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ON THE USE OF UNSYMMETRICALLY SUBSTITUTED FURANS IN THE FURAN-CARBONYL PHOTOCYCLOADDITION REACTION: SYNTHESIS OF A KADSURENONE-GINKGOLIDE HYBRID

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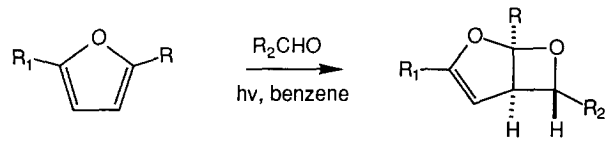
Abstract The Paterno-Buchi cycloaddition of aldehydes to silyl and stannyl substituted furans has been investigated. An application of this method to a short synthesis of a hybrid of two inhibitors of platelet activating factor (paf) receptor binding is described.

The furan-carbonyl photocycloaddition reaction has been utilized in the context of stereoselective synthesis, e.g., in the construction of bicyclic polyoxygenated ring systems.[1] One limitation encountered in these studies concerns a lack of chemoselectivity in the addition of aldehydes to unsymmetrically substituted furans. For example, the photochemical addition of benzaldehyde to 2-methyl furan provides a 1.3:1 mixture of oxetanes resulting from the exo-addition of the aldehyde to the more- and less-substituted furan olefins, respectively. This Letter describes the use of main group metals to (a) direct the site of addition and (b) participate in a transition metal catalyzed coupling reaction in the context of a specific synthetic objective.

The results of the photocycloaddition of aldehydes to silyl and stannyl substituted furans are shown in Table I. These experiments were performed on a mixture of the appropriate furan (2 mmol) in a 2 M solution of the aldehyde (1.1 mmol) in degassed benzene. The use of excess furan in the reaction is highly desirable due to the tendency of silyl (and presumably stannyl) furans to undergo unimolecular photorearrangement processes.[2] The reaction mixtures were buffered with anhydrous potassium carbonate in order to prevent acid catalyzed decomposition of the photoproducts. Chromatography was performed on neutral alumina or silica gel buffered with 2% triethylamine. *Under these conditions, the minor isomers (with metal substitution at the acetal carbon) were selectively destroyed.* The more stable vinyl substituted photoproducts were efficiently recovered without contamination of isomeric products.

The results in Table I indicate that among silicon substituted furans, the triisopropylsilyl group exhibits the highest degree of directing properties[3] (entry 4, ratios refer to the analysis of crude reaction mixtures). The use of propionaldehyde (entry 3) resulted in reduced selectivity of addition. The 2-tributylstannyl group exhibited directing properties in the same sense as the silicon counterpart, again with a noticeable dependency on the identity of the aldehyde addend (cf. entry 5 vs. 6). The stannyl group was examined in competition with a second substituent in entry 8. Irradiation of 2-tributylstannyl-5-methyl furan in benzene buffered with triethylamine produced a 2.5:1 mixture of regioisomeric photoproducts that was chromatographed to provide only the vinyl stannane product.

Table I Silyl and Stannyl Furan-Carbonyl Photocycloadditions[a]



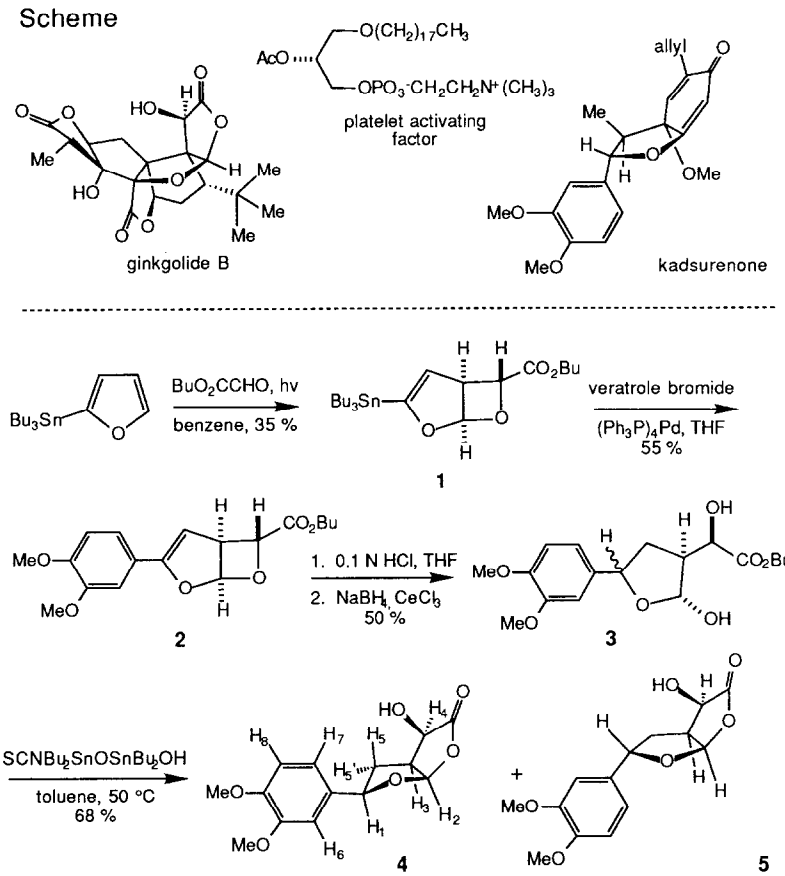
Entry	R	R_1	R_2	Time	Yield[b]	Ratio[c]
1	H	$SiMe_3$	Et	18 h	25%	1.2:1
2	H	$SiMe_3$	Ph	14 h	40%	2.5:1
3	H	$SiiPr_3$	Et	22 h	42%	4.0:1
4	H	$SiiPr_3$	Ph	17 h	56%	>20:1
5	H	$SnBu_3$	Ph	20 h	48%	2.5:1
6	H	$SnBu_3$	Et	24 h	30%	1.0:1
7	H	$SnBu_3$	CO_2Bu	24 h	35%	>20:1
8	CH_3	$SnBu_3$	Ph	18 h	41%	2.5:1

[a]Photoreactions were performed by irradiation of the furan (1.8 eq) and the aldehyde (1.0 eq) in degassed benzene with a 450 W Hanovia lamp equipped with Vycor filter. [b]Yields refer to pure major isomer isolated via flash chromatography. All compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, MS and HRMS (M^+) and/or microanalytical data. [c]Ratios refer to unpurified photoproducts, determined by integration of 250 MHz proton NMR signals. The minor component in all cases is the (unstable) isomer with the metal (Si, Sn) bonded to the acetal carbon.

An application of the stannyl directed furan carbonyl photocycloaddition reaction to a synthesis of a kadsurenone-ginkgolide hybrid is shown in the Scheme. The paf antagonists kadsurenone[4] and ginkgolide B[5] have been demonstrated to competitively inhibit paf binding to the paf receptor.[6] Based on the structural homology of these and related compounds, the structures of hybrid molecules have been formulated in order to further understand the requirements for binding to the paf receptor (for a discussion, see ref 6a). One such target (**5**) is depicted in the Scheme.

The synthesis of the target hybrid **5** began with the photoaddition of 2-tributylstannyl furan and butyl glyoxalate[7] and resulted in the stannyl substituted photoadduct **1**. The modest yield of this transformation reflects the photolability of the glyoxalate partner. Nevertheless, the highly selective formation of the complex oxetane **1** is noteworthy and central to the short synthesis of **5**. A Stille coupling[8] of bromoveratrole with the photoproduct then produced the crystalline arylated dihydrofuran **2** (mp 86-87 °C) in 55% yield. Attempted catalytic hydrogenation of the vinyl ether of **2** with rhodium on alumina provided several aldehyde containing products that were indicative of benzylic hydrogenolysis. As an alternative to the direct (but unsuccessful) reduction process, the arylated photoadduct was hydrolyzed[1c] and the crude hydrolysis mixture was subjected to conditions of the chemoselective Luche reduction.[9] This transformation allowed for the selective reduction of the aryl ketone in the presence of the aldehyde (hemiacetal) and provided lactol isomers in a 1:1 ratio (isomeric at the benzylic carbon). Various cyclization methods were then

Scheme



employed in an attempt to effect cyclization of the lactol moiety and the butyl ester. Acid catalyzed protocols (e.g., TFA, CH_2Cl_2) gave only cyclization of the lactol ring oxygen (in the open form of **3**) to afford six-membered ring lactone products. Base catalyzed methods (NaH, THF or DBU, benzene) gave similar results. However, success was achieved when the lactol mixture was treated with Otera's distannoxane transesterification catalyst[10] (toluene, 50 °C) under high dilution conditions to afford a 1:1 mixture of readily separable bicyclic compounds **4** and **5** that were isomeric at the benzylic carbon. When the Otera catalyst was employed in refluxing toluene, *only six membered ring lactone products were obtained*. The stereochemistry of the endo-isomer **4** was assigned on the basis of NOE difference measurements.[11]

In summary, a four step synthesis of a ginkgolide B-kadsurenone hybrid compound has been developed that illustrates the utility of a tributylstannyl directed furan-carbonyl photocycloaddition. Noteworthy in the synthesis is the mild distannoxane catalyzed intramolecular lactonization of a lactol and ester that engages the hemiacetal hydroxyl selectively at lower reaction temperatures. Further studies of the utility of this catalyst in organic synthesis are in progress. The paf receptor binding properties of **4** and **5** and related substances are currently under investigation.

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References and Footnotes

1. (a) Kozluk, T.; Zamojski, A. *Tetrahedron* **1983**, *39*, 805.
(b) Zamojski, A., Jarosz, S. *Tetrahedron* **1982**, *38*, 1447, 1453.
(c) Schreiber, S. L.; Hoveyda, A. H.; Wu, H-J. *J. Am. Chem. Soc.* **1983**, *105*, 660.
(d) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1983**, *105*, 6723.
(e) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186.
(f) Schreiber, S. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200.
(g) Schreiber, S. L. *Science*, **1985**, *227*, 857.
(h) Schreiber, S. L., Satake, K. *Tetrahedron Lett.* **1986**, *23*, 2575.
2. Barton, T. J.; Hussman, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6316.
3. Corey, E. J.; Cho, H.; Rucker, C. H.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
For a recent example of the use of the triisopropylsilyl as a furan blocking group see: Corey, E. J.; Wess, G.; Xiang, Y-B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.
4. Shen, T.-Y.; Hwang, S.-B.; Chang, M. N.; Doebber, T. W.; Lam, M. T.; Wu, M. S.; Wang, X.; Han, G. Q.; Li, R. Z. *Proc. Nat. Acad. Sci.* **1985**, *82*, 672.
5. Nakanishi, K. *Pure Appl. Chem.* **1967** *14*, 89.
6. (a) Schreiber, S. L.; Porco, J. A., Jr.; Hawley, R. C.; Desmaele, D. *New Methods in Drug Research* **1988** *3*, in press.
(b) Ponpipom, M. M.; Bugianesi, R. L.; Brooker, D. R.; Yue, B.-Z.; Hwang, S.-B.; Shen, T.-Y. *J. Med. Chem.* **1987**, *30*, 136.
(c) Braquet, P. In *Ginkgolides-Chemistry, Biology, Pharmacology and Clinical Perspectives* Braquet, P., Ed.; J. R. Prous Science: Barcelona, **1988**; p XV.
7. Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, *10*, 544.
8. McKean, D. R.; Pariello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 42.
9. Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
10. Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383; Otera, J.; Yano, T.; Himeno, Y.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 4501.
11. 250 MHz ^{1}H NMR data for compound **4**: δ1.98 (ddd, 1H, J= 4.1, 8.0, 14.0 Hz) $H_{5'}$, 2.55 (ddd, 1H, J= 6.5, 8.0,14.0 Hz) H_5, 2.64 (d, 1H, J= 2.5 Hz) OH, 3.5 (m, 1H) H_3, 3.88 (s, 3H) OMe, 3.89 (s, 3H) OMe, 4.74 (dd, 1H, J=2.5, 7.6 Hz) H_4, 5.33 (dd, 1H, J=6.5, 10.2 Hz) H_1, 6.05 (d, 1H, J=4.5 Hz) H_2, 6.8-6.92 (m, 3H) H_{6-8}. Selected NOE (250 MHz): Irradiation at δ3.5 ppm: 3.5% enhancement at δ4.74 ppm, 3.2% enhancement at δ6.05 ppm, 3.0% at δ2.55 ppm. Irradiation at δ5.33 ppm: 4.2% enhancement at δ2.55 ppm, 2.5% enhancement at δ3.5 ppm. Irradiation at δ2.55 ppm: 18% enhancement at δ5.33 ppm, 13% enhancement at δ3.5 ppm.

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