Pergamon

PII: S0040-4039(97)01262-8

Tetrahedron Letters, Vol. 38, No. 32, pp. 5579-5582, 1997

0040-4039/97 $17.00 + 0.00

Synthesis of Substituted Tetrahydrofuranones and Tetrahydropyranones: Photocycloaddition/Fragmentation Reactions of Dioxinones

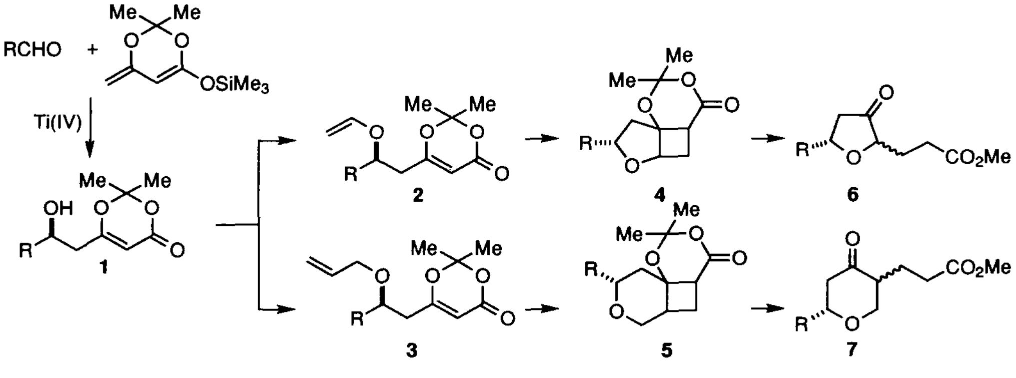
Jay H. Dritz and Erick M. Carreira*

Arnold and Mabel Beckman Laboratory of Chemical Synthesis
California Institute of Technology
Pasadena, California 91125

Abstract. The combination of dioxinone aldol addition methodology and [2+2]-photocycloaddition/fragmentation reactions can provide access to substituted tetrahydrofuran-3-ones and tetrahydropyran-4-ones, subunits abundantly found in biologically active natural products. Intramolecular photocyclization of vinyl and allyl ethers with dioxinones, followed by fragmentation in alkaline MeOH (K_2CO_3) leads to tetrahydrofuran-3-ones and tetrahydropyran-4-ones, providing a practical route to versatile building blocks for complex molecule synthesis. © 1997 Elsevier Science Ltd.

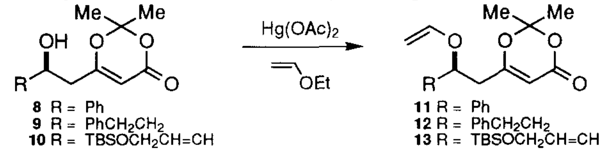
The use of [2+2]-photocycloaddition methods in synthesis permits access to a wide range of architecturally complex structures possessing stereochemical relationships not otherwise easily prepared. When strategically employed in the context of a complex molecule synthesis, such methodology imparts considerable efficiency to the synthetic route.[1] Important demonstrations of photochemical strategies in natural products syntheses are found in the construction of quinanes,[2] ingenanes,[3] alkaloids,[4] and bilobalides.[5] We have been interested in applications of [2+2]-cycloaddition reactions in combination with the asymmetric dienolate aldehyde addition reactions to the preparation of versatile, optically active synthetic building blocks (Scheme 1).[6,7] Herein we report the intramolecular [2+2]-cycloaddition of *O*-allyl and *O*-vinyl dioxinone ethers **2** and **3** to give intermediate fused tricyclic ring systems **4** and **5** which upon fragmentation under alkaline conditions give rise to 2,5-disubstituted tetrahydrofuran-3-ones **6** and 2,5-disubstituted-tetrahydropyran-4-ones **7**, commonly encountered structural subunits in natural products.[8]

Scheme 1

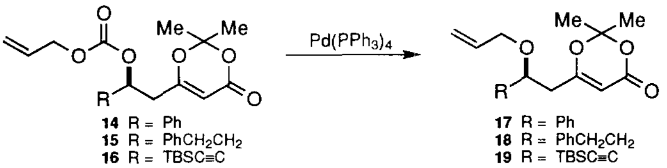


The use of dioxinone photochemistry for the diastereoselective synthesis of medium–sized carbocycles has been elegantly studied and developed by Winkler.[1c,9] In this general strategy, the intramolecular [2+2]–photocycloaddition of dioxinones with alkenes is followed by fragmentation of the cyclobutyl photoadducts to give the corresponding cycloalkanes.[10] We have examined the intramolecular [2+2]–cycloaddition reactions of racemic dioxinones and alkenes followed by photoadduct fragmentation to provide heterocycles. The availability of optically active starting alcohols via catalytic enantioselective methods[6] would allow for the diastereoselective synthesis of the corresponding optically active furanones and pyranones.

Preparation of the *O*–vinyl ether photosubstrates was readily effected upon treatment of alcohols **8–10** with ethyl vinyl ether and $Hg(OAc)_2$, giving **11–13** in 72–75% yields (Eq 1).[11] By contrast, the preparation of the homologous *O*–allyl ethers proved more difficult as a consequence of the propensity of compounds such as **1** to undergo retroaldolization under alkaline conditions. Thus, treatment of **8–10** with allyl triflate, iodide, or bromide and NaH, Ag_2O, 2,6–di–*tert*–butyl–4–methylpyridine, or 2–*tert*–butyl–2–diethylamino–1,3–dimethylperhydro–1,3,2–diazaphosphorine[12] in various solvents inevitably led to isolation of the desired allyl ethers **3** in only poor yields and recovery of the aldehyde and dioxinone retroaldol fragments. We subsequently examined the application of a two–step procedure for the preparation of **17–19** from intermediate mixed allyl carbonates **14–16**. Treatment of the corresponding secondary alcohols with allyl chloroformate[13] (pyridine, CH_2Cl_2, 0 °C→23 °C) delivered allyl carbonates **14–16**, which upon reaction with catalytic $Pd(PPh_3)_4$ in refluxing benzene furnished allyl ethers **17–19** in 65–87% yield (Eq 2).[14]



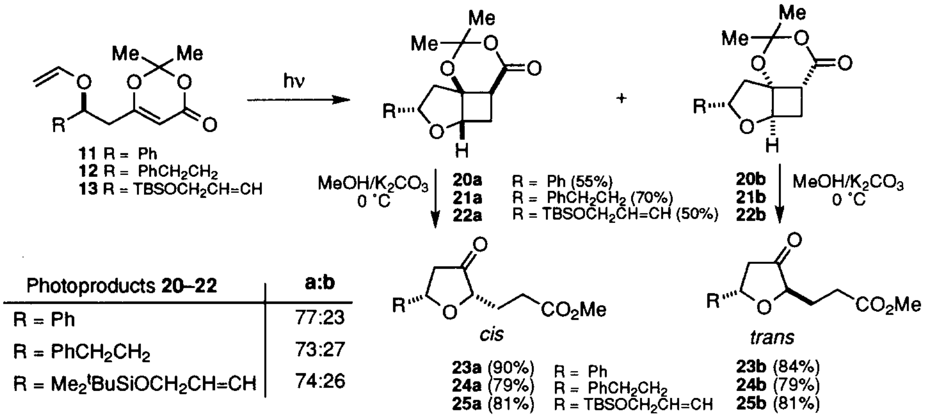
(1)



(2)

With suitable *O*–vinyl and *O*–allyl photosubstrates in hand, we proceeded to examine their photochemistry. Photocycloadditions were performed in 10% $Me_2CO/MeCN$ at ambient temperature with an Ace–Hanovia 450 W Hg medium–pressure UV lamp in a water–cooled quartz immersion apparatus through a Pyrex filter. Irradiation of *O*–vinyl ethers **11–13** yielded fused–cyclobutyl photoadducts **20–22** (50–70%) as ca. 3:1 mixtures of diastereomers[15] (Scheme 2), which upon fragmentation in alkaline MeOH (K_2CO_3) at 0 °C stereospecifically furnished tetrahydrofuran–3–ones **23–25** (79–90%). For example, adducts **20a** and **20b** produced the 2,5–*cis*–disubstituted tetrahydrofuran–3–one **23a** (90%) and 2,5–*trans*–disubstituted tetrahydrofuran–3–one **23b** (84%), respectively. For the cyclobutyl photoadducts and the fragmentation products, the stereochemistry was rigorously established through ^1H NMR nOe difference experiments.

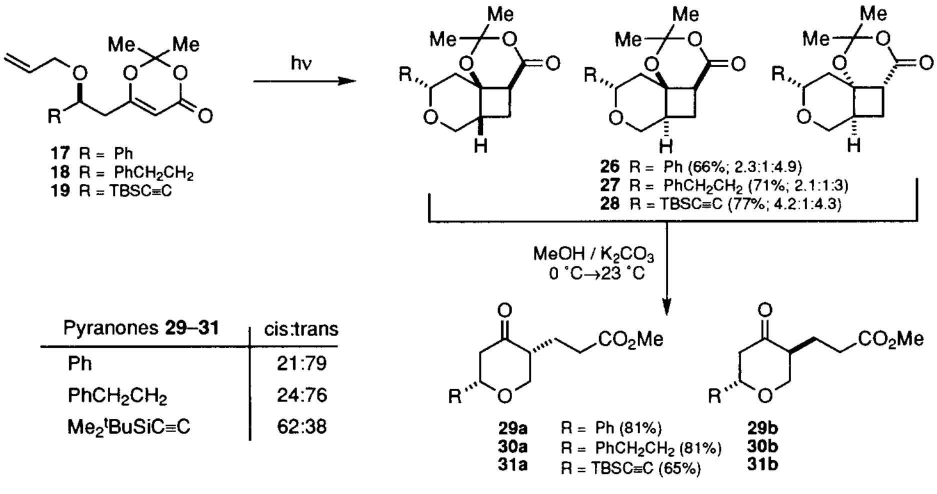
Scheme 2



Photoproducts **20–22**	a:b
R = Ph	77:23
R = PhCH$_2$CH$_2$	73:27
R = Me$_2$^{t}BuSiOCH$_2$CH=CH	74:26

In analogy to vinyl ethers **11–13**, the *O*–allyl homologs underwent [2+2]–cycloadditions to give cyclobutyl ring systems **26–28** in 66–77% yield as mixtures of diastereomers (Scheme 3). Although the diastereomeric photoproducts could be separated by chromatography on silica gel, we found that epimerization of the final tetrahydropyran–4–ones occurred under the alkaline conditions required for fragmentation, even at low temperature (–20 °C). Therefore, in practice, diastereomeric mixtures were submitted directly to fragmentation. Treatment of mixtures **26–28** with alkaline MeOH (K_2CO_3) at 0 °C→23 °C furnished diastereomeric mixtures of substituted tetrahydropyran–4–ones **29–31** (65–81%). These could be readily separated by chromatography on silica gel and, once separated, handled without epimerization. The diastereomeric ratios reported for **29–31** correspond to their expected equilibrium ratios, determined by integration of the ^{1}H NMR spectrum of the

Scheme 3



Pyranones **29–31**	cis:trans
Ph	21:79
PhCH$_2$CH$_2$	24:76
Me$_2$^{t}BuSiC≡C	62:38

crude reaction mixture after stirring in alkaline MeOH at 23 °C for 48 h.[16] In analogy to the tetrahydrofuran–3–one study, the stereochemistry of these systems was established by ^{1}H NMR nOe difference experiments.

The methodology we have described demonstrates that [2+2]–photocycloaddition reactions can provide a practical route to substituted tetrahydrofuran–3–ones and tetrahydropyran–4–ones. Such structures are abundant subunits in polyketide–derived natural products with important biological activity. Moreover, the ability to use substrates possessing alkenyl and alkynyl sidechains renders the heterocyclic products versatile as building blocks for complex molecule synthesis. Additionally, the availability of optically active starting alcohols via catalytic enantioselective methods would allow for the ready synthesis of the corresponding optically active furanones and pyranones. Further studies of such systems and applications to natural products synthesis are currently being pursued and will be the subject of future investigations.

Acknowledgment: JHD is grateful to the NSF for a predoctoral fellowship and California Institute of Technology for an Institute Fellowship. This research has been supported by the Sloan and Packard Foundations, NSF, NIH, and generous gifts from Lilly, Merck, Pfizer, Pharmacia–UpJohn, and Zeneca.

References and Footnotes

1. (a) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453. (b) Crimmins, M. T.; Reinhold, T. L. *Org. React.*; Wiley: New York, **1993**; Vol. 44, 297. (c) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.
2. (a) Crimmins, M. T.; DeLoach, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 800. (b) Birch, A. M.; Pattenden, G.; *J. Chem. Soc., Chem. Commun.* **1980**, 1195. (c) Dufour, C.; Iwasa, S.; Fabre, A.; Rawal, V. H. *Tetrahedron Lett.* **1996**, *37*, 7867. (d) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. (e) For an example of a [3+2] photocycloaddition, see: Wender, P. A.; von Geldern, T. W.; Levine, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 4858.
3. Winkler, J. D.; Hong, B.–C.; Bahador, A.; Kazanietz, M. G.; Blumberg, P. M. *J. Org. Chem.* **1995**, *60*, 1381.
4. (a) Koft, E. R.; Smith, A. B., III *J. Org. Chem.* **1984**, *49*, 832. (b) Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 5177. (c) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.
5. Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3146.
6. Carreira, E. M.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 12360.
7. For related work involving the stereoselective [2+2]–photocycloadditions of chiral allenes, see: (a) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622. (b) Shepard, M. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597.
8. (a) For a recent review in the synthesis of tetrahydropyrans and tetrahydrofurans, see: Alvarez, E.; Candenas, M.–L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem Rev.* **1995**, *95*, 1953. (b) Evans, P. A.; Roseman, J. D. *J. Org. Chem.* **1996**, *61*, 2252.
9. For early work on the photocycloaddition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one with alkenes, see: Baldwin, S. W.; Wilkinson, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 3634.
10. Winkler has reported an application of the dioxinone photocycloaddition reaction involving the [2+2]–photocycloaddition of vinylogous amide with a dioxinone as an approach to the synthesis of perhydrohistrionicotoxin, see: ref 4b and 4c.
11. All compounds described were prepared in racemic form.
12. Schwesinger, R.; Schlemper, H. *Angew. Chem., Ind. Ed. Engl.* **1987**, *26*, 1167.
13. Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3223.
14. Guibe, F.; Saint M'Leux, Y. *Tetrahedron Lett.* **1981**, *22*, 3591.
15. With the exception of **22**, these diastereomers could be separated by chromatography on silica gel.
16. The preference for an axial alkyne (**31a**) in dioxanes, under equilibrating conditions, has been discussed: Bailey, W. F.; Eliel, E. L. *J. Am. Chem. Soc.* **1974**, *96*, 1798.

(*Received in USA* 17 *May* 1997; *accepted* 11 *June* 1997)