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3-Bromopropenyl Methylcarbonate in Organic Synthesis: A Straightforward Approach to 4,5-Disubstituted 5-Vinyl-1,3-dioxolan-2-ones

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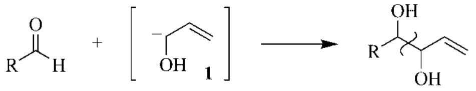
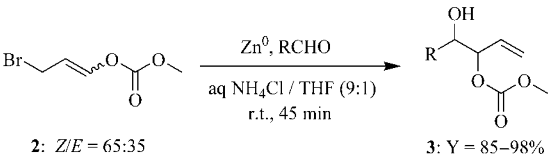
The reaction of 3-bromopropenyl methylcarbonate (**2**) with aliphatic or aromatic aldehydes, in the presence of indium metal in *N*,*N*-dimethylformamide, affords *cis* and *trans* 4,5-disubstituted 5-vinyl-1,3-dioxolan-2-ones **4** in very high isolated yields. Reactions may be run by adopting either one-pot Barbier conditions or a two-step Grignard protocol. The *cis*-**4**/*trans*-**4** ratio is controlled by the nature of the carbonyl compound: saturated aldehydes mainly afford *cis*-**4**, whereas conjugated aldehydes favor the formation of *trans*-**4**.

Introduction

As a part of our ongoing study on the development of new precursors of heterofunctionalized synthons **1** to be exploited in the α-hydroxyallylation reaction of carbonyl compounds (Scheme 1),[1] we recently proposed the use of 3-bromopropenyl methylcarbonate (**2**), easily accessible by radical bromination of allyl methylcarbonate,[2] in a straightforward and diastereoselective synthesis of monoprotected diols **3** using zinc in an aqueous medium (Scheme 2).



Scheme 1.



Scheme 2.

When we subjected carbonate **2** to typical Barbier–Luche conditions (zinc powder in a saturated aqueous NH_4Cl/THF mixture as the reaction medium, room temperature) in the presence of an aldehyde,[3] the result was the formation of a *syn*/*anti* mixture of open-chain adducts **3**. As for the diastereomeric composition, the same trend displayed by 3-bromopropenyl acetate was observed:[4] indeed, the *syn*-**3**/*anti*-**3** ratio mainly depended on the nature of the aldehyde. *Syn* adducts were preferentially formed in the case of conjugated aldehydes, whereas *anti* adducts prevailed when nonconjugated aldehydes were used (Scheme 2).

The extreme versatility of heterosubstituted allylic halides **2** in promoting oxidative addition reactions to suitable low valent metals allowed us to check a variety of solvents and reaction protocols, either with zinc or indium as the metal. We are now in a position to present two straightforward protocols for the synthesis of 4,5-disubstituted 5-vinyl-1,3-dioxolan-2-ones **4**, valuable intermediates in organic synthesis[5] and in material and polymer chemistry.[6]

Results and Discussion

The two synthetic protocols here proposed are based on the use of indium metal in *N*,*N*-dimethylformamide (DMF); the former is a typical Barbier one-pot process (protocol A), the second is a classic Grignard two-step process involving first the formation of the organoindium species and then the addition of the carbonyl compound (protocol B). In protocol A, an aldehyde and **2** are stirred in a suspension of indium metal in DMF at 0 °C for 1 h, and then the temperature is raised to 25 °C and maintained at that value for 1 h. Both the oxidative addition and the nucleophilic attack of the intermediate indium complex **5**[7] to the aldehyde take place readily at 0 °C,[8] leading to the intermediate indium alkoxide **6**, which, eventually, undergoes cyclization to the target cyclic carbonate **4** (Scheme 3). Raising the temperature to 25 °C allows the cyclization step go to completion.

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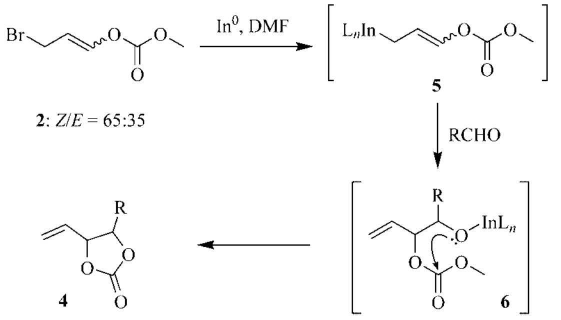

Scheme 3.

The results of a set of experiments, carried out with typical prochiral aliphatic and aromatic aldehydes, are reported in Table 1.

Table 1. Indium promoted synthesis of **4** in DMF according to protocol A.

Entry	R in RCHO	**4**, Yield (%)[a]	*trans*-**4**/*cis*-**4**
1	*n*-nonyl-	**4a**, 94	28:72
2	phenethyl-	**4b**, 93	18:82
3	cyclohexyl-	**4c**, 91	7:93
4	isopropyl-	**4d**, 98	13:87
5	*tert*-butyl-	**4e**, 88	35:65
6	phenyl-	**4f**, 93	90:10
7	4-methoxyphenyl-	**4g**, 97	77:23
8	4-fluorophenyl-	**4h**, 95	85:15
9	1-naphthyl-	**4i**, 91	95:5
10	(*E*)-styryl-	**4j**, 98	79:21

[a] Isolated yields after purification by flash-chromatography on silica gel.

The GC–MS profile of the crude reaction mixture is utterly simple, since no side-products are observed and no more than traces of starting materials are present. Correspondingly, very high recoveries of cyclic carbonates **4** are obtained after column chromatography, with overall chemical yields ranging from 88 to 98%.

As for the stereochemical outcome of the formal overall cycloaddition process, the usual stereocrossover previously described was observed. Indeed, saturated aldehydes afford *anti* adducts which spontaneously cyclize to *cis*-**4**, while conjugated aldehydes afford *syn* adducts, and hence, *trans*-**4**. Diastereomeric ratios (*dr*) were determined by GC–MS analysis of the crude reaction mixtures and by chromatographic separation of the pure products **4** over silica gel.[9] Values of *dr* (*trans*-**4**/*cis*-**4**) range from 35:65 to 3:97 and from 77:23 to 95:5 for saturated and conjugated aldehydes, respectively. The use of DMF as solvent and its role in favoring ring closure to **4** is crucial. It is well known that Barbier reactions between allyl halides and carbonyl compounds promoted by indium metal typically run most efficiently in water as solvent.[10] When we carried out the reaction between **2** and benzaldehyde using indium in water, the corresponding cyclic carbonates **4** were recovered in very low yields (15–20%), together with the unreacted aldehyde. The critical point was the acidity of the solution, which suddenly reached pH < 4 under these conditions,[11] an environment which catalyzed the hydrolysis of **2**. On the other hand, we knew that, in a buffered medium (saturated aqueous ammonium chloride),[12] both indium and zinc metals afforded the open chain monocarbonates deriving from the simple protonation of **6**, but zinc was found superior in terms of chemical yields, exactly as previously observed by Lu and Chan who used allylic bromides.[13]

In terms of reactivity, complex **5** added to a sterically demanding carbonyl compound such as 2,2-dimethylpropanal, affording the corresponding adducts in very high yield (entry 5). Moreover, **2** reacted with *p*-fluorobenzaldehyde (entry 8), while the analogous process based on the use of 3-bromopropenyl acetate did not work.[4c]

Protocol B involved the preliminary formation of **5** in DMF at 0 °C for 1 h. The temperature for the subsequent addition step to an aldehyde may be set at any value compatible with DMF (see Table 2), provided that stirring at 25 °C for 1 h is performed before quenching the reaction, to complete the cyclization of **6** to **4** (Scheme 3). We were astonished by the observation that, when we carried out the addition step at –50 °C for 3 h with four different aldehydes (Table 2, entries 1–4),[14] no significant change in diastereomeric ratios resulted with respect to entries 1,5,7, and 10 of Table 1, where the same aldehydes were used at 0 °C under Barbier conditions.[15]

Table 2. Indium promoted synthesis of 4 in DMF according to protocol B.

Entry	R in RCHO	*T*, *t*[a]	**4**, Yield (%)[b]	*trans*-**4**/*cis*-**4**
1	*n*-nonyl-	–50 °C, 3 h	**4a**, 55	30:70
2	*tert*-butyl-	–50 °C, 3 h	**4e**, 88	35:65
3	4-methoxyphenyl-	–50 °C, 3 h	**4g**, 89	75:25
4	(*E*)-styryl-	–50 °C, 3 h	**4j**, 87	75:25
5	4-nitrophenyl-	0 °C, 1 h	**4k**, 98	85:15

[a] Conditions relative to the addition step of preformed **5** to the aldehyde. [b] Isolated yields after purification by flash-chromatography on silica gel.

Protocol B, on the other hand, allowed us to force 4-nitrobenzaldehyde to react. Indeed, when protocol A was applied to 4-nitrobenzaldehyde, no reaction occurred, and in particular the insertion of indium into the C–Br bond of **2** did not occur at all, as if the metal surface was doped by the aldehyde. In contrast, preformed organoindium complex **5** added to *p*-nitrobenzaldehyde in an almost quantitative fashion (Table 2, entry 5).

Conclusions

In conclusion, a highly efficient, one-pot synthesis of cyclic carbonates **4** has been reported. Based on the in situ formation of **2**, excellent isolated yields of target products **4** are obtained. The control of *cis*/*trans* stereochemistry is governed by the nature of the aldehyde substituent. The *trans* adducts **4** are obtained in the case of aromatic and conjugated aldehydes, whereas the *cis* adducts **4** prevail when saturated aldehydes are used. A transition-state modeling study is in progress, aimed at identifying the geometrical constraints and electronic factors responsible for the observed stereochemical outcomes. The value of this route to 4,5-disubstituted 5-vinyl-1,3-dioxolan-2-ones **4** is further demonstrated on one hand by the possible adoption of Grignard two-step conditions, which allowed us to use an otherwise unreactive aldehyde, and, on the other, by the possible use of buffered aqueous solutions of either indium or zinc, to switch the process to the synthesis of the selectively monoprotected diols.

Experimental Section

General Remarks: All reactions were performed in flame dried glassware under dry argon and by using air-sensitive Schlenk techniques. All reagents were commercially available and were used without further purification, unless otherwise stated; indium powder (particle size –100 mesh, 99.99%), was purchased from Aldrich. NMR spectra were obtained with a Varian Inova 300 (300 and 75 MHz, for ^{1}H and ^{13}C, respectively) using $CDCl_3$ as internal standard; chemical shifts (δ) are reported in ppm relative to TMS. GC–MS analyses were performed with an HP 5890 II instrument connected to a quadrupole mass detector HP 5970.

Synthesis of 1,3-Dioxolan-2-ones (4), Protocol A: (Table 1, entries 1–10) 3-Bromo-propenyl methylcarbonate **2** (0.145 mL, 1.2 mmol) was added at 0 °C to a mixture of indium (0.094 g, 0.82 mmol) and the appropriate aldehyde (1 mmol) in DMF (2 mL); the heterogeneous solution was vigorously stirred at 0 °C for 1 h and at room temperature for 1 h. The crude reaction mixture was directly poured onto the top of a silica gel column (d = 2 cm, h = 15–18 cm) and chromatographed with cyclohexane/ethyl acetate mixtures, to give title compounds **4** as separated pure *cis* and *trans* isomers. Characterization data for compounds **4a**–**d** and **4f**–**j** are reported in ref.[3]

Synthesis of 1,3-Dioxolan-2-ones (4), Protocol B: (Table 2, entries 1–5) 3-Bromo-propenyl methylcarbonate **2** (0.145 mL, 1.2 mmol) was added at 0 °C to a suspension of indium (0.094 g, 0.82 mmol) in DMF (2 mL) and the heterogeneous mixture was vigorously stirred at 0 °C for 1 h. The desired aldehyde (1 mmol) was added, and the reaction mixture was stirred at 0 °C for 1 h or at –50 °C for 3 h, and at room temperature for 1 h. The crude reaction mixture was directly poured onto the top of a silica gel column (d = 2 cm, h = 15–18 cm) and eluted with cyclohexane/ethyl acetate mixtures, to give title compounds **4** as separated pure *cis* and *trans* isomers.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedure for the synthesis of 3-bromopropenyl methylcarbonate (**2**) and spectroscopic data for new compounds **4e** and **4k**.

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[7] In structure **5** the oxidation state of indium is not defined. To this purpose, we refer to an interesting NMR study of the interaction of In^0 and allyl bromide, which showed that, when the solvent is water, allyl In^I is the only complex detectable, whereas, when the solvent is DMF, signals assigned to both allyl In^I and allyl In^{III} complexes are observed, the former being the more reactive ones. See: T. H. Chan, Y. Yang, *J. Am. Chem. Soc.* **1999**, *121*, 3228–3229.

[8] The oxidative addition step is exceedingly sluggish at –20 °C, thus protocol A can not be conveniently run at $T < 0$ °C.

[9] Chromatographic properties of *cis*-**4** and *trans*-**4** show regular trends useful for stereochemical assignments: i) GC retention times (HP-5MS cross-linked 5% phenyl-methyl silicone glass capillary column, 0.25-µm film thickness) of *cis*-**4** are consistently shorter than those of the corresponding *trans*-**4**, and ii) chromatographic R_f of *cis*-**4** (silica gel, cyclohexane/ethyl acetate mixtures as the eluent solution) are regularly higher.

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[14] TLC and GC–MS controls clearly revealed that nucleophilic addition of **5** to RCHO had occurred at –50 °C before the temperature was raised in order to complete the cyclization of **6** to **4**.

[15] Examples of nucleophilic additions where stereoselectivity is invariant with respect to temperature are reported in the literature; in these cases, the Eyring plots of ln(*anti*/*syn*) vs. $1/T$ are represented by a horizontal line, meaning that selectivity is controlled by entropic rather than by enthalpic factors: a) R. Berardi, G. Cainelli, P. Galletti, D. Giacomini, A. Gualandi, L. Muccioli, C. Zannoni, *J. Am. Chem. Soc.* **2005**, *127*, 10669–10706, and references cited therein; b) M. Lombardo, S. Fabbroni, C. Trombini, *J. Org. Chem.* **2001**, *66*, 1264–1268.

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