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Double nucleophilic addition of bis(trimethylsilyl)ketene acetals to carbon–carbon double bonds of pyrazines: formation of polycyclic γ-lactones

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Abstract—The double activation of pyrazines upon their interaction with methyl chloroformate leading in the presence of bis-(TMS)ketene acetals to polycyclic N-containing γ-lactones parallels the interaction of the same ketene acetals with metal-activated aromatics. The fundamental role of the two oxygen–silicon bonds is outlined. This result broadens the scope of application of these ketene acetals as potential 1,3-dinucleophiles.

The transformation of aromatic molecules into alicyclic, functionalized and stereodefined compounds is still a matter of investigations. For that purpose, reactions mediated by transition metals are among the most recent routes.[1–6]

As part of our efforts to synthesize molecules of potential biological interest, we investigated a few years ago the functionalization of aromatic systems by means of enolates derived from bis(trimethylsilyl)ketene acetals **1** and tricarbonylchromium arene complexes. Interestingly, we observed, besides the expected α-arylcarboxylic acids due to a classical mononucleophilic addition of the trimethylsilyl ester enolate, a rewarding *one pot dearomatization* resulting in the formation of *bicyclic γ-lactones*.[7,8] In these instances, the ketene acetals behaved as 1,3 (C, O) dinucleophiles **2** (Scheme 1).[9]

In contrast, pyridine and its derivatives, as well as pyrazines are known to undergo such nucleophilic additions but in the absence of any metal.[10–12,15] In this regard, we have demonstrated recently that the one pot addition of ketene acetals **1** to pyridines activated by methyl chloroformate,[13] followed by iodine gave also lactones, in that special case, δ-iodolactones again as the result of a double nucleophilic addition of the ketene acetals to the azaaromatic ring system.[14]

As a consequence of this result, we reasoned that 1,4-diazaaromatics might behave such as arenes upon their interaction with bis(trimethylsilyl)ketene acetals and methyl chloroformate, and lead to γ -lactones, the metal being here replaced twice by an activated nitrogen atom. And this was indeed the case. Thus, when a threefold excess of methyl chloroformate in dichloromethane was added, at room temperature, to a mixture of pyrazine **3** (1 equiv) and bis(trimethylsilyl)ketene acetal **1a** (1.1 equiv) in the same solvent, and the mixture stirred for 1 h, then a new crystalline product **4a**† (47%, white

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† Compound **4a**: white crystals, mp = 70 °C; 47% ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.09 (s, 3H, Me); 1.35 (s, 3H, Me); 3.73 and 3.76 (s, 6H, CO_2Me); 4.80 and 4.89 (d, J = 9 Hz, 1H, NCH) ; 6.2 (m, 3H, NCHO and =CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.8 and 25.9 (Me); 44.3 (C_q); 53.7 and 53.9 (OMe); 60.6–61.2 (NC); 80.0–81.1 (NCO) ; 110.4 and 111.4 (C=); 152.9 and 153.6 (CO_2Me); 178.2 (CO_2); IR ν_{CO} = 1718 and 1782 cm^{-1}; MS 302 (M+NH_3). Compound **4b**: white crystals, mp = 130 °C; 58%. Compound **6a**: white crystals, mp = 135 °C; 53%; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.08 (s, 3H, Me); 1.13 (s, 3H, Me); 3.53 (s, 3H, CO_2Me); 3.70 (s, 6H, CO_2Me); 4.3 (m, 1H, OH); 4.57 (m, 1H, NCH); 5.8–6.2 (m, 3H, NCHO and =CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 21.7, 23.4 and 23.7 (Me); 45.8 (C_q); 52.3 and 53.6 (OMe); 60.0 and 60.3 (NC); 71.8 and 72.3 (NCOH); 105.9–108.8 (C=); 152.3, 152.8 and 154.7 (CO_2Me); 175.7 (CO_2); IR ν_{CO} = 1718 cm^{-1}; MS 334 (M+NH_3).

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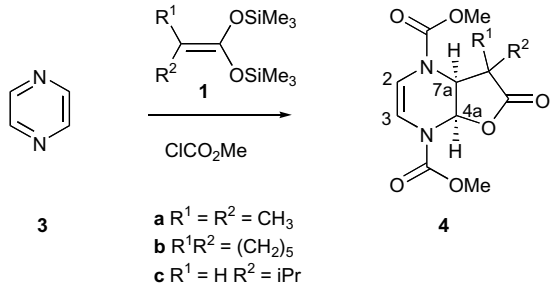
Scheme 1.



Scheme 2.

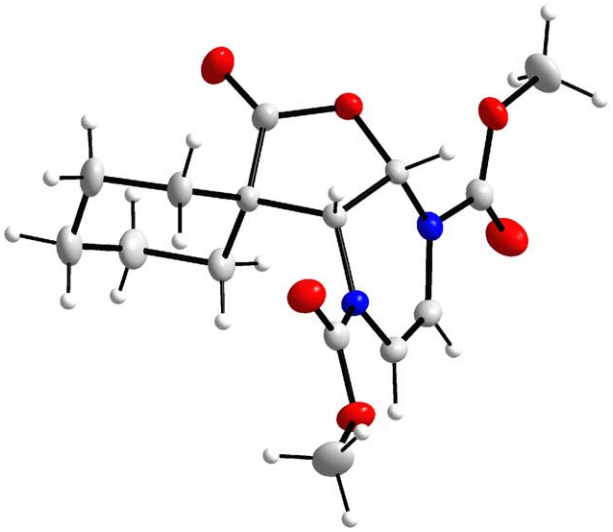


Figure 1. *Diamond* view of **4b**.

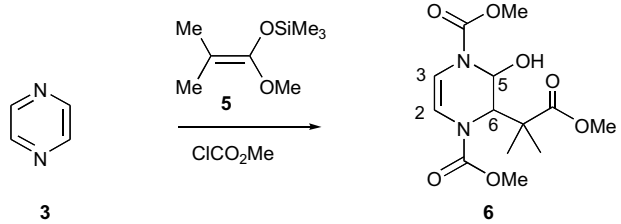
solid, mp = 70 °C) was obtained after work up and silica gel chromatography (Scheme 2).

Both the mass spectrum, NMR and IR data confirmed the formation of a bicyclic lactone upon addition of one equivalent of the deprotonated carboxylate to the doubly activated pyrazine moiety.

Especially diagnostic signals appeared in the ^{1}H NMR spectrum at δ 3.76 and 3.73 for two carbomethoxy groups, and at δ 1.35 and 1.09 for only two methyl groups originating from the ketene acetal **1a**, whereas the ^{13}C NMR (δ_{CO} 178.2, 153.6 and 152.9 ppm) and IR spectra (ν_{CO} 1782 and 1718 cm^{-1}) were in agreement with the presence of both a γ-lactone and the carbomethoxy functions. Similarly, pyrazine and the ketene acetals **1b**,**c** led, respectively, to **4b** (58%) and **4c** (36%). Crystals of **4b** suitable for an X-ray structure[‡] determination were grown from dichloromethane/hexane solutions: a *Diamond* projection appears in Figure 1.[20] It confirmed the formation of a bicyclic γ-lactone upon a double nucleophilic addition of the ketene acetal **1b** to two vicinal carbons of pyrazine, a carbomethoxy group being introduced on each nitrogen atom. In order to clearly establish the importance of the structure of the ketene acetals, the following reactions were carried out. First, the interaction of pyrazine with the ketene acetal **5** containing only one silicon–oxygen bond led to a product **6** different from **4a** in 53% yield. The NMR data were in agreement with the introduction of both the ketene acetal as an ester (ν_{CO} 1718 cm^{-1}, δ_{CO} 175.7 ppm) and of two carbomethoxy groups (δ_{OMe} 3.53 (3H) and 3.70 (6H) ppm). That a monoaddition of the C-centred anion took place at C-6 appeared clearly in the NMR spectra (δ_C, 60 ppm, δ_H, 4.57, d). The chemical shift of C-5, 72 ppm, is indicative of the presence of a second heteroatom on this carbon (δ_H, 6.0 ppm), here a hydroxyl group (δ_{OH}, 4 ppm). Thus, in the absence of a second Si–O bond, although the reaction between methyl chloroformate and the second nitrogen atom still took place, the resulting iminium salt was trapped by water. [15] The presence of a second silicon–oxygen bond is thus of a central role in the formation of the lactones (Scheme 3).

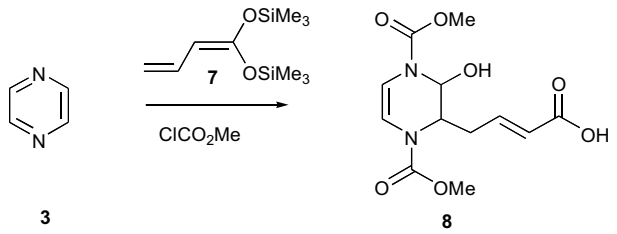
Second, the reaction of pyrazine with the ketene acetal **7** led to the compound **8**, reminiscent of **6**. Though two silicon–oxygen bonds are present in the ketene acetal **7**, no double addition reaction with formation of an (unfavourable) seven-membered lactone took place. A γ-addition of the ketene acetal (thermodynamic product) was observed, followed by the trapping of the second iminium salt by water leading to **8** (Scheme 4).[16–18]

Adding an extra ring to pyrazine did not modify the course of the reaction since quinoxaline **9** led to the tricyclic γ-lactones **10a**,**b** (75% and 50% yields) (Scheme 5).

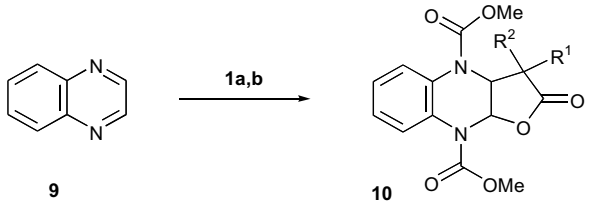


Scheme 3.

[‡]X-ray structural determination of **4b** $C_{15}H_{20}N_2O_6$: Crystals of **4b** were grown at 5 °C from a solution of the compound in a dichloromethane/hexane mixture. Data were collected at room temperature. The compound crystallizes in space group *C*2/*c*, with a = 18.190(2), b = 6.8221(5), c = 24.766(3) Å, V = 3060.2(6) $Å^3$. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-233001. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).



Scheme 4.



Scheme 5.

As a conclusion, two points must be stressed: first, on a formal point of view, the metal, which is essential in the case of aromatic substrates devoid of heteroatom is here replaced by the nitrogen atoms, which render the aromatic rings twice electrophilic upon their successive interactions with methyl chloroformate. Second, the ketene acetals interact *stepwise* with the azaaromatics without a preliminary base-induced activation confirming their high nucleophilicity.[19]

Work is in progress to extend this new type of additions to other heterocyclic systems and to further functionalize the nitrogen-containing lactones.

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20. Experimental procedure: a dichloromethane solution (5 mL) of methylchloroformate (6 mmol) was added to a solution of bis(trimethylsilyl)ketene acetal (2.3 mmol) and pyrazine (2 mmol), at room temperature. Stirring for 1 h followed by evaporation of the solvent and chromatography (PE/AcOEt) on silica gel gave the products **4**.