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Proton-catalysed *E-Z* isomerisation and Pd(II) assisted carbon–carbon cleavage on 3-phenyl-4-(2,4,6-trimethoxyphenyl)methyleneisoxazolin-5-one

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Abstract—Proton electrophilic addition to 3-phenyl-4-(2,4,6-trimethoxyphenyl)methyleneisoxazolin-5-one can either catalyse *E-Z* isomerisation or a Pd(II) assisted cleavage of the exocyclic sp^2-hybridised C–C bond in dependence on the proton site attack.

The activity of 4-aryl-methyleneisoxazolin-5-ones as 1–4 Michael acceptors,[1] conjugated oxadienes in Diels–Alder reactions[2,3] or dipolarophiles[4–6] is well documented. Due to 1,3 steric interactions between aryl substituents the 3-phenyl derivatives were believed to exist only in the *Z* form (like **2** and **2a** in Fig. 1) both in solution[7] and in the solid state.[8]

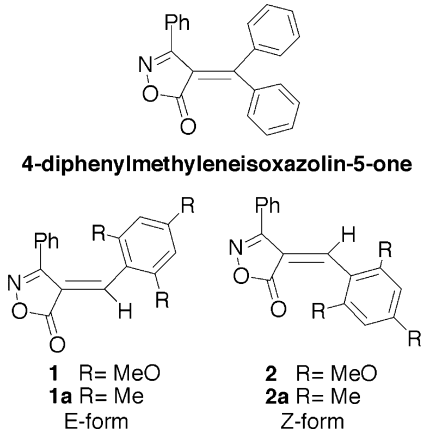

Figure 1.

Nonetheless, the formation of 4-diphenylmethyleneisoxazolin-5-one[9] (Fig. 1) witnesses the possibility that the 4-arylmethylenes can exist in the *E*-form, and a theoretical study on aryl derivatives of cynnamic acid owning similar steric features suggests, indeed, a comparable thermodynamic stability for the two isomers despite of the bigger steric hindrance claimed for the *E* form.[10]

Our ^{1}H NMR[11] and 2D NOESY[12] spectra show the trimethoxy derivative, as solved in chloroform, in the pure *E* form **1** that slowly interconverts in to the *Z* isomer **2**, reaching an equilibrium composition ratio **1** to **2** of 1.4 in about 8 days. In the same way we proved that although fresh chloroform solutions of trimethyl derivative, contains almost exclusively the *Z* form **2a**, slow isomerisation leads to equilibrium composition similar to that reported for the trimethoxy derivative (**1a** to **2a** ratio about 1.3). On the other side, slow evaporation of chloroform from the mixtures of, respectively, the trimethoxy and trimethyl derivatives at equilibrium, again separates pure crystals of **1** and **2a**, whereas fast evaporation in both cases yields mixtures of the two isomers with the approximate equilibrium composition. Thus, in accord with the theoretical conclusions,[9] we found that in solution *E* and *Z* forms have approximately equal potential energy, and that, in chloroform, the selective crystallisation of a single pure isomer is driven by its lower solubility. The isomerisations require several days to take place, either in protic or aprotic solvents, however, as assessed for analogue

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derivatives,[13] the reactions are dramatically catalysed by protons. In acid CD_3OD at room temperature, interconversion occurs in the NMR timescale so that the kinetic process can be analysed, at the equilibrium, by magnetisation transfer experiments.[14,15] By this procedure we found that the pseudo-first-order **1** to **2** interconversion rate constant (k_{obs}) obeys to the following kinetic law:[16]

$$k_{obs} = a[D^+]/(1+b[D^+]);$$

$a = 9.5\pm0.8$ s^{-1} mol^{-1}; $b = 0.9\pm 0.2$ mol^{-1}; in methanol at 298 K.

Proton addition to **1** and **2** derivatives leads to intermediates **3** and **4**, respectively, whose energetic rotational barrier is dramatically reduced because of the mesomeric shift of the exocyclic double bond toward the isoxazolinone ring. In alternative electrophilic addition of a proton to the aromatic electron-rich *ipso*-carbon of **1** and **2** leads to intermediates **5** and **6** which prevent the isomerisation.

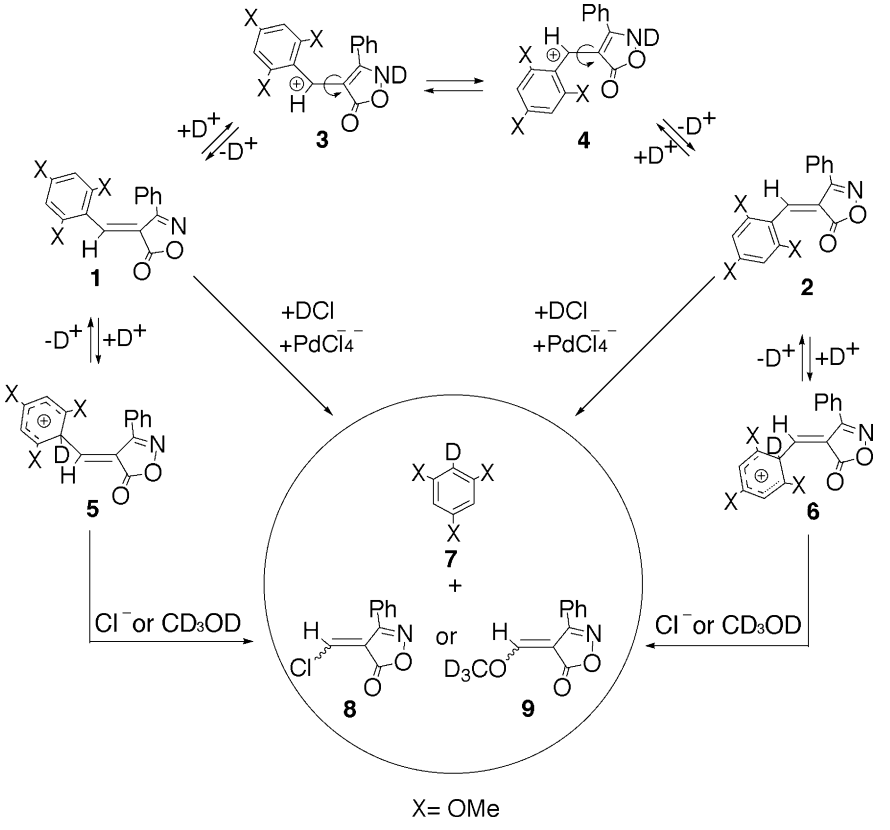
Addition of $PdCl_4^{2-}$ does not affect significantly the isomerisation rate, however the complex greatly speeds the rate of a much slower process that leads to the release of 1,3,5-trimethoxybenzene (over 85% yields). The rate of this process, monitored by periodic integration of the methoxy resonance of **7** at 3.75 ppm, shows, in the reported experimental conditions,[17] a pseudo-first-order kinetic dependence on the **1-2** concentration (*E-Z* fast equilibrium), in accord with the following kinetic rate law:

$$k'_{obs} = (a' + a''[PdCl_4^{2-}])[D^+]/(1+b'[D^+]);$$

$a' = 0.5\pm0.1$ h^{-1} mol^{-1}; $a'' = 15.3\pm2$ h^{-1} mol^{-2}; $b' = 3.7\pm 0.5$ mol^{-1}; in methanol at 323 K.

A mechanism of both isomerisation and palladium assisted reaction, consistent with our experimental results, is reported in Scheme 1.

Experimental evidence for the proposed mechanism: (i) the kinetic rate laws; (ii) mass spectra proving the progressive formation of **7**, **8**, and **9** (small amounts) in the reaction mixture; (iii) NMR spectra in acid CD_3OD, showing progressive transformation of the methoxy resonances of **1** and **2** in to the single resonance at 3.75 ppm, correspondent to that of an authentic sample of 1,3,5-trimethoxybenzene. Further NMR and mass spectra monitoring of the acid CD_3OD solution indicate slower complete deuteration of the residual aromatic protons of **7**. The reaction here reported is, to our knowledge, the first example of carbon–carbon sp^2 hybridised exocyclic cleavage in mild conditions. We did not observe an analogous cleavage in **1a** and **2a**, probably because activation of the exocyclic carbon–carbon bond requires very electron rich aryls. Cleavage and functionalisation of strong C–C single bonds by transition metal complexes is an important transformation, relevant to Ziegler Natta and other organometallic processes.[18–20] Pd-aryl *ipso*-carbon η_1 interaction has been proposed as a likely intermediate of C_{aryl}–C_{alkyl} activation[21]. A recent structural characterisation of similar complexes highlighted a length of about 156 pm for the crucial exocyclic linkage.[22] On



Scheme 1.

this basis the authors predicted for this class of compounds potential easy C–C cleavage (deinsertion) analogous to that occurring in our system.

References

1. Risitano, F.; Grassi, G.; Bruno, G.; Nicolò, F. *Liebgs Ann. Recueil* **1997**, 441–445 and references cited therein.
2. De Simoni, G.; Tacconi, G. *Gazz. Chim. Ital.* **1968**, 1329–1342.
3. De Simoni, G.; Gamba, A.; Righetti, P. P.; Tacconi, G. *Gazz. Chim. Ital.* **1971**, 899–922.
4. Lo Vecchio, G.; Grassi, G.; Risitano, F.; Foti, F. *Tetrahedron Lett.* **1973**, *39*, 3777–3780.
5. Clerici, F.; Erba, E.; Mornatti, P.; Trimarco, P. *Chem. Ber.* **1989**, *122*, 295–300.
6. Abbass, J. M.; Mosselhy, M. A. N.; Abdallah, M. A.; Shawali, A. S. *J. Chem. Res.* **1995**, 190–191.
7. Maquestiau, A.; Van Haverbeke, Y.; Muller, R. N. *Tetrahedron Lett.* **1972**, *12*, 1147–1150.
8. Meunier-Piret, P. J.; Piret, P.; Germain, G.; Putzeys, J.-P.; Van Meerssche, M. *Acta Crystallogr.* **1972**, *B28*, 1308–1311.
9. Harhash, A. H.; Elnagdi, M. H.; Tunsi Hussein, N. S.; Fahmi, S. M. *Indian J. Chem.* **1973**, *11*, 1.
10. Kortvelyesi, T.; Lovas, S.; Murphy, R. F.; Kiss, G.; Palinkò, I. *Internet J. Chem.* **1999**, *2*, 2.
11. Selected ^{1}H NMR data ($CDCl_3$, 300 MHz, 298 K); **1**: δ 3.40 (s, 6H, *o*-OCH_3), 3.79 (s, 3H, *p*-OCH_3), 5.81 (s, 1H, CH), 7.18–7.37 (m, 5H, Ph), 8.09 (s, 2H, Ar). **2**: $\delta=3.82$ (s, 6H, *o*-OCH_3), 3.87 (s, 3H, *p*-OCH_3), 6.10 (s, 1H, CH), 7.47–7.68 (m, 5H, Ph), 7.80 (s, 2H, Ar). **7**: $\delta=3.75$ (s, 9H, *o*-OCH_3), $\delta=6.06$ (s, 2H, Ar).
12. (a) Bax, A.; Davies, D. G. *J. Magn. Reson.* **1985**, *65*, 355–360; (b) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; Weinheim, 1989; pp. 253–305.
13. Palinkò, I.; Burrichter, A.; Rasul, G.; Torok, B.; Prakash, G. K. S.; Olah, G. A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 379–385.
14. Forsen, S.; Hoffman, R. A. *J. Chem. Phys.* **1963**, *39*, 2892.
15. Forsen, S.; Hoffman, R. A. *J. Chem. Phys.* **1964**, *40*, 1189.
16. 0.01 mmol of **1** and 0.25–0.05 mmol of DCl were dissolved in 0.5 mL of CD_3OD with 5% of D_2O. Pseudo-first-order **1**–**2** interconversion rates at equilibrium were obtained plotting the 3.40 ppm resonance intensity (2,5-OCH_3 of **1**), as a function of the selective saturation time of the 3.82 ppm resonance (2,5-OCH_3 of **2**). Corrections for the relaxation rate, calculated by the residual relative intensity of the 3.40 ppm resonance after long selective irradiation at 3.82 ppm, went from 5 to 18%. The ionic strength was maintained constant at $\mu=0.5$ by addition of anhydrous LiCl.
17. 0.01 mmol of **1** and 0.25–0.05 mmol of DCl were dissolved in 0.5 mL of CD_3OD with 5% of D_2O. From 0.0 to 0.05 mmol of $PdCl_2$ were added to the solutions. Pseudo-first-order rates of **7** formation from the acid mixtures of **1**–**2** at equilibrium were obtained by periodic monitoring of the trimethoxy-benzene resonance intensity at 3.75 ppm. The ionic strength was maintained constant at $\mu=0.5$ by addition of anhydrous LiCl.
18. Murai, S. *Topics in Organometallic Chemistry*: *Activation of Unreactive Bond and Organic Synthesis*; Springer-Verlag: Berlin, 1999.
19. Simhai, N.; Iverson, C. N.; Edelbach, B. L.; Jones, W. D. *Organometallics* **2001**, *20*, 2759–2766.
20. Edelbach, B. L.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2843–2853.
21. Campora, J.; Gutierrez-Puebla, E.; Lopez, J. A.; Monge, A.; Palma, P.; del Rio, D.; Carmona, E. *Anghew. Chem., Int. Ed* **2001**, *40*, 3641–3644.
22. Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336–4346.