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Reactions of 2-methylthiazolines and N-methyl cyclic ketene-N,S-acetals with acid chlorides

Aihua Zhou and Charles U. Pittman, Jr.*

Department of Chemistry, Mississippi State University, Mississippi State, MS 39762, USA

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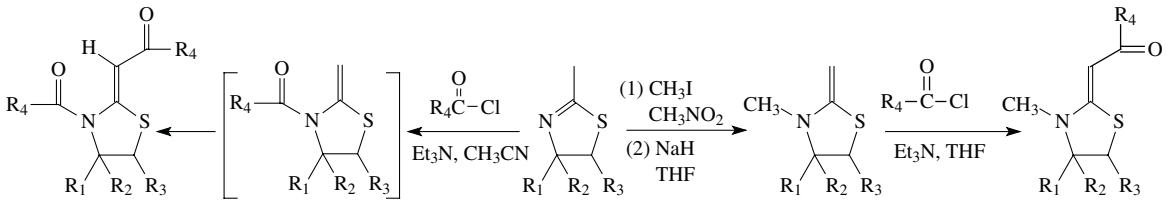
Abstract—Carbon–carbon bond formation occurs under mild conditions when 2-methylthiazolines react with acid chlorides to form N-acyl-β-keto cyclic ketene-N,S-acetals. N-Methyl cyclic ketene-N,S-acetals, generated from 2-methyl-thiazolines, can react further with acid chlorides to form N-methyl-β-keto cyclic ketene-N,S-acetals.

Carbon–carbon bond formation is one of the most important reactions in organic synthesis. Formation of C–C bonds under mild conditions is especially valuable. We demonstrate, herein, facile nucleophilic additions of both 2-methylthiazolines **1** and N-methyl cyclic ketene-N,S-acetals [e.g., 2-(3-substituted thiazolidin-2-ylidene)-1-alkyl- or arylethanones] **2** to acid chlorides to form N-substituted-β-keto cyclic ketene-N,S-acetals [e.g., 2-(3-substituted thiazolidin-2-ylidene)-1-alkyl- or arylethanones], **3** and **4**, respectively, under mild conditions.[1,2] 2-Methylthiazolines have been prepared and employed in organic synthesis for about 70 years.[3,4] They appear in drugs[5,6] and natural products.[7] However, their reactions with acid chlorides to form N-acyl-β-keto cyclic ketene-N,S-acetals **3** have not been reported previously. N-Methyl cyclic ketene-N,S-acetals **2** have never been reported. Their structure combines both an enamine and a thioether function, which suggests they should be explored as a new class of carbon nucleophiles.

2-Methylthiazolines **1** were converted into the more nucleophilic N-methyl cyclic ketene-N,S-acetals **2** by N-methylation followed by treatment with sodium hydride.[8–10] Treating **2** with acid chlorides formed the corresponding N-methyl-β-keto cyclic ketene-N,S-acetals **4** (Scheme 1). The 4-keto analogs of **4** have been reported.[11,12]

Reacting 2-methylthiazolines **1a–d** with 3 equiv of acid chloride and 3 equiv of triethylamine in refluxing acetonitrile generated N-acyl-β-keto cyclic ketene-N,S-acetals **3a–f**. (Table 1). High yields of N-acyl-β-keto cyclic ketene-N,S-acetals **3a–f** were achieved when benzoyl and trimethylacetyl chlorides were used. These acid chlorides have no α-protons. Acid chlorides, which have α-protons, were also tried. N-Acyl-β-keto cyclic ketene



3 **1** **2** **4**

Scheme 1.

Keywords: 2-Methylthiazolines; N-Methyl cyclic ketene-N,S-acetals; Acid chlorides.
* Corresponding author. Tel.: +1 601 325 7616; fax: +1 601 325 7611; e-mail: cpittman@ra.msstate.edu

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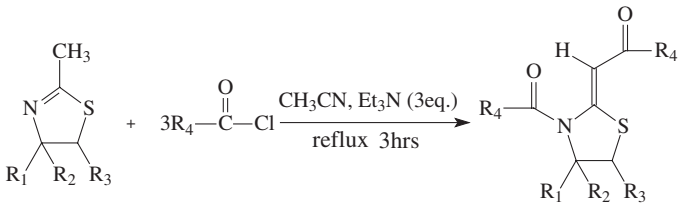
Table 1. The reaction of 2-methylthiazoline with acid chlorides



Entry	Substituents in **1**			R_4 in RCOCl	Product **3**	Yield **3** (%)
	R_1	R_2	R_3			
1a	H	H	H	C_6H_5	**3a**	92
1b	H	H	CH_3	C_6H_5	**3b**	88
1c	Et	H	H	C_6H_5	**3c**	85
1d	CH_3	CH_3	H	C_6H_5	**3d**	90
1a	H	H	H	$(CH_3)_3C$	**3e**	93
1b	H	H	CH_3	$(CH_3)_3C$	**3f**	85
1a	H	H	H	$(CH_3)_2CH$	**3g**	0
1a	H	H	H	$CH_3(CH_2)_2$	**3h**	0

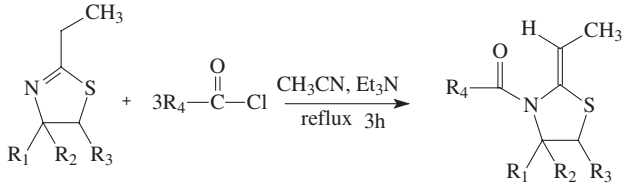
The ratio of **1**/acid chloride/Et_3N = 1:3:3. All yields are isolated yields.

acetals **3g**–**h** did not form using propionyl chloride and *iso*-butyryl chloride. Competing base-catalyzed elimination of HCl from acid chlorides containing α-protons occurred to form the corresponding ketenes, which leads to other reactions.

2-Ethylthiazolines **5** were also synthesized and reacted with benzoyl and trimethylacetyl chlorides, generating N-acyl cyclic ketene-N,S-acetals **6** (Table 2). Unlike the reactions in Table 1, N-acyl-β-keto cyclic-N,S-ketene acetals were not formed. A second equivalent of acid chloride does not react with N-acyl-cyclic ketene-N,S-acetals **6a**–**c**. Indeed, N-acyl-cyclic ketene-N,S-acetals **6a**–**c** were stable enough to be separated by column chromatography. In each case, only the isomer with the methyl *cis* to sulfur was obtained.

The formation of **3a**–**f** and **6a**–**c** may proceed as shown in Scheme 2. The consumption of 1 equiv of acid chloride generates intermediate **7**. Loss of a proton from **7** to NEt_3 produces the reactive intermediate N-acyl cyclic ketene-N,S-acetal **8**. Nucleophilic attack by electron-rich **8** on a second equivalent of acid chloride generates **9** and then **10**, which loses a proton to give **3**. The β-carbon nucleophilicity of N-acyl cyclic ketene acetals derives from the electron-donating ability of both nitrogen and sulfur and the high stability of the resulting 2-substituted thiazolinium cation, even with an N-acyl group present. Thus, a second acid chloride can continue to react with intermediate **8** to form N-acyl-β-keto cyclic ketene-N,S-acetal **3**.

Table 2. The reaction of 2-ethylthiazoline with acid chlorides

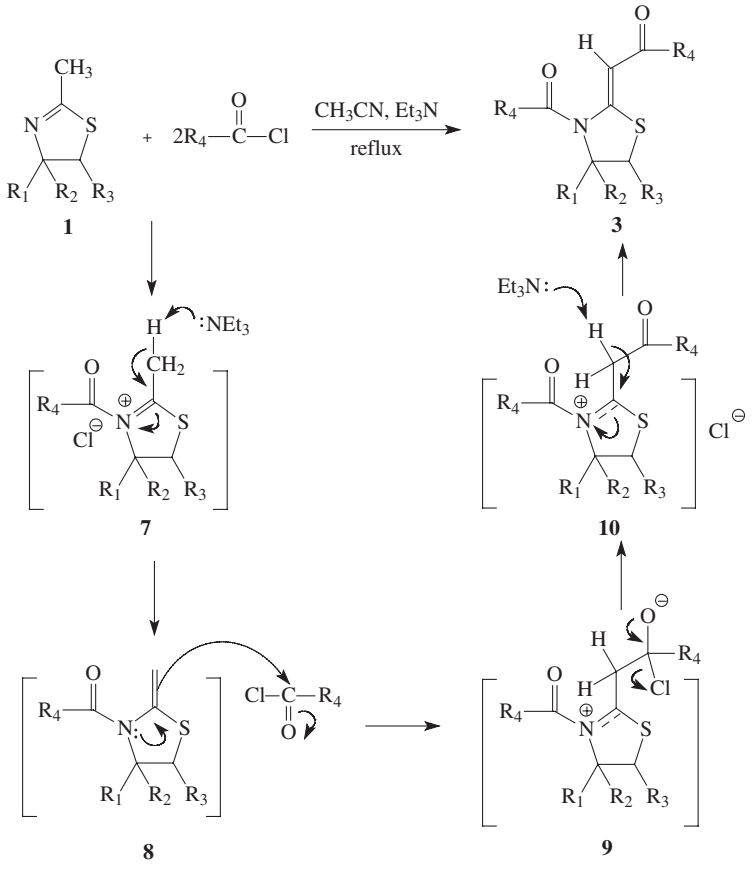


Entry	Substituents in **5**			R_4 in RCOCl	Product **6**	Yield **6** (%)
	R_1	R_2	R_3			
5a	H	H	H	$(CH_3)_3C$	**6a**	87
5b	H	H	CH_3	$(CH_3)_3C$	**6b**	84
5c	H	H	H	C_6H_5	**6c**	89

The ratio of **5**/acid chloride/Et_3N = 1:3:3. All yields are isolated yields.

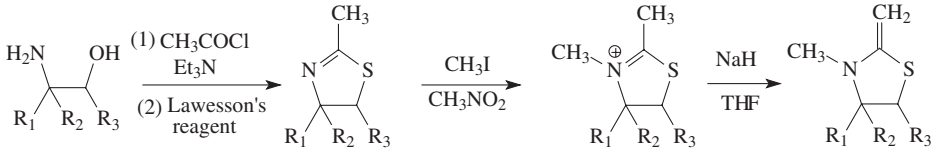
Replacing the N-acyl function of **8** with a methyl group should increase the β-carbon's nucleophilicity. Thus, N-methyl cyclic ketene-N,S-acetals **2** were synthesized and characterized for the first time (Table 3). These compounds are extremely sensitive to acids, acidic surfaces and water. Thus, the isolation of **2a**–**d** requires basic media or base-treated glassware surfaces. To prepare **2a**–**d**, amino alcohols **11** were reacted with acetyl chloride plus Et_3N in dichloromethane to afford 2-hydroxyamides, followed by the treatment with Lawesson's reagent (or P_2S_5) to generate the corresponding 2-methylthiazolines **1a**–**d**.[13,14]. N-Methylation of **1a**–**d** with iodomethane in nitromethane afforded N-methyl-2-methylthiazolinium iodides **12a**–**d**.[15–17] Treatment of **12a**–**d** with sodium hydride in THF generated the very acid sensitive and previously unreported N-methyl cyclic ketene-N,S-acetals **2a**–**d** (Table 3). Their N,O analogs have been reported.[18,19]

N-Methyl cyclic ketene-N,S-acetals **2a**–**d** combine both a thioether and an enamine structure within the same functional group. Due to their high reactivity, they were used immediately after being prepared and characterized. N-Methyl cyclic ketene-N,S-acetals reacted with acid chlorides in THF at room temperature in the presence of Et_3N to form N-methyl-β-keto cyclic ketene-N,S-acetals **4** in good isolated yields (Table 4).



Scheme 2. The reaction mechanism for 2-methylthiazoline with acid chlorides.

Table 3. The synthesis of N-methyl cyclic ketene-N,S-acetals



11 **1** **12** **2**

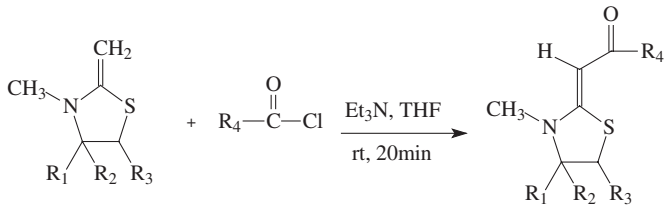
Entry	Substituents in **11**			**1**	**12**	**2**	Yield of **2** from **11** (%)
	R_1	R_2	R_3				
11a	H	H	H	**1a**	**12a**	**2a**	43
11b	H	H	CH_3	**1b**	**12b**	**2b**	41
11c	Et	H	H	**1c**	**12c**	**2c**	36
11d	CH_3	CH_3	H	**1d**	**12d**	**2d**	40

All yields are isolated yields starting from **11**.

Acid chlorides, with or without α-protons, could be employed. The reactions were completed within 10 min. The conversion of **2a** to the corresponding N-methyl-β-keto cyclic ketene-N,S-acetals **4i–o**, using acid chlorides with α-protons, contrasts sharply with the failed of attempts to convert **1a** to **3g**,**h** (in Table 1). N-Methyl cyclic ketene-N,S-acetals **2a–d**, are stronger carbon nucleophiles than their N-acyl analogs, **6**, so reactions of **2a–d** with acid chlorides are faster. Thus, the conversions of **2a** to **4i–o**, occur before competing formation of ketenes occurs. This faster rate allows the use of ambient temperature and shorter reaction times.

Do N-methyl β-keto cyclic ketene-N,S-acetals have enough nucleophilicity to react with a second acid chloride at higher temperatures as illustrated by the conversion of **4i** to **13** (in Scheme 3)? To test this question, **4i** was reacted with benzoyl chloride in refluxing THF in the presence of Et_3N. Surprisingly, the main product of the reaction was **4a** (82%) instead of **13**. Different

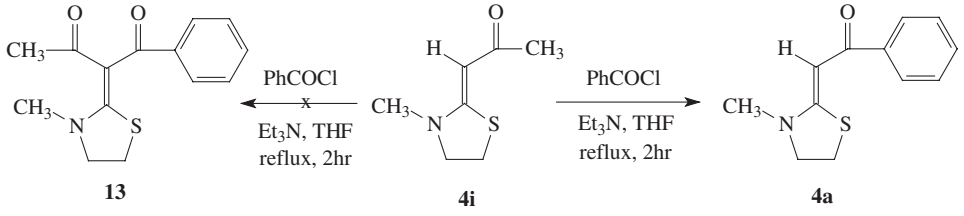
Table 4. The reaction of N-methyl cyclic ketene-N,S-acetals with acid chlorides



2 **4**

Entry	Substituents in **2**			R_4 in RCOCl	Product **4**	Yield **4** (%)
	R_1	R_2	R_3			
2a	H	H	H	C_6H_5	**4a**	78
2b	H	H	CH_3	C_6H_5	**4b**	75
2c	Et	H	H	C_6H_5	**4c**	71
2d	CH_3	CH_3	H	C_6H_5	**4d**	74
2a	H	H	H	$(CH_3)_3C$	**4e**	81
2b	H	H	CH_3	$(CH_3)_3C$	**4f**	76
2c	Et	H	H	$(CH_3)_3C$	**4g**	68
2d	CH_3	CH_3	H	$(CH_3)_3C$	**4h**	69
2a	H	H	H	CH_3	**4i**	82
2a	H	H	H	CH_3CH_2	**4j**	77
2a	H	H	H	$CH_3(CH_2)_2$	**4k**	74
2a	H	H	H	$(CH_3)_2CH$	**4l**	79
2a	H	H	H	$CH_3(CH_2)_3$	**4m**	75
2a	H	H	H	$(CH_3)_2CHCH_2$	**4n**	78
2a	H	H	H	$CH_3(CH_2)_6$	**4o**	75

The ratio of **2**/acid chloride/Et_3N = 1:2:2.1. All yields are based on isolated yields.

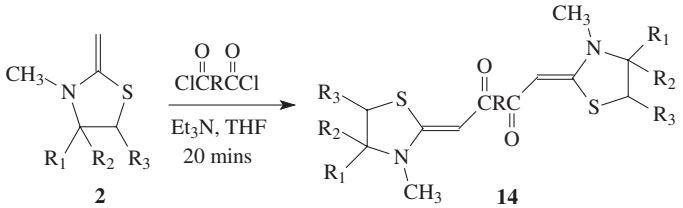


13 **4i** **4a**

Scheme 3. The reaction of N-methyl-β-keto cyclic ketene-N,S-acetals with benzoyl chloride.

reaction times (from 20 min to 20 h) and different acid chlorides (with α-protons) were also tried, but diketo products were not generated. Clearly, once N-methyl cyclic ketene-N,S-acetals **2** react to form N-methyl-β-keto cyclic ketene-N,S-acetals **4**, a sharp drop in nucleophilicity occurs. Thus, the competing reactions of acid

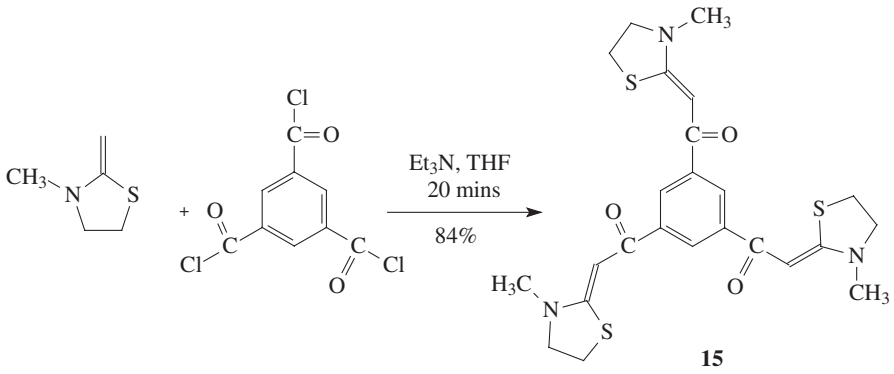
Table 5. The reaction of cyclic ketene-N,S-acetals with diacid chlorides



2 **14**

Entry	Substituents in **2**			R	Product	Yield (%)
	R_1	R_2	R_3			
2a	H	H	H	$>C(CH_3)_2$	**14a**	88
2c	Et	H	H	$>C(CH_3)_2$	**14b**	79
2a	H	H	H	*p*-C_6H_4	**14c**	80

The ratio of **2**/diacid chloride/Et_3N = 2.2:1:2.5. All yields are isolated yields.



Scheme 4. The reaction of cyclic ketene-N,S-acetals with 1,3,5-benzenetricarbonyl trichloride.

chlorides to form ketene by loss of HCl would dominate, leading to other side reactions.

The reactions of N-methyl cyclic ketene-N,S-acetals **2** with diacid chlorides, which have no α-protons, proceed readily in the same way to form the bis-α,β-unsaturated ketones **14a**–**c** in high yields (Table 5). Using diacid chlorides with α-protons (succinyl chloride and glutaryl dichloride) did not afford the analogous products. Compound **14b** was obtained as a pair of racemic diastereomers, which have almost equivalent NMR chemical shifts. Reacting **2** with 1,3,5-benzenetricarbonyl chloride led to the tris-α,β-unsaturated ketone **15** in 84% isolated yield; using a ratio of **2a**/triacid chloride/Et_3N = 3.6:1:4 (Scheme 4).

In summary, we have successfully demonstrated two C–C bond-forming reactions of 2-methyl thiazolines and N-methyl cyclic ketene-N,S-acetals with acid chlorides. These reactions proceed under mild conditions with good yield of N-substituted β-keto cyclic ketene-N,S-acetals. Further applications of these reactions in organic synthesis are being investigated in our lab.

Acknowledgements

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Supplementary data

The detailed synthetic and isolation procedures and the full spectral identifications of all compounds are provided in supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.182.

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