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Three-component synthesis of functionalized five-membered ring lactones under Barbier-like conditions

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ABSTRACT

Five-membered ring lactones have been synthesized using a straightforward three-component reaction among in situ-generated arylzinc reagents, dimethyl itaconate and aromatic aldehydes. This Barbier-like procedure, which is characterized by its simplicity, allows the concise synthesis of a range of highly functionalized 4,5-substituted γ-butyrolactones.

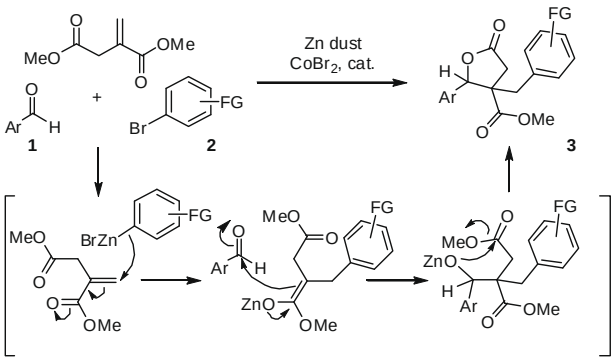
Substituted γ-butyrolactones, in particular those bearing a carboxyl group at the β position (paraconic acids) constitute an important family of biologically active compounds displaying antitumour and antibiotic activities.[1] They also represent important building blocks in the preparation of natural products of pharmaceutical interest.[2] Accordingly, during the last years, numerous procedures have been developed for the synthesis of paraconic acids and derivatives.[3]

Surprisingly, although multicomponent reactions provide a rapid access to highly functionalized scaffolds[4] such processes have not been employed so far for the synthesis of functionalized 4,5-substituted γ-butyrolactones.[5]

Recently, our group has developed a Mannich-type three-component reaction among organozinc reagents, amines and aldehyde derivatives.[6] As a prospect, we envisaged to extend this methodology to an array of multicomponent reactions involving in situ-generated arylzinc reagents as nucleophiles. Thus, as a first disclosure, we describe herein a cascade conjugate addition-aldolization-cyclization process as a useful tool for the synthesis of γ-butyrolactones.

The putative synthesis of γ-butyrolactones was based on the observation that the addition of arylzinc compounds to aldehyde **1** is generally slow. Thus, we conceived that a 1,4 addition of these organometallic reagents, generated in situ from aryl bromides **2**, on a suitable Michael acceptor like dimethyl itaconate might be the faster pathway. The resulting enolate might then react with aldehyde **1**[7] to induce the formation of an alcoholate which would further cyclize to provide the expected γ-butyrolactone **3** (Scheme 1).

In a preliminary experiment, we tried to undergo a three-component cascade reaction between benzaldehyde **1a**, dimethyl itaconate and 4-bromoanisole **2a**. We chose to employ experimental conditions similar to those described in a previous work regarding the in situ activation of aryl bromides into the corresponding arylzinc compounds[8] and their three-component reaction with aldehydes and amines.[6e] Thus, **2a** was allowed to react with dimethyl itaconate and benzaldehyde **1a** in the presence of zinc dust and cobalt bromide at room temperature (Scheme 2).



Scheme 1. Principle of the three-component cascade reaction.

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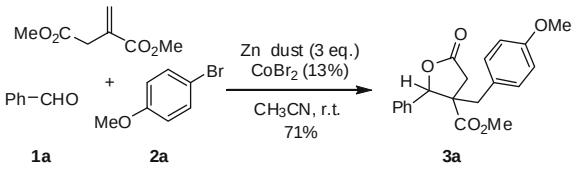
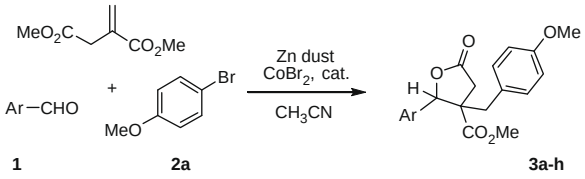
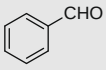
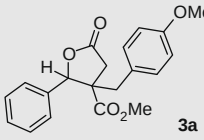
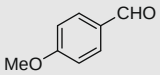
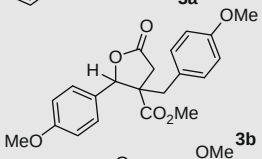
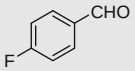
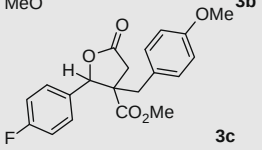
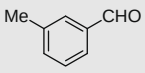
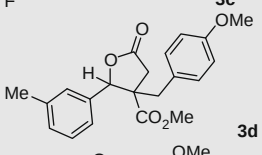
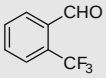
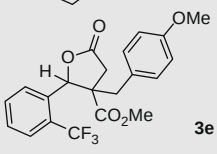
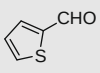
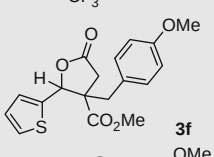
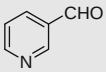
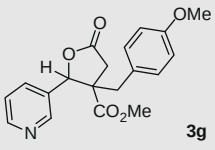
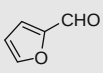
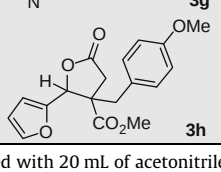


Scheme 2. Preliminary experiment involving 4-bromoanisole, benzaldehyde and dimethyl itaconate.

Table 1
Scope of aromatic aldehydes[a]



Entry	Aromatic aldehyde	Product **3**	Yield[b] (%)
1		 **3a**	95
2		 **3b**	41
3		 **3c**	98
4		 **3d**	79
5		 **3e**	56
6		 **3f**	75
7		 **3g**	–[c]
8		 **3h**	49

[a] All experiments were conducted with 20 mL of acetonitrile, 2.7 g (15 mmol) of bromoanisole, 10 mmol of the aldehyde, 7.9 g (50 mmol) of dimethyl itaconate, 3 g (46 mmol) of zinc dust and 0.44 g (2 mmol) of $CoBr_2$. Reactions were carried out for 0.75–2 h.
[b] Isolated yield.
[c] No reaction.

Under these conditions, we were satisfied to observe the formation of the expected lactone in good yield, as a one-to-one ratio of diastereoisomers.

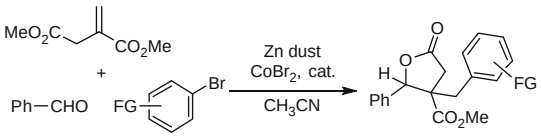
We then started to investigate the scope of this reaction system. In a first series of experiments, dimethyl itaconate and 4-bromoanisole **2a**, taken as the model halide, were allowed to react with a range of aromatic aldehydes **1** for 0.75–2 h.[9] Results are reported in Table 1.

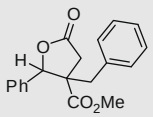
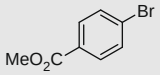
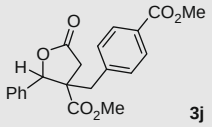
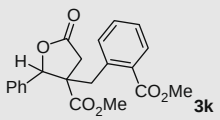
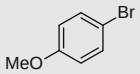
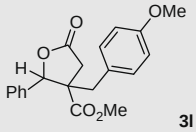
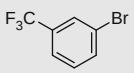
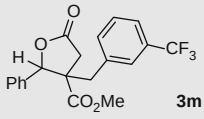
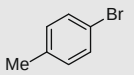
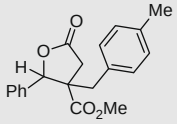
Yields obtained with benzaldehyde derivatives generally range from moderate to excellent and it can be noted that the reaction tolerates an important variety of functionalized aromatic aldehydes bearing electron-withdrawing as well as electron-donating groups. Starting from heteroaromatic aldehydes, the corresponding lactones are obtained in satisfactory to good yields except starting from 3-pyridine carboxaldehyde (Table 1, entry 7). In that case, no coupling is observed, even after 24 h at 60 °C.

In a second set of experiments, we turned our attention to the variation of the aromatic bromide. Results are reported in Table 2.

Very satisfactory yields are generally obtained with both electron-rich and electron-deficient aryl bromides. Moreover, we were

Table 2
Scope of aromatic bromides[a]



Entry	Aromatic bromide	Product **3**	Yield (%)[b]
1		 **3i**	64
2		 **3j**	99
3		 **3k**	52
4		 **3l**	95
5		 **3m**	46
6		 **3n**	69

[a] All experiments were conducted with 20 mL of acetonitrile, 15 mmol of the aryl bromide, 1.1 g (10 mmol) of benzaldehyde, 7.9 g (50 mmol) of dimethyl itaconate, 3 g (46 mmol) of zinc dust and 0.44 g (2 mmol) of $CoBr_2$. Reactions were carried out for 1–3 h.
[b] Isolated yield.

satisfied to observe that hindered bromides can undergo the coupling, even if in this case a slight decrease of the reaction yield (Table 2, entries 3 and 5) is noticed.

In summary, we have developed a simple and efficient method for the synthesis of 4,5-substituted γ-butyrolactones via a multicomponent one-pot reaction between dimethyl itaconate, aryl bromides and carbonyl compounds. This cascade procedure, which involves in the same experimental step the formation of an organozinc reagent, a Michael addition, an aldol coupling and a final cyclization provides a reliable access to a wide variety of lactones, making this strategy suitable for parallel synthesis. Further developments of this promising reaction system are currently in progress.

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9. *General procedure*: a dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (20 mL). Dodecane (0.2 mL), zinc dust (3 g, 46 mmol), dimethylitaconate (7.9 g, 50 mmol), aromatic aldehyde (10 mmol) and aryl bromide (15 mmol) were added under stirring. Cobalt bromide (0.44 g, 2 mmol), trifluoroacetic acid (0.1 mL) and 1,2-dibromoethane (0.2 mL) were added successively to the mixture which was heated at 60 °C until complete consumption of the aryl bromide (45 min to 3 h, monitored by gas chromatography). The reaction mixture was then filtered through Celite. Celite was washed several times with diethyl ether and the combined organic fractions were concentrated in vacuo. The crude reaction product was purified via flash column chromatography over silica gel using a pentane/diethyl ether mixture (1:0 to 0:1) as an eluant to afford the pure lactone **3**.