Pergamon

Tetrahedron Letters 43 (2002) 5301–5304

TETRAHEDRON LETTERS

Efficient Mn^{III}-mediated synthesis of functionalized *trans*-3,4-disubstituted-γ-butyrolactones

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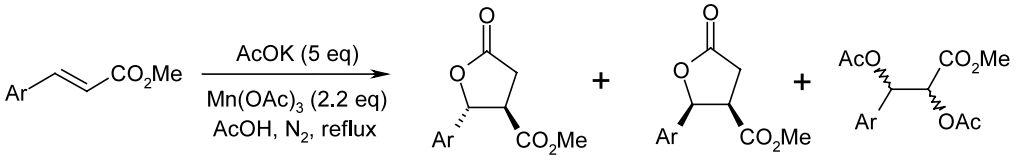
Received 17 May 2002; accepted 30 May 2002

Abstract—The Mn^{III}-induced addition of malonic acid (instead of acetic acid) to cinnamic esters affords in one step functionalized *trans*-3,4-disubstituted-γ-butyrolactones in a greatly improved yield which can be further optimized by conducting the reaction in either acetic or formic acid, depending on the substrate. © 2002 Elsevier Science Ltd. All rights reserved.

The Mn^{III}-promoted addition of acetic acid to 1,2-disubstituted alkenes enables the preparation, in a single step, of γ-butyrolactones possessing two contiguous stereogenic centers. Nevertheless, this synthetically attractive reaction suffers from severe limitations which preclude its general use: it is often poorly regio- and diastereoselective (giving rise to a mixture of isomers) and the yield in isolated lactone(s) is seldom good due to the low reactivity of many alkenes and/or the formation of side products (mainly mono-, di- and hydroxyacetates).[1]

However, we have shown previously that the Mn^{III}-induced addition of potassium monomethyl malonate to substituted cinnamic esters furnishes a single (all-*trans*) diastereomer of functionalized 2,3,4-trisubstituted-γ-butyrolactones, in good yield provided that the reaction is carried out in either acetic or formic acid, depending on the substrate.[2]

Owing to the continuing interest in the preparation of 3,4-disubstituted-γ-butyrolactones of defined stereochemistry, especially those possessing a 4-aryl substituent,[3] we thought that we could capitalize on our previous findings in order to also obtain stereodefined functionalized 3,4-disubstituted-γ-lactones in a practically useful yield. Few results concerning the addition of acetic acid to unsubstituted cinnamic derivatives could be found in the literature: despite some dis-



1a-g

a Ar = C_6H_5
b Ar = 4-MeC_6H_4
c Ar = 2,4-$Me_2C_6H_3$
d Ar = 4-$MeOC_6H_4$
e Ar = 2,4-$(MeO)_2C_6H_3$
f Ar = 3,4-$(MeO)_2C_6H_3$
g Ar = 3,4-$(OCH_2O)C_6H_3$

2 **3** **4** **5**

Scheme 1.

Keywords: manganese(III) acetate; oxidative addition; γ-butyrolactones; malonic acid.
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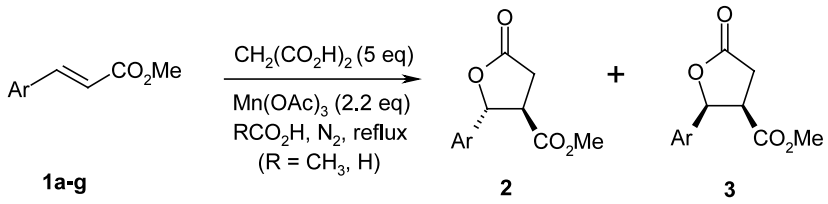
PII: S0040-4039(02)01022-5



Scheme 2.

crepancies (due in particular to the different reaction conditions employed and to the mode of assessment of the yield), a single or a highly predominant *trans*-3,4-disubstituted-γ-lactone seemed to be formed in moderate yield.[4] Moreover, this oxidative addition failed with the only substituted cinnamic substrate tested, 3,4-methylenedioxycinnamyl acetate.[4d]

Our preliminary study was thus focused on re-examining the addition of acetic acid to a series of cinnamic esters possessing diverse substitution patterns, under standardized conditions, while measuring the yield in isolated lactone(s) relative to the starting alkene (Scheme 1 and Table 1).[5a]

As expected, the addition of acetic acid to cinnamic esters **1a–f** is totally regioselective and highly diastereoselective, giving the two epimeric lactones **2** and **3** (readily separable by flash chromatography) with **2**:**3** ≥ 96:4. However, the yield in isolated lactone **2** is moderate (42–46%) in three cases (entries 2–4) and poor (10–29%) in three others (entries 1, 5 and 6). Finally, when starting from **1g**, no lactone was ever detected after 24 h. The incomplete consumption of **1** (entries 1–3) and the formation of side products **4** and **5** (entries 4–6) both account for the overall unsatisfactory yield in lactone **2**. Clearly, a more reactive substitute of acetic acid was needed in order to obtain better yields of the desired **2**. In addition, this could also allow us to perform the reaction in formic acid (which proved highly beneficial for the preparation of trisubstituted γ-lactones).[2] Malonic acid seemed a good candidate provided that the first-formed α-carboxylactone could be readily decarboxylated under the reaction conditions. The use of malonic acid had previously been examined but abandoned as an alternative for preparing monolactones presumably because, in each instance, it gave overwhelmingly spirodilactones (0.5 equiv. of malonic acid relative to the alkene were used and cinnamates were not among the few substrates tested).[6] Yet, when using methylmalonic acid (which could not obviously give rise to spirodilactones), Kurosawa cleanly obtained α-methyl-α-carboxy-γ-lactones in moderate to good yields (AcOH, 100°C, 2.5–10 min). Three of them were subsequently decarboxylated by prolonged heating (5.5–9 h) in refluxing acetic acid, allowing the preparation of α-methyl-γ-butyrolactones (in 34–72% yield over two steps) from styrene or 1,1-diarylethenes. Interestingly, in one instance (AcOH, 70°C, 14 days) the α-methyl-γ-lactone was directly obtained in 81% yield.[7] These results prompted us to investigate more systematically the addition of malonic acid to cinnamic esters aiming to define an experimental procedure which could lead to a less time-consuming one-pot synthesis of lactones **2**. After much effort, we were pleased to find that, by employing the modified protocol depicted in Scheme 2 (R = CH_3) and Table 2, no spirodilactone was ever observed: the only products are the two lactones **2** and (when formed, entries 4 and 5) **3**.[5b]

The comparison between Tables 1 and 2 shows that, for each entry, **1** is consumed to a greater extent and the yield in **2** is consistently better (34–55%) when using malonic acid. Furthermore, under these conditions, lactone **2g** (entry 7) is formed and can be isolated in fair yield (55%).

To gain an overview of the benefits afforded by the use of malonic acid, we then completed our study by carrying out the same reactions in refluxing formic acid (Scheme 2, R = H).[5b] The results are displayed in Table 3.

In this solvent, no lactone is formed in two instances (entries 5 and 6). In all the other entries, except for

Table 1. Addition of acetic acid to cinnamates **1a–g**

Entry	Cinnamate	Time (h)	**2**:**3**:**4**:**5**[a]	**2** (yield, %)[b]	**4** (yield, %)[c]	**5** (yield, %)[b]	Unreacted **1** (%)[b]
1	**1a**	4	97:3:0:0	29	–	–	32
2	**1b**	6	97:3:0:0	43	–	–	29
3	**1c**	6	97:3:0:0	46	–	–	38
4	**1d**	3.5	69:3:28:0	42	12 (50:50)	–	16
5	**1e**	4	20:0:26:54	10	11 (67:33)	18	13
6	**1f**	1.5	35:0:65:0	18	23 (47:53)	–	22
7	**1g**	24	–	–	–	–	62

[a] Determined by ^{1}H NMR on the crude product.
[b] Pure isolated compound.
[c] Inseparable mixture of *erythro*:*threo* diastereomers.

Table 2. Addition of malonic acid to cinnamates **1a–g** in acetic acid

Entry	Cinnamate	Time (h)	**2**:**3**[a]	**2** (yield, %)[b]	**3** (yield, %)[b]	Unreacted **1** (%)[b]
1	**1a**	3	100:0	50	–	12
2	**1b**	2	100:0	46	–	32
3	**1c**	2.5	100:0	54	–	25
4	**1d**	2.5	98:2	55	–	19
5	**1e**	2	87:13	43	7	9
6	**1f**	2.5	100:0	34	–	9
7	**1g**	2.5	100:0	55	–	28

[a] Determined by ^{1}H NMR on the crude product.
[b] Pure isolated compound.

Table 3. Addition of malonic acid to cinnamates **1a–g** in formic acid

Entry	Cinnamate	Time (h)	**2**:**3**[a]	**2** (yield, %)[b]	**3** (yield, %)[b]	Unreacted **1** (%)[b]
1	**1a**	3	100:0	38	–	–
2	**1b**	3	86:14	60	7	10
3	**1c**	3	77:23	48	14	–
4	**1d**	2.5	88:12	59	8	3
5	**1e**	3	–[c]	–	–	–
6	**1f**	3	–[c]	–	–	–
7	**1g**	4	87:13	18	3	40

[a] Determined by ^{1}H NMR on the crude product.
[b] Pure isolated compound.
[c] Complex mixture of unidentified compounds.

entry 1, the addition is far less diastereoselective giving more lactone **3** than in acetic acid. Nonetheless, from a practical point of view, in two cases the yield in isolated **2** is even better in formic than in acetic acid (entries 2 and 4).

We have thus demonstrated that, by a simple experimental modification combining the use of malonic acid (instead of acetic acid) and the proper choice of the solvent (acetic or formic acid), it is possible to conveniently and rapidly prepare diverse racemic *trans*-3,4-disubstituted-γ-butyrolactones in greatly enhanced isolated yield (from 0–46 to 34–60%) by a one-pot free-radical oxidative addition/decarboxylation from readily accessible starting materials. Current work is in progress toward the generalization of this protocol (including further yield improvements) in order to synthesize other types of substituted γ-butyrolactones and toward the development of an asymmetric version.

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5. General procedure for the preparation of **2**: (a) Cinnamic ester **1** (1 mmol), AcOK (490 mg, 5 mmol) and $Mn(OAc)_3{\cdot}2H_2O$ (590 mg, 2.2 mmol) were heated in refluxing AcOH (10 mL) under nitrogen for the time indicated in Table 1. After cooling, H_2O was added and the mixture was extracted with Et_2O. The organic extracts were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent afforded the

crude product which was purified by flash chromatography (hexane/Et_2O: from 16:1 to 1:1); (b) the same procedure was used, only replacing AcOK by malonic acid (520 mg, 5 mmol) and conducting the reaction in refluxing AcOH or HCO_2H (10 mL) for the time indicated in Table 2 or Table 3, respectively. All isolated compounds exhibited spectral (IR, NMR) and analytical characteristics consistent with their structure.

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