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Notes

Diastereoselectivity in the Paterno−Büchi Reaction of Enol Acetates and Benzaldehydes

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The Paterno−Büchi reaction[1] represents a direct avenue to oxetanes that will accommodate a variety of olefin and aldehyde substitution patterns. The presence of a 3-acetoxyoxetane subunit in taxol[2] raised the prospect of using a Paterno−Büchi reaction of enol acetates and benzaldehydes to introduce this particular moiety. The success of the methodology would depend upon the yields in the photoaddition reaction as well as a subsequent oxidative degradation[3] of the aromatic ring and decarboxylation.[4] Prior reports of the photoaddition of enol ethers,[5] trimethylsilyl enol ethers,[6] methyl vinyl sulfides,[7] and 2,3-dihydrooxazoles[8] with aldehydes suggested that the regiochemistry desired in the taxol situation was favored, but precedent for the photoaddition of enol acetates was lacking. We report a study of the photoaddition of isopropenyl acetate (**1**), 1-acetoxycyclododecene[9] (**2**), and 4-*tert*-butyl-1-acetoxycyclohexene[10] (**3**) with various benzaldehydes **4**.

As shown in Scheme 1 and summarized in Table 1, the photolysis of variously substituted benzaldehydes **4** with an excess of cyclic or acyclic enol acetates led to 2-aryl-3-acetoxyoxetanes and not the isomeric 2-aryl-4-acetoxyoxetanes. The yields for these photoadditions were modest, although prolonged photolysis times led, as indicated in Table 1, to some improvements in yield. The observed regioselectivity of the photoaddition was consistent with literature precedent for related 2,3-dihydrofuran[5a,b] and with the appearance of the C-2 methine proton as a *singlet* in the ^{1}H NMR spectrum of the 2-aryl-3-acetoxyoxetanes produced from **1**−**3**.

The stereoselectivity[11] of the Paterno−Büchi reaction of various benzaldehydes and these unsymmetrical enol acetates **1**−**3** varied considerably. The photolysis of isopropenyl acetate (**1**) with pentafluorobenzaldehyde (**4a**) led to a 1.1:1 mixture of isomeric 3-acetoxyoxetanes **5** and **6**. These stereochemical assignments were based principally upon the anisotropic shift of the C-3α methyl group in the ^{1}H NMR spectrum by the *cis*-oriented C-2α pentafluorophenyl group in **6** relative to the isomer **5**.

Pentafluorobenzaldehyde (**4a**) displayed considerably more stereoselectivity in photoadditions with cyclic enol acetates than with isopropenyl acetate (**1**). The photolysis of an *E*/*Z* mixture of 1-acetoxycyclododecene[9] (**2**) with **4a** led to a single product **7**. No other isomers were detected. The *cis*-relationship between the aryl and acetoxy groups in **7** was again assigned on the basis of ^{1}H NMR data. Collapse of the presumed diradical intermediate in a transition state that minimized steric interactions between the aryl group and the cyclic hydrocarbon portion of the enol acetate presumably accounted for this stereochemical outcome. The *cis*- or *trans*-arrangement between the acetoxy group and the methine hydrogen of the ring fusion in **7** was not, however, apparent from spectral data alone and was established through an X-ray structure determination.[12]

The photolysis[13] of 4-*tert*-butyl-1-acetoxycyclohexene[10] (**3**) with various benzaldehydes gave a single 2-aryl-3-acetoxyoxetane in which the regiochemical and stereochemical outcome with respect to the aryl and the acetoxy groups was consistent with the previous case. The photolysis of an excess of **3** in the presence of pentafluorobenzaldehyde (**4a**) gave preferentially an oxetane **8a** possessing a *cis*-relationship of the pentafluorophenyl and acetoxy groups. Once again, however, it was more difficult to resolve the remaining stereochemical issue in **8a** as to the selectivity of facial attack by **4a** on the diastereotopic faces of **3**. Unfortunately, the C-6α methine hydrogen in **8a** was not well resolved. However,

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[1] (a) Paterno, E.; Chieffi, G. *Gazz. Chim. Ital.* **1909**, *39*, 341. (b) Büchi, G.; Inman, C. G.; Lipinsky, E. S. *J. Am. Chem. Soc.* **1954**, *76*, 4327. For recent reviews, see: (a) Jones, G., II. *Organic Photochemistry*; Marcel Dekker: New York, 1981; Vol. 5, pp 1−122. (b) Braun, M. *Org. Synth. Highlights* **1991**, 105.

[2] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggan, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

[3] (a) Caputo, J. A.; Fuchs, R. *Tetrahedron Lett.* **1967**, *8*, 4729. (b) Klein, H.; Steinmetz, A. *Ibid.* **1975**, *16*, 4249. (c) Deno, N. C.; Greigger, B. A.; Messer, L. A.; Meyer, M. D.; Stroud, S. G. *Ibid.* **1977**, *18*, 1703.

[4] (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. (b) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285. (c) Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (d) Pfenninger, J.; Heuberger, C.; Graf, W. *Ibid.* **1980**, *63*, 2328.

[5] For examples of Paterno−Büchi reactions with furan and 2,3-dihydrofuran, see: (a) Griesbeck, A. G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1990**, *112*, 1281. (b) Griesbeck, A. G.; Stadtmüller, S. *Chem. Ber.* **1990**, *123*, 357. (c) Griesbeck, A. G.; Mauder, H.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Ibid.* **1991**, *124*, 407. (d) Zagar, C.; Scharf, H. D. *Ibid.* **1991**, *124*, 967. (e) Buschmann, H.; Hoffmann, N.; Scharf, H. D. *Tetrahedron Asymmetry* **1991**, 2, 1429.

[6] Bach, T. *Tetrahedron Lett.* **1991**, *32*, 7037.

[7] (a) Morris, T. H.; Smith, E. H.; Walsh, R. *J. Chem. Soc., Chem. Commun.* **1987**, 964. (b) Khan, N.; Morris, T. H.; Smith, E. H.; Walsh, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 865

[8] (a) Weuthen, M.; Scharf, H. D.; Runsink J. *Chem. Ber.* **1987**, *120*, 1023. (b) Weuthen, M.; Scharf, H. D.; Runsink J.; Vassen, R. *Ibid.* **1988**, *121*, 971.

[9] (a) Leonard, N. J.; Owens, F. H. *J. Am. Chem. Soc.* **1958**, *80*, 6039. (b) Waelchli, R.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 2178. (c) Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971.

[10] House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935.

[11] For a photoaddition of benzophenone to norbornadiene in which the product was presumed to be *endo*, see: Bryce-Smith, D.; Gilbert, A.; Johnson, M. G. *J. Chem. Soc. C* **1967**, 383. For a photoaddition of benzophenone and 4,4′-dimethylbenzophenone to norbornene in which the product was reported to be exo, see: Aarnold, D. R.; Hinman, R. L.; Glick, A. H. *Tetrahedron Lett.* **1964**, *5*, 1425. For a photoaddition of acetyl cyanide to norbornene in which 40% of *exo*- and 37% yield of *endo*-oxetanes were obtained, see: Shigemitsu, Y.; Odaira, Y.; Tsutsumi, S. *Tetrahedron Lett.* **1967**, *8*, 55. For a photoaddition of diethyl oxomalonate and norbornene gave a 3:1 ratio of *exo*-:*endo*-oxetanes; see: Hara, M.; Odaira, Y.; Tsutsumi, S. *Tetrahedron Lett.* **1967**, *8*, 2981.

[12] Brock, C. P.; Watt, D. S.; Morita, H. *Acta Crystallogr.*, in press.

[13] For a leading reference to the photolysis of cyclohexene and benzaldehyde, see: Bradshaw, J. S. *J. Org. Chem.* **1966**, *31*, 237.

0022-3263/94/1959-4677$04.50/0

Scheme 1

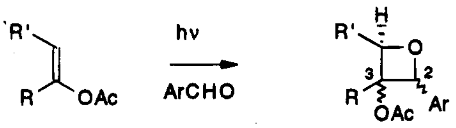
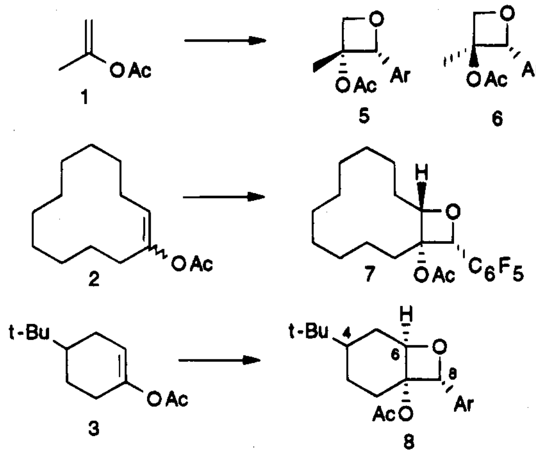


Table 1. Paterno−Büchi Reaction of Enol Acetates 1−3 with Benzaldehyde 4

enol acetate	benzaldehyde ArCHO (**4**)	irradn time (h)	products and isolated yield (%)
1	**4a**, Ar = C_6F_5	24	**5**:**6** (1:1; 10)
1	**4a**, Ar = C_6F_5	48	**5**:**6** (1:1; 28)
2	**4a**, Ar = C_6F_5	24	**7** (10)
3	**4a**, Ar = C_6F_5	20	**8a** (11)
3	**4a**, Ar = C_6F_5	72	**8a** (17)
3	**4b**, Ar = C_6H_5	20	**8b** (14)
3	**4c**, Ar = 3-$(CH_3O)C_6H_4$	20	**8c** (6)
3	**4d**, Ar = 3-ClC_6H_4	24	**8d** (14)

Scheme 2



the ^{1}H NMR spectrum of the analogous products, **8b**, **8c**, and **8d** (Table 1), displayed the C-6α methine hydrogen as a doublet of doublets with coupling constants, $J_{5\alpha,6\alpha}$ = *ca.* 6 Hz and $J_{5\beta,6\alpha}$ = *ca.* 3 Hz, consistent with an oxetane product having two widely different dihedral angles. In agreement with this finding, molecular mechanics calculations[14] produced a minimized structure for **8a** in which $\Phi_{5\alpha,6\alpha} = 16°$ and $\Phi_{5\beta,6\alpha} = 131°$. An X-ray structure[15] again provided final confirmation for the structural assignment in **8a**.

This assignment meant that the triplet pentafluorobenzaldehyde underwent a preferential addition *syn* to the *tert*-butyl group in **3**. The factors which guide this unexpected diastereospecificity in this situation are unclear, but the steric influence of the *tert*-butyl group on attack by triplet would appear to be minimal. A kinetic preference for addition to the *re*-face of the enol acetate may reflect a transition state in which the acetyl group preferentially shields the *si*-face. Molecular mechanics calculations[14] of 4-*tert*-butyl-1-acetoxycyclohexene (**3**) suggested that a conformation with the acetyl group twisted toward the *si*-face was more stable than other conformations with the acetyl in a quadrant above the *re*-face.

In summary, application of the Paterno−Büchi reaction to the synthesis of 2-aryl-3-acetoxyoxetanes proceeds in modest yield. The result, in the particular case of the *syn*-addition of pentafluorobenzaldehyde (**4a**) to 4-*tert*-butyl-1-acetoxycyclohexene (**3**), suggests that diastereoselectivity in these cycloadditions may take an unexpected turn on the basis of steric considerations alone. The uncertain prospect for improving the yield for these Paterno−Büchi reactions also suggests that a significant modification of this reaction will be necessary before it might find application in a taxol synthesis. We are currently investigating intramolecular variants[16] of this process in which the aryl ring and the acetoxy group of the enol acetate are linked through an expendable bridge.

Experimental Section

2α-(2,3,4,5,6-Pentafluorophenyl)-3α-acetoxy-3β-methyloxetane (5) and 2α-(2,3,4,5,6-Pentafluorophenyl)-3β-acetoxy-3α-methyloxetane (6). To 500 mg (2.55 mmol, 1 equiv) of pentafluorobenzaldehyde (**4a**) in 15 mL of degassed, anhydrous benzene was added 511 mg (5.94 mmol, 2.3 equiv) of isopropenyl acetate (**1**). The mixture was irradiated at 25 °C for 24 h using a 400-W high-pressure Hg lamp (Shigemi Corp.) with a Pyrex filter. The mixture was chromatographed on a silica gel preparative plate using 1:9 EtOAc−hexane to afford 112 mg (15%) of **5** and 101 mg (13%) of **6**. Spectral data for **5**: IR (TF) 1747 (C=O) cm^{-1}; exact mass spectrum calcd for $C_{12}H_9O_3F_5$ 296.1955, found 296.1906. Spectral data for **6**: IR (TF) 1744 (C=O) cm^{-1}; exact mass spectrum calcd for $C_{12}H_9O_3F_5$ 296.1955, found 296.1948.

***trans*-1α-Acetoxy-14α-pentafluorophenyl-13-oxabicyclo[10.2.0]tetradecane (7).** To 514 mg (2.62 mmol, 1 equiv) of pentafluorobenzaldehyde (**4a**) in 40 mL of degassed, anhydrous benzene was added 1.15 g (5.10 mmol, 1.95 equiv) of (1ζ)-1-acetoxycyclododecene (**2**). The mixture was irradiated at 25 °C for 24 h using a 450-W Hanovia lamp using a Pyrex filter. The mixture was chromatographed on a silica gel preparative plate using 1:1 hexane−benzene to afford 97 mg (9%) of **7** as a white solid: mp 76−77 °C (from ethanol); IR (KBr) 1745 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{25}F_5O_3$: C, 59.99; H, 5.99. Found: C, 60.09; H, 6.03.

***cis*-1α-Acetoxy-4β-*tert*-butyl-8α-(2,3,4,5,6-pentafluorophenyl)-7-oxabicyclo-[4.2.0]octane (8a).** The procedure described in the preparation of **8b** was repeated using 104 mg (0.53 mmol, 1 equiv) of pentafluorobenzaldehyde (**4a**) and 182 mg (0.93 mmol, 1.75 equiv) of 1-acetoxy-4-*tert*-butyl-1-cyclohexene[10] (**3**) in 9 mL of benzene to afford, after irradiation for 20 h at 25 °C and chromatography on silica gel using benzene, 24 mg (11%) of **8a** as a white solid: mp 82−84 °C; IR (KBr) 1733 (C=O) cm^{-1}; ^{13}C NMR (CDCl$_3$) δ 20.5, 21.1, 27.0, 29.4, 30.6, 32.9, 41.3, 78.1, 79.2, 85.1 (t, J_{CF} = 3.3 Hz), 110−114 and 138−148 (multiplets), 169.1. Anal. Calcd for $C_{19}H_{21}F_5O_3$: C, 58.16; H, 5.39. Found: C, 58.26; H, 5.42.

***cis*-1α-Acetoxy-4β-*tert*-butyl-8α-phenyl-7-oxabicyclo[4.2.0]-octane (8b).** To 108 mg (1.02 mmol, 1 equiv) of benzaldehyde (**4b**) in 18 mL of degassed, anhydrous benzene was added 349 mg (1.78 mmol, 1.75 equiv) of **3**. The mixture was irradiated at 25 °C for 20 h using a 450-W Hanovia lamp using a Pyrex filter. The mixture was chromatographed on silica gel using 1:10 EtOAc−hexane to afford 43 mg (14%) of **8b** as a colorless oil: IR (TF) 1740 (C=O) cm^{-1}; ^{13}C NMR (CDCl$_3$) δ 20.5, 21.0, 27.1, 29.4, 31.1, 32.9, 41.3, 79.3, 84.6, 87.3, 127.0, 127.79, 127.83, 137.7, 169.3. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.36; H, 8.69.

***cis*-1α-Acetoxy-4β-*tert*-butyl-8α-(3-methoxyphenyl)-7-oxabicyclo[4.2.0]octane (8c).** The procedure described in the preparation of **8b** was repeated using 173 mg (1.27 mmol, 1 equiv) of 3-anisaldehyde (**4c**) and 439 mg (2.22 mmol, 1.75 equiv) of **3** in 23 mL of benzene to afford, after irradiation for 20 h at 25 °C and chromatography on silica gel using 1:10:10 EtOAc−hexane−benzene, 26 mg (6%) of **8c** as a colorless oil: IR (TF) 1733 (C=O) cm^{-1}; ^{13}C NMR (CDCl$_3$) δ 20.5, 21.1, 27.1, 29.4, 31.3,

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[14] Molecular mechanics calculations were performed using MM+ in HyperChem (Release 3), Autodesk, Inc., Sausalito, CA 94965.

[15] Brock, C. P.; Lloyd, M. A.; Vasudevan, S.; Watt, D. S.; Morita, H. *Acta Crystallogr.* in press.

[16] For a relevant intramolecular example involving an enol ether, see: Carless, H. A. J.; Beanland, J.; Mwesigye-Kibende, S. *Tetrahedron Lett.* **1987**, *28*, 5933.

32.9, 41.4, 55.2, 79.2, 84.6, 87.0, 112.1, 113.5, 119.3, 128.9, 139.4, 159.4, 169.4. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.02; H, 8.56.

***cis*-1α-Acetoxy-4β-*tert*-butyl-8α-(3-chlorophenyl)-7-oxabicyclo[4.2.0]octane (8d).** The procedure described for the preparation of **8b** was repeated using 99 mg (0.70 mmol, 1 equiv) of 3-chlorobenzaldehyde (**4d**) and 241 mg (1.23 mmol, 1.75 equiv) of **3** in 12 mL of benzene to afford, after irradiation at 25 °C for 24 h using a 450-W Hanovia lamp using a Pyrex filter and chromatography on silica gel using benzene, 34 mg (14%) of **8d** as a colorless oil: IR (TF) 1733 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 20.5, 21.0, 27.0, 29.3, 31.2, 32.9, 41.3, 79.1, 84.7, 86.4, 125.2, 126.9, 127.9, 129.1, 133.9, 140.0, 169.2. Anal. Calcd for $C_{19}H_{25}ClO_3$: C, 67.75; H, 7.48. Found: C, 67.83; H, 7.48.

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Supplementary Material Available: ^1H NMR data and assignments for **5**, **6**, **7**, and **8a–d** and copies of ^1H NMR spectra for **5** and **6** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.