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Vicinal dianions of diethyl α-aroylsuccinates: a general synthetic route to α-aroyl- and α-arylidene-γ-butyrolactones

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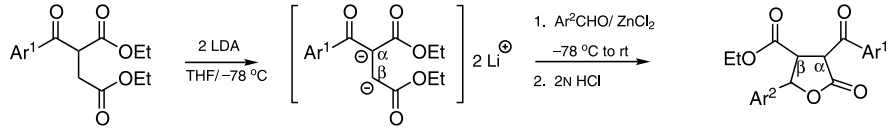
Abstract—Vicinal dianions derived from diethyl α-aroylsuccinates were found to react with carbonyl compounds β-regioselectively to afford α-aroyl-γ-butyrolactones, which were converted into α-arylidene-γ-butyrolactones by reduction with H_2/Pd–C followed by elimination employing methanesulfonyl chloride in pyridine. The method provides a general and convenient route to α-aroyl- and α-arylidene-γ-butyrolactones.

Carbon–carbon bond forming reactions based on the reactions of dianions are of interest, because high regio- and stereoselectivities towards electrophiles have been achieved.[1] Among these dianions, the vicinal dianions of succinic acid derivatives were extensively demonstrated to be useful reagents for the preparation of various classes of compounds.[2] In the course of our study on using succinic acid derivatives as versatile building blocks for synthesis of some natural products containing the γ-butyrolactone nucleus including lignans, we have recently reported the syntheses of (±)-lichesterinic acid, (±)-phaseolinic acid, (±)-nephromopsinic acid and (±)-dihydroprotolichesterinic acid by making use of the vicinal dianion derived from triethyl ethanetricarboxylate.[3] In continuation of our above results, we wish to report herein the reactions of vicinal dianions of α-aroylsuccinic esters with carbonyl compounds. It could be envisaged that these vicinal dianions would react with carbonyl compounds β-regioselectively to provide α-aroyl-γ-butyrolactones, which would be useful as the precursors for many synthetic manipulations. In this communication, the preparation of α-arylidene-γ-butyrolactones[4] from α-aroyl-γ-butyrolactones is also reported.

The vicinal dianion **2a** was readily generated by treatment of α-benzoylsuccinic ester **1a**[5] with lithium diisopropylamide (LDA, 2.1 equiv.) in tetrahydrofuran (THF) at −78°C for 1 h. The reaction of the vicinal dianion **2a** with benzaldehyde (1.1 equiv.) in the presence of $ZnCl_2$ (1.1 equiv.) at −78°C for 2 h, followed by slowly warming up to rt overnight afforded the expected α-aroyl-γ-butyrolactone **3a** in 74% yield as a mixture of diastereomers after quenching with 2N HCl. The formation of γ-butyrolactone **3a** revealed that the vicinal dianion **2** combined with benzaldehyde regioselectively at the β-carbon to furnish the β-hydroxy adduct which underwent lactonisation upon acidic



1a Ar^1= Ph
1b Ar^1= 3,4-Methyenedioxyphenyl
1c Ar^1= 4-Methoxyphenyl

2

3

Scheme 1.

Keywords: dianions; diethyl α-aroylsuccinates; α-arylidene-γ-butyrolactones; α-aroyl-γ-butyrolactones.
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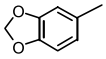
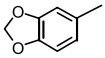
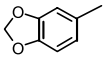
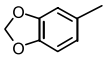
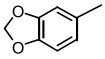
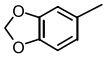
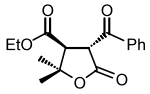
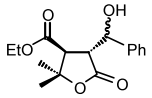
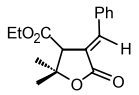
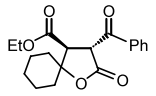
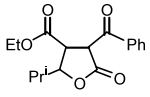
work-up. Exclusive β-regioselectivities of the vicinal dianion **2a** with other aromatic aldehydes and isobutyraldehyde, as well as acetone and cyclohexanone (Table 1, entries 1–3 and 10–12) were observed (Scheme 1). Moderate to good yields of the corresponding γ-butyrolactones **3** as diastereomeric mixtures were obtained. The reactions of vicinal dianions **2b** and **2c** with aromatic aldehydes under the same conditions gave moderate yields of γ-butyrolactones **3** as mixtures of diastereomers (Table 1, entries 4–9). The 3,4-*trans*-4,5-*cis*-isomer (TC-isomer) of γ-butyrolactones **3a–i** could be obtained in pure form by preparative thin-layer chromatography (silica gel). The relative stereochemistries of the TC-isomer of **3a** was concluded from NOE experiments.[6]

Table 1. Preparation of α-aroyl-γ-butyrolacones **3** and α-arylidene-γ-lactones **5**

Entry	**1**	Electrophile	Ar^1	Ar^2	% Yields		
					3[a, b, c]	**4**[a] (diastereomeric ratio)	**5**[a]
1	**1a**	Benzaldehyde	Ph	Ph	**3a**, 74 (61)	**4a**, quant. (90 :10)	**5a**, 60[f]
2	**1a**	Piperonal	Ph		**3b**, 71 (63)	**4b**, 61 (84 : 16)	**5b**, 92
3	**1a**	4-Methoxybenzaldehyde	Ph	4-MeOPh	**3c**, 65 (52)	**4c**, 65 (88 : 12)	**5c**, 91
4	**1b**	Benzaldehyde		Ph	**3d**, 50 (43)	**4d**, quant.[d]	**5d**, 75[f]
5	**1b**	Piperonal			**3e**, 47 (37)	**4e**, 93[e]	**5e**, 90
6	**1b**	4-Methoxybenzaldehyde		4-MeOPh	**3f** , 51 (43)	**4f**, quant. (90 :10)	**5f**, 75[f]
7	**1c**	Benzaldehyde	4-MeOPh	Ph	**3g** , 64 (55)	**4g**, 80 (88 : 12)	**5g**, 95
8	**1c**	Piperonal	4-MeOPh		**3h**, 65 (56)	**4h**, 87[d]	**5h**, 91
9	**1c**	4-Methoxybenzaldehyde	4-MeOPh	4-MeOPh	**3i**, 57 (50)	–[g]	–[g]
10	**1a**	Acetone			**3j** (50)	 **4i**, 83 (65 : 35)	 **5i**, 83
11	**1a**	Cyclohexanone			**3k** (70)	–[g]	–[g]
12	**1a**	Isobutyraldehyde			**3l**, 63	–[g]	–[g]

[a] Isolated yields.

[b] Yields of the isolated 3,4-*trans*-4,5-*cis*-isomers of **3a-i** and the *trans*-isomers of **3j** and **3k** are given in parentheses.

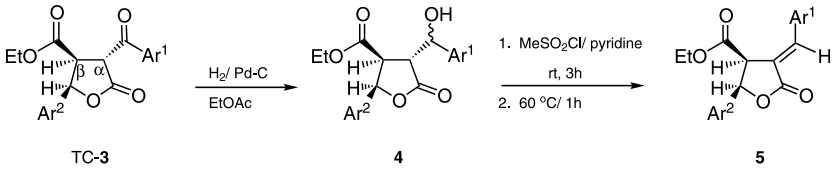
[c] Obtained as mixtures of diastereomers.

[d] The ratio of diastereomers was not determined.

[e] Obtained as a single diastereomer.

[f] Overall yields based on compounds **3a**, **3d** and **3f**.

[g] The reactions were not carried out.



Scheme 2.

Having obtained functionalized γ-butyrolactones **3** in an efficient way, we next demonstrated the synthetic utility of these γ-butyrolactones as precursors for syntheses of α-arylidene-γ-butyrolactones **5**. These synthetic transformations could be simply accomplished by successive reduction and elimination reactions. Thus, TC-**3a** was subjected to a catalytic hydrogenation (H_2/Pd–C/EtOAc) to furnish alcohol **4a** as a 90:10 mixture of diastereomers, which was further treated with methanesulfonyl chloride in pyridine at rt for 3 h followed by heating at 60°C for 1 h to give *E*-benzylidene-γ-butyrolactone **5a** in 60% overall yield (Scheme 2). As shown in Table 1, compounds **5b–i** were prepared in good overall yields as *E*-isomers.[7] The explanation for the formation of the *E*-isomer as the sole product could be due to the fact that elimination of the initially formed mesylate group of compound **4** proceeded via an E_2-elimination followed by a conjugate addition–elimination of pyridine to the initially formed α-arylidene-γ-butyrolactones to lead to the thermodynamically more stable *E*-isomer. An E_{1cb} mechanism may also be responsible for these results. The *cis*-stereochemistry at C-4 and C-5 was confirmed by the NOE experiments of compound **3h**.[8]

In summary, we have shown that the vicinal dianions derived from α-aroylsuccinic esters react with carbonyl compounds regioselectively at the β-carbon in the presence of $ZnCl_2$ to furnish α-aroyl-γ-butyrolactones in moderate yields. These compounds could be used as useful precursors for the preparation of α-arylidene-γ-butyrolactones. Thus, our method described herein provides a general synthetic route to α-arylidene-γ-butyrolactones.

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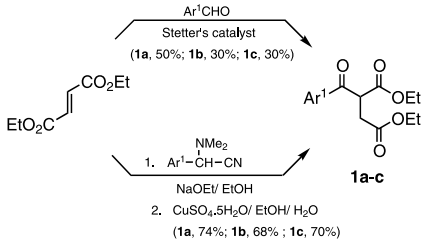
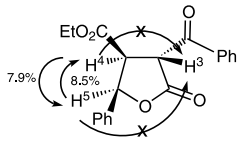
5. α-Aroylsuccinic esters **1** were prepared by reacting α-*N*,*N*-dimethylaminonitriles derived from aromatic aldehydes with diethyl fumarate in ethanol employing NaOEt as a base followed by hydrolysis of the resulting adducts with $CuSO_4$.[9] Alternatively, these compounds could also be achieved by conjugate addition of aromatic aldehydes to diethyl fumarate catalysed by Stetter's catalyst [3-benzyl-5-(2-dihydroxy-ethyl)-4-methylthiazolium chloride] in ethanol at 80°C for 15 h.[10]

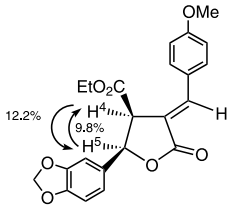


6. Irradiation of H-4 resulted in 7.9% enhancement of H-5, but there was no effect on H-3. The enhancement of 8.5% of H-4 was observed, when H-5 was irradiated, but there was no enhancement of H-3.



TC-**3a**

7. The chemical shifts of the benzylidene protons of compounds **5** appeared as doublets ($J=1.5$–1.8 Hz) at δ 7.6–7.75 ppm, comparable to the chemical shifts of the *E*-isomers of some related compounds reported in the literature, see for examples: (a) Hwang, E.-I.; Yun, B.-S.; Kim, Y.-K.; Kwon, B.-M.; Kim, H.-G.; Lee, H.-B.; Jeong, W.-J.; Kim, S.-U. *J. Antibiot*. **2000**, *53*, 903–911; (b) Banerji, J.; Das, B.; Chatterjee, A.; Shoolery, J. N. *Phytochemistry* **1984**, *23*, 2323–2327; (c) Stevens, D. R.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 633–637.
8. Enhancements of 9.8 and 12.2% of H-4 and H-5 of **5h** were observed upon irradiation of H-5 and H-4, respectively.



5h

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