HETEROCYCLES, Vol. 63, No. 7, 2004, pp. 1659 - 1665
Received, 23rd March, 2004, Accepted, 10th May, 2004, Published online, 11th May, 2004

REACTION OF 3,5-DICYANOISOXAZOLES WITH NUCLEOPHILES

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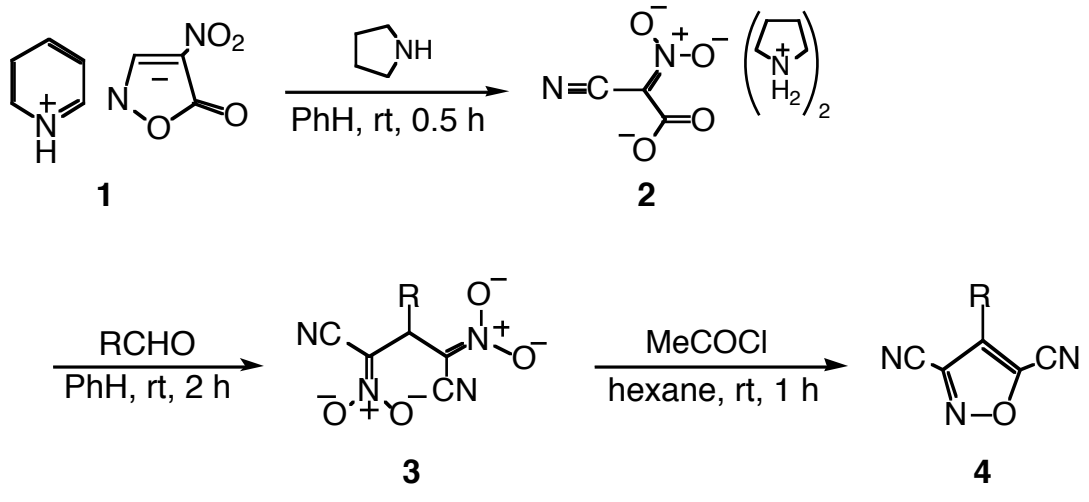
Abstract – Cyano groups on 3,5-dicyanoisoxazole readily caused nucleophilic addition of alcohols (or amines) to give corresponding imidates (or amidines). Dicyanoisoxazoles was also converted to 3,5-bis(imidazolinyl)isoxazoles upon treatment with 1,2-diamines.

INTRODUCTION

4-Nitroisoxazolin-5(*2H*)-ones have multi-functionalities, and the structural features cause versatile reactivities to afford polyfunctionalized compounds. 2-Methylated derivative, for example, behaves as the precursor for nitrile oxide,[1] nitropyrroles,[2] amidoximes[3] and nitroketene aminals.[3] Active anionic isoxazolone (**1**) afforded easily 3,5-dicyanoisoxazoles (**4**)[4] via dianionic intermediates, cyano-*aci*-nitroacetates (**2**)[5] and di-*aci*-nitropentanedinitriles (**3**),[6] under mild conditions in one pot as shown in Scheme 1. In this preparation of **4**, it is easy to modify the substituent at the 4-position by changing aldehydes.

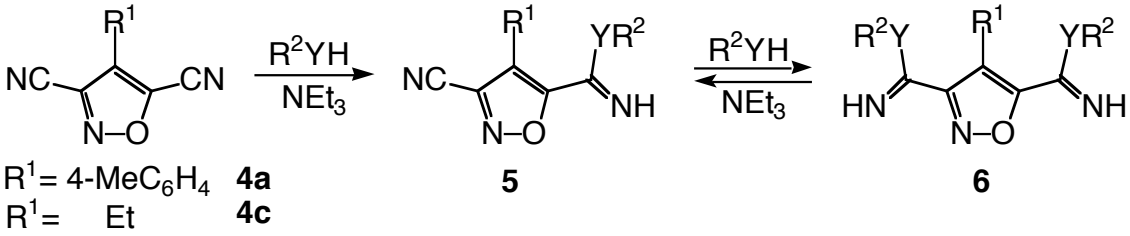


1 **2** **3** **4**

Scheme 1

Although numerous isoxazoles have been used as biologically active compounds such as medicines and agricultural chemicals,[7] preparation of new isoxazole derivatives is one of the important projects in this area. Since **4** has two cyano groups which diminish electron density each other through the isoxazole ring, nucleophilic addition with alcohols (or amines) leading to imidates[8] (or amidines) is considered to be facile.

Table Nuculeophilic Addition to Cyano Groups of **4**



R^1= 4-MeC_6H_4 **4a**
R^1= Et **4c**

5 **6**

							Ratio[a]	
Run	R^1	R^2	Y	Time/d	Temp/°C		**5**	**6**
1	4-MeC_6H_4	Me	O	1	rt	**a**	60	40
2				4	rt		0	100
3				6	65		15	85
4	4-MeC_6H_4	Et	O	5	rt	**b**	94	6
5				12	rt		90	10
6				2	80		56	44
7				8	80		67	33
8	Et	Me	O	1	rt	**c**	10	90
9				4	rt		0	100
10[b]	4-MeC_6H_4	Pr	NH	3	rt	**d**	20[c]	—

a) Isoxazoles (**4**) were quantitatively converted to **5** and **6**, and their ratio was determined by ^{1}H-NMR spectrometry.

b) Propylamine (20 equiv.) was added to a solution of **4a** in benzene.

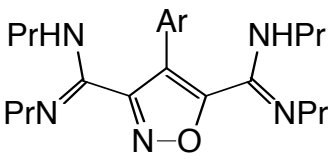
c) Isolated yield.

RESULTS AND DISCUSSION

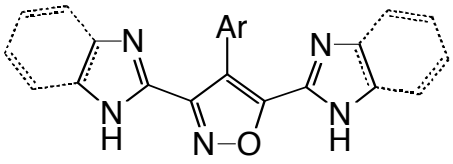
When isoxazole (**4a**) was treated with triethylamine in methanol for 1 day, monoimidate (**5a**) and diimidate (**6a**) were afforded in 60% and 40% yields respectively (Table, Run 1). Although we have not obtained enough evidence, the first addition of alcohol may occur at the 5-position adjacent to the more

electronegative oxygen. 4-Nitrobenzonitrile having an electron deficient cyano group was also allowed to react under the same conditions for comparison of reactivity with **4a**, however no change was observed. Thus, the cyano group was concluded to be more reactive than that of nitrobenzonitrile. Prolonged reaction time realized the quantitative addition of methanol to both cyano groups of **4a** (Run 2).

On the other hand, monoimidate (**5a**) was not completely consumed under heated conditions, which suggested the presence of equilibrium between **5a** and **6a** (Run 3). Actually, monoimidate (**5a**) was formed in 16% yield when isolated **6a** was heated in methanol under reflux for 1 h in the presence of triethylamine, which indicated that both addition and elimination of methanol were assisted by triethylamine. When a solution of **4a** in ethanol was stirred at room temperature in the presence of triethylamine, ethylmonoimidate (**5b**) was formed, however longer reaction time was not effective for double addition (Runs 4 and 5). Furthermore, isopropanol and *tert*-butanol caused no change even at elevated temperature. Thus, the present addition was sensitive to bulkiness of the nucleophile. The yield of **6b** was considerably increased when reaction temperature was elevated, and the equilibrium between **5b** and **6b** was also observed (Runs 5-7). 4-Ethylisoxazole (**4c**) was easily converted to diimidate (**6c**) (Runs 8 and 9). The less bulky substituent at the 4-position might facilitate the approach of methanol to the cyano group. Employment of more reactive propylamine as the nucleophile gave a complicated reaction mixture, and amidine (**5d**) was obtained in 20% yield (Run 10). In the present reaction, several adducts having more than two *N*-propyl groups such as **7d** were additionally obtained. These adducts were formed by reactions of **5d** with extra amines. This experimental fact prompted us to study the conversion of the substituents of **4** and **6** to imidazolinyl groups.

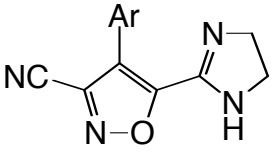


7d



7e,f

Ar = 4-MeC_6H_4



8e

When dicyanoisoxazole (**4a**) was allowed to react with 2 equivalents of ethylenediamine in tetrahydrofuran, imidazolinylisoxazoles (**7e**) and (**8e**) were furnished in 64% and 36% yields, respectively. To the contrary, 4-nitrobenzonitrile was intact under the same conditions, which also proved the high reactivity of the cyano groups of **4**. Although the reaction of **4a** with phenylenediamine did not proceed, more reactive diimidate (**6a**) gave bis(benzoimidazol-2-yl)isoxazole (**7f**) in 31% yield.

In summary, cyano groups of 3,5-dicyanoisoxazoles (**4**) were found to be highly reactive, and could be converted into corresponding imidates (**5**) and amidines (**6**) under mild conditions with simple experimental manipulations. Furthermore, these nucleophilic reactions were applied to construction of new isoxazole derivatives (**7**) and (**8**) having imidazolinyl groups.

EXPERIMENTAL

Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. The IR spectra were recorded on a Horiba FT-200 infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured on a Brucker DPX-400 at 400 MHz and at 100 MHz respectively with TMS as an internal standard. ^{13}C NMR assignments (s, d, t and q) were made from DEPT experiments. MS spectra were recorded on a JEOL JMS-AX505HA, and elemental microanalyses were performed using a Yanaco MT-3 CHN corder. All reagents and solvents were commercially available and used as received.

Preparation of Dicyanoisoxazole (4a).[4] To a suspension of pyridinium salt (**1**, 418 mg, 2.0 mmol) in benzene (6 mL), pyrrolidine (0.35 mL, 4.2 mmol) was added, and the mixture was stirred at rt for 0.5 h. To the resultant solution, 4-methylbenzaldehyde (0.12mL, 1.0 mmol) was added. After 2 h stirring, hexane (20 mL) was added, and the mixture was stood overnight. Upper solution was decanted off, and hexane (12 mL) and acetyl chloride (0.36 mL, 5.0 mmol) were added. After 1 h stirring, the upper solution was decanted, and the residual oil was extracted with hexane (20 mL x 3). The combined hexane solution was concentrated to give almost pure **4a**. Further purification was performed by column chromatography on silica gel to afford **4a** as pale yellow solid (117mg, 56%). Isoxazole (**4c**) was prepared in a similar way.

Typical procedure for preparation of 5 and 6. To a solution of dicyanoisoxazole (**4a**, 209 mg, 1.0 mmol) in methanol (10 mL), triethylamine (0.14 mL, 1.0 mmol) was added, and the resultant solution was stirred at rt for 4 days. After removal of solvent, the residue was almost pure diimidate (**6a**) without detection of any other signals in the ^{1}H NMR spectrum. Reactions using other isoxazoles and alcohols were carried out in the same way. When the reaction was conducted for 1 day, formation of monoimidate (**5a**) was confirmed by ^{1}H NMR spectrum of the reaction mixture, however **5a** could not be isolated, because of easy decomposition in the silica gel column (chloroform). Further purification was performed by recrystallization with mixed solvent of chloroform and hexane.

3,5-Bis(methylimidocarbomethoxy)-4-(4-methylphenyl)isoxazole (6a)

Colorless needles (from chloroform and hexane); mp: 105-107 °C; IR (KBr) 3332, 1651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.81 (s, 6H), 7.19 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.93 (s, 1H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (q), 53.4 (q), 53.5 (q), 119.7 (s), 124.0 (s), 129.4

(d), 129.7 (d), 139.4 (s), 156.1 (s), 157.3 (s), 157.9 (s), 160.1 (s); MS (FAB) 274 (M^++1, 100%). Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.34; H, 5.45; N, 15.09.

3-Cyano-5-methylimidocarbomethoxy-4-(4-methylphenyl)isoxazole (5a)

The formation of monoimidate (**5a**) was confirmed with ^{1}H NMR spectrum, however isolation of **5a** could not be performed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.86 (s, 3H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 8.44 (s, 1H).

3-Cyano-5-methylimidocarboethoxy-4-(4-methylphenyl)isoxazole (5b)

Colorless needles (from chloroform and hexane); mp: 78-79 °C; IR (KBr) 3311, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 2.43 (s, 3H), 4.32 (q, *J* = 7.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 8.31(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (q), 21.4 (q), 62.8 (t), 109.2 (s), 121.7 (s), 122.5 (s), 129.3 (d), 129.6 (d), 140.3 (s), 141.6 (s), 156.5 (s), 157.5 (s); MS (FAB) 256 (M^++1, 100%). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.00; H, 5.42; N, 16.19.

3,5-Bis(methylimidocarboethoxy)-4-(4-methylphenyl)isoxazole (6b)

The formation of diimidate (**6b**) was confirmed with ^{1}H NMR spectrum, however isolation of **6b** could not be performed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.4 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 4.21 (m, 4H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.97 (s, 1H), 8.02 (s, 1H).

3-Cyano-4-ethyl-5-(methylimidocarboethoxy)isoxazole (5c)

The formation of monoimidate (**5c**) was confirmed with ^{1}H NMR spectrum, however isolation of **5c** could not be performed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.6 Hz, 3H), 2.79 (q, *J* = 7.6 Hz, 2H), 4.00 (s, 3H), 8.42 (s, 1H).

3,5-Bis(methylimidocarboethoxy)-4-ethylisoxazole (6c)

Colorless needles (from hexane): mp: 50-52 °C; IR (KBr) 3307, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.5 Hz, 3H), 2.79 (q, *J* = 7.5 Hz, 2H), 3.97 (br s, 6H), 6.6-9.7 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9 (q), 16.3 (t), 53.6 (q), 53.7 (q), 119.8 (s), 157.3 (s), 157.6 (s), 158.8 (s), 160.7 (s); MS (FAB) 212 (M^++1, 100%).

Reaction of 4a with propylamine. To a solution of dicyanoisoxazole (**4a**, 63 mg, 0.3 mmol) in benzene (3 mL), propylamine (0.48 mL, 6.0 mmol) was added, and the mixture was stirred at rt for 3 days. The reaction mixture after evaporation was a complex mixture of isoxazoles having plural *N*-propyl groups. Since these products had similar property, it was difficult to separate the mixture, and **5d** was

obtained as somewhat crude product in 20% yield on treatment with column chromatography on silica gel (eluted with ethyl acetate).

3-Cyano-5-*N*^{1}-propylamidino-4-(4-methylphenyl)isoxazole (5d)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.25 (s, 1H), 1.60 (tq, *J* = 7.3 Hz, *J* = 7.3 Hz), 2.43 (s, 3H), 3.26 (br t, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H).

Reaction of 4a with diamines. To a solution of dicyanoisoxazole (**4a**, 213 mg, 1.0 mmol) in tetrahydrofuran (10 mL) ethylenediamine (0.14 mL, 2.1 mmol) was added, and the mixture was heated under reflux for 5 days. After removal of solvent, the residual yellow solid was a mixture of **7e** and **8e** in 64% and 36% yields, which were determined by ^{1}H NMR spectrum. The reaction using phenylenediamine was carried out in the same way.

Reaction of 6a with diamines. To a solution of dicyanoisoxazole (**6a**, 273 mg, 1.0 mmol) in tetrahydrofuran (10 mL), ethylenediamine (0.14 mL, 2.1 mmol) was added, and the mixture was heated under reflux for 5 days. The precipitated **7e** was collected by filtration in 38% yield. Further purification was performed by recrystallization with mixed solvent of chloroform and hexane. The reaction using phenylenediamine was carried out in the same way.

3,5-Bis(imidazolinyl)-4-(4-methylphenyl)isoxazole (7e)

Colorless needles (from chloroform and hexane); mp: 208-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.32 (s, 3H), 2.9-4.1 (br, 8H), 6.7-7.2 (br, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.8 (q), 119.4 (s), 124.4 (s), 128.0 (d), 130.2 (d), 137.3 (s), 153.9 (s), 155.1 (s), 155.3 (s), 157.7 (s). Two broadened signals were observed near 50 ppm, which were assigned for imidazolinyl ring carbons.; MS (FAB) 176 (100%), 232 (97%), 296 (M^++1, 68%); Anal. Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.40; H, 5.75; N, 23.38.

3,5-Bis(benzoimidazol-2-yl)-4-(4-methylphenyl)isoxazole (7f)

White powder; mp: > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.36 (s, 3H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.2 – 7.4 (m, 4H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.5 – 7.7 (m, 4H), 13.30 (s, 1H), 13.44 (s, 1H); MS (FAB) 176 (100%), 232 (67%), 289 (58%), 307 (75%), 391 (M^+, 33%); Anal. Calcd for $C_{24}H_{17}N_5O$: C, 73.64; H, 4.38; N, 17.89. Found: C, 73.47; H, 4.30; N, 17.68.

3-Cyano-5-imidazolinyl-4(4-methylphenyl)isoxazole (8e)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.6 - 3.9 (br, 4H), 6.9 - 7.1 (br, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H).

REFERENCES

1. N. Nishiwaki, T. Uehara, N. Asaka, Y. Tohda, M. Ariga, and S. Kanemasa, *Tetrahedron Lett*., 1998, **39**, 4851.
2. N. Nishiwaki, M. Nakanishi, T. Hida, Y. Miwa, M. Tamura, K. Hori, Y. Tohda, and M. Ariga, *J. Org. Chem*., 2001, **66**, 7535.
3. N. Nishiwaki, Y. Okajima, M. Tamura, N. Asaka, K. Hori, Y. Tohda, and M. Ariga, *Heterocycles*, 2003, **60**, 303.
4. N. Nishiwaki, T. Nogami, T. Kawamura, N. Asaka, Y. Tohda, and M. Ariga, *J. Org. Chem.,* 1999, **64**, 6476.
5. N. Nishiwaki, Y. Takada, Y. Inoue, Y. Tohda, and M. Ariga, *J. Hetrocycl. Chem*., 1995, **32**, 473.
6. N. Nishiwaki, T. Nogami, C. Tanaka, F. Nakashima, Y. Inoue, N. Asaka, Y. Tohda, and M. Ariga, *J. Org. Chem.,* 1999, **64**, 2160.
7. S. A. Lang, Jr., Y.-i Lin, *Isoxazoles and Their Derivatives*; in *Comprehensive Heterocyclic Chemistry*, Vol. 6, pp. 1-130, ed. by K. T. Potts, Pergamon Press, Oxford, 1984.
8. R. J. Grout, *Biological Reactions and Pharmaceutical Uses of Imidic Acid Derivatives,* in *The Chemistry of the Amidines and Imidates*, pp. 255-282, ed. by S. Patai, John Wiley & Sons, London, 1975.