Facile, One-Pot Synthesis of Bicyclic 2-Pyridones from Acyl Isocyanates, *N*-Phenylmaleimide and Trimethylsilyldiazomethane

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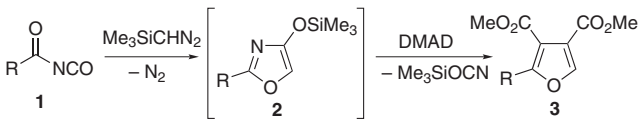
Received 28 February 2005; revised 4 April 2005

Abstract: The hetero-Diels–Alder reaction of 2-substituted 4-trimethylsiloxyoxazoles, prepared in situ from trimethylsilyldiazomethane and acyl isocyanates, with *N*-phenylmaleimide followed by treatment with a catalytic amount of 10-camphorsulfonic acid efficiently gave bicyclic 2-pyridones in a one-pot process.

Key words: acyl isocyanates, Diels–Alder reaction, 2-pyridones, oxazoles, trimethylsilyldiazomethane

Since it was found by Kondrat'eva that oxazoles act as heterodienes in Diels–Alder reactions,[1] numerous studies on Diels–Alder reactions of various oxazole derivatives with alkenes or alkynes giving pyridines or furans have been reported to date.[2,3] Although 4(5*H*)-oxazolones instead of oxazoles have also been reported to be usable for the synthesis of pyridine or furan derivatives, the yields were low to moderate.[4] In these cases, the reaction proceeds by a 1,3-dipolar cycloaddition process via a mesoionic intermediate, and not by a Diels–Alder addition process.

Very recently, we have found that the 2-substituted 4-trimethylsiloxyoxazoles **2** [the silyl enol ethers of 4(5*H*)-oxazolones], easily generated in situ from acyl isocyanates **1** and trimethylsilyldiazomethane (Me_3SiCHN_2), are quite useful as electron-rich heterodienes in the Diels–Alder reaction. Thus, a one-pot synthesis of multi-substituted furans by reaction of **2** with electron-deficient alkynes, such as dimethyl acetylenedicarboxylate (DMAD) or ethyl propiolate, followed by retro-Diels–Alder reaction with the loss of Me_3SiOCN from the initial [4+2] cycloadduct to form 3,4-dimethoxycarbonylfurans has been achieved (Scheme 1).[5] Our continuous interest in the reactivities of 4-trimethylsiloxyoxazoles as heterodienes has led us to investigate the Diels–Alder reaction of **2** with alkenes giving pyridine derivatives.



Scheme 1 One-pot furan synthesis from acyl isocyanates using trimethylsilyldiazomethane.

Reaction of **2a**, generated in situ from benzoyl isocyanate (**1a**) and Me_3SiCHN_2, with *N*-phenylmaleimide as an electron-deficient alkene in MeCN under reflux conditions slowly proceeded to give the tricyclic compound **4a** (28%) (Table 1), formed from the initial [4+2] cycloadduct **5a** by hydrolysis during work-up, without yielding any 2-pyridone **6a** (entry 1). The stereochemistry of **4a** was confirmed to be in an *exo*-form, because the proton at position 7 was observed as a singlet by ^1H NMR measurement.[6] Changing the reaction solvent from MeCN to toluene with higher boiling point led to a considerable improvement in the reaction efficiency and gave a mixture of the desired **6a** (22%) and **4a** (50%) (entry 2). The use of xylene as the reaction solvent caused a significant decrease in the yields of **4a** and **6a** (entry 3). We thought that the cycloadduct **5a** could be converted to the 2-pyridone **6a** by a ring-opening reaction, followed by dehydration. Thus, the effect of an additive for the conversion of **5a** (or **4a**) to **6a** was investigated. When AcOH or pyridine as an additive was used, no increase in the yield of **6a** was observed (entries 4 and 5). On the other hand, 10-camphorsulfonic acid (CSA) was quite effective as an additive and the desired **6a** was obtained in 70% yield (entry 6). The use of a catalytic amount of CSA led to the complete conversion of **5a** (or **4a**) to **6a** in high yield, though prolonged reaction time was required (entry 7).

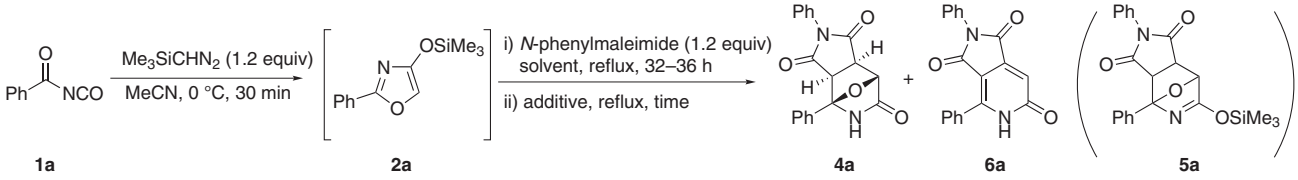
Unfortunately, other electron-deficient alkenes, such as dimethyl fumarate, maleic anhydride, fumaronitrile, phenyl vinyl sulfone or *trans*-β-nitrostyrene, gave no characterizable products.

Next, under the same reaction conditions as shown in entry 7 in Table 1, the one-pot synthesis of pyridones using other acyl isocyanates **1b–f** was performed (Table 2). Various aliphatic acyl isocyanates **1b–d** smoothly gave the corresponding 2-pyridones **6b–d** in 76–85% yields, respectively (entries 1–3). Interestingly, the siloxyoxazole **2e** generated from **1e** has two reactive sites (oxazole and furan rings) in the molecule, but the reaction selectively occurred at the oxazole moiety, and the 2-pyridone **6e** was obtained in high yield (entry 4). Similarly, the styryl derivative **2f** containing a 1-azabuta-1,3-diene moiety also afforded the desired **6f** in a regioselective manner (entry 5).

Finally, we examined the one-pot synthesis of **6** from the amides **7**, precursor of acyl isocyanates. As shown in Scheme 2, four successive treatments of benzamide **7a** with i) oxalyl chloride (preparation of acyl isocyanate), ii)

SYNTHESIS 2005, No. 13, pp 2147–2150
Advanced online publication: 07.07.2005
DOI: 10.1055/s-2005-870002; Art ID: F04605SS

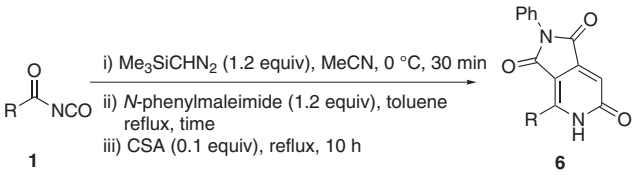
Table 1 Optimization of the Synthesis of 6-Phenyl Bicyclic Pyridones



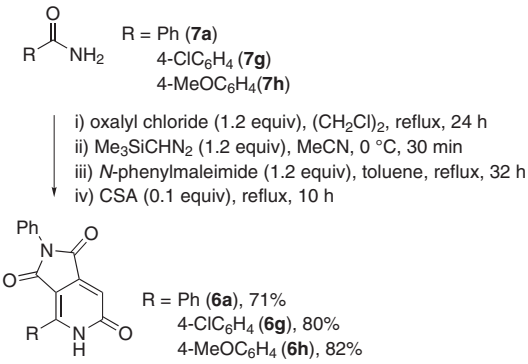
Entry	Solvent	Additive[a]	Time (h)	Yield (%)	
				4a	**6a**
1	MeCN	–	–	28	–
2	toluene	–	–	50	22
3	xylene	–	–	35	6
4	toluene	AcOH (1.2 equiv)	10	71	24
5	toluene	pyridine (1.2 equiv)	10	59	23
6	toluene	CSA (1.2 equiv)	1	–	70
7	toluene	CSA (0.1 equiv)	10	–	85

[a] CSA = 10-Camphorsulfonic acid.

Table 2 Synthesis of 6-Substituted Bicyclic Pyridones



Entry	R	Time (h)	Product	Yield (%)
1	cyclohexyl	32	**6b**	85
2	benzyl	9	**6c**	84
3	*n*-pentyl	19	**6d**	76
4	2-furyl	31	**6e**	83
5	*trans*-β-styryl	32	**6f**	88



Scheme 2 One-pot synthesis of 6-substituted bicyclic pyridones from amides.

$TMSCHN_2$, iii) *N*-phenylmaleimide, and then iv) CSA in one-pot gave the 2-pyridone **6a** in 71% yield. An electron-withdrawing group on the benzene ring of **7** such as the chlorine atom did not affect the reaction and the desired **6g** was obtained in 80% yield. Moreover, the use of *p*-methoxybenzamide (**7h**) bearing an electron-donating group also smoothly afforded **6h** in 82% yield.

In conclusion, we have succeeded in the one-pot synthesis of various 6-substituted bicyclic 2-pyridones from acyl isocyanates, *N*-phenylmaleimide, and $TMSCHN_2$.

All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX-270 spectrometer (^1H, 270 MHz; ^{13}C, 67.8 MHz). Mass spectra were recorded on a JEOL JMS-SX-102A spectrometer.

One-Pot Synthesis of Bicyclic Pyridones from Acyl Isocyanates; 2,4-Diphenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6a); Typical Procedure

To a solution of benzoyl isocyanate (**1a**; 101 mg, 0.69 mmol) in MeCN (5 mL), was added Me_3SiCHN_2 (1.63 M in hexane solution, 0.51 mL, 0.82 mmol) at 0 °C under argon. After stirring for 0.5 h, the solvent was removed in vacuo under moisture-free conditions. Then, toluene (5 mL) and *N*-phenylmaleimide (143 mg, 0.82 mmol) were added under argon and the mixture was refluxed for 32 h. After the addition of 10-camphorsulfonic acid (15.8 mg, 0.07 mmol),

the mixture was refluxed for further 10 h. The solvent was then removed in vacuo. The residue was purified by flash column chromatography (Fuji Silysia PSQ 60B, $CHCl_3$–EtOAc, 1:0 to 8:1) to give the desired compound **6a** (186 mg, 85%); white powder; mp >266 °C.

IR (Nujol): 1728, 1672 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.08 (1 H, s), 7.37–7.63 (8 H, m), 7.80 (2 H, d, *J* = 6.9 Hz), 9.83 (1 H, br s).

^{13}C NMR (DMSO-d_6): δ = 112.3, 126.8, 127.4, 127.7, 128.3, 129.2, 130.6, 131.5, 142.3, 149.7, 162.9, 163.3, 164.0.

EI-MS: *m*/*z* = 316 (M^+).

Anal. Calcd for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86. Found: C, 72.08; H, 3.91; N, 8.47.

The data of **4a** formed in the reaction not involving CSA (Table 1) is given below.

2,4-Diphenyl-4,7-oxa-1*H*-tetrahydropyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,3a*H*)-trione (4a)
Colorless crystals; mp 220–225 °C ($CHCl_3$–Et_2O, dec.).

IR (Nujol): 1738, 1697 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.68 (1 H, d, *J* = 6.8 Hz), 3.90 (1 H, d, *J* = 6.8 Hz), 5.21 (1 H, s), 6.48 (1 H, br s), 7.18 (2 H, d, *J* = 6.8 Hz), 7.34–7.59 (8 H, m).

^{13}C NMR (DMSO-d_6): δ = 46.5, 55.7, 79.3, 97.0, 125.4, 126.5, 128.0, 128.4, 128.9, 129.0, 131.7, 131.9, 171.4, 173.1, 173.8.

EI-MS: *m*/*z* = 334 (M^+), 161.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{14}N_2O_4$: 334.0954; found: 334.0965.

The following pyridones **6b–f** were prepared by adopting the typical procedure.

4-Cyclohexyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6b)
Colorless crystals; mp >285 °C ($CHCl_3$–Et_2O).

IR (Nujol): 1772, 1732, 1661, 1609, 1593 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.32–1.93 (10 H, m), 3.78 (1 H, tt, *J* = 3.0, 12.2 Hz), 6.95 (1 H, s), 7.38–7.54 (5 H, m), 11.6 (1 H, br s).

^{13}C NMR ($CDCl_3$): δ = 25.4, 26.1, 30.3, 38.6, 103.8, 113.3, 126.4, 128.4, 129.0, 131.2, 142.7, 158.4, 164.4, 164.7, 165.0.

EI-MS: *m*/*z* = 322 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{18}N_2O_3$: 322.1317; found: 322.1339.

4-Benzyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6c)
Yellow crystals; mp 269–270 °C ($CHCl_3$–Et_2O).

IR (Nujol): 1722, 1666 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.45 (2 H, s), 6.97 (1 H, s), 7.31–7.53 (10 H, m), 11.8 (1 H, br s).

^{13}C NMR ($CDCl_3$): δ = 35.7, 105.2, 113.7, 126.4, 127.8, 128.5, 129.1, 129.3, 131.1, 134.9, 142.8, 151.6, 164.1, 164.7, 165.5.

EI-MS: *m*/*z* = 330 (M^+).

Anal. Calcd for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48. Found: C, 72.46; H, 4.29; N, 8.61.

4-Pentyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6d)
Colorless crystals; mp 146–148 °C (hexane–EtOAc).

IR (Nujol): 1769, 1718, 1662, 1649, 1612 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.92 (3 H, t, *J* = 6.9 Hz), 1.35–1.46 (4 H, m), 1.82 (2 H, tt, *J* = 7.5, 7.5 Hz), 3.12 (2 H, t, *J* = 7.5 Hz), 6.94 (1 H, s), 7.38–7.52 (5 H, m), 13.0 (1 H, br s).

^{13}C NMR ($CDCl_3$): δ = 13.9, 22.2, 28.7, 29.9, 31.2, 105.2, 112.7, 126.2, 128.3, 128.9, 131.1, 142.8, 154.6, 164.3, 164.5, 166.0.

EI-MS: *m*/*z* = 310 (M^+), 254.

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.80; H, 5.92; N, 9.07.

4-(2-Furyl)-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6e)
Colorless crystals; mp >295 °C ($CHCl_3$–Et_2O).

IR (Nujol): 1697, 1670, 1589 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.76 (1 H, s), 6.83 (1 H, dd, *J* = 2.1, 1.0 Hz), 7.39–7.54 (5 H, m), 8.07–8.08 (2 H, m), 12.3 (1 H, br s).

^{13}C NMR (DMSO-d_6): δ = 112.4, 113.4, 119.4, 127.5, 128.4, 128.9, 131.9, 137.5, 143.0, 143.2, 147.1, 163.0, 164.0, 164.5.

EI-MS: *m*/*z* = 306 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{10}N_2O_4$: 306.0641; found: 306.0641.

2-Phenyl-4-[(*E*)-2-phenylethenyl]-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6f)
Yellow powder; mp >295 °C.

IR (Nujol): 1720, 1668, 1641 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.76 (1 H, s), 7.41–7.61 (10 H, m), 7.77 (1 H, d, *J* = 16.8 Hz), 8.08 (1 H, d, *J* = 16.8 Hz), 12.5 (1 H, br s).

^{13}C NMR (DMSO-d_6): δ = 112.8, 115.3, 126.7, 127.2, 127.7, 128.3, 128.8, 129.8, 131.4, 134.6, 139.2, 141.8, 145.1, 162.9, 164.1, 164.4.

EI-MS: *m*/*z* = 342 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{14}N_2O_3$: 342.1004; found: 342.0998.

One-Pot synthesis of Bicyclic Pyridones 6a,g,h from Amides 7a,g,h; 2,4-Diphenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6a); Typical Procedure
To a solution of benzamide (**7a**; 125 mg, 1.03 mmol) in 1,2-dichloroethane (5 mL), was added oxalyl chloride (0.11 mL, 1.24 mmol). After stirring under reflux for 24 h, the solvent was removed in vacuo under moisture-free conditions. The residue [benzoyl isocyanate (**1a**)] was dissolved to MeCN (5 mL) and Me_3SiCHN_2 (1.94 M in hexane solution, 0.64 mL, 1.24 mmol) was added at 0 °C under argon. After stirring for 0.5 h, the solvent was removed in vacuo under moisture-free conditions. Then, toluene (5 mL) and *N*-phenylmaleimide (215 mg, 1.24 mmol) were added under argon and the mixture was refluxed for 32 h. After the addition of 10-camphorsulfonic acid (23.8 mg, 0.10 mmol), the mixture was refluxed for further 10 h. The solvent was removed in vacuo. The residue was purified by flash column chromatography (Fuji Silysia PSQ 60B, $CHCl_3$–EtOAc, 1:0 to 8:1) to give the desired compound **6a** (227 mg, 71%). For analytical and spectral data of **6a**, see above.

4-(4-Chlorophenyl)-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6g)
White powder; mp >295 °C.

IR (Nujol): 1776, 1728, 1666, 1629, 1610, 1593 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.84 (1 H, s), 7.35–7.52 (5 H, m), 7.59 (2 H, d, *J* = 8.6 Hz), 7.76 (2 H, d, *J* = 8.6 Hz), 12.7 (1 H, br s).

^{13}C NMR (DMSO-d_6): δ = 99.4, 112.5, 126.8, 127.6, 127.8, 128.2, 128.4, 131.2, 131.5, 135.6, 142.3, 148.4, 163.1, 163.5, 164.0.

EI-MS: *m*/*z* = 350 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{11}ClN_2O_3$: 350.0458; found: 350.0437.

4-(4-Methoxyphenyl)-2-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,6(2*H*,5*H*)-trione (6h)
Yellow powder; mp >295 °C.

IR (Nujol): 1767, 1728, 1670, 1604 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.83 (3 H, s), 6.77 (1 H, s), 7.06 (2 H, d, *J* = 8.7 Hz), 7.36–7.52 (5 H, m), 7.72 (2 H, d, *J* = 8.7 Hz), 12.5 (1 H, br s).

^{13}C NMR (DMSO-d_6): δ = 55.4, 102.8, 112.3, 113.2, 121.2, 127.2, 128.0, 128.6, 131.5, 131.7, 142.8, 149.7, 161.5, 163.4, 163.9, 164.4.

EI-MS: *m*/*z* = 346 (M^+).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{14}N_2O_4$: 346.0954; found: 346.0952.

Acknowledgment

This work was financially supported by a Grant-in-Aid for Scientific Research (KAKENHI) (to T.A.), and a Grant-in-Aid for The Japan Securities Scholarship Foundation (to Y.H.).

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