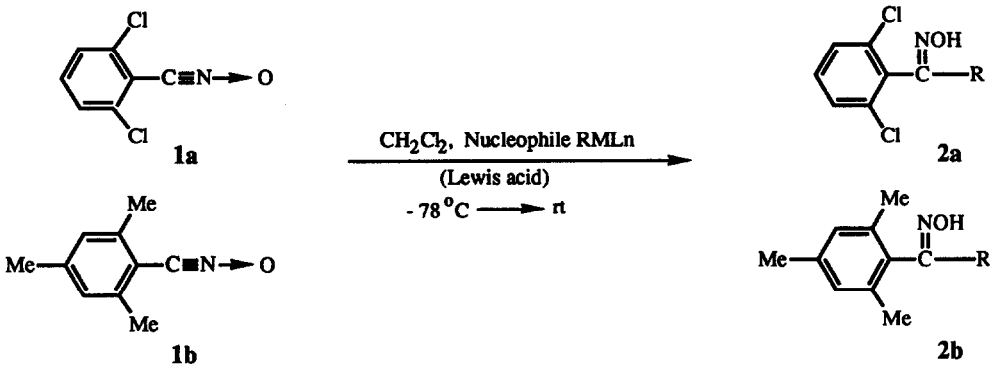
Summary: *Nitrile oxides react with some organometallic compounds with or without the aid of Lewis acid depending on the organometallic nucleophiles to give oxime derivatives in good yields.*

Nitrile oxides cycloadd with many unsaturated compounds leading to heterocyclic compounds.[1] They also react with many kinds of heteroatom containing nucleophiles such as amines, alcohols, water, thiols, carboxylates, azide, thiocyanate, cyanide, and chloride ions to give 1,3-addition products.[2] However, only a few studies have been reported on the reaction of nitrile oxide with carbon nucleophiles involving important carbon-carbon bond formation. Previously reported carbon nucleophiles included lithium salt of 1,3-dithiane,[3a] acetaldehyde,[3b] and methyl phenylacetate.[3c]

Recently we reported on the reaction of nitrile oxides with aromatic compounds with the aid of Lewis acid to increase the electrophilicity of the carbon atom of nitrile oxide.[4] In a continued program, we have studied the reactions of nitrile oxides with some organometallic compounds such as RLi, RMgX, R_2Zn, and organotin compounds. To examine the intrinsic reactivity of nitrile oxide toward these organometallic compounds, we chose 2,6-dichlorobenzonitrile oxide (**1a**) and 2,4,6-trimethylbenzonitrile oxide (**1b**) as substrates due to their stability toward dimerization to furoxan.[2a] The results obtained from the reaction of **1a-b** with some selected organometallic compounds are listed in **Table 1**. As shown in **Table 1**, **1a-b** reacted well without the aid of Lewis acid with organolithium compounds and Grignard reagents (entries 1-5 and 11-12),[5] whereas Lewis acid such as $BF_3{\cdot}OEt_2$ was needed in the case of diethylzinc and organotin compounds (entries 6-7, 9-10, and 13-15).[6] As shown in entry 8, the reaction of **1a** with allyltributyltin in the absence of $BF_3{\cdot}OEt_2$ afforded the [3+2] cycloaddition product[7] quantitatively instead of the 1,3-addition product. The use of other Lewis acids such as $AlCl_3$ or $TiCl_4$ found to be not effective in the reaction.

We also examined the reactivity of Grignard reagents as organometallic nucleophiles with some hydroximoyl chlorides, the precursor of nitrile oxides. Treatment of hydroximoyl chloride with 1.0 equivalent of Grignard reagent produced the corresponding nitrile oxide complexed with Lewis acid MgClX as Kanemasa et al. have reported,[8] which was then treated with additional Grignard reagent to give the desired oxime derivatives as shown in **Scheme 1** and **Table 2**.

Table 1. The reaction of **1a-b** with organometallic nucleophiles RMLn.

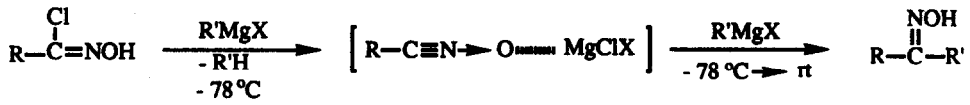


Entry	Nitrile Oxide	Lewis Acid (equiv)	Nucleophiles RMLn (equiv)	Time (h)	Product (R)	Yield[a] (%)
1	**1a**	-	MeLi (1.3)	5	**2a** (Me)	45
2	**1a**	-	*n*-BuLi (1.3)	5	**2a** (*n*-Bu)	94
3	**1a**	-	MeMgCl (1.2)	5	**2a** (Me)	95
4	**1a**	-	EtMgBr (1.2)	5	**2a** (Et)	95
5	**1a**	-	PhMgCl (1.2)	5	**2a** (Ph)	97
6	**1a**	-	Et_2Zn (1.1)	24	**2a** (Et)	30
7	**1a**	$BF_3{\cdot}OEt_2$ (1.1)	Et_2Zn (1.1)	24	**2a** (Et)	99
8	**1a**	-	CH_2=CH-$CH_2Sn(n\text{-}Bu)_3$ (1.2)	24	**b**	99
9	**1a**	$BF_3{\cdot}OEt_2$ (1.2)	CH_2=CH-$CH_2Sn(n\text{-}Bu)_3$ (1.2)	24	**2a** (-CH_2CH=CH_2)	75
10	**1a**	$BF_3{\cdot}OEt_2$ (1.2)	CH_3CH=$CHCH_2Sn(n\text{-}Bu)_3$ (1.2)	24	**2a** (-CH(CH_3)-CH=CH_2)	85
11	**1b**	-	*n*-BuLi (1.1)	5	**2b** (*n*-Bu)	58
12	**1b**	-	PhMgCl (1.2)	5	**2b** (Ph)	96
13	**1b**	$BF_3{\cdot}OEt_2$ (1.1)	Et_2Zn (1.1)	24	**2b** (Et)	93
14	**1b**	$BF_3{\cdot}OEt_2$ (1.2)	CH_2=CH-$CHSn(n\text{-}Bu)_3$ (1.2)	24	**2b** (-CH_2CH=CH_2)	75
15	**1b**	$BF_3{\cdot}OEt_2$ (1.2)	CH_3CH=$CHCH_2Sn(n\text{-}Bu)_3$ (1.2)	24	**2b** (-CH(CH_3)-CH=CH_2)	72

[a]Isolated yields of pure products and identified by MS, ^{1}H NMR, and ^{13}C NMR spectroscopy. [b][3+2] Cycloaddition product was obtained in 99% isolated yield (see reference 7).

The reaction of Grignard reagents with benzohydroximoyl chlorides as well as aliphatic hydroximoyl chloride (entry 5) afforded the corresponding oxime derivatives in moderate to good yields.[9]

In conclusion, we have examined the reactivity of nitrile oxides and hydroximoyl chlorides toward some organometallic compounds and developed an important carbon-carbon bond forming reactions.



Scheme 1

Table 2. The Reaction of Hydroximoyl Chlorides with Grignard Reagents.

Entry	Hydroximoyl Chloride (R)	R'MgX (equiv)	Time (h)	Yield[a] (%)
1	C_6H_5-	PhMgCl (2.4)	5	96
2	2,4,6-$Me_3C_6H_2$-	PhMgCl (2.4)	5	97
3	2,6-$Cl_2C_6H_3$-	EtMgBr (2.4)	5	94
4	2,3,5,6-F_4C_6H-	PhMgCl (2.4)	5	95
5	CH_3-$(CH_2)_4$-	PhMgCl (2.4)	5	65

[a]Isolated yields of pure products and identified by MS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Acknowledgement. We thank the Ministry of Science and Technology for financial support.

References and Notes

1. (a) D. P. Curran, Advances in Cycloaddition; JAI: Greenwich, CN, 1988; p129. (b) V. Jäger, I. Muller, R. Schohe, M. Frey, R. Ehrler, B. Hafele, and D. Schroter, *Lect. Heterocycl. Chem.*, **1985**, *8*, 79-98. (c) A. P. Kozikowski, *Acc. Chem. Res.*, **1984**, *17*, 410-416. (d) K. B. G. Torssell, Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis; VCH: New York, 1988. (e) S. Kanemasa and O. Tsuge, *Heterocycles*, **1990**, *30*, 719-736. (f) P. G. Baraldi, A. Barco, S. Benetti, G. P. Pollini, and D. Simoni, *Synthesis*, **1987**, 857-869.
2. (a) C. Grundmann and J, M, Dean, *J. Org. Chem.*, **1965**, *30*, 2809-2812. (b) C. Grundmann and H. D. Frommeld, *J. Org. Chem.*, **1966**, *31*, 157-162. (c) A. Dondoni and G. F. Pedulli, *J. Org. Chem.*, **1972**, *37*, 3564-3566. (d) H. Gozlan, R. Michelot, C. Riche, and R. Rips, *Tetrahedron*, **1977**, *33*, 2535-2542. (e) J. Plenkiewicz, *Tetrahedron*, **1978**, *34*, 2961-2966. (f) A. Q. Hussein, M. M. El-Abadelah, and W. S. Sabri, *J. Heterocycl. Chem.*, **1983**, *20*, 301-304.
3. (a) T. Yamamori and I. Adachi, *Tetrahedron Lett.*, **1980**, *21*, 1747-1750. (b) L. Di Nunno and A. Scilimati, *Tetrahedron*, **1987**, *43*, 2181-2189. (c) G. Dannhardt, S. Laufer, I. Obergrusberger, *Synthesis*, **1989**, 275-280. For theoretical studies on the reaction of nitrile oxide with nucleophiles, see: (d) K. J. Dignam, A. F. Hegarty, and P. L. Quain, *J. Org. Chem.*, **1978**, *43*, 388-393. (e) G. Leroy, M. T. Nguyen, M. Sana, K. J. Dignam, and A. F. Hegarty, *J. Am. Chem. Soc.*, **1979**, *101*, 1988-1994.
4. J. N. Kim and E. K. Ryu, *Tetrahedron Lett.*, **1993**, *34*, 3567-3570.
5. Typical procedure for the formation of **2a** (R = *n*-Bu) from **1a** and *n*-BuLi (entry 2 in **Table 1**): To a stirred

solution of 2,6-dichlorobenzonitrile oxide (**1a**, 283 mg, 1.5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise *n*-BuLi (2.5 M solution in hexane, 0.78 mL, 1.95 mmol) at -78 °C during 5 min. The reaction mixture was warmed to room temperature slowly and stirred for 5 h, and poured into saturated aqueous NH_4Cl solution. The reaction mixture was extracted with ether (50 mL x 2), and the organic layers were washed with 1 *N* HCl solution, brine, and dried with $MgSO_4$. Removal of solvents gave the desired product **2a** (R= *n*-Bu). Analytically pure product was obtained by silica gel column chromatography (hexane/ether, 8:2) as a white solid, 345 mg (94%); MS (70 eV) m/z (rel intensity) 47 (24), 49 (23), 84 (100), 86 (61), 168 (4), 246 (M^++1, 2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, *J* = 7.09 Hz, 3H), 1.25-1.41 (m, 4H), 2.69 (m, 2H), 7.17-7.32 (m, 3H), 9.33 (brs, 1H, oxime proton); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.70, 23.01, 27.07, 28.78, 128.02, 129.96, 134.55, 134.92, 157.84.

6. Typical procedure for the formation of **2a** (R = $-CH_2CH{=}CH_2$) from **1a** and allyltributyltin (entry 9 in **Table 1**): To a stirred solution of 2,6-dichlorobenzonitrile oxide (**1a**, 376 mg, 2.0 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of $BF_3{\cdot}OEt_2$ (340 mg, 2.4 mmol) in dry CH_2Cl_2 (0.5 mL) at -78 °C during 5 min. After stirred 5 min, a solution of allyltributyltin (795 mg, 2.4 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise during 5 min. The reaction mixture was warmed to room temperature slowly and stirred 24 h, and poured into saturated aqueous NH_4Cl solution . The reaction mixture was extracted with ether (50 mL x 3), and the organic layers were washed successively with 1 *N* HCl solution, 0.5 *N* KOH solution, water and dried with $MgSO_4$. After removal of solvents followed by silica gel column chromatography (hexane/ether, 8:2) pure product **2a** (R = $-CH_2CH{=}CH_2$) was obtained as a white solid, 345 mg (75%); MS (20 eV) m/z (rel intensity) 41 (45), 124 (44), 185 (100), 186 (71), 187 (100), 198 (100), 199 (61), 200 (100), 212 (51), 230 (M^++1, 50), 232 (27); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.48-3.52 (m, 2H), 4.94-5.13 (m, 2H), 5.63-5.77 (m, 1H), 7.18-7.34 (m, 3H), 9.05 (brs, 1H, oxime proton); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.56, 118.68, 127.92, 130.21, 130.81, 133.93, 134.92, 155.82.

7. Characterization of the [3+2] cycloaddition product: a colorless oil (entry 8 in **Table 1**); MS (20 eV) m/z (rel intensity) 231 (25), 233 (32), 235 (40), 291 (30), 460 (29), 461 (31), 462 (M^+-Bu, 45), no M^+; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80-1.00 (m, 15H), 1.05-1.70 (m, 14H), 2.80 (dd, *J* = 16.60 and 7.60 Hz, 1H), 3.35 (dd, *J* = 16.60 and 9.85 Hz, 1H), 4.99-5.08 (m, 1H), 7.24-7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.35, 13.61, 16.64, 27.28, 29.03, 44.96, 82.48, 127.98, 129.34, 130.70, 135.07, 153.49.

8. S. Kanemasa, S. Kobayashi, M. Nishiuchi, H. Yamamoto, and E. Wada, *Tetrahedron Lett.*, **1991**, *32*, 6367-6370.

9. Typical procedure for the formation of **2b** (R' = Ph) from 2,4,6-trimethylbenzohydroximoyl chloride and PhMgCl (entry 2 in **Table 2**): To a stirred solution of 2,4,6-trimethylbenzohydroximoyl chloride (297 mg, 1.5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise PhMgCl (2.0 M solution in THF, 1.8 mL, 3.6 mmol) at -78 °C during 5 min. The reaction mixture was warmed to room temperature slowly and stirred 5 h. After following the same workup procedure as shown in reference 5, pure product was obtained as a white solid, 348 mg (97%); MS (20 eV) m/z (rel intensity) 120 (21), 144 (78), 222 (100), 224 (57), 239 (M^+, 31); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 6H), 2.31 (s, 3H), 6.89 (s, 2H), 7.30-7.69 (m, 5H), 9.45 (brs, 1H, oxime proton); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.80, 21.10, 128.02, 128.45, 129.50, 130.05, 132.34, 133.24, 137.10, 138.02, 155.36.

(Received in Japan 30 March 1993; accepted 11 June 1993)