Pergamon

Tetrahedron Letters, Vol. 35, No. 45, pp. 8349-8352, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01821-9

Stereoselective Synthesis of Substituted Tetrahydrofurans and Butyrolactones by a New Nickel Catalyzed Carbozincation.

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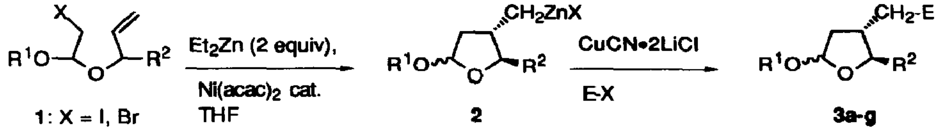
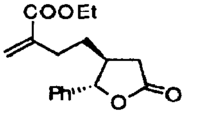
Summary: 2-Iodo- and 2-bromoethyl allyl ethers undergo a highly diastereoselective ring closure producing *trans*-4,5-disubstituted lactols. After oxidation with *m*-chloroperbenzoic acid, *trans*-4,5-disubstituted butyrolactones are obtained. This one-pot stereoselective approach to *trans*-4,5-disubstituted butyrolactones (2-furanones) proceeds in satisfactory overall yield (45-56 %; > 99% *trans*) for a range of substituted precursors **1** (R^2 = phenyl, *n*-hexyl or *i*-propyl). The use of cyclic 2-iodoacetals as precursors for the ring closure leads to new bicyclic heterocycles, such as **6a** and **6b**, with high *endo*-selectivity (> 96% *endo*). An *endo*-selective preparation of a pyrrolidine is also reported (*endo* > 96%), although in this case, the intermediate zinc reagent could only be trapped effiently by deuterolysis, due to its low reactivity.

Substituted tetrahydrofurans are structural units which are found in many natural products, and the stereoselective preparation of these heterocycles has been extensively investigated.[1] Recently, we reported a diethylzinc mediated palladium catalyzed carbozincation of 5-hexenyl iodides leading to substituted cyclopentylmethylzinc iodides in which the relative stereochemistry of up to three chiral centers could be controlled.[2] Unfortunately, attempts to extend this method to the preparation of substituted tetrahydrofurans were not successful and provided in many cases mixtures of cyclized and uncyclized products. We wish now to report that the use of nickel(II) acetylacetonate as catalyst (2-3 mol%) allows the cyclization of various unsaturated iodo- and readily available unsaturated *bromo*-acetals of type **1** in the presence of diethylzinc (2 equiv) at 25 °C (ca. 0.5 h). The resulting cyclic zinc compounds of type **2** can react, after a transmetalation with CuCN·2LiCl, with a range of electrophiles (allylic halides, ethyl propiolate, alkylidenemalonates, 3-iodo-2-cyclohexenone and acid chlorides) providing the 2-alkoxytetrahydrofurans **3a-g** in 60-70% overall yield (eq. 1, Table 1).

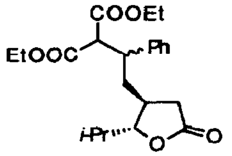


(1)

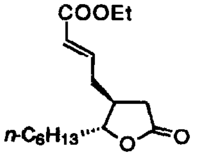
The ring closure proceeds via a radical mechanism[2] initiated by the nickel catalyst, but still produces an organometallic reagent **2** which can be readily further functionalized.[3] The relative stereochemistry between the substituents attached to C(4) and C(5) of compounds **3** is *trans* (>98% selectivity), as predicted by the transition-state model for radical cyclizations proposed by Beckwith.[4] The *trans*-stereochemistry observed between C(2) and C(4) is obtained with lower selectivity (ca. 9 : 1, see products **3a-c** of Table 1), however the lactols **3** can be readily oxidized with *meta*-chloroperbenzoic acid in the presence of boron trifluoride etherate (15 mol%)[5] affording pure *trans* -4,5-disubstituted butyrolactones[6] (2-furanones) in high yields. This reaction sequence can be performed in a one-pot procedure affording the lactones **4a-d** (> 99% *trans*) in 45-56% overall yield (see typical procedure).[7]



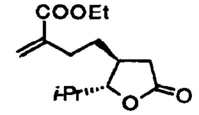
4a : 45 % overall yield (> 99 % *trans*)



4b : 53 % overall yield (> 99 % *trans*)

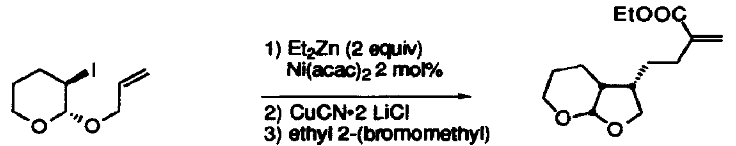


4c : 56 % overall yield (> 99 % *trans*)



4d : 50 % overall yield (> 99 % *trans*)

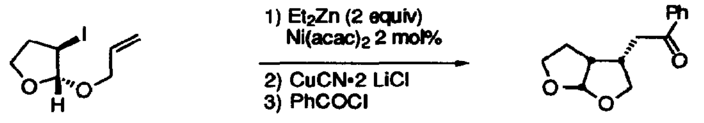
By using unsaturated *cyclic* iodo-acetals, such as **5a** and **5b**, as precursors,[8] bicyclic heterocyclic zinc reagents are produced (Et_2Zn (2 equiv), 0° C, 0.5 h). A transmetalation with CuCN·2LiCl and quenching with ethyl 2-(bromomethyl)acrylate (-78° C to 0° C, 0.5 h) or with benzoyl chloride (0°C, 12 h) affords the bicyclic heterocycles **6a** (66% overall yield) and **6b** (62% overall yield; eq 2 and 3). These cyclizations proceed with very high *endo*-selectivity (> 96%)[9,10]. This result can be explained by assuming that for the intermediate radical **7** the oxygen (O(1)) belonging to the ring will prefer to occupy an axial position due to stabilization by the anomeric effect, whereas the carbon chain attached to C(3) will occupy an equatorial position in the transition state (eq 4).



5a

6a : 66 %; *endo* : *exo* = 96 : 4

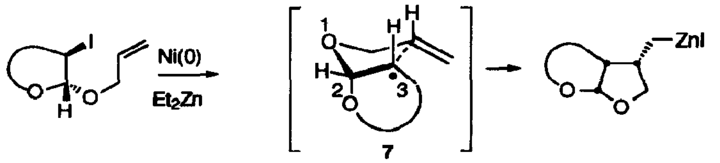
(2)



5b

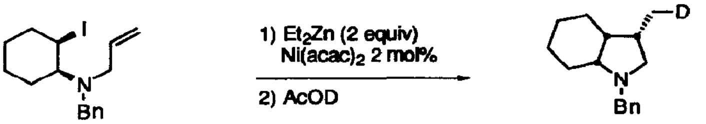
6b : 62 %; *endo* : *exo* > 98 : 2

(3)



7

(4)



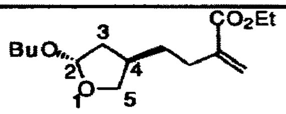
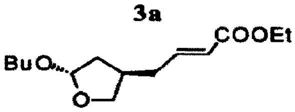
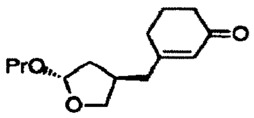
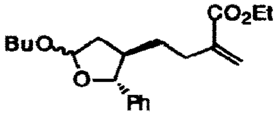
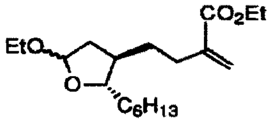
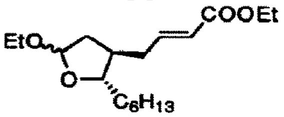
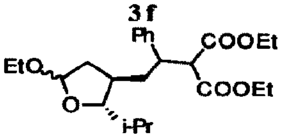
8

9 : 73 %; *endo* :*exo* > 96 : 4
100 % *d* incorporation

(5)

The ring closure of the β-iodo N-allylamino derivative **8**[11] provides a cyclized organozinc iodide which, due to its complexation with the amino group, has a reduced reactivity and can be trapped in high yields only by protonation or deuterolysis. A 100% deuterium incorporation is found in **9**, indicating that the organozinc species was formed as expected (eq 5).

Table 1. Polyfunctional Tetrahydrofurans **3a-g** Obtained by the Cyclization of Unsaturated Haloacetals of Type **1** with Diethylzinc in the Presence of $Ni(acac)_2$ Followed by the Quenching of the Corresponding Zinc-Copper Reagents with an Electrophile (E-X).

R^1	R^2	Electrophile	Product 3	d.r. C_4-C_5[a]	Yield(%)[b]
Bu	H	ethyl (2-bromomethyl)acrylate	 **3a**	c	70[d]
Bu	H	ethyl propiolate	 **3b**	c,e	61[d]
n-Pr	H	3-iodo-2-cyclohexenone	 **3c**	c	62[d]
Bu	Ph	ethyl (2-bromomethyl)acrylate	 **3d**	>99:1[f]	69[d]
Et	C_6H_{13}	ethyl (2-bromomethyl)acrylate	 **3e**	98:2	61[d]
Et	C_6H_{13}	ethyl propiolate	 **3f**	98:2[e]	60[g]
Et	*i*-Pr	diethyl benzylidenemalonate	 **3g**	>99:1	60[g]

[a] The diastereomeric ratio was determined by ^{13}C-NMR. [b] Overall yield of analytically pure products. [c] Cis:trans mixture between C(2) and C(4): ca. 12:88. [d] An iodo-acetal of type **1** was used [e] The unsaturated ester is > 99% E. [f] The relative stereochmistry between C(4) and C(5) has been assigned by ^{1}H ^{1}H NOESY experiments on the corresponding lactone. The proton attached to C(4) shows a strong NOE effect with the protons of the phenyl substituent attached to C(5). [g] A bromo-acetal of type **1** was used.

In summary, we have shown that a nickel(II) catalysis performed in the presence of diethylzinc allows the cyclization of various unsaturated iodo- and bromo-acetals leading to 4,5-disubstituted lactols, which after peracid oxidation, afford polyfunctional 4,5-disubstituted butyrolactones with high *trans*-diastereoselectivity and satisfactory overall yields. By using monocyclic iodo-acetals, condensed oxygen heterocycles, such as **6a** and **6b**, can be prepared with almost complete "*endo*" selectivity. Further extensions of the method, as well as applications directed towards natural product synthesis are under way.

Acknowledgment. We thank the DFG (SFB 260), the Fonds der Chemischen Industrie for the generous support of this research. We thank also WITCO AG (Bergkamen) and the BASF AG (Ludwigshafen) for a generous gift of chemicals.

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(7) *Typical procedure: trans*-4-(3-carbethoxy-3-butenyl)- 4,5-dihydro-(3H)-5-isopropyl-2-furanone (**4d**). To a suspension of Ni(acac)$_2$ (60 mg, 0.25 mmol), LiI (160 mg, 1.25 mmol) and 1-bromo-2-ethoxy-4-isopropyl-3-oxa-5-hexene (**1a** : X = Br; R^1 = Et; R^2 = *i*-Pr) (1.25 g, 5.0 mmol) in THF (5 mL) was added diethylzinc (1.0 mL, 10 mmol) at -78°C. The reaction mixture was warmed up to 25 °C within an hour, leading to a black solution. The cyclization reaction was completed by heating the mixture at 40 °C for 12 hours. A THF solution (15 mL) of CuCN (1.33 g, 15 mmol) and LiCl (1.26 g, 30 mmol) was added at -60 °C. The reaction mixture was stirred for 20 min. at 0°C, ethyl (2-bromomethyl)acrylate (2.95 g, 15 mmol) was added at -78 °C and the reaction mixture was warmed to 25 °C, poured after 5 min. into a saturated aqueous NH$_4$Cl- solution (50 mL) and extracted with ether (3 x 100 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over MgSO$_4$ and concentrated, affording the crude tetrahydrofuran derivative which was directly converted to the lactone in the following way. To a solution of *m*-chloroperbenzoic acid (1.64 g, 9.6 mmol, 50% purity ; the CH$_2$Cl$_2$ solution of the peracid was dried prior use with MgSO$_4$ (ca. 2g)) in CH$_2$Cl$_2$ (10 mL) was added successively at 25 °C boron trifluoride etherate (0.2 mL, 1.58 mmol) and the previously obtained crude oil dissolved in CH$_2$Cl$_2$ (2-3 mL). After stirring for one hour, the mixture was diluted with ether (30 mL) and washed successively with a saturated aqueous solution of sodium thiosulfate (2 x 20 mL), a saturated aqueous solution of K$_2$CO$_3$ (10 mL) and brine (2 x 20 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated. The crude product was purified by chromatography (hexanes : ether 4 : 1) affording the *trans*-γ-butyrolactone **4d** (0.63 g, 50% overall yield).

(8) The iodo-acetal **5a** is prepared by the reaction of dihydropyran, N-iodosuccinimide and allyl alcohol in CH$_2$Cl$_2$ (-30 to 0 °C, 3 h; 64% yield). The iodo-acetals **1a-e** and **5b** were obtained similarly (70-87% yield). Simpkins, N.S.; Middleton, D.S. *Synth. Commun.* **1989**, *19*, 21.

(9) The relative stereochemistry has been established with the aid of two dimensional NMR-spectrosopy.

(10) Compare with (a) RajanBabu, T.V.; Fukunaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296. (b) RajanBabu, T.V.; Fukunaga, T.; Reddy, G.S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

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(*Received in Germany* 26 *August* 1994; *accepted* 15 *September* 1994)