Acylation of Heterocyclic Ketene Aminals with Benzoyl Chloride

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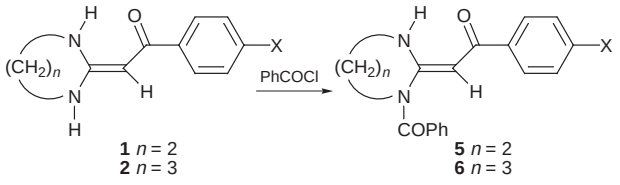
Jian-Chao Wang, Li-Ben Wang and Zhi-Tang Huang*
Institute of Chemistry, The Chinese Academy of Sciences, Beijing 100080, China

Heterocyclic ketene aminals **1** or **2** react with benzoyl chloride to give the regiospecifically mono-*N*-benzoylated products **5** or **6**, while *N*-methyl heterocyclic ketene aminals **3** or **4** react under the same conditions, to give a more complex mixture of products.

Heterocyclic ketene aminals are important intermediates for the synthesis of a wide variety of new heterocycles and fused heterocycles. Therefore, the synthesis and reactions of heterocyclic ketene aminals have received much attention and have been reviewed.[1] Heterocyclic ketene aminals are ambident nucleophiles, for substituted heterocyclic ketene aminals, the electrophiles may attack in three different ways, *N*-, *C*- and *O*-attack, to give different products. The alkylation of heterocyclic ketene aminals, both *C*-alkylation[2–15] or *N*-alkylation,[15–20] have been extensively studied. Recently, the *O*-glucosylation of heterocyclic ketene aminals was also reported.[21,22] By contrast, the acylation of heterocyclic ketene aminals has scarcely been studied.[23,24] Herein, the results of acylation of heterocyclic ketene aminals with benzoyl chloride are reported.

Heterocyclic ketene aminals **1** or **2** react readily with benzoyl chloride in acetonitrile solution at room temperature to give the regiospecifically mono-*N*-benzoylated products **5** or **6** in good to excellent yields (Scheme 1).

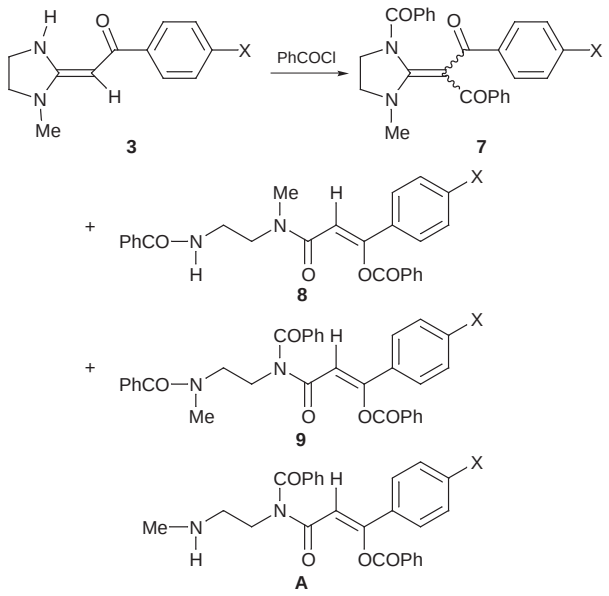


Scheme 1

The constitution of **5** and **6** is determined by elemental analyses and mass spectrometry, and indicates that the products are monoacylated heterocyclic ketene aminals. The presence of an ethylenic proton signal in the ^{1}H NMR spectrum and a carbonyl absorption in IR spectrum of the products exclude *C*- or *O*-acylated derivatives, and the retention of one nitrogen proton signal in the ^{1}H NMR spectrum and a NH absorption in IR spectrum of the products confirm further that the products are the *N*-benzoylated derivatives **5** and **6**. The *E*-configuration of **5** and **6** is determined based on the presence of an intramolecular hydrogen bond, as indicated by the downfield shift of the nitrogen proton in the ^{1}H NMR spectrum and the bathochromic shift of the carbonyl absorption in the IR spectra.

When the *N*-methyl heterocyclic ketene aminals **3** react with benzoyl chloride under the same conditions, the reaction is more complex (Scheme 2). Three products **7**, **8** and **9** are isolated by silica gel column chromatography.

The constitution of **7**–**9** is determined by elemental analyses and mass spectrometry. Compounds **7** are dibenzoylated products as indicated by the disappearance of the N–H and ethylenic proton signal in the ^{1}H NMR spectrum and the absence of an ester carbonyl absorption in the IR spectrum which establish that both *N*- and *C*- benzoylation have taken place. However, the configuration for **7b**–**d** (*E* or *Z*) is not determined. In general, the *E*- or *Z*-forms of **7b**–**d** are difficult to separate by column chromatography and cannot readily be distinguished spectroscopically; **7b**–**d** may well occur as a mixture of *E*- and *Z*-forms.



Scheme 2

From elemental analysis and mass spectrometric data, compounds **8** are also dibenzoylated derivatives in which one molecule of water has been added to cause cleavage of the imidazolidine ring. The presence of the ethylenic proton signal in the ^{1}H NMR spectra and ester carbonyl absorption in the IR spectra of **8** indicate that benzoylation occurs at the nitrogen and oxygen atoms. A provisional X-ray data study suggests that the structure **8** is as shown and not as given by **A**, but this is not established.

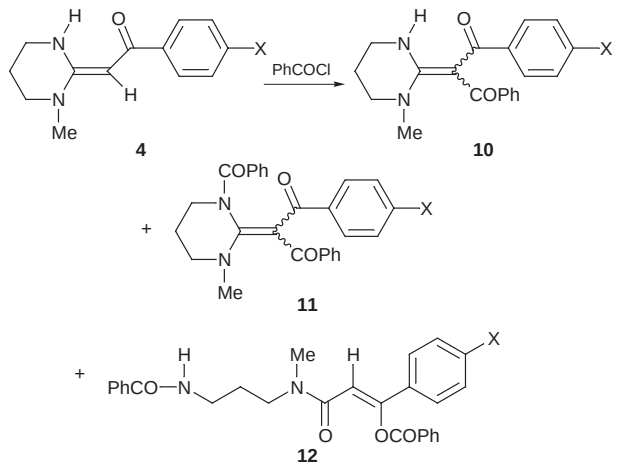
From the elemental analyses and mass spectrometric data, the third product is a tribenzoylated moiety in which one molecule of water has been added to cause ring cleavage. The retention of the ethylenic proton signal in the ^{1}H NMR spectrum and the presence of ester carbonyl absorption indicate that the structure of the product is **9**.

When *N*-methyl ketene aminals **4** with a six-membered hexahydropyramidine ring react with benzoyl chloride under the same conditions, three products **10**, **11** and **12** are isolated by column chromatography (Scheme 3).

From the elemental analysis and mass spectrometric data, two of these products are mono- and di-benzoylated derivatives. The disappearance of the ethylenic proton signal in the ^{1}H NMR spectrum and retention of N–H signal and absorption in the ^{1}H NMR and IR spectrum indicate that compounds **10** are *C*-benzoylated products. The spectra of **11** are similar to **7**, with **11** being both *N*-and *C*-benzoylated products. As for **7b**–**d** above, the *E*- or

* To receive any correspondence (*e-mail*: huangzt@public.bta.net.cn).

Z-configuration of **10b–d** and **11b–d** could not be determined. The third products resemble **8**, and compounds **11** are bibenzoylated products in which cleavage of the hexahydropyrimidine ring has occurred. In the reaction of **3** and **4** with benzoyl chloride, **4** is more likely to undergo *C*-acylation, as observed in other reactions.[27]



Scheme 3

From the above results, we conclude that heterocyclic ketene aminals **1** and **2** react with benzoyl chloride to give the regiospecifically mono-*N*-benzolyated products. In comparison with the results of **1** or **2** with aliphatic acid chlorides, such as propionyl chloride,[23] in which both *N*- and *C*-acylated products are formed, and the regiospecifically *N*-acylated products are only formed under strongly basic conditions;[24] it is seen that the regioselectivity of acylation is higher for benzoyl chloride. While *N*-methyl heterocyclic ketene aminals **3** and **4** react with benzoyl chloride under the same conditions, the reactions are more complex; besides *N*- and *C*-benzoylation, *O*-benzoylation and heterocyclic ring cleavage also occur and hence the regioselectivity is diminished.

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Techniques used: IR, UV, ^{1}H and ^{13} NMR, mass spectrometry

Schemes: 4

References: 27

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