DOI: 10.1002/ejoc.200601130

C–O Insertion Reaction of Nucleophilic Carbene: Facile Synthesis of Isochromane Cage

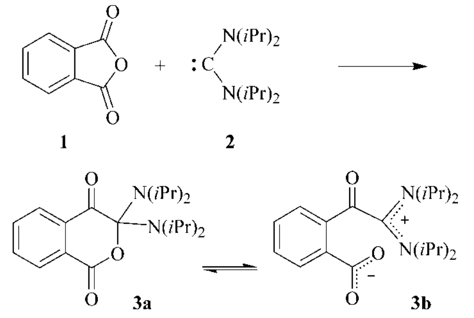
Dmytro Poliakov[a] and Igor Shevchenko*[a]

Keywords: Carbenes / Insertion / Isochromane / Zwitterions / Hydrogen bonds

Bis(diisopropylamino)carbene easily reacts with phthalic anhydride to give quantitatively an isochromane derivative which undergoes unusual isomerization with the formation of a strained azetidine ring and a very short intramolecular hydrogen bond.

The possibility of stabilization of a carbene center by steric amino groups and the isolation of stable nucleophilic aminocarbenes have renewed the interest in the chemistry of carbenes in the last decade.[1] Some general properties of nucleophilic carbenes have become known during this time. For example, such carbenes are able to react with multiple bonds to form complexes with Lewis acids and transition metals and to enter insertion reactions with C–H, N–H, and O–H acids. Nevertheless, many chemical properties of singlet nucleophilic carbenes and their use in preparative chemistry remain uninvestigated. In contrast to unstable electrophilic triplet carbenes,[2,3] insertion reactions of nucleophilic carbenes into C–O and C–S bonds are unknown.

This paper is devoted to a novel formal insertion reaction of a stable singlet diaminocarbene into a single C–O bond. We have found that phthalic anhydride (**1**) easily reacts with bis(diisopropylamino)carbene (**2**) to give quantitatively isochromane derivative **3**, which can be isolated after crystallization as yellow crystals in high yield (Scheme 1). The mechanism of this reaction probably includes a nucleophilic attack of carbene **2** at the C atom of the carbonyl group with subsequent rearrangement, analogous to that proposed for the ring-opening polymerization of lactones catalyzed by N-heterocyclic carbenes.[4]



Scheme 1.

The X-ray analysis revealed some interesting properties of compound **3**. The crystal structure consists of an equal number of molecules of two structural isomers assembled in alternate layers. Each layer is composed of molecules of either the closed isochromane structure **3a** or the opened zwitterionic form **3b** (Figures 1 and 2).[5] The length of the C8–O2 bond in **3a** (1.494 Å) is substantially longer than the adjacent C7–O2 bond (1.338 Å), which is equal to the average length of the C–O bond in anhydrides. The distance between the C8 and O2 atoms in the zwitterionic isomer is 2.497 Å. The facile heterolytic cleavage of the C8–O2 bond in **3a** is accounted for by the presence of carboxylic CO_2 and amidinium CN_2 moieties in the molecule which stabilize negative and positive charges in zwitterionic structure **3b**. Indeed, because of the delocalized positive charge, the C8 atom has a flat configuration and short C8–N1 and C8–N2 bonds (1.345 and 1.333 Å, respectively). Analogously, because of the negative charge, the C7–O2 bond in **3b** (1.263 Å) is shorter than that in closed form **3a** (1.338 Å).

It is logical to suppose that in solution the two isomers should exist in equilibrium with each other. However, in different solvents either closed isomer **3a** or zwitterionic isomer **3b** was found. For example, in hexane, benzene, and THF, compound **3** existed exclusively in closed isochromane form **3a**, whereas in CD_2Cl_2 or $CDCl_3$, only zwitterionic form **3b** was detected. The rapid exchange between the two structural isomers (on the NMR time-scale) was registered by ^{1}H NMR spectroscopy at 20 °C in a benzene solution containing about 20% chloroform.

Both isomers of compound **3** are stable in the crystalline form. Closed isochromane isomer **3a** is stable in hexane, benzene, and THF even at 80 °C and shows no tendency to decompose. However, the opening of the heterocycle in

---

[a] Institute of Bioorganic Chemistry and Petrochemistry,
Murmanskaya Street 1, 02094 Kiev, Ukraine
Fax: +380-44-5732552
E-mail: igorshevchenko@yahoo.com

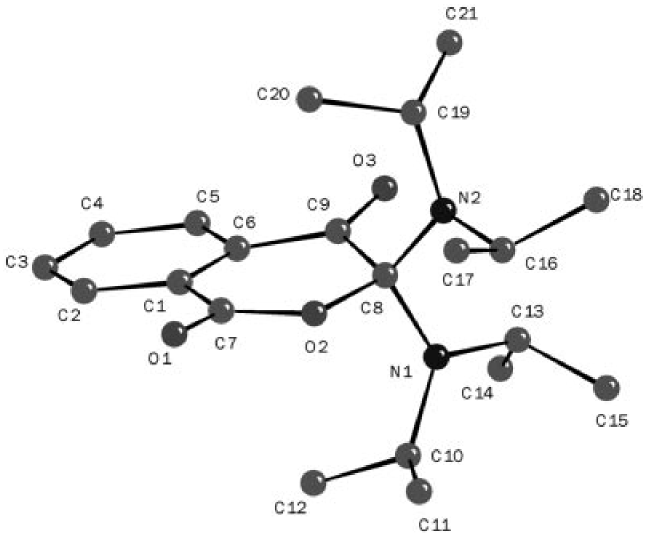


Figure 1. Crystal structure of **3a**. Selected bond lengths [Å] and angles [°]: C7–O1 1.211; C7–O2 1.338; C8–O2 1.494; C8–N1 1.448; C8–N2 1.419, N1–C8–N2 112.54.

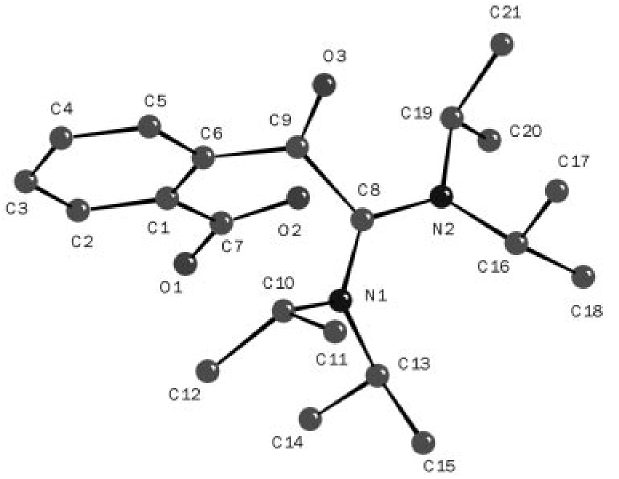
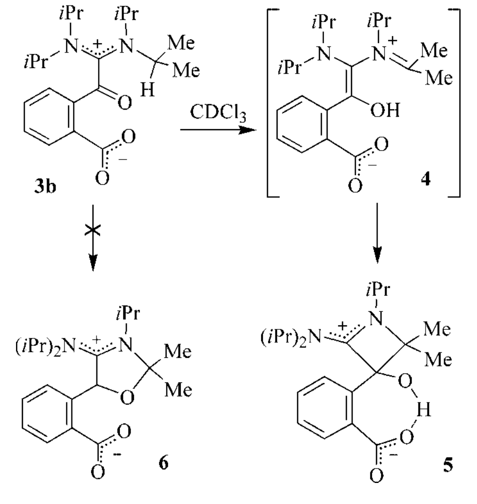


Figure 2. Crystal structure of **3b**. Selected bond lengths [Å] and angles [°]: C7–O1 1.237; C7–O2 1.263; C8–O2 distance 2.497; C8–N1 1.345; C8–N2 1.333; N1–C8–N2 123.78; N1–C8–C9 118.03; N2–C8–C9 117.39.

dichloromethane or in chloroform makes the structure of zwitterionic isomer **3b** unstable. In solution, it undergoes an interesting quantitative irreversible rearrangement into the third structural isomer **5** (Scheme 2). This process is slow and takes about 20 h at room temperature. The X-ray analysis of the new isomer revealed that zwitterionic structure **5** contains a four-membered ring and an OH group which resulted from the intramolecular addition of a CH fragment of one of the isopropyl groups to the carbonyl CO function (Figure 3).[5]

At first sight, the alternative direction of the intramolecular cyclization of **3b** leading to the less acidic CH bond and less strained five-membered oxazolidine derivative **6** would be more preferable. The mechanism of the formation of structural isomer **5** is likely to involve intramolecular hydrogen shift leading to azamethine intermediate **4** followed



Scheme 2.

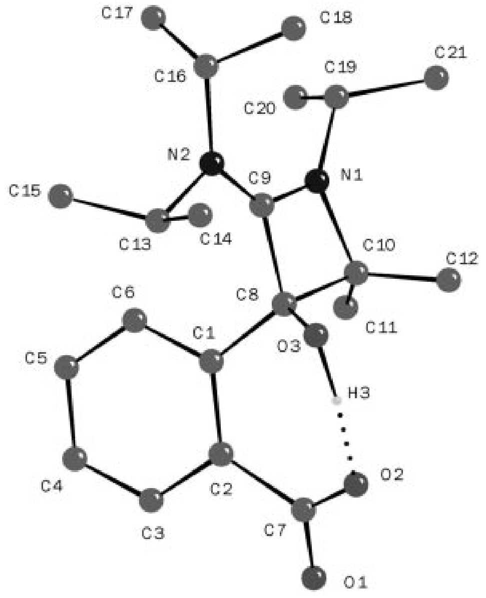


Figure 3. Crystal structure of **5**. Selected bond lengths [Å], angles [°], and torsion angles [°]: O3–H3 1.06(6); O2–H3 1.40(6); O2–O3 distance 2.450; C9–N1 1.307(4); C9–N2 1.325(4); O2–H3–O3 174.69; C8–O3–H3 98(3); C9–C8–C10 84.5(3); N1–C10–C8 86.3(2); C9–C8–C10–N1 4.9(2); C19–N1–C9–N2 13.8(7); C10–C8–C1–C6 91.7(3).

by ring-closure. This process has something to do with the recently reported transient formation of an azomethine ylide from a stable aminocarbene.[6] The reason why the strained four-membered ring is thermodynamically more stable is not quite clear. At least partially, this is accounted for by another interesting peculiarity of structure **5**, namely, by the abnormally short hydrogen bond between the hydroxy group and one of the carboxylic oxygen atoms (O3···O2 intramolecular distance is 2.450 Å). The H3···O2 distance [1.40(6) Å] is equal to that of the shortest intramolecular OH···O hydrogen bond known.[7] Thus, the O–H–O triade is incorporated into the seven-membered cycle and the whole molecule adopts a spirocyclic structure. It is interesting that the C8–O3–H3 angle inside the seven-membered ring is unusually narrow (98° instead of 109.5°).

The ^{1}H NMR spectrum of this compound in chloroform displayed an unexpectedly low-field chemical shift of the H(3) proton at δ = 13.03 ppm, which is even higher than that of benzoic acid. This may indicate the partial delocalization of negative charge on the O3 oxygen atom.

We believe that the insertion reaction described here can be extended to other systems with a properly activated C–O bond. Because of the relative accessibility of carbene **2**, the reaction may not only have a theoretical but also a practical interest.

Experimental Section

3: A mixture of phthalic anhydride (**1**; 0.5 mmol, 74 mg) and bis(diisopropylamino)carbene (**2**;[8] 0.5 mmol, 106 mg) in benzene (0.5 mL) was stirred for 2 h at 20 °C until complete dissolution of **1** was observed. Benzene was evaporated, the residue was dissolved in boiling hexane (2 mL), and the solution was left at –15 °C overnight to give **3** as yellow crystals (yield: 144 mg, 80%). Crystals suitable for X-ray analysis were grown from a hexane/Et_2O solution at –15 °C. M.p. 117–119 °C. **3a**: ^{1}H NMR (400 MHz, C_6D_6, 20 °C): δ = 0.97 (d, $^3J_{H,H}$ = 6.84 Hz, 12 H), 1.15 (d, $^3J_{H,H}$ = 6.84 Hz, 12 H), 3.71 (sept., $^3J_{H,H}$ = 6.84 Hz, 4 H), 7.10 (m, 2 H), 8.02 (m, 1 H), 8.18 (m, 1 H) ppm. ^{13}C NMR (100 MHz, C_6D_6, 20 °C): δ = 23.14, 23.52, 46.54, 115.41, 127.00, 129.5, 130.16, 133.07, 133.48, 134.16, 161.88, 187.36 ppm. **3b**: ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 1.26 (m, 24 H), 3.98 (sept., $^3J_{H,H}$ = 6.84 Hz, 4 H), 7.35 (t, $^3J_{H,H}$ = 7.82 Hz, 1 H), 7.48 (t, $^3J_{H,H}$ = 7.82 Hz, 1 H), 7.73 (d, $^3J_{H,H}$ = 7.82 Hz, 1 H), 8.19 (d, $^3J_{H,H}$ = 7.82 Hz, 1 H) ppm.

5: A solution of **3** (0.03 mmol, 110 mg) in chloroform (0.7 mL) was left at 20 °C overnight. The solvent was evaporated in vacuo, the residue was heated at reflux in toluene (1 mL) for 5 min to give, after cooling, **5** as a beige precipitate (yield: 92 mg, 84%). Crystals suitable for X-ray analysis were grown from a $CHCl_3$/THF solution at –15 °C. M.p. 200–202 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 0.99 (s, 3 H), 1.07 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 1.17 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 1.23 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 1.33 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 1.37 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 1.49 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 1.67 (s, 3 H), 3.86 (sept., $^3J_{H,H}$ = 6.84 Hz, 1 H), 4.31 (sept., $^3J_{H,H}$ = 6.84 Hz, 1 H), 4.33 (sept., $^3J_{H,H}$ = 6.84 Hz, 1 H), 6.66 (d, $^3J_{H,H}$ = 7.82 Hz, 1 H), 7.20 (t, $^3J_{H,H}$ = 7.82 Hz, 1 H), 7.24 (t, $^3J_{H,H}$ = 7.24 Hz, 1 H), 8.22 (d, $^3J_{H,H}$ = 7.82 Hz, 1 H), 13.03 (br., 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 19.06, 19.90, 20.40, 20.54, 21.34, 22.90, 24.69, 25.66, 46.24, 51.54, 55.89, 86.28, 124.06, 128.11, 128.34, 134.48, 135.96, 139.22, 163.77, 171.14 ppm.

---

[1] D. Bourissou, O. Guerret, F. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39–91.

[2] K. Ito, T. Katsuki, *Chem. Lett.* **1994**, 1857–1860.

[3] J. Buschmann, R. Damerius, R. Gerhardt, D. Lentz, P. Luger, R. Marshall, D. Preugschat, K. Seppelt, A. Simon, *J. Am. Chem. Soc.* **1992**, *114*, 9465–9469.

[4] G. W. Nyce, T. Glauser, E. F. Connor, A. Möck, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2003**, *125*, 3046–3056.

[5] **3** (CCDC-624633): $C_{21}H_{32}N_2O_3$, M = 360.49, triclinic, a = 9.3553(6), b = 14.2731(9), c = 15.3322(9) Å, α = 99.518(4), β = 99.162(4), γ = 90.620(4)°, U = 1991.9(2) Å^3, T = 293 K, space group $P\bar{1}$, Z = 4, μ(Mo-K_α) = 0.08 mm^{-1}, 19693 reflections measured, 9442 unique (R_{int} = 0.0393). The final $R1$ = 0.0598, $wR(F_2)$ 0.1709 for 6553 observed reflections [$I > 2\sigma(I)$]. **4** (CCDC-624632): $C_{25}H_{40}N_2O_4$, M = 432.59, orthorhombic, a = 15.3456(4), b = 8.4830(3), c = 19.0773(4) Å, α = 90, β = 90, γ = 90°, U = 2483.42(12) Å^3, T = 293 K, space group $Pca2_1$, Z = 4, μ(Mo-K_α) = 0.078 mm^{-1}, 7308 reflections measured, 3738 unique (R_{int} = 0.039). The final $R1$ = 0.0592, $wR(F_2)$ 0.1386 for 2809 observed reflections [$I > 2\sigma(I)$]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[6] X. Cattoën, S. Solé, Ch. Pradel, H. Gornitzka, K. Miquen, D. Bourissou, G. Bertrand, *J. Org. Chem.* **2003**, *68*, 911–914.

[7] C. Bilton, F. H. Allen, G. P. Shields, J. A. K. Howard, *Acta Crystallogr., Sect. B* **2000**, *56*, 849–856.

[8] R. W. Alder, P. R. Allen, M. Murray, A. G. Orpen, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1121–1123.

Received: December 28, 2006