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# A Simple One-Pot Preparation of 2-Pyridones from Acyl Isocyanates Utilizing Trimethylsilylketene

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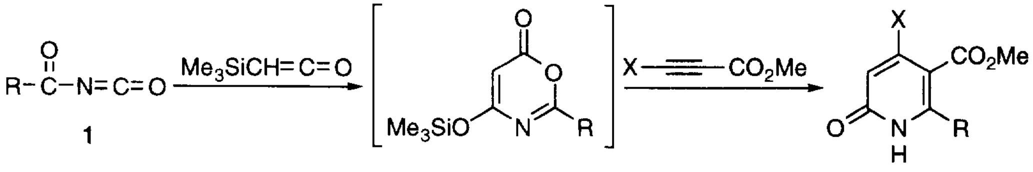
***Abstract*** — *Trimethylsilylketene reacts with acyl isocyanates to give 4-trimethylsiloxy-1,3-oxazin-6-ones which smoothly undergo the Diels-Alder reaction with dimethyl acetylenedicarboxylate and methyl propiolate to furnish 2-pyridones.* Copyright © 1996 Elsevier Science Ltd

Recent publications from our laboratories have disclosed the first example of the [4+2] cycloaddition reaction of silylketenes with electron-rich 1,3-dienes and *o*-quinodimethanes,[1] and the novel type of cycloaddition reaction of silylketenes with enamines.[2] Our continued interest in the reactivity of silylketenes has led us to investigate the reaction of trimethylsilylketene (TMSCH=C=O) with acyl isocyanates **1**.[3] Although the [4+2] cycloadducts **2** from this reaction were labile, we have found that they easily react with some acetylenes to give 2-pyridones **3** or **4**.

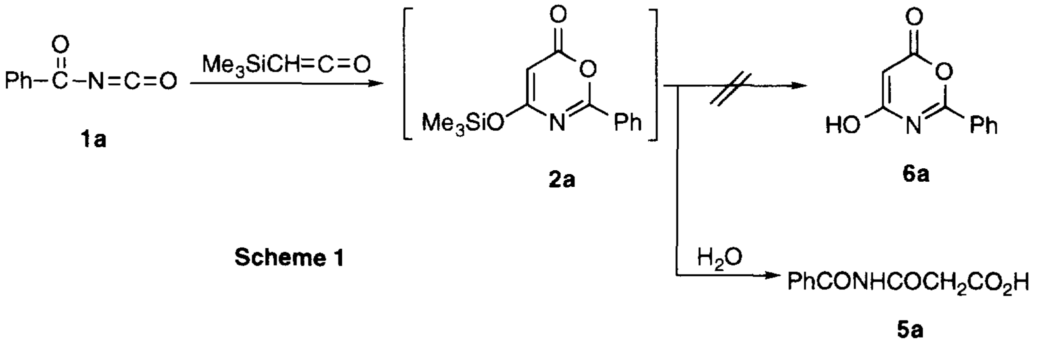


**2**

**3** : X = $CO_2Me$

**4** : X = H

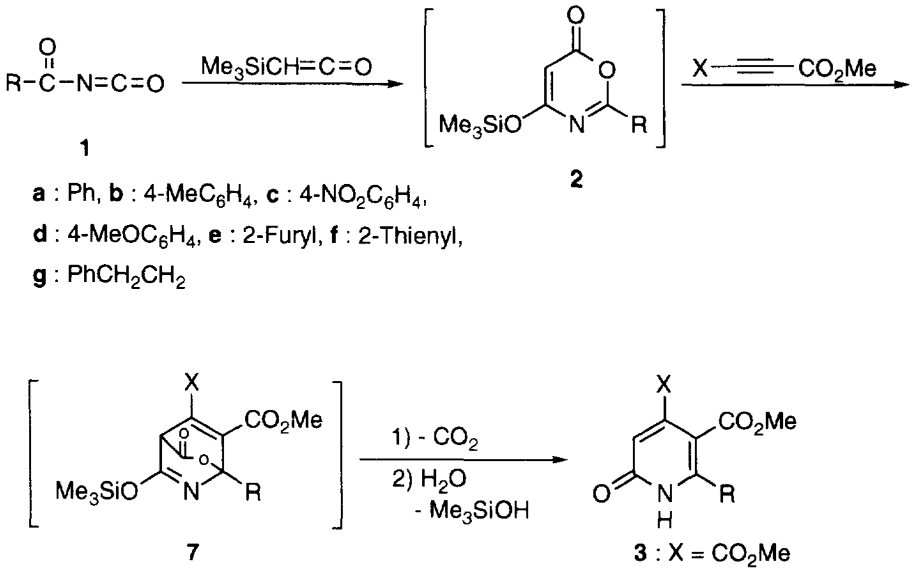
First, TMSCH=C=O was allowed to react with benzoyl isocyanate (**1a**) in benzene at reflux for 3 h, as shown in Scheme 1. Purification of the crude products by recrystallization gave the acid **5a** in 84% yield, and no [4+2] cycloadduct **2a** or **6a** could be detected. The $^1H$ NMR of the crude reaction mixture showed the signal of an olefinic proton at 5.24 ppm as a singlet in addition to the signal of the TMS group at 0.32 ppm. The IR spectrum exhibited an absorption at 1753 $cm^{-1}$, characteristic of the 1,3-oxazin-6-one structure.[4] These data indicated that the reaction of TMSCH=C=O with **1a** would first give the [4+2] cycloadduct, 4-trimethylsiloxy-1,3-oxazin-6-one (**2a**). The adduct **2a** would be very sensitive to moisture and was immediately hydrolyzed to **5a** during recrystallization.[5] In contrast to the results, the reaction of ketene with **1a** has been reported to give **6a** as an isolable product.[4]



**Scheme 1**

We thought that **2a** could be trapped by appropriate dienophiles if **2a** acts as a diene component of the Diels-Alder reaction.[6] In fact, treatment of **2a**, generated *in situ*, with dimethyl acetylenedicarboxylate (DMAD) in benzene at reflux gave the 2-pyridone **3a** though the yield was very low as shown in Scheme 2. However, changing the reaction solvent to *o*-dichlorobenzene or *o*-dimethoxybenzene led to a significant improvement in the yield. The obvious intermediate will be the cycloadduct **7** which will spontaneously loose carbon dioxide to give 2-pyridones **3** or **4**.

Thus, we have found that TMSCH=C=O smoothly reacts with acyl isocyanates **1** to give the 1,3-oxazin-6-one intermediates **2** which easily undergo the Diels-Alder reaction with DMAD or methyl propiolate to furnish the corresponding 2-pyridones **3** or **4** after expulsion of carbon dioxide.



**a** : Ph, **b** : 4-$MeC_6H_4$, **c** : 4-$NO_2C_6H_4$,
**d** : 4-$MeOC_6H_4$, **e** : 2-Furyl, **f** : 2-Thienyl,
**g** : $PhCH_2CH_2$

**Scheme 2**

A typical experimental procedure is as follows: A mixture of **1** (1 mmol) and TMSCH=C=O (1.2 eq. ) in a solvent (3 ml) was heated at 90°C for 2~3 h under argon. DMAD (2 eq.) or methyl propiolate (4 eq.) was then added and the mixture was stirred at reflux (for *o*-dichlorobenzene) or at 195°C (for *o*-dimethoxybenzene) for 3~7 h. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (BW-200, Fuji Davison, hexane then hexane: AcOEt=5:1~1:5) to give the 2-pyridone **3** or **4**.

The results are summarized in the Table. Various aromatic and heteroaromatic acyl isocyanates were smoothly converted to the corresponding 2-pyridones **3** and **4**. Aliphatic acyl isocyanate such as 3-phenypropionyl isocyanate also underwent the reaction to give **3g** though the yield was moderate. Unfortunately, cyclohexylcarbonyl isocyanate and pivaloyl isocyanate were completely inert. Both *o*-dichlorobenzene and *o*-dimethoxybenzene were the solvent of choice when using DMAD, but *o*-dimethoxybenzene was preferable when using methyl propiolate. Substituents at the 4-position on the benzene ring of **1** considerably affected the yield. The substitution of the electron-withdrawing group increased the yield of **3** and **4**, while the yield decreased with the substitution of the electron-donating group. Excess (2~4 equivalents) acetylene is required to smoothly conduct the reaction, since the reaction proceeded slowly with the use of a slight excess of acetylenes. The other acetylenes such as phenylacetylene and diphenylacetylene were unreactive to **2**.

Table.[a] A One-Pot Preparation of 2-Pyridones **3** and **4**

| Compd. No. | R | X | Solvent[b] | Reaction Time (h) | Yield (%) | IR(nujol) $cm^{-1}$, NHC=O | $^1H$ NMR($CDCl_3$) ppm, C(3)-H | mp[c, d] (°C) |
|---|---|---|---|---|---|---|---|---|
| **3a** | Ph | $CO_2Me$ | A | 3 | 75 | 1665 | 6.90(s) | 194-195 |
| **3b** | 4-$MeC_6H_4$ | $CO_2Me$ | A | 3 | 76 | 1669 | 6.99(s) | 233-235 |
| **3c** | 4-$NO_2C_6H_4$ | $CO_2Me$ | A | 3 | 84 | 1663 | 6.98(s) | 252-253 |
| **3c** | 4-$NO_2C_6H_4$ | $CO_2Me$ | B | 3 | 99 | 1663 | 6.98(s) | 252-253 |
| **3d** | 4-$MeOC_6H_4$ | $CO_2Me$ | A | 4 | 64 | 1661 | 6.98(s) | 225-227 |
| **3e** | 2-Furyl | $CO_2Me$ | A | 3 | 92 | 1657 | 7.02(s) | 205-208 |
| **3f** | 2-Thienyl | $CO_2Me$ | A | 3 | 54 | 1651 | 7.03(s) | 183-185 |
| **3g** | $Ph(CH_2)_2$- | $CO_2Me$ | A | 3 | 23 | 1669 | 6.71(s) | 208-210 |
| **4a** | Ph | H | B | 6 | 49 | 1651 | 6.52(d)<br>(J=9.57 Hz) | 176-178 |
| **4c** | 4-$NO_2C_6H_4$ | H | B | 7 | 65 | 1663 | 6.54(d)<br>(J=9.57 Hz) | 257-258 |
| **4d** | 4-$MeOC_6H_4$ | H | B | 4 | 22 | 1653 | 6.50(d),<br>(J=9.57 Hz) | 207-208 |
| **4e** | 2-Furyl | H | B | 5 | 63 | 1640 | 6.45(d)<br>(J=9.57 Hz) | 180-181 |

a) All new products gave satisfactory elemental analysis and spectral data. b) A = *o*-dichlorobenzene, B = *o*-dimethoxybenzene. c) Recrystallized from tetrahydrofuran-hexane. d) Melting points were measured on a hot-plate.

In the case of methyl propiolate, the reaction was completely regioselective and no regioisomer of **4** could be detected. The observed high selectivity of the addition can be explained by calculated data of the atomic charges of **1a** and methyl propiolate as shown in Fig.1.[7]

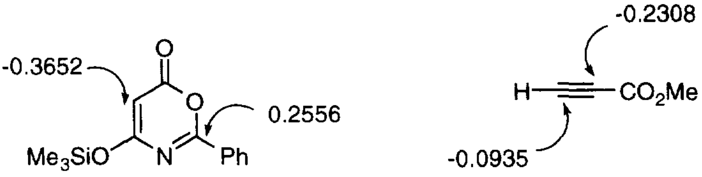


**Fig. 1**

In conclusion, the present method using TMSCH=C=O makes possible the conversion of acyl isocyanates to 2-pyridones in a one-pot process and will provide added flexibility in the pyridone synthesis.

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5. 2-Phenethyl-4-trimethylsiloxy-1,3-oxazin-6-one (**2g**), prepared from the reaction of TMSCH=C=O and 3-phenylpropionyl isocyanate (**1g**), could be isolated by distillation (bp 190°C/1mmHg) in 41% yield. Again, **2g** was hydrolyzed with water within a few minutes to give the corresponding acid **5g**. **2g**: IR(neat): 1762, 1625 cm$^{-1}$. $^{1}$H NMR (CDCl$_3$) δ: 0.32 (s, 9H), 2.90-3.10 (m, 4H), 5.28 (s, 1H), and 7.18-7.31 (m, 5H).
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