Ring Opening Reaction of the Pyridinium Salt of 4-Nitro-3-isoxazolin-5-one: A Preparation of Trifunctionalized Methane Derivatives

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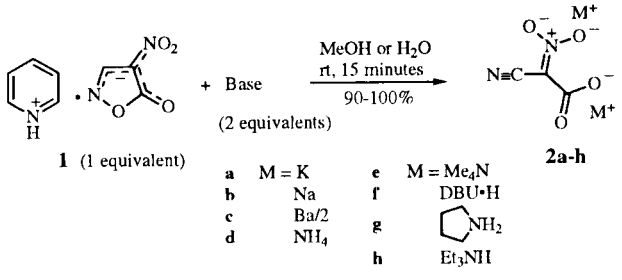
Received November 23, 1994

The ring cleavage of the pyridinium salt of 4-nitro-3-isoxazolin-5-one **1** was found to proceed under mild basic conditions and to give cyano-*aci*-nitroacetates **2** in quantitative yields. The ring opened products **2** have three different functional groups at the same carbon atom, and are worth applying as a useful building block to syntheses of polyfunctionalized compounds.

J. Heterocyclic Chem., **32**, 473 (1995).

3-Isoxazolin-5-ones bearing an electron withdrawing group are considered to show versatile reactivities owing to their various functionalities. The greater part of the reports about them dealt with 4-ethoxycarbonyl derivatives [1-3], and only in a few instances were the 4-nitro derivatives utilized for preparation of 1-oxa-2,6,8-triazaspiro[4.4]nonane ring systems [4,5]. We have reported that 4-nitro-3-isoxazolin-5-one derivatives possess interesting reactivity [6,7]. Now, ring opening studies of the anionic isoxazolone system **1** was conducted to extend the synthetic utility of this compound. In the present paper, we wish describe the ring cleavage of **1** yielding trifunctionalized methane derivatives. Although a number of ring opening reactions of isoxazolinones were published [1-3,8-13], there was no report about the transformation from the anionic isoxazolinone into trifunctionalized methane derivatives to our knowledge.

Scheme 1



1 (1 equivalent)

2a-h

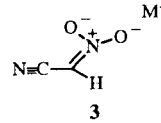
a	M = K	**e**	M = Me_4N
b	Na	**f**	DBU•H
c	Ba/2	**g**	
d	NH_4	**h**	Et_3NH

The readily available pyridinium salt of 4-nitro-3-isoxazolin-5-one **1** [14] was treated with potassium hydroxide at room temperature to afford dipotassium cyano-*aci*-nitroacetate (**2a**, M = K) in 98% yield as a pale yellow precipitate. The structure of **2a** was supported by the characteristic infrared absorption of the nitrile group at 2214 cm^{-1} which was as strong as that of carbonyl group.

The present reaction proceeded under sufficiently mild conditions (room temperature) as compared with similar ring opening reactions requiring severe conditions [10,11]. This difference was presumably due to the activation of the isoxazoline ring by the nitro group.

The ring opened-product **2a** has a synthetically interesting structure, namely three different functional groups, cyano, carboxylate and *aci*-nitro groups, are connected at the same carbon atom. Although esters of cyano-*aci*-nitroacetic acid were widely reported [15-18], there is no description about the dianion except barium salt **2c** [19]. These esters and dianion had not been utilized for organic syntheses because of the difficulty to prepare and to treat them in organic solvents.

The dianion **2a** was thermally stable, but decarboxylation easily occurred to afford nitroacetonitrile under acidic conditions below *p*H 4. Decarboxylation also proceeded when the aqueous solution of **2a** was passed through ion-exchange resin (IRC-50). In this case, the potassium salt of nitroacetonitrile **3a** [16] was obtained in 79% yield.



3

Figure

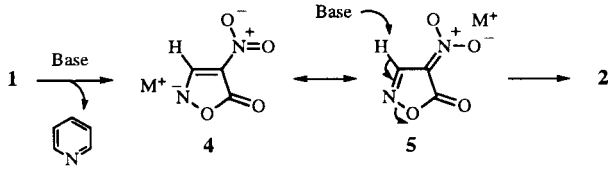
Some other bases were investigated under the same conditions as used for potassium hydroxide. The reaction of the pyridinium salt **1** with sodium hydroxide and sodium hydrogen carbonate gave disodium salt **2b** (M = Na). Sodium ethoxide, which is more nucleophilic and frequently attacks the carbonyl group [12,13], also furnished **2b**. Dianions **2c** [19], **2d** and **2e** were prepared by using barium hydroxide, diammonium carbonate and tetramethylammonium hydroxide, respectively. However, it was difficult to apply dianions **2a-e** to organic syntheses as they were almost insoluble in even polar organic solvents such as dimethyl sulfoxide, *N,N*-dimethylformamide, acetonitrile, methanol and pyridine.

Hence, organic bases were employed in order to increase the solubility of the dianion **2** in organic solvents. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and pyrrolidine

afforded the corresponding quaternary salts **2f** and **2g**, but only cation exchanged product **4h** was afforded in the case of triethylamine. When a solution of the pyridinium salt **1** was refluxed with triethylamine in acetonitrile having a large dielectric constant, the dianion **2h** was not as yet detected and the decarboxylated product **3h** was yielded quantitatively. According to expectations, the quaternary salts **2f** and **2g** were soluble in several organic solvents such as benzene, chloroform, methanol, ethanol, acetonitrile, *etc.*

The ring opening reaction of the pyridinium salt **1** was considered to proceed in a following manner. The first molecule of the base is used for exchange of the counter cation of **1** to give **4**. The proton at the 3-position of *aci*-nitro type anion **5**, one of resonance structures, is attacked by the second molecule of the base. Successive cleavage of the N-O bond occurred to produce **2**.

Scheme 2



The reaction mechanisms mentioned above were easily followed by ^{1}H nmr. To a solution of **1** in dimethyl sulfoxide-d_6, an equimolar amine, DBU or triethylamine, was added. In each case, a singlet signal of the proton at the 3-position (δ 8.47) was unchanged and all of protons of a pyridine ring shifted to higher field. The signals of the amines were observed at lower fields than those of the free amines. These observations showed the formation of the ammonium salt **4f** and **4h** instead of the pyridinium salt **1**. Disappearance of the signal at δ 8.47 of **4f** by addition of one more equivalent of the DBU suggested that **4f** was transformed to the dianion **2f**. A similar treatment of **4h** with additional triethylamine left the whole signals of **4h** intact.

In summary, the dianions **2** were readily prepared by the ring-opening reaction of 4-nitroisoxazolinone **1**. They are considered to be a useful synthetic intermediate of polyfunctionalized compounds. The reactions of **2** with various electrophiles such as carbonyl compounds, alkyl halides and ethers are under investigation.

EXPERIMENTAL

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. All reagents and solvents were commercially available and used as received. The ir spectra were recorded on a Horiba FT-200 infrared spectrometer and the ^{1}H nmr spectra were measured on a Hitachi NMR R-1200 at 60 MHz with tetramethylsilane as an internal standard. Elemental microanalyses were performed using a Yanaco MT-3 CHN corder.

Pyridinium Salt of 4-Nitro-3-isoxazolin-5-one **1** [14].

To a solution of 16.10 g (100 mmoles) of methyl 3-methoxy-2-nitropropenoate [20] dissolved in 161 ml of ethanol, 7.73 g (120 mmoles) of hydroxylamine hydrochloride and 20.2 ml (250 mmoles) of pyridine were added. The mixture was heated at 60 ° for 3 hours and cooled. Pale yellow needles were collected and air-dried to yield 14.84 g (71 mmoles) of **1**, mp 141-142° dec; ir (Nujol): ν 1693 (CO), 1533, 1335 (NO_2) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.10 (dd, 2H, J = 8.0, 6.0 Hz), 8.46 (s, 1H, 3-H), 8.50 (t, 1H, J = 8.0 Hz), 8.95 (d, 2H, J = 6.0 Hz), 9.1-9.7 (br, 1H).

General Procedure for the Preparation of Cyano-*aci*-nitroacetates **2**.

The pyridinium salt of 4-nitro-3-isoxazolin-5-one **1** (2.09 g, 10 mmoles) was dissolved in 40 ml of 0.5 *M* potassium hydroxide in methanol and stirred at room temperature for 15 minutes. A pale yellow precipitate was observed during the stirring. The solid was collected and air-dried to afford 2.01 g (9.76 mmoles, 98%) of dipotassium cyano-*aci*-nitroacetate (**2a**), mp >300°; ir (Nujol): 2214 (CN), 1626 (br, CO) cm^{-1}. The presence of the potassium was confirmed by the flame reaction.

Anal. Calcd. for $C_3N_2O_4K_2$: C, 17.47; H, 0.00; N, 13.58. Found: C, 17.33; H, 0.27; N, 13.79.

The other dianions **2b-g** were prepared by a similar method. Sodium hydroxide and organic bases were employed as 0.5 *M* solutions in methanol. In the case of sodium hydrogen carbonate, barium hydroxide, diammonium carbonate and tetramethylammonium hydroxide, 0.5 *M* aqueous solutions were used. Dianions **2b-g** were obtained in 90-100% yields. Since diammonium salts **2d-g** were hygroscopic and/or readily decarboxylated, satisfactory elemental analytical data were not obtained.

Disodium Cyano-*aci*-nitroacetate (**2b**).

This compound was obtained as a colorless solid, mp >300°; ir (Nujol): 2218 (CN), 1608 (CO) cm^{-1}.

Anal. Calcd. for $C_3N_2O_4Na_2$: C, 20.71; H, 0.00; N, 16.10. Found: C, 20.61; H, 0.19; N, 16.07.

Diammonium Cyano-*aci*-nitroacetate (**2d**).

This compound was obtained as a pale yellow solid, mp 120-137 ° dec; ir (Nujol): 2212 (CN), 1660 (CO) cm^{-1}.

Bis(tetramethylammonium) Cyano-*aci*-nitroacetate (**2e**).

This compound was obtained as a colorless solid, mp 38-41°; ir (neat): 2193 (CN), 1633 (CO) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 3.13 (s).

Bis(1,8-diazabicyclo[5.4.0]undec-7-enium) Cyano-*aci*-nitroacetate (**2f**).

This compound was obtained as brown oil; ir (neat): 2193 (CN), 1645 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.7-2.3 (m, 16H), 2.6-2.9 (m, 4H), 3.3-3.7 (m, 12H), 5.7-6.0 (br, 2H).

Dipyrrolidinium Cyano-*aci*-nitroacetate (**2g**).

This compound was obtained as a yellow oil; ir (neat): 2197 (CN), 1630 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.7-2.3 (m, 8H), 3.0-3.5 (m, 8H), 7.3-7.8 (br, 4H).

Decarboxylation of Dianion **2a**.

A solution of 485 mg (2.35 mmoles) of dipotassium salt **2a** dissolved in water (10 ml) was passed through 50 ml of ion-exchange resin (IRC-50). The resin was washed with water. The aqueous solution was concentrated *in vacuo* to afford monopotassium salt **3a** [16] as pale yellow plates, 230 mg (1.86 mmoles, 79%), mp 174-176°; ir (Nujol): 2224 (CN) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 5.61 (s); The presence of the potassium was confirmed by the flame reaction.

Anal. Calcd. for $C_2HN_2O_2K$: C, 19.35; H, 0.81; N, 22.57. Found: C, 19.46; H, 0.79; N, 22.85.

Triethylammonium Salt of Nitroacetonitrile **3H,**

This compound was obtained as a yellow oil; ir (neat): 2196 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (t, 9H, J = 7.4 Hz), 3.14 (q, 6H, J = 7.4 Hz), 5.0-7.5 (br, 2H). Since ammonium salt **3h** was hygroscopic, satisfactory elemental analytical data were not obtained. The salt **3h** was converted to potassium salt **3a** by adding a solution of potassium hydroxide in methanol.

REFERENCES AND NOTES

[1] H. Ulrich, J. N. Tilley and A. A. Sayigh, *J. Org. Chem.*, **27**, 2160 (1960).

[2] D. J. Woodman, C. H. Borman, N. Tontapanish and P. M. Stonebraker, *J. Org. Chem.*, **34**, 2981 (1969).

[3] C. Donati, W. K. Janowski, P. H. Prager, M. R. Taylor and L. M. Vilkins, *Aust. J. Chem.*, **42**, 2161 (1989).

[4] R. Nesi, S. Chimichi, F. De Sio, R. Pepino and P. Tedeschi, *Tetrahedron Letters*, **23**, 4397 (1982).

[5] R. Nesi, S. Chimichi, D. Giomi, P. S. Fantoni and P. Tedeschi, *J. Chem. Soc., Perkin Trans. 1*, 1005 (1987).

[6] S. Higashida, H. Nakashima, Y. Tohda, K. Tani, N. Nishiwaki and M. Ariga, *Heterocycles*, **34**, 1511 (1992).

[7] N. Nishiwaki, Y. Takada, K. Tani, Y. Tohda and M. Ariga, *Chem. Express*, **7**, 845 (1992).

[8] D. J. Woodman, W. H. Cambell and E. F. DeRose, *Heterocycles*, **7**, 247 (1977).

[9] A. Mustafa, W. Asker, A. H. Harhash and N. A. L. Kassab, *Tetrahedron*, **19**, 1577 (1963).

[10] L. D. Quin and D. O. Pinion, *J. Org. Chem.*, **35**, 3130 (1970), (refluxed for 23 hours in methanol).

[11] F. De Sarlo and G. Dini, *J. Heterocyclic Chem.*, **4**, 533 (1967); (heated with sodium hydroxide or sodium ethoxide at 60° for 12 hours).

[12] A. Silveria Jr. and S. K. Satra, *J. Org. Chem.*, **44**, 873 (1979).

[13] F. De Sarlo and G. Renzi, *Tetrahedron*, **22**, 2995 (1966).

[14] M. Ariga, Y. Tohda, H. Nakashima, K. Tani, Y. Mori and E. Matsumura, *Bull. Chem. Soc. Japan*, **64**, 3544 (1991).

[15] M. Conrad and A. Schulze, *Ber.*, **42**, 735 (1909).

[16] C. O. Parker, *Tetrahedron*, **17**, 109 (1962).

[17] C. Grundmann, G. W. Nickel and R. K. Bansal, *Liebigs Ann. Chem.*, 1029 (1975).

[18] T. D. Ladyzhnikova, A. G. Tyrkov, K. V. Altukhov, V. P. Pozdnyakov, M. O. Dekaprilevich and K. I. Rezchikova, *J. Org. Chem. U.S.S.R.*, 700 (1993); Translated from *ZH. Org. Chem.*, **28**, 912 (1992).

[19] C. Ulpiani, *Gazz. Chim. Ital.*, **42**, 209 (1912), detailed information about the dianion **2** was not obtained.

[20] Propenoate derivative was prepared from nitromethane *via* 3 steps. From nitromethane to methyl nitroacetate (2 steps): S. Zen, M. Koyama and S. Koto, *Org. Synth.*, Coll Vol **6**, 797 (1988); From methyl nitroacetate to 2-methoxy-3-nitropropenoate: M. J. Kamlet, *J. Org. Chem.*, **24**, 714 (1959).