



Radical–polar crossover domino reactions involving organozinc reagents and β -(allyloxy)-enoates

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ARTICLE INFO

Article history:

Received 26 March 2008

Revised 17 April 2008

Accepted 18 April 2008

Available online 23 April 2008

Keywords:

Domino reactions

Radical–polar crossover

Organozinc reagents

Radicals

Furans

ABSTRACT

Organozinc reagents (organozinc halides, diorganozincs and mixed copper–zinc reagents) react with β -(allyloxy)-enoates via a radical–polar crossover process to afford substituted furans in one single synthetic step following a domino reaction involving Michael addition and carbocyclisation. Reversal of diastereoselectivity can be obtained varying the organometallic and/or the reaction conditions.

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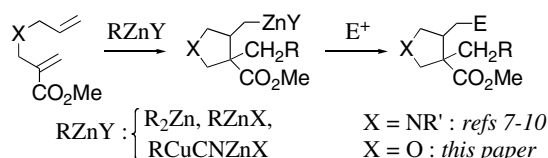
Organozinc chemistry has witnessed over the last decades a remarkable regain of interest from synthetic chemists.¹ Being less reactive than the corresponding organolithium and Grignard reagents it is possible to prepare organozinc reagents bearing functional groups such as esters or nitriles. However, this reduced reactivity also implies the use of metallic or organic catalysts or promoters to provoke reactions with electrophiles.^{2,3} Thus, the mastering of these activating methods remains essential to take full advantage of the potential of such unique functionalised organometallic reagents. Of particular interest is the use of organozinc reagents as radical precursors following oxidation or reaction with carbon or heteroatom-centred radicals. Known since their discovery,⁴ this possibility has only been started to be exploited for synthetic purposes rather recently.⁵

As part of our ongoing interest in carbometallation of unactivated alkenes by zinc enolates,⁶ we have recently shown that dialkylzincs (Bu_2Zn),^{7,8} organozinc reagents (RZnX)⁸ and mixed copper–zinc reagents ($\text{R}(\text{CuCN})\text{ZnX}$)^{9,10} react with (*N*-allyl)-aminoenoates to give substituted (pyrrolidylmethyl)zinc derivatives through a domino 1,4-addition/carbocyclisation sequence involving the transformation of a simple readily available organozinc into a more elaborated one via a radical chain transfer mechanism (vide infra).^{11,12} We reasoned that this radical–polar crossover transformation, unlike reactions involving metal enolates that would most

likely lead to β -elimination, should also be suitable for substrates bearing an oxygen in β position.^{12b,d} Reaction with β -(allyloxy)-enoates, readily available by reaction of the corresponding allylic alcohol with methyl 2-(bromomethyl)acrylate, should thus offer a new multi-component approach to substituted furans (Scheme 1).

We initiated our work with a model study on substrate **1**¹³ derived from allyl alcohol (Table 1). We were very glad to see that reaction with $n\text{Bu}_2\text{Zn}$ under our previously reported conditions (Et_2O , 16 h, room temperature)⁸ led, after acidic quench, to furan **2** in 64% yield and 75:25 (cis:trans) diastereoselectivity (entry 1). Using the dialkylzinc reagent obtained by mixing ZnBr_2 and $n\text{BuLi}$ (written as $n\text{Bu}_2\text{Zn}-2\text{LiBr}$) resulted in a slight increase in selectivity, albeit with a loss of yield (entry 2).

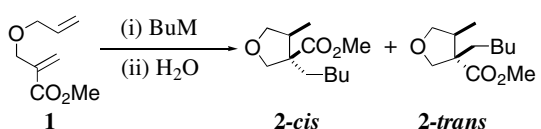
Other organometallic reagents were also surveyed. Organozinc ($n\text{BuZnX}$) reagents also perform the 1,4-addition/cyclisation reaction (Table 1, entries 3–6). Without additives, $n\text{BuZnBr}-\text{LiBr}$ obtained by transmetallation of $n\text{BuLi}$ with ZnBr_2 gave the corresponding furan **2-cis** in good yield (65%) but quite low selectivity (cis:trans = 58:42). In presence of two extra equivalents of



Scheme 1.

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Table 1
Domino reaction between alkylzincs and β -(allyloxy)-enoate **1**



Entry	<i>n</i> BuM (equiv)	Additive (equiv)	dr ^a (cis:trans)	2 ^b (%)
1	ZnBu ₂ (2)	—	75:25	64
2	ZnBu ₂ -2LiBr ^c (2.5)	—	80:20	41
3	BuZnBr-LiBr ^c (2.4)	—	58:42	65
4	BuZnBr-LiBr ^c (2.3)	ZnBr ₂ (2.3)	19:81	48
5	BuZnBr-LiCl ^c (2.2)	ZnCl ₂ (2.2)	38:62	45
6	BuZnBr (2.7)	ZnBr ₂ (2)	62:38	62
7	Bu(CuCN)ZnBr-LiBr ^d (1)	ZnBr ₂ (0.5)	50:50	48
8	Bu(CuCN)ZnBr-LiBr ^d (1)	ZnBr ₂ (1)	31:69	28
9	Bu(CuCN)ZnBr-LiBr ^d (1)	ZnBr ₂ (3)	22:78	10

Conditions: (i) BuM (equiv), Et₂O, rt, 16 h; (ii) HCl (1 M) or (ii) NH₄Cl (2)/NH₃ (1) for entries 7–9.

^a Determined by NMR analysis of the crude material.

^b Combined yield of isolated diastereomers after chromatography.

^c Prepared from salt-free *n*BuLi and ZnX₂.

^d Prepared from salt-free *n*BuLi, CuCN and ZnBr₂.

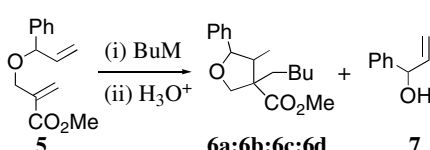
ZnBr₂, reversal of selectivity was observed and **2-trans** was obtained with reasonable selectivity (cis:trans = 19:81) but moderate yield. The use of ZnCl₂ as zinc salt also led to **2-trans** but with lower diastereoselectivity. Salt free *n*BuZnBr was prepared by equilibration between ZnBu₂ and ZnBr₂ via the Schlenk equilibrium. Reaction with **1** led quite unexpectedly to **2-cis** furan even with excess ZnBr₂ (entry 6), in a behaviour that matches rather the dialkylzinc case and contrasts with our observations with aminoenoates.⁸

Copper–zinc mixed reagents were also found to react with **1** to afford **2** but with very disappointing results (Table 1, entries 7–9). As for BuZnX, addition of ZnBr₂ was necessary to obtain some levels of diastereoselectivity in favour of the trans diastereomer but it also resulted in a dramatic loss of yield due to extensive degradation.

The presence of the intermediate (furan)methylzinc resulting from the domino sequence was confirmed by an iodine quench following the reaction of **1** with *n*Bu₂Zn which afforded iodides **3-cis** and **3-trans** in a 75:25 ratio (Scheme 2). The structure of the major diastereomer was determined after refluxing the mixture of inseparable isomers in toluene. The major **3-cis** compound afforded quantitatively bicyclic lactone **4** while the minor **3-trans** one remained unchanged.¹⁴

The domino reaction was next investigated with substrate **5** bearing a Ph substituent in allylic position (Table 2). *n*Bu₂Zn afforded furan **6** in good yield (68%) albeit as a mixture of 4 diastereomers (62:14:17:7). The stereoselectivity was enhanced using *n*BuZnBr-LiBr with excess ZnBr₂, as only two diastereomers (66:34:0:0) were obtained. By contrast, salt containing *n*Bu₂Zn-

Table 2
Domino reaction between alkylzincs and β -(allyloxy)-enoate **5**



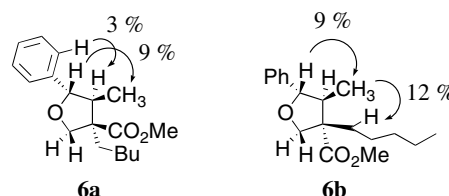
Entry	<i>n</i> BuM (equiv)	Additive (equiv)	6 (a:b:c:d) ^{a,b} (%)	7 ^c (%)
1	ZnBu ₂ (2)	—	68 (62:14:17:7)	0
2	BuZnBr-LiBr (2)	ZnBr ₂ (2)	51 (66:34:0:0)	0
3	ZnBu ₂ -2LiBr (2)	—	0	85

Conditions: (i) BuM (equiv), Et₂O, rt, 16 h; (ii) HCl (1 M).

^a Determined by NMR analysis of the crude material.

^b Combined yield of isolated diastereomers after chromatography.

^c Isolated yield.



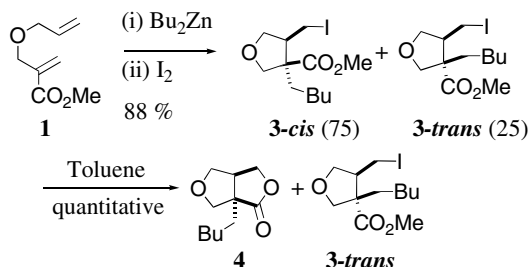
Scheme 3.

2LiBr only resulted in β -elimination. Unlike the non-substituted case, the same major isomer was observed with the dialkylzinc and the organozinc reagents. The structure of the two diastereomers obtained using BuZnBr was determined by NOE experiments (Scheme 3).

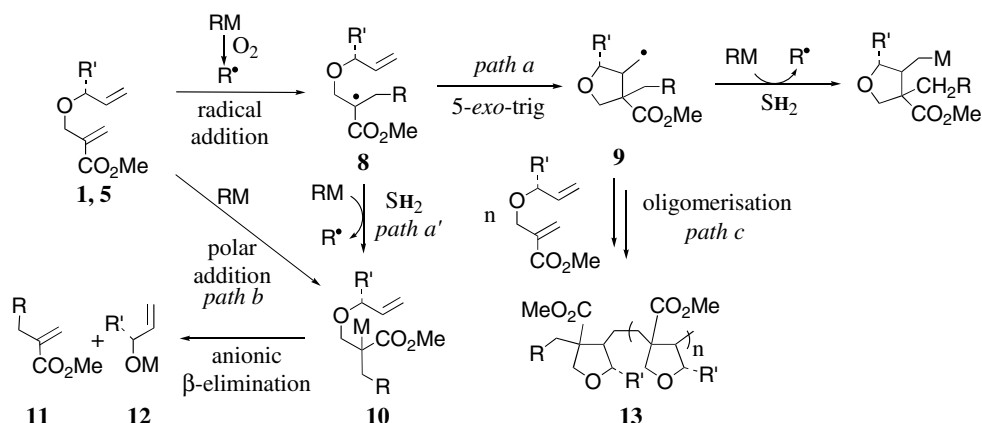
The observed transformations are believed to follow the radical–polar mechanism that we evidenced for the related reactions involving (*N*-allyl)-aminoenoates (Scheme 4, path a).⁸ Initial oxidation of the organometallic species by traces of oxygen produces a radical that undergoes 1,4-addition onto the Michael acceptor to afford an enoxy radical **8**. Subsequent 5-*exo*-trig cyclisation and reduction of the alkyl radical **9** by the organometallic species give the (tetrahydrofuran)methylzinc intermediate and a new radical that propagates the chain.

The formation of allylic alcohol **7** from **5** in the presence of formed LiBr in contrast with the salt free reaction is unexpected, as it arises most likely from anionic β -elimination of zinc enolate **10**. Formation of **10** cannot arise from the polar conjugate addition of ZnBu₂ alone,⁸ but could possibly be the result of a polar conjugate addition of a putative ate-complex such as ZnBu₂Br⁻Li⁺ formed from ZnBr₂ and LiBr (Scheme 4, path b). Alternatively, on the basis of a radical mechanism, it could also arise from homolytic substitution at zinc of radical **8** (Scheme 4, path a'). Even though tertiary alkyl-substituted α -alkoxycarbonyl radicals are believed not to undergo homolytic substitution at zinc,¹⁵ the increased SH2 rate might again be related to the formation of an ate-complex such as ZnBu₂Br⁻Li⁺, as observed for the reduction of similar α -alkoxycarbonyl radicals by alkylmercury derivatives,¹⁶ or it can also result from an increase of the electrophilicity of radical **8** by coordination of the Lewis-acid to the carbonyl moiety.¹⁷ Additionally, it has also been suggested that the ease for α -alkoxycarbonyl radicals to undergo SH2 at zinc is dependent on the possibility to form chelated enolates.⁵

Whatever its origin, this observation sheds some light on other salt effects observed in reactions with substrate **1** as indeed addition of Lewis acids generally results in significant yield decreases (Table 1, entry 1 vs 2, entry 3 vs 4,5 and entry 7 vs 8,9). Even though neither of the two expected β -elimination products (**11**



Scheme 2. Reagents and conditions: (i) Bu₂Zn (3 equiv), Et₂O, rt, 16 h; (ii) I₂, THF, rt, 3 h.



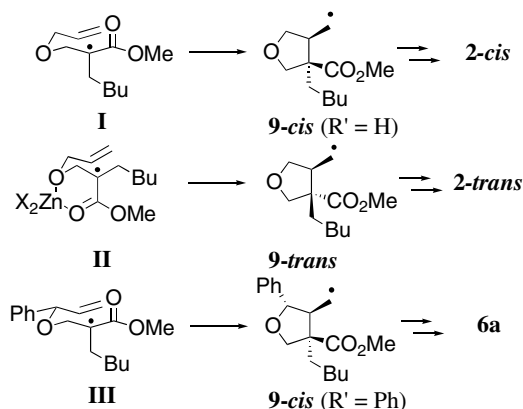
Scheme 4. Mechanism for the radical–polar crossover domino reaction.

($R = \text{Bu}$) and **12** ($R' = \text{H}$)) were detected (allyl alcohol obtained from **12** is too volatile and **11** presumably polymerises in the reaction media), we strongly suspect the formation of zinc enolate **10** leading to fragmentation to be the reason for the observed yield loss.

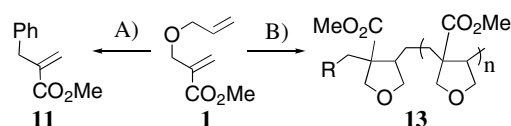
Concerning the diastereoselectivity, the observed results can be understood using the model we proposed previously for reactions with aminoenoates.⁸ The diastereoselectivity of the domino process results from the diastereoselectivity of the 5-*exo*-cyclisation (Scheme 5). The *cis* isomer results from cyclisation via **I** where, following the Beckwith–Houk model,^{18,19} for $A^{1,3}$ strain²⁰ and intramolecular dipole–dipole effect minimisation,²¹ the carbomethoxy moiety adopts a pseudo-equatorial position. This is the case for dialkylzincs and, unlike for aminoenoates and to a lesser extent, also for organozinc and copper–zinc mixed reagents. Addition of extra Lewis acids (ZnX_2) makes the cyclisation occur preferentially via **II** where chelation between the oxygen atom, the carbonyl group and the metal salt counterbalances $A^{1,3}$ -strain minimisation, thus leading to the *trans* isomer. However, the impact of LiBr on the diastereoselectivity (Table 1, entry 4 vs 6) remains unexplained.

For substrate **5** bearing an allylic substituent, cyclisation starting from Bu_2Zn occurs mainly via the non-chelated intermediate **III** where the phenyl group adopts a pseudo-equatorial position. It is also the case using BuZnBr-LiBr despite the presence of added ZnBr_2 , presumably because steric hindrance prevents coordination to the allylic oxygen atom, hence chelation of the zinc salt.

Finally, we explored the possibility to use arylzinc reagents (Scheme 6). Neither PhZnBr-LiBr nor PhZn(CuCN)Br-LiBr gave the domino addition/cyclisation products after reaction with **1**.



Scheme 5.



Scheme 6. Reagents and conditions: (A) (i) PhZn(CuCN)Br-LiBr , Et_2O , 16 h, rt; (ii) NH_4Cl (2)/ NH_3 (1); (B) (i) PhZnBr-LiBr , Et_2O , 16 h, rt; (ii) HCl (1 M).

With the former, only oligomeric material **13**, spectroscopically (^{13}C NMR) identical to the previously reported radical polymerisation product of **1**,¹³ was isolated, evidencing that alkyl radical **9** does not undergo homolytic substitution at zinc with the aryl zinc compound (Scheme 4, path c). With the latter, only product **11** ($R = \text{Ph}$) was obtained.

In conclusion, we have shown that the radical–polar domino 1,4-addition/carbocyclisation process that we described with (*N*-allyl)-aminoenoates can be extended to β -(allyloxy)-enoates thus providing polysubstituted furans. The general features of the sequence remain the same in both cases: the use of dialkylzincs leads to 2,3-*cis* furans, while the use of organozinc and copper–zinc mixed reagents (though the latter in much lower yields) leads to 2,3-*trans* furans. Nevertheless, some limitations have been evidenced. In first place, competitive 1,4-addition/fragmentation often hampers the efficiency of the reaction, especially in the presence of Lewis acids. In particular, it precludes the use of copper–zinc mixed reagents. Further studies are currently underway to determine whether the formation of the intermediate zinc enolate leading to β -elimination results from an initial polar addition or from reduction of the intermediate enoxy radical as a consequence of a less favourable 5-*exo*-cyclisation step than for the nitrogen containing substrates.^{22,23} The latter would imply that tertiary alkylsubstituted α -alkoxycarbonyl radicals can undergo homolytic substitution at zinc, a transformation that is, to the best of our knowledge, unprecedented. In second place, for reactions leading to the *trans* diastereomers, both as a result of its lower Lewis basicity and for geometrical reasons, chelation of zinc salts by the oxygen atom and the carbonyl group is less favourable, giving lower levels of selectivity.

Acknowledgement

The authors thank E. Caytan for help with NOE experiments.

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