CYANOCARBONYLATION OF AMINES WITH 5-TOSYLOXYIMINO-2,2-DIMETHYL-1,3-DIOXANE-4,6-DIONE[#]

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Abstract —— 5-Tosyloxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (**3**), prepared by the reaction of 5-hydroxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione sodium salt (**2**) with tosyl chloride, was treated with various amines (**4a-c** and **6a,b**) in the presence of triethylamine to give the corresponding *N*-cyanocarbonyl derivatives (**5a-c** and **7a,b**). However, reaction of **3** with benzyl alcohol gave rise to the formation of dibenzyl carbonate (**10**).

5-Hydroxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (**A**),[1,2] prepared easily by nitrosation of 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**: Meldrum's acid) has become of interest in recent years in the field of synthetic chemistry.[3] Previously, we found that thermolysis of **A** generated a new reaction intermediate, nitrosoketene.[4-6] This intermediate readily underwent [3+2] cycloaddition with various ketones to produce cyclic nitrones (**B**) which were found to be versatile reagents for the EPC (enantiomerically pure compound) synthesis of nonproteinogenic amino acids.[7-9] When a C=N double bond of carbodiimides was used as a $\pi 2$ component in the [3+2] cycloaddition, the expected compound was not obtained but *N*-cyanocarbonylurea derivative (**C**), an intermediate of parabanic acid, was formed.[10] Methylation of **A** with diazomethane also showed an interesting reaction to form nitrone (**D**) concomitant with the formation of *O*-methyl derivative.[11] Though a C=N bond of **A** did not behave as a dienophile in hetero Diels-Alder reaction, the *O*-acetylated **E** reacted with electron-rich olefins under high pressure to form [4+2] cycloadduct (**F**).[12] We considered that the *O*-tosyl derivative (**G**) was more reactive than **E** as a dienophile. We then planned to synthesize **G** and to examine its Diels-Alder reaction. During this study, Renslo and Danheiser reported that **G** was a versatile dienophile for hetero Diels-Alder reaction and reacted with

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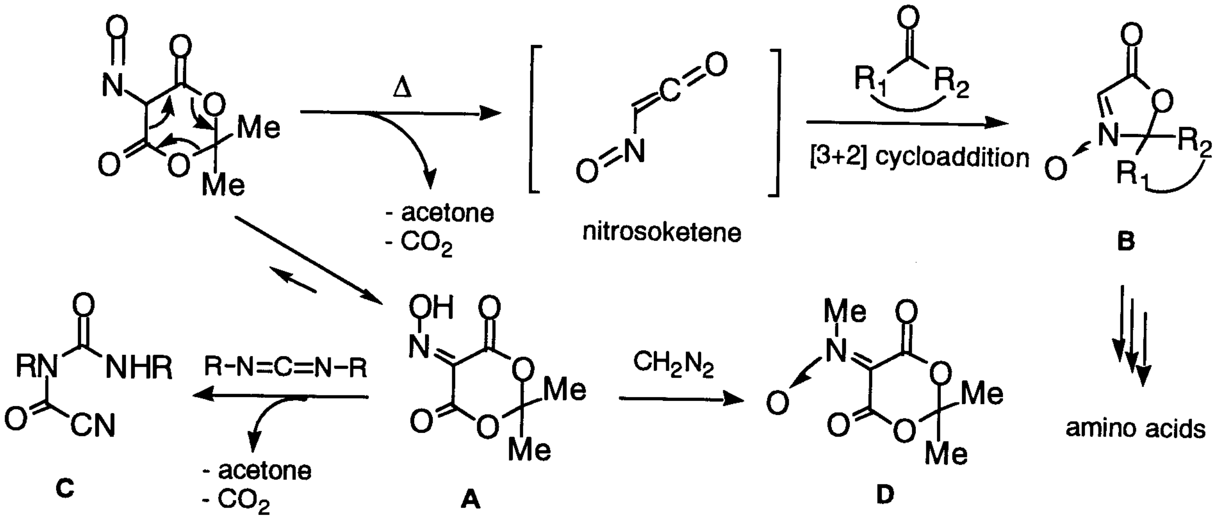
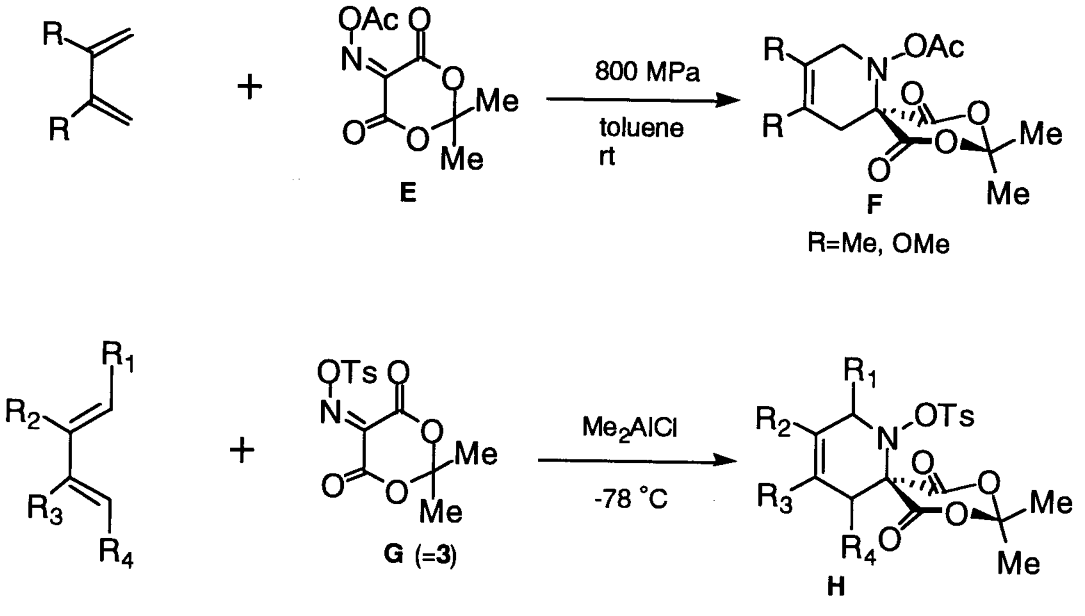
[#] This paper is dedicated to the celebration of the 73rd birthday of Prof. Teruaki Mukaiyama.



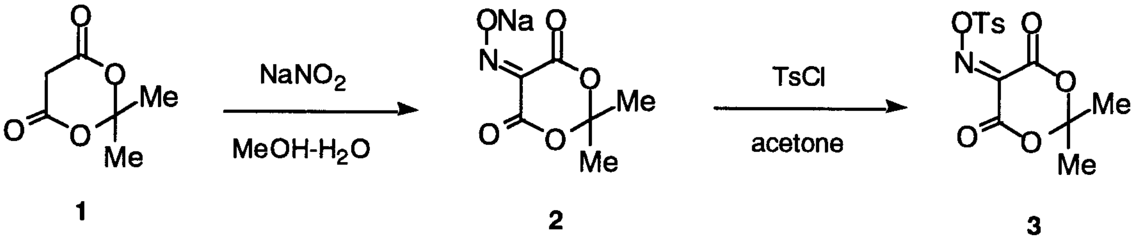
Scheme 1

various dienes in the presence of dimethylaluminium chloride to give [4+2] cycloadducts (**H**) which could be transformed to substituted pyridines.[13] In connection with our continuing interest in the 5-imino-1,3-dioxane-2,4-dione chemistry directed towords the synthesis of new heterocycles, we studied on the reaction of **G** with amines to form *N*-cyanocarbonyl derivatives.



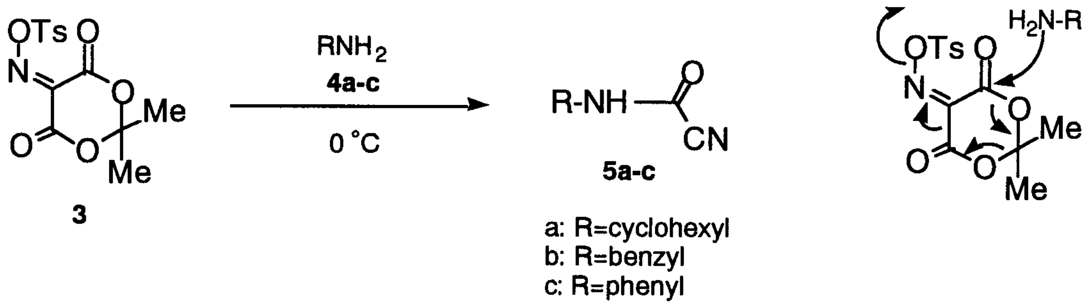
Scheme 2

The oximinosulfonate (**3**) was prepared by slightly different Danheiser's method. Meldrum's acid (**1**) was treated with sodium nitrite in methanol to give the sodium salt (**2**) of **A** in 72% yield. Compound (**2**) was then reacted with tosyl chloride in acetone to form the desired oximinosulfonate (**3**) in 79% yield. First, the reaction of **3** with various primary amines was examined. The results were shown in the Table. When **3** was allowed to react with amines (**4a-c**) in toluene or THF under ice-cooling, the corresponding *N*-cyanocarbonyl derivatives (**5a-c**)



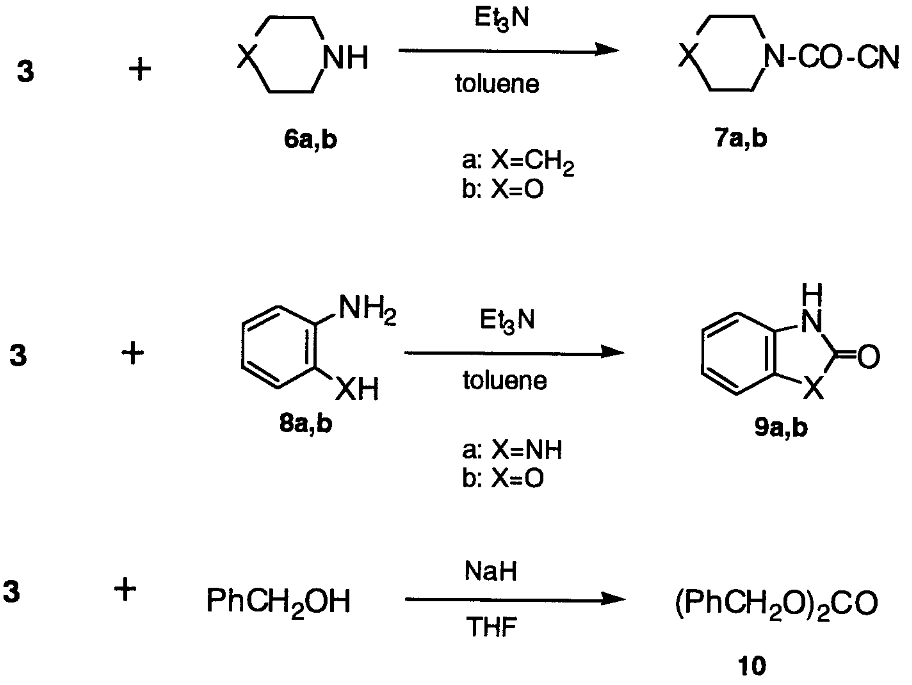
Scheme 3

Table. Reaction of **3** with Primary Amines (**4a-c**) under Various Conditions



Entry	Amines	Solvent	Reaction time (h)	Yield of **5** (%)
1	**4a**	toluene	3	48
2	**4b**	toluene	3	43
3	**4c**	THF	3	45
4	**4a**+NEt$_3$ (1eq.)	toluene	0.5	73
5	**4b**+NEt$_3$ (1eq.)	THF	0.5	68
6	**4c**+NEt$_3$ (1eq.)	THF	0.5	70

were obtained in low yields (43%-48%). The yields were improved and the reaction time was shortened when the reactions were carried out in the presence of triethylamine (1 eq.). Secondary amines (**6a,b**) also reacted with **3** under the same conditions to give *N*-cyanocarbonyl derivatives (**7a,b**) in good yields. Next, the reaction of *o*-functionalized aniline derivatives (**8a,b**) with **3** was examined. The reaction of *o*-phenylenediamine (**8a**) with **3** in the presence of triethylamine in toluene proceeded smoothly with the evolution of carbon dioxide. However, the product was not a *N*-cyanocarbonyl derivative but 2(3*H*)-benzimidazolone (**9a**). Compound (**9a**) was formed by *N*-cyanocarbonylation followed by ring closure with elimination of hydrogen cyanide. In a similar fashion, 2-aminophenol (**8b**) reacted with **3** to give 2-benzoxazolinone (**9b**) in 53% yield. Finally, we examined the reaction of **3** with benzyl alcohol. The reaction did not proceed even in the presence of triethylamine. However, when the reaction was carried out in the presence of sodium hydride, dibenzyl carbonate (**10**) was obtained in 45% yield. This reaction could be considered to proceed through the analogous mechanism to that for the formation of **9**.



Scheme 4

In conclusion, we have found that 5-tosyloxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (**3**) serves as a reagent for the *N*-cyanocarbonylation of amines. Further investigation of the reaction of **3** with C-nucleophiles is in progress.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. IR spectra were measured on a JASCO-102 spectrophotometer and ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI, Hitachi R-3000, and Varian Gemini-300L spectrometer with tetramethylsilane as an internal standard. Wakogel (C-200) and Merck Kiesel-gel 60F 254 were employed for silica gel column and thin layer chromatography (TLC), respectively. The ratios of solvent mixtures for chromatography are shown as volume / volume.

5-Tosyloxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (3)

To a suspension of **2**[1] (1.95 g, 10 mmol) in acetone (40 mL) was added tosyl chloride (1.90 g, 10 mmol) with stirring at rt. After being stirred for 5 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a crystalline substance which was recrystallized from $CHCl_3$-hexane to afford **3** (2.59 g, 79%) as colorless needles.

3: mp 152-153 °C (*lit.*,[13] mp 155-156 °C). *Anal.* Calcd for $C_{13}H_{13}NO_7S$: C, 47.71; H, 4.00; N, 4.28; S, 9.80. Found: C, 47.57; H, 3.97; N, 4.29; S, 9.34. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.80 (6H, s, $C(CH_3)_2$), 2.48 (3H, s, CH_3), 7.42 (2H, d, J = 8.2 Hz), 7.96 (2H, d, J = 8.2 Hz).

General Procedure for the Reaction of 3 with Primary Amines (4a-c)

1) without triethylamine

To a solution of **3** (327 mg, 1 mmol) in toluene or THF(4 mL) was added each amine(**4a-c**)(1.01 mmol) with stirring under ice-cooling. The mixture was stirred for 3 h under ice-cooling. After evaporation of the solvent *in vacuo*, the residue was submitted to silica gel (50 g) column chromatography. Elution with hexane-ethyl acetate (5:1) gave the corresponding *N*-cyanocarbonyl derivative (**5a-c**).

5a: mp 81-82 °C (*lit.*,[10] mp 81-82 °C), colorless prisms ($CHCl_3$ - hexane). **5a** was identical with the authentic specimen[10] in all respects.

5b: mp 72 °C, colorless needles (AcOEt - hexane). *Anal.* Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.70; H, 5.24; N, 17.75. IR ($CHCl_3$): 3425, 2240, 1705 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 4.49 (2H, d, J = 5.8 Hz, CH_2), 6.85 (1H, br, NH), 7.2-7.4 (5H, m, phenyl).

5c: mp 127-129 °C, colorless needles ($CHCl_3$ - hexane). *Anal.* Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.50; H, 4.24; N, 19.05. IR ($CHCl_3$): 3420, 2250, 1710 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz) δ: 7.2-7.5 (5H, m, phenyl), 8.13 (1H, br, NH).

2) in the presence of triethylamine

To a solution of **3** (327 mg, 1 mmol) in toluene or THF (4 mL) was added a solution of each amine(**4a-c**)(1.01 mmol) and triethylamine (101 mg, 1 mmol) in toluene or THF (1 mL) with stirring under ice-cooling. The mixture was stirred for 30 min under ice-cooling. After evaporation of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$ (20 mL). The solution was washed with water (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*, successively. The obtained crystalline substance was recrystallized from an appropriate solvent to give the corresponding product (**5a-c**).

N-Cyanocarbonylpiperidine (7a)

To a solution of **3** (1.18 g, 4 mmol) in toluene (8 mL) was added a solution of piperidine (**6a**)(340 mg, 4 mmol) and triethylamine (404 mg, 4 mmol) in toluene (2 mL) with stirring under ice-cooling. The mixture was stirred for 1 h at rt. The reaction mixture was washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*, successively. The residue was submitted to silica gel (50 g) column chromatography. Elution with hexane-ethyl acetate (5:1) gave **7a** (260 mg, 95%) as colorless oil.

7a: colorless oil. *Anal.* Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.36; H, 7.54; N, 19.98. IR ($CHCl_3$): 2230, 1676 cm^{-1}.

N-Cyanocarbonylmorpholine (7b)

According to the procedure described above, **7b** (393 mg) was obtained in 70% yield from the reaction of **3** (1.18 g, 4 mmol) with morpholine(**6b**)(348 mg, 4 mmol).

7b: mp 54-55 °C, colorless needles (hexane-ether). *Anal.* Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.13; H, 5.94; N, 19.75. IR ($CHCl_3$): 2245, 1680 cm^{-1}.

2(3*H*)-Benzimidazolone (9a)

To a solution of **3** (1.18 g, 4 mmol) in THF (8 mL) was added a solution of *o*-phenylenediamine (**8a**)(432 mg, 4 mmol) and triethylamine (404 mg, 4 mmol) in THF (2 mL) with stirring under ice-cooling. The mixture was stirred for 1 h and kept overnight at rt. After removal of the solvent *in vacuo*, a crystalline residue was washed with $CHCl_3$ (20 mL). Recrystallization from MeOH gave **9a** (318 mg, 59%) as colorless plates.

9a: mp >300 °C. *Anal.* Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.30; H, 4.59; N, 20.68. IR (Nujol): 3250-2650, 1736cm^{-1}. The IR spectrum of **9a** was identical with that of an commercially available sample.

2-Benzoxazolinone (9b)

To a solution of **3** (1.18 g, 4 mmol) in toluene (8 mL) was added a suspension of 2-aminophenol(**8b**)(436 mg, 4 mmol) and triethylamine (404 mg, 4 mmol) in toluene (2 mL) with stirring under ice-cooling. The mixture was stirred for 1 h at rt. After removal of the solvent *in vacuo*, the residue was dissolved in AcOEt (20 mL). The AcOEt solution was washed with water (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*, successively. After removal of the solvent *in vacuo*, the residue was submitted to silica gel (100 g) column chromatography. Elution with hexane-ethyl acetate (2:1) gave **9b** (345 mg, 53%).

9b: mp 137-138 °C, pale yellow prisms (hexane-ether). *Anal.* Calcd for $C_7H_5NO_2$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.33; H, 3.87; N, 10.39. IR ($CHCl_3$): 3480, 1768 cm^{-1}. The IR spectrum of **9b** was identical with that of a commercially available sample.

Dibenzyl Carbonate (10)

To a solution of **3** (327 mg, 1 mmol) in anhydrous THF (5 mL) was added a solution of sodium benzyloxide, prepared by reaction of benzyl alcohol (119 mg, 1.1 mmol) with 60% sodium hydride (44 mg, 1.1 mmol) in anhydrous THF (5 mL), with stirring under ice-cooling. The mixture was stirred for 1 h under ice-cooling. After removal of the solvent *in vacuo*, the residue was submitted to silica gel (50 g) column chromatography. Elution with hexane-ethyl acetate (10:1) gave **10** (109 mg, 45%) as colorless oil.

10: IR ($CHCl_3$): 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.17 (2H, s, CH_2), 7.36 (5H, s, phenyl). The IR spectrum of **10** was identical with that of a commercially available sample.

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