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Direct vinylogous aldol addition of γ-butyrolactones and γ-butyrolactams

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Abstract

Deprotonation of *N*-benzyl-3-phenylselenylpyrrol-2(5*H*)-one **3** and furan-2(5*H*)-one **4** and reaction with aldehydes affords regioselectively 5-(1′-hydroxy)-γ-butyrolactones and the aza-analogous butyrolactams with good diastereoisomeric excesses. The presence of Lewis acids enhances the diastereoisomeric ratios.

This methodology is an alternative to Lewis acid mediated silyloxydiene condensation.

Keywords: regioselective aldol reaction; furanones; pyrrolidones.

The 5-(1′-hydroxy)-γ-butyrolactone and γ-butyrolactam moieties are present in many naturally occurring molecules of biological and pharmaceutical interest.[1] Although oxygenated five-membered compounds are more widespread in nature than the corresponding aza-analogues,[2] the aza derivatives of the butyrolactones can exhibit more interesting biological activity than the corresponding oxygenated heterocycles.[3] Furthermore, compounds such as **1** have been employed as useful intermediates in organic synthesis as a growing literature witnesses (Fig. 1).[4]

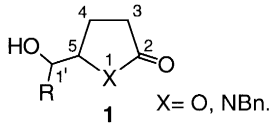

Fig. 1.

Herein we describe a new and efficient protocol for the regio and diastereoselective functionalization of the C5 position of suitable furan-2(5*H*)-ones and pyrrol-2(5*H*)-ones by direct vinylogous aldol condensation with aldehydes. Usually, these reactions, carried out on simple model compounds, such as butyrolactones and butyrolactams, give rise to the formation of mixtures of both regioisomeric and diastereoisomeric products (C3 and C5 alkylation).[5] Several methodologies have been introduced to overcome the drawback of the limited selectivity of this reaction. Some procedures have utilized

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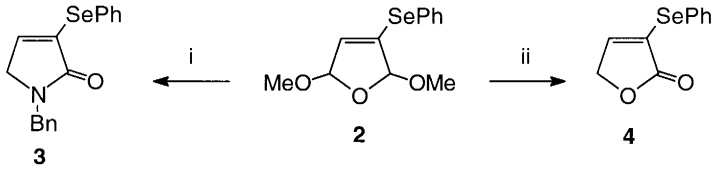
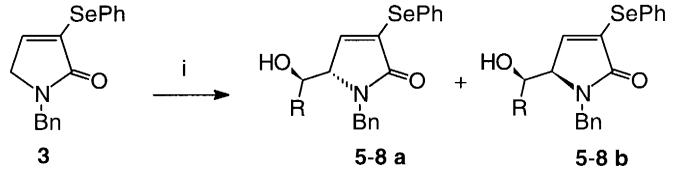
3- or 4-substituted heterocycles, such as methyl tetronate or methyl tetramate.[6] A few years ago, Ricci and co-workers described a multi-step sequence, which includes a base promoted enolization of the starting butyro-lactones or -lactams, followed by silyl triflate trapping with formation of the corresponding heterocyclic silyloxy diene, which can be functionalized only at the C5 position in the reaction with electrophiles.[7] In the last decade, Casiraghi's group as well as other authors have exploited this methodology to develop stereocontrolled syntheses of a large number of biologically interesting molecules.[8] In our method, we selected the phenylselenium moiety as a 'protective group' for the C3 position; particularly we utilized *N*-benzyl-3-phenylselenylpyrrol-2(5*H*)-one **3** and 3-phenylselenylfuran-2(5*H*)-one **4**. They can be easily prepared on large scale as single regioisomers starting from 2,5-dimethoxy-3-phenylselenyl-(2,5*H*)-furan **2** (Scheme 1).[9] It is noteworthy that the synthesis of similar unsaturated heterocyclic systems is not as straightforward as the preparation of the analogous saturated ones[10] which are inexpensive and commercially available.



Scheme 1. Reagents and conditions. i, $BnNH_2$, CH_3COOH, 4 days, 60% acetone; ii, HCl (aq.), CH_3CN, 85% or HCl (aq.), 65%

With the precursors in hand, the direct aldol condensation, conveniently performed by reaction of the corresponding enolate of our synthons, generated in situ by the action of LHMDS in THF, with model aldehydes, gave only the C5 functionalized products. The *anti* aldol products were predominantly obtained in all reactions involving the *N*-benzyl-3-phenylselenylpyrrol-2(5*H*)-one **3** (Scheme 2); both the yield (from 40% up to 80%) and the diastereoselectivity ratio (up to 50:1) were increased by using stoichiometric amounts of Lewis acids (Table 1 entry 2–4 and 6–8). [11] These results show clearly the pivotal role played by a transition state in which a boron or a tin enolate is involved. It is known that these enolates show lower interatomic distances with respect to lithium enolates,[12] and that the diastereoselectivity is increased because the transition state presents a more restricted geometry.



Scheme 2. Reagents and conditions. i, LHMDS, THF, 30 min, aldehyde (Table 1) then H_2O

On the other hand, the aldol condensation of the analogous 3-phenylselenylfuran-2(5*H*)-one **4** with benzaldehyde affords the corresponding alcohol as a 2:1 *anti*:*syn* mixture of diastereoisomers[13] (Scheme 3 and Table 2 entry 1); this *anti*:*syn* ratio is increased up to 6:1 if $Zn(OTf)_2$ is used as Lewis acid and toluene as solvent. The reverse diastereoselectivity is observed in the presence of $BF_3 \cdot Et_2O$ (1:6 *anti*:*syn*). When the addition reaction was performed with crotonaldehyde, only the formation of the 1,2-addition product was observed, with no detectable traces of the 1,4-adduct.

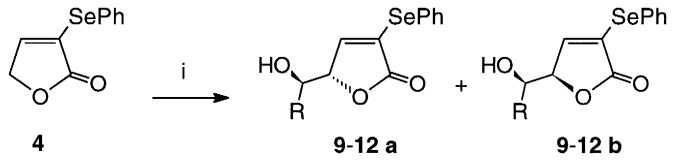
All the compounds described above were then treated under a deselenylation protocol based upon the use of in situ generated nickel boride which resulted in simultaneous reduction of the olefinic double bond (Scheme 4). We were usually able to obtain clean products in high yields without the need for chromatographic purification; both the reductive deselenylation of alkyl or vinylic selenides and the removal of the double bond in these heterocyclic systems have already been reported.[14]

In conclusion, our method allows the regioselective functionalization of *N*-benzyl-3-substituted-pyrrol-2(5*H*)-ones and furan-2(5*H*)-ones at the C5 position in reactions with aldehydes, affording either 5-

Table 1
Aldol reaction between **3** and various aldehydes

Entry	Products	Aldehyde	Lewis Acid[a]	*Anti/Syn*	Yield,[b] %
1	**5a-b**	PhCHO	None	1.5 :1	35
2	**5a-b**	PhCHO	$Sn(OTf)_2$	8 :1	60
3	**5a-b**	PhCHO	$BF_3{\cdot}Et_2O$	4 :1	50
4	**5a-b**	PhCHO	Bu_2BOTf	8 :1	70
5	**6a-b**	*o*-NO_2PhCHO	None	4 :1	40
6	**6a-b**	*o*-NO_2PhCHO	$Sn(OTf)_2$	12 :1	60
7	**6a-b**	*o*-NO_2PhCHO	$BF_3{\cdot}Et_2O$	20 :1	40
8	**6a-b**	*o*-NO_2PhCHO	Bu_2BOTf	50 :1	60
9	**7a-b**	$PhCH_2CH_2CHO$	Bu_2BOTf	1 :1	30
10	**8a-b**	Crotonaldehyde	Bu_2BOTf	1 :1	45

[a] 1 eq. of Lewis acid was employed. [b] Yields refer to pure isolated products.

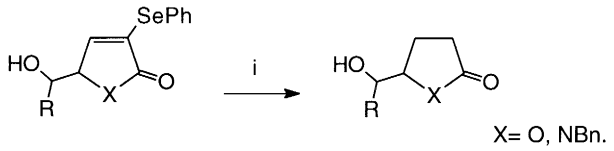


Scheme 3. Reagents and conditions. i, LHMDS, 30 min; aldehyde (Table 2) then H_2O

Table 2
Aldol reaction between **4** and various aldehydes

Entry	Products	Aldehyde	Solvent	Lewis Acid[a]	*Anti/Syn*	Yield,[b] %
1	**9a-b**	PhCHO	THF	none	2 :1	60
2	**9a-b**	PhCHO	THF	$BF_3{\cdot}Et_2O$	1 :6	83
3	**9a-b**	PhCHO	THF	$Zn(OTf)_2$	4 :1	83
4	**9a-b**	PhCHO	THF	$Sn(OTf)_2$	3.5 :1	60
5	**9a-b**	PhCHO	Toluene	$BF_3{\cdot}Et_2O$	1 :1	95
6	**9a-b**	PhCHO	Toluene	$Zn(OTf)_2$	6 :1	50
7	**10a-b**	*o*-NO_2PhCHO	THF	$BF_3{\cdot}Et_2O$	6 :1	70
8	**11a-b**	Crotonaldehyde	THF	$BF_3{\cdot}Et_2O$	1 :1	75
9	**12a-b**	*n*-$C_{14}H_{29}CHO$	THF	$BF_3{\cdot}Et_2O$	1 :1	95

[a] 1 eq. of Lewis acid was employed. [b] Yields refer to pure isolated products.



Scheme 4. Reagents and conditions. i, $NaBH_4$, $NiCl_2$, THF/MeOH; X=O, yields from 40 to 60%; X=NBn yields from 90 to 95%

(1′-hydroxy)-ɣ-butyrolactones or ɣ-butyrolactams with modest to excellent diasteroisomeric excesses, in particular if tin or boron Lewis acids are employed. The reaction involves a ‘free’ carbanion that is more nucleophilic than the heterocyclic silyloxy dienes activated with a Lewis acid and the overall transformation is the first general example of synthesis of molecules such as **1** via the direct aldol condensation.

Further studies to apply this reactivity to electrophiles other than aldehydes as well as to the synthesis of more complex molecules are in progress in our laboratory.

Acknowledgements

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11. Procedure for direct aldol reaction: To a cooled (−78°C) solution of 100 mg (0.305 mmol) of crystalline **3** in 2 ml of dry THF, LHMDS, 0.32 ml (1 M solution in THF, 1.05 equiv.) was added dropwise. The reaction mixture was stirred at this temperature for 30 min during which the colour of the solution changed from pale yellow to purple. A THF (1 ml) solution of Lewis acid (0.305 mmol, 1.00 equiv., see Table 1) was then added followed by the addition of a THF (1 ml) solution of aldehyde (0.457 mg, mmol 1.5 equiv., see Table 1). After 5 min NH_4Cl (2 M solution, 5 ml) was added and the mixture was diluted with ethyl acetate (10 ml) and diluted with brine. The organic layer was dried (Na_2SO_4) and evacuated in vacuo to give an oil that was further purified by chromatographic column on silica gel (eluant hexane:ethyl acetate 3:1) to give a mixture of compounds **5**–**8a**–**b**.
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