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First [2+2]-cycloaddition of a 3,4-didehydropyridine and a ketene dialkyl acetal

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Abstract—The 3- or 4-halopyridines and a ketene dialkyl acetal were shown to permit the synthesis of pyrido[*b*]cyclobutene derivatives. This finding constitutes the first published report of cycloadditions involving an olefin and a 3,4-pyridyne partner. The reaction is totally regioselective and the structure of the cycloadduct is determined unambiguously by NMR experiments.

Benzocyclobutenes have been shown to be transient intermediates in several organic syntheses.[1] Stevens and Bisacchi have found a simple and straightforward method for the synthesis of benzocyclobutenones **1**,[2] as they have shown that 1,1-dimethoxyethylene participates in a [2+2] reaction with benzynes. Recently, we have shown that 2-methylene-1,3-dioxepane, which is commercially available, could also be used for this synthesis.[3] However, cycloaddition reactions are much less well-known in heterocyclic series.[4]

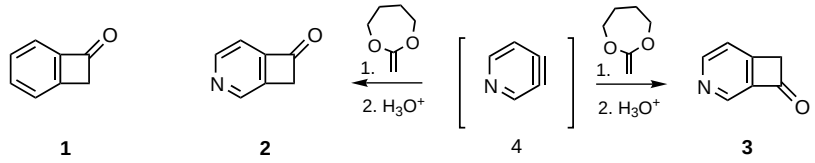
As an extension of our studies and based on the same approach, we have investigated the possibility to prepare the pyridine analogues of **1**, pyrido[*b*]cyclobuten-4-one **2** and/or pyrido[*b*]cyclobuten-3-one **3** by cycloaddition of 2-methylene-1,3-dioxepane and 3,4-pyridyne **4** (Scheme 1).

It is known that hetarynes are less easily generated than benzynes. Pyridynes (didehydropyridines) are reactive intermediates formally derived from a pyridine ring.[5] Of the two possible regioisomers, 3,4-pyridyne **4** is the best described of the hetarynes and has received the most synthetic attention.[6] The use of 3,4-pyridyne seemed of interest. However, compared to its carbocyclic analogue, benzyne, generated by similar methods, the yields of trapped product remain low, limiting the use of pyridynes as synthetic intermediates. Moreover, 3,4-pyridyne **4** has a less predictable dipolarophilic character than benzyne.[7]

In the present communication, we report for the first time the [2+2] cycloaddition of a 3,4-pyridyne to a ketene dialkyl acetal.

Using the usual conditions of cycloaddition, reaction of 3-bromopyridine **7a** with 2 equiv. of $NaNH_2$ in the presence of 2-methylene-1,3-dioxepane failed to give the desired product (Scheme 2).

After several attempts, it emerged that pyridyne could be generated by treatment of halopyridine **7** or **8** with 4 equiv. of LiHMDS and 10 of 2-methylene-1,3-dioxepane. Under these conditions, the cycloadduct **5** was isolated in yields varying from 6 to 11%. The nature of



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

Scheme 1.

Keywords: hetaryne; pyridocyclobutene; [2+2] cycloaddition; 2-methylene-1,3-dioxepane; diethoxyethylene.

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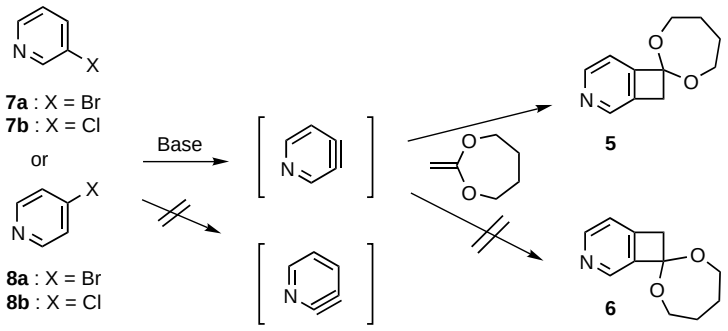


Scheme 2.

the base proved to be important. Quite surprisingly, 3,4-pyridyne was only generated by using LiHMDS. With other bases (LDA, $NaNH_2$, *t*BuOK) and in contrast to the reactions with benzynes,[1] none of the pyridocyclobutenes were obtained; the only product detected was the starting material.

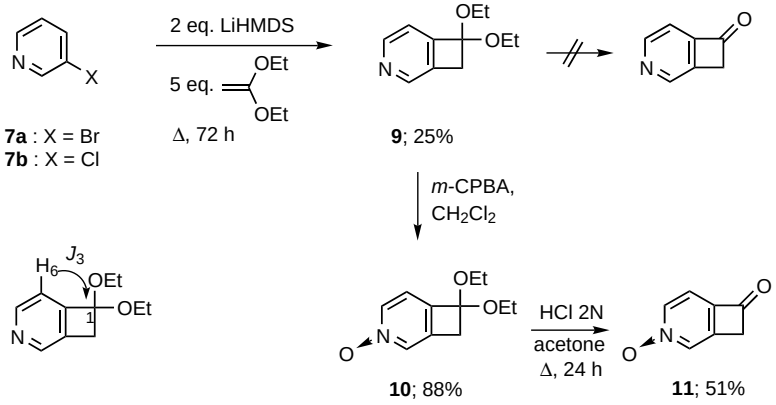
Although this was a pleasing and promising result, as it was the first time that such a product was isolated by this approach, it proved difficult to prepare the pyridocyclobutene in good yield. Nevertheless, this observation is in agreement with the results obtained with benzynes.

Interesting was the remarkable regioselectivity of the reaction. We observed the formation of a single isomer **5**, which was characterized by its physical data. Mass, ^{1}H NMR and ^{13}C NMR spectra were in agreement with the pyridocyclobutenic structure, and the position of the nitrogen was determined by 2D NMR experiments.[8]

The next step of our work was the deprotection of the ketal function. Unfortunately and much to our surprise, all attempts conducted on **5** using various conditions (HCl,[9] *p*-toluenesulfonic acid,[10] $CAN/H_2O/CH_3CN$,[11]…) failed to give the desired ketone; the starting material remaining unchanged or degraded. So, we undertook the preparation of a new ketal by using the acyclic 1,1-diethoxyethylene in place of the 2-methylene-1,3-dioxepane.

In this case, the use of 2 equiv. of LiHMDS and 5 equiv. of diethoxyethylene was sufficient to give the desired cycloadduct with 25% yield. Here too, the reaction is totally regioselective and the structure was also confirmed unambiguously by NMR experiments. The same regioisomer **9** as indicated in Scheme 3 was formed, but all attempts of deprotection failed to give the desired ketone. It is worth pointing out a contrast with the work we previously described,[12] as we have never observed any problem at equivalent steps in the carbocyclic series. So, we concluded that this reaction was affected by the presence of the nitrogen atom of the pyridyl ring. This unexpected result was resolved by oxidation of **9** with *m*-CPBA[13] to produce the target *N*-oxide **10** in 88% yield. A classic acid hydrolysis of **10** with HCl 2N in acetone, provided the desired ketone **11** in 51% yield.[14]

Conclusion: In this paper, we report the first total synthesis of an analogue of pyrido[*b*]cyclobuten-4-one, prepared by hydrolysis of the ketal which is generated from 3- or 4-halopyridine and LiHMDS reacted in the presence of a ketene dialkyl acetal. Its structure was supported by complete proton and carbon NMR assignments made with the aid of 2D experiments. The method herein described of 3,4-pyridyne formation should allow us to develop a novel general approach to 3-pyridyl-*N*-oxide steroids. We are currently exploring this avenue of research and will report our results in due course.



Scheme 3.

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8. Spectral data of **5**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75 (s, 4H); 3.47 (s, 2H); 3.85 (m, 4H); 7.10 (dd, 1H, $J=1.1$, 4.8 Hz); 8.44 (bs, 1H); 8.51 (d, 1H, $J=4.9$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.1; 46.5; 65.1; 105.3; 115.0; 137.5; 144.8; 148.3; 156.4. MS calcd for $C_{11}H_{13}NO_2$: (M^+) 191.0946, found (M^+) 191.0944.
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14. Spectral data of **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.68 (s, 2H); 7.20 (bs, 1H); 8.10 (bd, 1H); 8.15 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6; 125.7; 127.4; 133.3; 137.9; 139.8; 169.8.