Conjugate addition of 2-trifluoromethyl-1,3-dioxin-4-ones–π-facial selectivity

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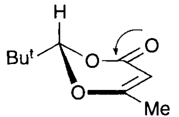
The π-facial selectivity of 2-trifluoromethyl-1,3-dioxin-4-ones in conjugate addition and catalytic hydrogenation is described and an explanation of the selectivity by the Cieplak effect and anomeric effect is given.

Previously[1] we proposed an explanation for the π-facial selectivity in the conjugate addition of a series of 1,3-dioxin-4-ones (**1**, **2**, **3**, **4** and **5**: arrows indicate the preferred side of attack). Since the enone carbons in these dioxinones pyramidalize,[2] without exception, towards the top, this explanation provided the first rationale for the violation of the link between ground-state distortions (*i.e.* pyramidalization) and face selection.[4] In order to explain the selectivity, we proposed that one must assume respective single sofa conformations for the dioxinones in solution [*cf.* the ones depicted] and then consider the corresponding transition states.[1] Thus, while the top-face preference of **1**, **2** and **5** is explained by the Cieplak effect,[3] the bottom face preference of **3** and **4** where there is an anomeric effect is explained by steric hindrance.

In continuation of this work, we examined the cuprate addition of the two titled newly synthesized dioxinones (**6a** and **7a**) bearing a CF_3 group (the most electronegative group among sp^3 carbon species) at the 2-position and a related dioxinone **8a** (the preferred side of attack in the cuprate addition is again indicated by arrows). Compounds **6–8** were prepared by the cycloaddition of acetylketene or formylketene with ketones according to the literature.[1] The conformations depicted for **6b** and **8b** were verified by X-ray crystallographic analysis.

Here, we report our results as well as the conformation of the derived dioxanones. Firstly we carried out the conjugate addition of **6a** with MeMgBr–CuI. Two 6-methyldioxanones (**9** and **10**) were obtained in 63 and 11% yields, respectively.† Whilst the twist-chair conformation of **9** was clearly indicated by ^1H NMR spectroscopy (500 MHz), the C_6-H signal at δ 4.040 ($J_{H6-H5_{trans}}$ 8.0 Hz), the ^1H NMR spectrum of **10** revealed that it exists in a twist-boat conformation (δ 4.664, $J_{H6-H5_{trans}}$ 11.0 Hz).[5] Since the 1,3-diaxial interaction between C-2 and C-6 substituents is quite large in the dioxanes,[6,7] the twist-boat conformation is the only possible conformation avoiding the *cis*-1,3-diaxial relationship (*cf.* **10′**). The high field shift of the C_6-H signal of **9** relative to that of **10** demonstrated that the shielding effect of the phenyl group is operative in **9** and hence the phenyl group and C_6-H of **9** are in a *cis*-diaxial-relationship. It is clear, therefore, that conjugate addition had occurred preferentially from the trifluoromethyl group side.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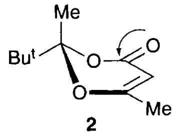
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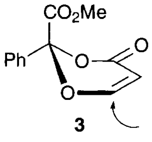
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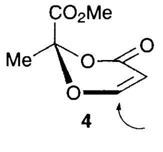
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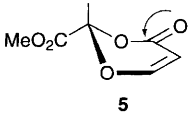
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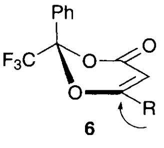
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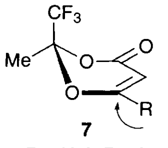
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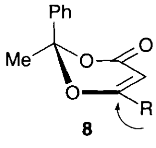
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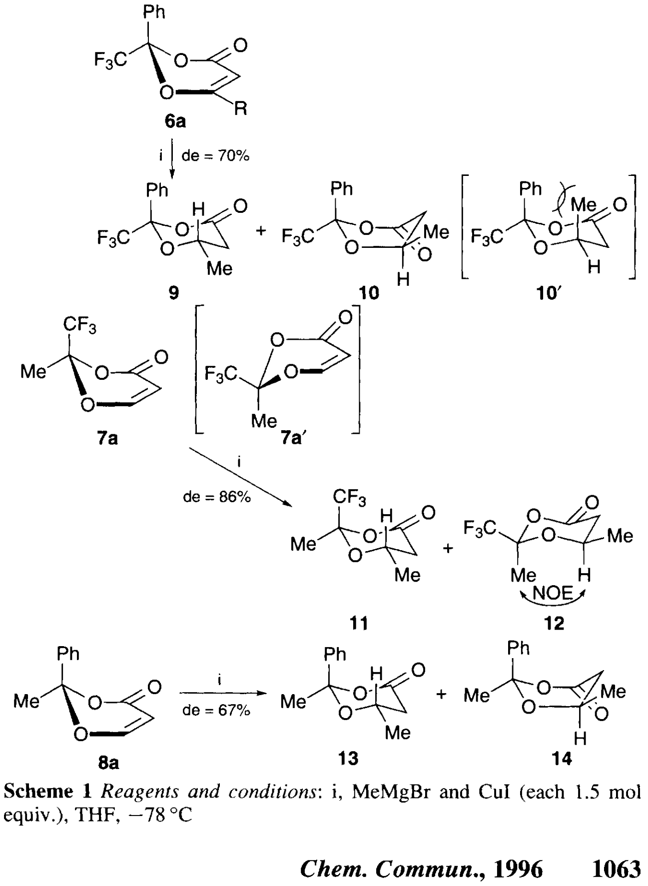
a R = H, **b** R = Me

Next, the same addition reaction was applied to **7a**. Two products (**11** and **12**) were obtained in 92 and 7% yields, respectively (de = 86%). ^1H NMR spectra revealed that the C_6-H of the major product **11** appeared at a lower field (δ 4.449, $J_{H6-H5_{trans}}$ 8.0 Hz) than that of the minor product **12** (δ 4.214, $J_{H6-H5_{trans}}$ = 11.4 Hz). The lower field shift of the signal of **11** is attributable to the deshielding effect of the trifluoromethyl group and hence suggests the *cis*-relationship between CF_3 and C_6-H. This assumption was verified further by NOE (7%) between Me and C_6-H in the minor product **12**. The result demonstrated clearly that the attack has occurred preferentially from the 2-methyl group side.

Finally, the conjugate addition of **8a** was examined. Two products **13**: δ of C_6-H = 3.856; $J_{H6-H5_{trans}}$ 11 Hz and **14**: δ C_6-H 4.233; $J_{H6-H5_{trans}}$ 8.5 Hz) were obtained in the respective yields of 64 and 13% (de = 66%). Based on the chemical shifts



Scheme 1 *Reagents and conditions*: i, MeMgBr and CuI (each 1.5 mol equiv.), THF, −78 °C

of the C_6-H signals, it is evident that the attack occurred preferentially from the 2-methyl group side.

In order to analyse the result, X-ray crystallographic analyses of **6b** and **8b**‡ were carried out and demonstrated that both take sofa conformations with axial phenyl groups. Similar to 1-methyl-1-phenylcyclohexane which exists solely in the conformation having an axial phenyl group,[8] the axial phenyl ring in these two dioxinones adopts a conformation perpendicular to the plane bisecting the six-membered ring through C_2 and C_5 (*cf.* Fig. 1).

The same preference (axial orientation and perpendicularity of the phenyl ring) was also observed in the related 2-methyl-2-phenyl-1,3-oxazine-4,6-dione.[9] Hence, it is reasonable to assume that the anomeric effect is not operative for the CF_3 group[10] and the preference of the conformations (**6a**) is due to steric hindrance.[12]

To summarize the result of the cuprate addition of **6a** and **8a**, the preferred side of attack is the reverse to the side of pyramidalization. The observed selectivity is accounted for by the Cieplak effect in the corresponding transition states. Thus, the lowest de (67%) found in the case of **8a** can be explained by the Cieplak effect which facilitates the top side attack to give the minor product **14**. The corresponding Cieplak effect should be less for **6a**, since the strong inductive effect of the CF_3 group lowers the energy level of σ^* (C_2-C_6H_5) and hence increases the anomeric effect. The conformation of **7a** has not yet been determined, but if one considers the predominant existence of equatorial CF_3 in the other conformation,[11,§] the same facial selectivity can be predicted from the Cieplak effect. It is obvious that the prediction based on the Cieplak effect is more reliable than that based on pyramidalization.

Finally, catalytic hydrogenation of **6b** and **7b** was carried out. In accordance with the above explanation, the hydrogenation of **7b** occurred from the same side as in the case of the cuprate addition to give **12** as the sole product (quant.). Very interestingly, the hydrogenation of **6b** resulted in the formation of **9** which was the same as the major product derived from the cuprate addition to **6a**. This abnormal selectivity is at present considered to be due to an attractive stacking between the phenyl group and the catalyst. The perpendicular phenyl ring orientation of **6b** seems to be the origin of this anomalous selectivity.

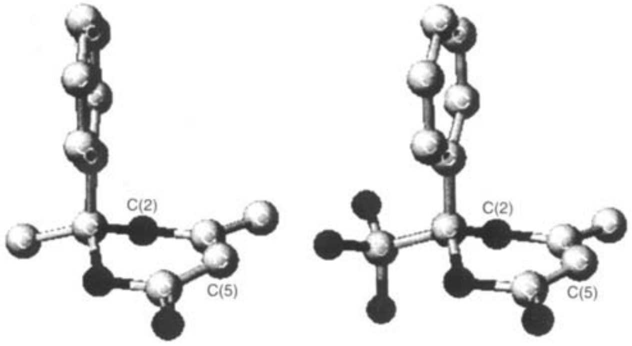
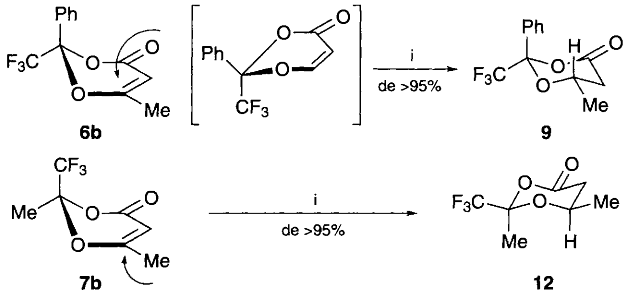


Fig. 1 Molecular structures of **6b** and **8b**



Scheme 2 *Reagents and conditions*: i, H_2 (1 atm.)/5%-Rh-Al_2O_3, AcOEt, room temp.

Footnotes

† All new compounds gave satisfactory spectral data (IR, ^1H NMR, and MS) and microanalytical or high resolution MS data.

‡ *Crystal data* for **6b**: mp 83–84 °C, $C_{12}H_9F_3O_3$, triclinic, space group $P\bar{1}$, a = 7.150(2), b = 12.691(6), c = 6.518(4) Å, α = 96.87(4), β = 92.83(4), γ = 77.30(3)°, U = 572.7(5) Å^3, Z = 2, D_c = 1.497 g cm^{-3}. 1698 unique reflections were collected, of which 1490 were observed with $I > 3.0\sigma(I)$. R (R_w) = 0.044 (0.048). For **8b**: mp 93–94 °C, $C_{12}H_{12}O_3$, space group $P2_1/c$, a = 9.587(3), b = 8.440(2), c = 13.216(3) Å, β = 94.01(2)°, U = 1066.8(4) Å^3, Z = 4, D_c = 1.272 g cm^{-3}. 1589 unique reflections were collected, of which 1336 were observed with $F > 3.0\sigma(F)$. R (R_w) = 0.049 (0.063). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/32.

§ It should be noted that in ^{19}F NMR spectroscopy all dioxinones and dioxanones having a quasi-equatorial CF_3 group (**6b**, **9** and **12**) showed the signal at a higher field (δ −85 to −83) than that having an axial CF_3 group (**11**, δ −79.2). It is reasonable therefore that the preferred conformation of the 2-methyl-2-trifluoromethyldioxinone (**7b**: δ −83.1) is a sofa with CF_3 group in an equatorial orientation (*e.g.* **7a′**).

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11 It should be also noted that the preference of bulkier group in an equatorial orientation in 1,3-dioxanes (having much shorter distance between C_2 and O_1 and O_3) is more pronounced than the corresponding cyclohexanes whose corresponding bond distances are much longer. F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, 3rd edn., part A: *Structure and Mechanisms*, Plenum Press, New York and London, 1993, p. 144.

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