Intramolecular cyclization of bis(2,4,6-trialkylphenyl) ketenes to isochromenes

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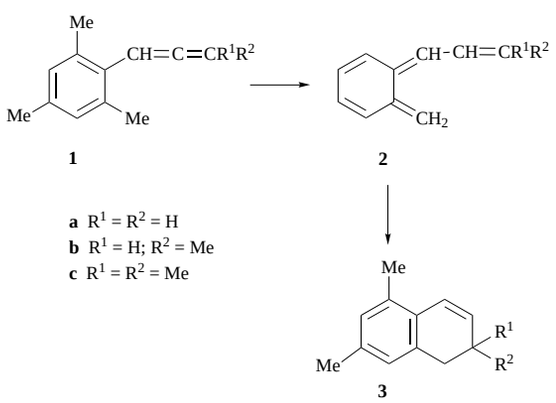
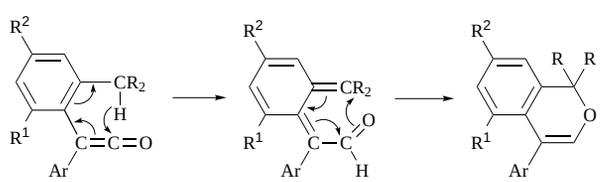
The crowded ketenes, $(2,4,6\text{-}R_3C_6H_2)_2C{=}C{=}O$, R = Pr^i, Me, undergo intramolecular cyclization of the ketene oxygen on an *o*-alkyl group to give substituted isochromenes. The reaction is two orders of magnitude faster at 170 °C for R = Pr^i than for R = Me. A stepwise reaction involving a 1,5-sigmatropic rearrangement to a conjugated tetraenal which does not accumulate and rapidly cyclizes to the isochromene is suggested.

Simple ketenes or allenes dimerize to cyclic derivatives and undergo intermolecular cycloadditions with doubly bonded substrates.[1] Intramolecular cyclization takes place when the molecules have special structural features. When an allenic moiety is attached to a bulky aromatic substituent intramolecular cyclization, as in the case of mesitylallene (**1a**) which undergoes intramolecular cyclization to the 1,2-dihydronaphthalene derivative (**3a**) in decane at 170 °C, takes place. Its monomethyl derivative (**1b**) gives the analog (**3b**), together with the pentaene, **2a**, whereas 1-mesityl-3,3-dimethylallene (**1c**) gives only **2c** (Scheme 1).[2] The cyclization mechanism suggested involves an



Scheme 1

initial 1,5-sigmatropic hydrogen shift from the aromatic methyl to form **2** with the correct geometry for cyclization. 1,5-Sigmatropic hydrogen shifts which generate aldehydes from ketenes have been reported,[3,4] *e.g.*, the suggested first step (**4a**→**5b**) in the di-*o*-tolylketene (**4a**) rearrangement to 4-*o*-tolylisochromene (**6a**) (Scheme 2).[2]



Scheme 2

The latter reaction is the only one known to us which gives an isochromene directly from a precursor ketene. The reaction is

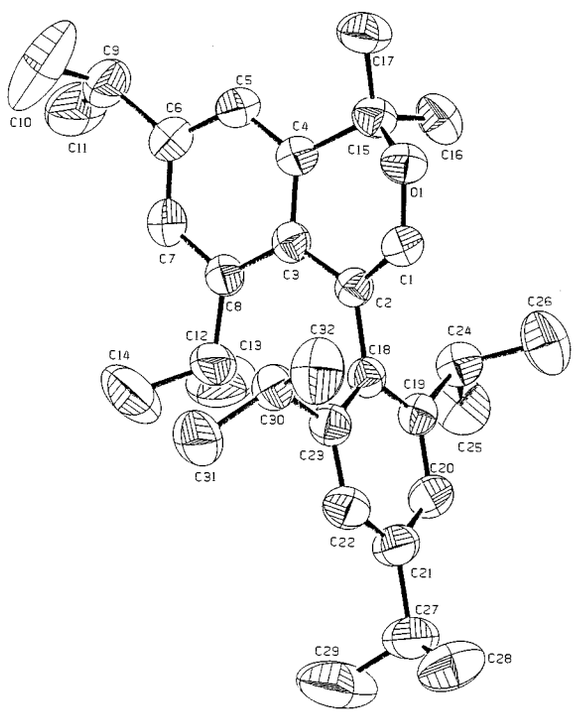


Fig. 1 ORTEP drawing of the X-ray diffraction of **6b**. O(1)–C(1) = 1.359(2); O(1)–C(15) = 1.451(2); C(1)–C(2) = 1.335(3) Å.

quoted[3b,4,5] as taken from a thesis[4b] but the details were not given except that it was conducted at 250 °C and **5a** was suggested as an intermediate. We note that acylcyclobutanes rearrange thermally to isochromenes by an initial thermal ring-opening to the corresponding tetraenones.[4a,6]

In an unrelated study, when the crowded ditipyl ketene **4b**[7] (tipyl = Tip = 2,4,6-triisopropylphenyl) was heated in toluene, an analogous intramolecular cyclization reaction was recorded (Scheme 2). In the ^{1}H NMR spectra one of the isopropyl doublets of the symmetrical ketene **4b** was converted to a six hydrogen singlet, indicating the loss of the isopropyl methine hydrogen, and the number of the other isopropyl doublets increased, indicating the loss of symmetry in the product. The product was identified as the isochromene **6b** by a single crystal X-ray diffraction (Fig. 1)[8] and had the appropriate NMR and mass spectra.

Whereas the cyclization in refluxing toluene required >10 h, the reaction was complete in <1 h in refluxing decane (*ca.* 170 °C). An appropriate rate constant of the apparently clean reaction, based on the intensity decrease of the aromatic NMR signals of **4b**, or the build-up of the aromatic or vinylic proton signals of **6b** is $k \sim 8.10^{-4}$ s^{-1} at 170 °C ($\tau_{\frac{1}{2}}$ = 15 min). No inter-

mediate was observed in this study. Since data on the cyclization of **4a** were not published[4] quantitative comparison is impossible, except that since the reaction of **4a** proceeds at 250 °C, the reaction of **4b** is at least two orders of magnitude faster.

In order to get a rough estimation of the substituent effect, the reaction of dimesitylketene (**4c**)[9] in refluxing decane was also investigated. Cyclization to the isochromene **6c** also took place (Scheme 2), and only 7.5% of **6c** was formed after 10 h, although this value was not very reproducible. This suggests that **4b** reacts *ca*. 200 times faster than **4c** and that the reactivity of **4c** resembles that of **4a**.

The suggested mechanism involves a rate determining 1,5-H transfer to form the intermediate tetraenals (**5b** and **c**) which then undergo a faster electrocyclization to the isochromenes **6**, gaining the lost aromaticity.

The intramolecular electrocyclization may be sufficiently slow to enable trapping of the tetraenal (**5**) by an external dienophile. However, when a six-fold excess of tetracyanoethylene was added to **4b**, no new signals were formed. Hence, the intermediate **5** is not trapped under these conditions.

The faster cyclization of **4b** than of **4c** is consistent with substituent effects on a rate determining sigmatropic H-shift. Without recourse to a specific mechanism, the transition state of the reaction generates a partial double bond $=CR_2$ (if concerted) or a radical $^{\bullet}CR_2$ (if proceeding *via* a biradical) and in both cases methyl groups (R = Me) will stabilize the transition state more than hydrogens (R = H), as was indeed observed.

Experimental

NMR spectra were recorded with a Bruker AMX 400 instrument operating at 400 (for ^{1}H) and 100 MHz (for ^{13}C), using Me_4Si as a reference. *J* Values are given in Hz.

Cyclization of ditipylketene

Synthetic method. Ditipylketene (**4b**) (100 mg, 0.224 mmol) was refluxed in dry toluene (25 ml) for 50 h. TLC showed the presence of traces of ditipylacetic acid and of a new compound, **6b**. The solvent was evaporated and the residual solid (60 mg, 60%) was crystallized from MeCN, giving **6b**, mp 102 °C; $\delta_H(CDCl_3)$ 0.79, 1.13, 1.17, 1.24, 1.26 (5 × 6 H, 5 d, *J* 6.7–7.0, Pr^i–Me), 1.68 (6 H, s, 2 Me), 2.71, 2.84, 2.90 (3 × 1 H, 3 septets, *J* 6.9–7.1, Pr^i–C*H*), 3.02 (2 H, 2 overlapping septets, *J* 6.8, Pr^i–C*H*), 6.20 (1 H, s, H-1), 6.86, 6.97 (2 × 1 H, d, *J* 1.5, H-5 and H-7), 6.99 (2 H, s, H-20 and H-22); $\delta_C(CDCl_3)$ 22.77, 23.95, 24.22, 24.79, 26.36 (Pr^i–Me), 27.10 (C-12), 28.25 (C-16, C-17, Me), 30.53 (C-24, C-30), 33.99, 34.29 (C-9, C-27), 78.77 (C-15), 114.37 (C-2), 118.96, 120.80 (C-20, C-22), 124.22 (C-5, C-7), 138.25 (C-18), 143.21 (C-1), 144.54 (C-4), 148.00 (C-19, C-23), 125.11, 134.31, 147.10 (C-4, C-3, C-8); [HRMS: 446.3512 (67%, Calc. for $C_{32}H_{46}O$: 446.3548), 431.3356 (B, *M* − Me, Calc. 431.3313). Calc. for $C_{32}H_{46}O$: C, 86.04; H, 10.38. Found: C, 85.7; H, 10.21%].

Crystallographic data.[8] Space group $P2_1/c$; $a = 13.167(3)$, $b = 14.393(3)$, $c = 16.214(2)$ Å, $\beta = 110.73(2)°$; $V = 2873.8(8)$ Å^3, $Z = 4$, $D_c = 1.03$ g cm^{-3}, μ(Cu-Kα) = 4.20 cm^{-1}; no. of unique reflections 4468, no. of reflections with $3\sigma_I = 3563$, $R = 0.057$, $R_w = 0.090$.

Product analysis by ^{1}H NMR. Ditipylketene (30 mg, 0.067 mmol) was refluxed in decane for 8–60 min. Samples were withdrawn, the solvent was evaporated and the samples were analyzed by ^{1}H NMR after 8, 12 and 16 min, giving *ca*. 20, 40 and 55% of **6b**, respectively. The only signals observed during the reaction were those of **4b** and **6b**. After longer reaction times (>20 h) new signals started to form, but these were not investigated.

Reaction in the presence of TCNE. Ditipylketene (30 mg, 0.067 mmol) and tetracyanoethylene (50 mg, 0.256 mmol) were refluxed in decane for 90 min. Evaporation of the solvent and ^{1}H NMR analysis of the crude material showed only signals of **6b**.

Cyclization of dimesityl ketene

A solution of dimesitylketene (**4c**) (200 mg, 0.72 mmol) in decane (23 ml) was refluxed for 10 h. After cooling, the solution was diluted with diethyl ether (30 ml) and stirred with 30% aqueous $NaHCO_3$. The organic layer was separated, washed with water, dried ($MgSO_4$) and the solvent was evaporated. The remaining solid was chromatographed on silica using 1:3 diethyl ether : low boiling light petroleum eluent. Crystallization of the first yellowish solid fraction from MeCN gave colorless crystals (15 mg, 7.5%) of **6c**, mp 96–98 °C; $\delta_H(CDCl_3)$ 1.59 (3 H, s, Me), 2.21 (6 H, 2 s, 2 Me), 2.31, 2.34 (2 × 3 H, 2 s, 2 Me), 5.04 (2 H, s, CH_2), 6.45 (1 H, s, =CH), 6.81, 6.82 (2 × 1 H, 2 br s, Ar-H), 6.29 (2 H, s, Ar-H); $\delta_C(CDCl_3)$ 69.54 (C-15), 145.02 (C-1), 117.64 (C-2), 123.75, 132.68 (C-5, C-7), 128.18 (C-20, C-22), 132.24 (C-8), 137.62 (C-19, C-23), 126.80, 130.21, 134.77 (C-6, C-10, C-18), 136.21, 136.70 (C-9, C-18); *m*/*z* (+DCI, isobutane): 279 (MH^+, B), 277 (23%, *M* − H), 249 (4, Mes_2C − H), 235 (3, Mes_2C − Me). ν_{max}(Nujol)/cm^{-1} 1382, 1460 (s), 2900 (vs) (Calc. for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 85.97; H, 8.20%).

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