Synthesis of 2,3-Difunctionalized 4-Nitropyrroles

Nagatoshi Nishiwaki,*,† Masataka Nakanishi,† Takahiko Hida,† Yuko Miwa,† Mina Tamura,† Kazushige Hori,‡ Yasuo Tohda,‡ and Masahiro Ariga*,†

Department of Chemistry, Osaka Kyoiku University, and Division of Natural Science, Osaka Kyoiku University, Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan

ariga@cc.osaka-kyoiku.ac.jp

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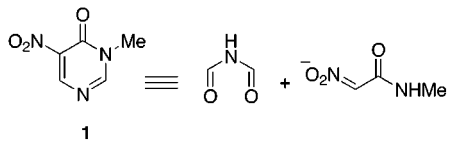
Introduction

It is often difficult to introduce a functional group into heterocyclic compounds or to construct polyfunctionalized ring systems. The ring transformation reaction has been employed to address these problems.[1] Highly electron-deficient heterocyclic compounds having a good leaving group are suitable substrates for this reaction. We have shown that 3-methyl-5-nitropyrimidin-4(3*H*)-one (**1**) leads to functionalized azaheterocycles.[2] Another system, 2-methyl-4-nitroisoxazolin-5(2*H*)-one (**2a**),[3] is also expected to behave as the synthetic equivalent of 1,3-dipolar nitroenamine with loss of a good leaving group, CO_2. We decided to synthesize 4-nitropyrroles functionalized at the 2-position by using 1,3-dicarbonyl compounds as a dipolar building block.



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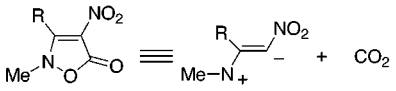

2a R = H
2b Me

The β-nitropyrrole skeleton plays an important role in the biological and pharmacological fields.[4] 2,3-Dichloro-4-nitropyrrole and its *N*-alkyl derivatives are known as the pyrromycin family and display antifungal and antibiotic activities.[5] On the other hand, 4-nitropyrroles are easily converted to 4-aminopyrroles by reduction. Both 4-nitro- and 4-aminopyrrole-2-carboxylic acid derivatives are composed of main chains of oligopyrrole peptides such as diastamycin A[6a,b] (with antibiotic, antiviral, and oncolytic properties; from *Streptomyces distallicus*), netropsin[6b] (with a wide range of antimicrobial activity; from *Streptomyces netropsis*), anthelvencin A,[6c] and so on. The first two agents are also of interest in molecular biology because they bind in the minor groove of double-helical DNA.[6] Recently, it has been energetically investigated to design nonnatural ligands for sequence-specific recognition in the DNA.[7] Various types of oligopyrroles have been prepared, and synthetic methods for them have been dramatically developed.[8] 2-Acyl-4-nitropyrroles are also used in the synthesis of oligopyrroles.[9] In addition, 4-nitropyrroles having a carbonyl group at the 2-position are useful precursors of functionalized porphyrins,[10] calixarene ionophores,[11] and chiral NADH model compounds.[12]

Although electrophilic substitution is a powerful method for introduction of a nitro group, α-nitration predominantly takes place in the case of pyrrole ring. Thus, the deactitvating occupation of the 2-position with electron-withdrawing group is necessary for causing the nitration at the 4-position. However, introduction of a carbonyl group into the pyrrole ring often accompanies multistep reactions and troublesome manipulations.[13] The condensation of sodium nitromalonaldehyde with glycine ester hydrochloride is also an available method leading to 4-nitropyrrole-2-carboxylic acid derivatives.[14] Sodium nitromalonaldehyde is a useful reagent for the preparation of nitro compounds, but it should be handled as an explosive material before purification.[15] Either of these traditional methods is still employed even now despite the restrictions mentioned above.

In the past decade, new preparative methods for 2-carbonylated 4-nitropyrroles have been developed. Ono et al. synthesized 2-formyl-4-nitropyrroles from nitroalkene on treatment with tosylmethylisocyanide following by Vilsmeier reaction.[16] Approaches with ring transformation using 3-benzoylamino-5-nitro-2,4,6-trimethylpyr-

* To whom correspondence should be addressed. Tel: +81-729-78-3398. Fax: +81-729-78-3399.
† Department of Chemistry.
‡ Division of Natural Science.

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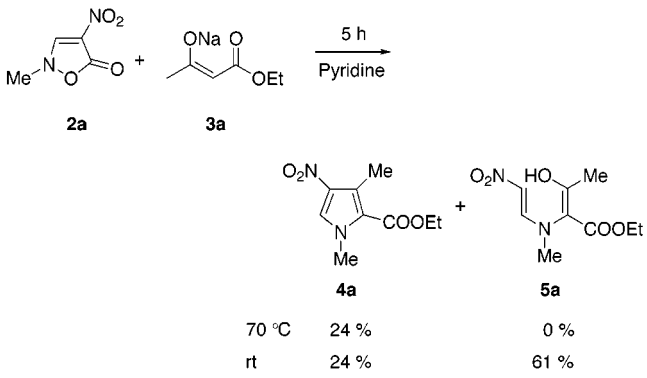
Scheme 1



idinium salt[17] or 2-methyl-3-nitrochromone are also found in the literature.[18]

Surprisingly, to the best of our knowledge, there is no report dealing with 1,3-disubstituted 4-nitropyrrole having a carbonyl group at the 2-position except for a single description.[19] This fact encouraged us to investigate the ring transformation of nitroisoxazolone **2a** with 1,3-dicarbonyl compounds affording a new class of compounds, 2,3-difunctionalized 4-nitropyrroles.

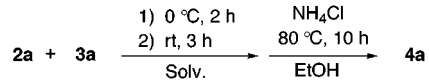
Results and Discussion

The reaction of nitroisoxazolone **2a** with sodium enolate **3a** affords a complex mixture under heated conditions. The desired 2-ethoxycarbonyl-1,3-dimethyl-4-nitropyrrole (**4a**) was isolated in 24% yield on treatment with column chromatography. Spectral and analytical data are consistent with this structure. The final confirmation of the structure is performed by comparison of spectral and physical data with those of the authentic sample.[20] Although the reaction mixture affords many unidentified side products, the complication of the crude product is solved with lowering the reaction temperature. In this case, nitroenamine **5a** is obtained as a main product (Scheme 1).

Although nitroenamine, a typical push−pull alkene, is widely used for organic syntheses,[21] only a few preparative methods for functionalized nitroenamines are known.[15a,21,22] Thus, the present reaction will be a novel procedure for preparation of N-functionalized nitroenamine. Since product **5a** has both nucleophilic and electrophilic sites in the enamine and the enol moieties respectively, it is considered to be possible to form a C−C bond between these positions leading to pyrrole **4a**. Actually, heating of **5a** with NH_4Cl effectively performed the ring closure.

These two reactions can be conducted successively in one pot, and pyrrole **4a** is isolated in 48% yield. During the addition of enolate **3a**, lower temperature is effective. In this reaction, DMF is also applicable as the solvent. It is found that considerable improvement of the yield up to 79% is observed when a larger amount of enolate is used (Table 1).

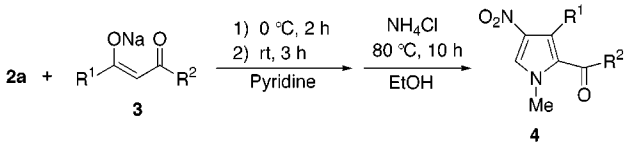
Table 1



solvent	yield (%)
DMF	47
MeCN	12
pyridine	48
pyridine	79[a]

[a] 3 molar equiv of **3a** was used.

Table 2



R^1	R^2		yield (%)
Me	Me	**b**	42
Me	Ph	**c**	44
Ph	OEt	**d**	0
CF_3	OEt	**e**	0
CH_2COOEt	OEt	**f**	33
COOEt	OEt	**g**[a]	74

[a] **3g** is commercially available.

Reactions of isoxazolone **2a** with other enolates **3b**−**g** are performed under the optimized conditions for acetoacetate **3a** (Table 2). In the cases of β-diketones **3b** and **3c**, the corresponding 2-acyl-4-nitropyrroles **4b** and **4c** are obtained in moderate yields. Preparation of 2,3-difunctionalized 4-nitropyrroles is similarly studied using several other β-keto esters. Stable enolates **3d** and **3e** derived from benzoylacetate, and trifluoroacetoacetate caused no change under the present conditions. Pyrrole **4f** having an ethoxycarbonylmethyl group is obtained in 33% yield, though the reaction mixture is somewhat complicated because of side reactions caused by the other active methylene. The ring transformation of **2a** with the sodium salt of oxalacetoacetate **3g** effectively proceeds to furnish pyrrole-2,3-dicarboxylic acid derivative **4g**. On the other hand, the pyrroline derivative is not furnished in the reaction with ethyl α-methylacetoacetate. Since all of the pyrroles prepared here are hitherto unknown, the properties of these compounds intrigued us, and they will be used for synthetic intermediates of novel functionalized systems possessing a pyrrole ring.

In the nitroisoxazolone ring, the oxygen atom at the 1-position diminishes electron density on the adjacent nitrogen atom. In addition, nitro and carbonyl groups withdraw electrons through a double bond. Hence, the 2- and 3-positions of **2a** are highly reactive toward the nucleophile. When the 2-position is attacked by enolate **3a** (N-attack), decarboxylation immediately takes place to give anionic nitroenamine **5′**, and the intramolecular cyclization followed by aromatization leads to pyrrole **4a**. In the case of Michael addition at the 3-position (C-attack),[23] enolate ion **6** is formed. Rearrangement of **6** via aziridine intermediate **7** also affords anionic nitroenamine **5′**. Isolation of nitroenamine **5a** supports the

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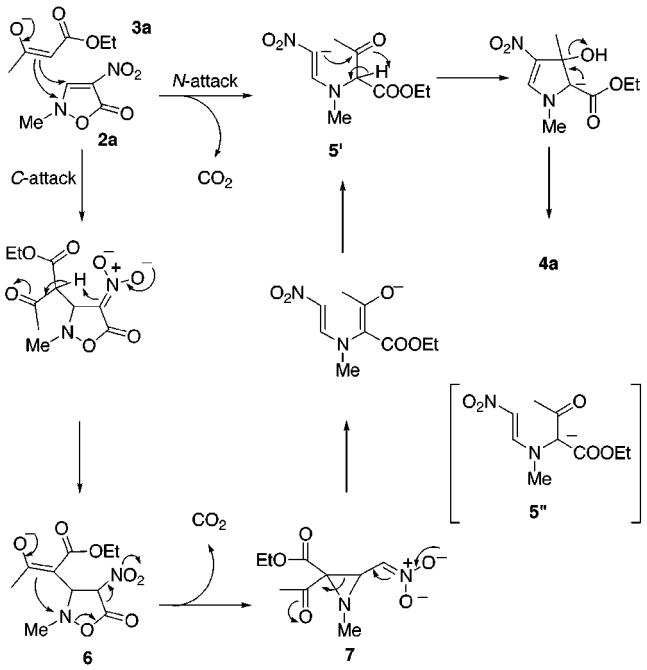
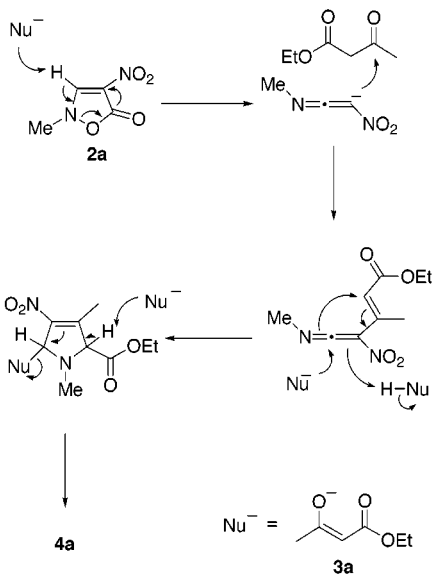
Scheme 2



Scheme 3



speculation that reaction proceeds in either of these paths (Scheme 2). Since intermediate **5′** is easily transformed to stable anion **5″**, cyclization hardly proceeds under basic conditions. Hence, the addition of NH_4Cl is effective for cyclization.

The above mechanism in Scheme 2, however, cannot rationalize enough the effect of larger amount of enolate increasing the yield of **4a**. Furthermore, isoxazolone **2b** (R = Me)[24] blocked at the 3-position is inert under the same conditions with quantitative recovery. This result might be due to steric hindrance of the methyl group; however, it is known that the proton at the 3-position of nitroisoxazolone is highly acidic.[25] Thus, we took into consideration another mechanism that is initiated with deprotonation at the 3-position. There is a possibility that the reaction proceeds in both reaction paths as shown in Schemes 2 and 3.

In summary, a novel preparative procedure for pyrroles is provided. The ring transformation of nitroisoxazolone **2a** with enolates **3** conveniently furnishes 3-functionalized 4-nitropyrrole-2-carboxylates and 2-acyl-4-nitropyrroles. This methodology will contribute to synthetic chemistry for pyrrole derivatives.

Experimental Section

General Methods. Solvents and Me_2SO_4 were dried by the usual method and distilled before use. 1,3-Dicarbonyl compounds were commercially available and were used without further purification.

2-Methyl-4-nitroisoxazolin-5(2*H*)-one 2a. The pyridinium salt of nitroisoxazolone (4.18 g, 20 mmol)[25] was heated with Me_2SO_4 (2.27 mL, 24 mmol) without solvent at 65 °C for 3 h. The reaction mixture was cooled to room temperature, and H_2O (100 mL) was added. Generated white precipitates were collected and washed with H_2O (50 mL), MeOH (30 mL), and PhH (30 mL) to afford *N*-methylisoxazolone **2a** (2.26 g, 15.7 mmol, 79%). Further purification was performed by recrystallization from EtOH. 2,3-Dimethylisoxazolone **2b** was also prepared in a similar way.

General Procedure for Ring Transformation. Na (690 mg, 30 mmol) was dissolved in dry EtOH (20 mL), and one-fifth of the solution (4 mL) was transferred to another flask. To this solution was gradually added ethyl acetoacetate (0.84 mL, 6.6 mmol), and the mixture was dried under reduced pressure to give sodium enolate **3a** (1.17 g) as a white solid. The enolate **3a** was dissolved in pyridine (8 mL). To this solution was added a solution of isoxazolone **2a** (288 mg, 2.0 mmol) in pyridine (22 mL) over 30 min on an ice bath. The resultant yellow solution was stirred for an additional 2 h at the same temperature. The mixture was warmed to room temperature and was stirred for 3 h. The reaction was quenched with 1 M HCl (6.0 mL, 6.0 mmol). The reaction mixture was dried under reduced pressure. To a solution of the residue in EtOH (50 mL) was added NH_4Cl (215 mg, 4.0 mmol), and the mixture was heated at 80 °C for 10 h. After removal of EtOH, the residual yellowish brown solid was extracted with hot hexane (50 mL × 3). The organic layer was dried ($MgSO_4$), concentrated, and treated with column chromatography on SiO_2 to afford pyrrole **4a** (335 mg, 1.58 mmol, 79%) as a white solid.

Reactions of isoxazolone **2a** with other 1,3-dicarbonyl compounds are conducted similarly.

1,3-Dimethyl-2-ethoxycarbonyl-4-nitropyrrole 4a: white solid; mp 150.7−150.9 °C; IR (KBr) 3139, 1689, 1552, 1322 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.1 Hz, 3H), 2.64 (s, 3H), 3.93 (s, 3H), 4.36 (q, J = 7.1 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (q), 14.5 (q), 39.1 (q), 61.0 (t), 121.4 (s), 125.8 (s), 128.5 (d), 134.7 (s), 161.5 (s). Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.72; H, 5.68; N, 13.32.

2-Acetyl-1,3-dimethyl-4-nitropyrrole 4b: brown plates; mp 142.0−142.3 °C; IR (KBr) 3135, 1654, 1546, 1336 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 2.69 (s, 3H), 3.91 (s, 3H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3 (q), 31.2 (q), 39.7 (q), 123.9 (s), 129.4 (d), 129.9 (d), 134.2 (s), 190.2 (s). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.56; H, 5.62; N, 15.53.

2-Benzoyl-1,3-dimethyl-4-nitropyrrole 4c: reddish white solid; mp 169.8−170.1 °C; IR (KBr) 3153, 1633, 1544, 1319 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.91 (s, 3H), 7.51 (dd, J = 7.6, 7.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (q), 37.6 (q), 123.3 (s), 128.6 (d), 128.8 (d), 129.5 (s), 129.5 (d), 133.4 (d), 135.2 (s), 138.8 (s), 188.1 (s). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.79; H, 4.87; N, 11.20.

2,3-Bis(ethoxycarbonyl)-1-methyl-4-nitropyrrole 4f: white solid; mp 90.1−90.3 °C; IR (KBr) 3145, 1743, 1702, 1504, 1330 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 3.98 (s, 3H), 4.32 (q, J = 7.1 Hz, 2H),

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4.36 (q, $J = 7.1$ Hz, 2H), 7.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (q), 14.0 (q), 38.3 (q), 61.6 (t), 61.6 (t), 120.0 (s), 120.6 (s), 127.0 (d), 132.3 (s), 159.1 (s), 163.2 (s). Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 49.02; H, 5.30; N, 10.20.

2-Ethoxycarbonyl-3-ethoxycarbonylmethyl-1-methyl-4-nitropyrrole 4g: yellow plates; mp 86.2−86.5 °C; IR (KBr) 3133, 1726, 1712, 1554, 1322 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, $J = 7.1$ Hz, 3H), 1.37 (t, $J = 7.1$ Hz, 3H), 3.96 (s, 3H), 4.27 (s, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 4.34 (q, $J = 7.1$ Hz, 2H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7 (q), 16.7 (q), 33.9 (t), 41.8 (q), 63.7 (t), 63.8 (t), 123.8 (s), 124.7 (s), 129.9 (d), 136.9 (s), 159.4 (s), 173.2 (s). Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.94; H, 5.79; N, 9.91.

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