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Vicinal dianions of diethyl α-aroylsuccinates: preparation of functionalized-2,3-dihydrofurans and -furans, and diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes

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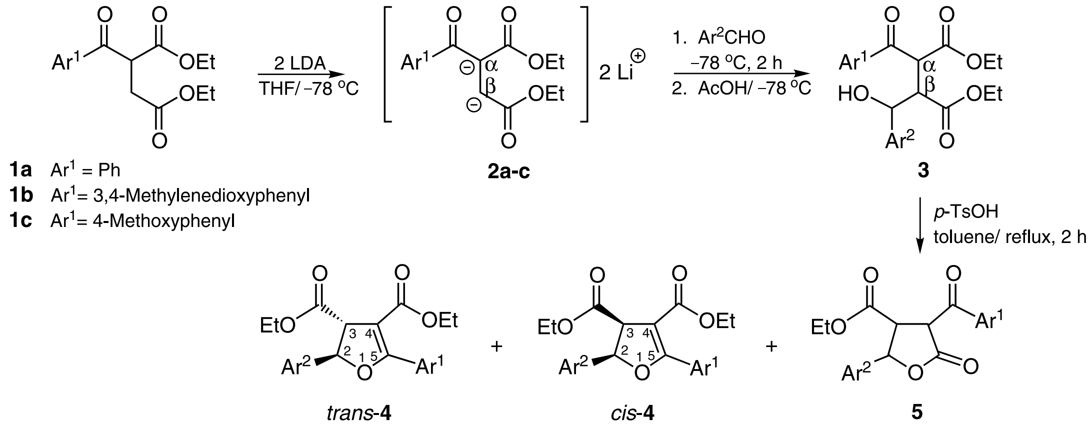
Abstract—Vicinal dianions of diethyl α-aroylsuccinates react with aromatic aldehydes to provide functionalized 2,3-dihydrofurans as the major products together with γ-butyrolactones after treatment of the adducts obtained with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene. *cis*-2,3-Dihydrofurans are used as precursors for the preparation of tetrasubstituted furans and diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes.

Substituted 2,3-dihydrofurans and furans are important classes of compounds due to their presence in a wide range of biologically active synthetic and natural products.[1] Moreover, some of them have been shown to be useful synthetic intermediates.[2] Therefore, efficient and general synthetic routes to these heterocycles[3,4] are of interest. As part of our program devoted to the development of synthetic routes to these classes of compounds, a general method for the synthesis of substituted 2,3-dihydrofurans and furans based on the chemistry of vicinal dianions derived from α-aroylsuccinic esters was investigated. We have recently described that these vicinal dianions react with carbonyl compounds in the presence of $ZnCl_2$ exclusively at the β-carbon to provide α-aroyl-γ-butyrolactones, which were demonstrated as useful intermediates for the preparation of naturally occurring α-arylidene-γ-butyrolactones.[5] In connection with these results, we wish to report the preparation of functionalized-2,3-dihydrofurans and -furans as well as diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes utilizing the vicinal dianions of diethyl α-aroylsuccinates as shown in Schemes 1 and 2.



Scheme 1.

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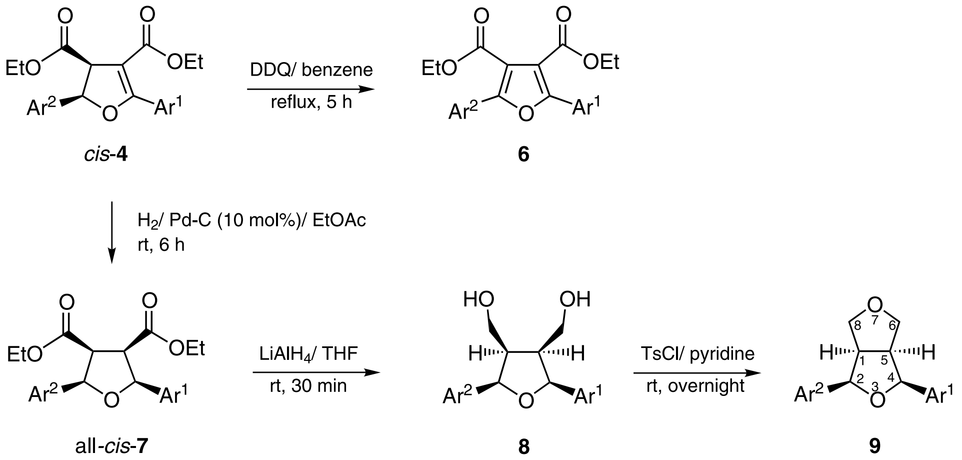

Scheme 2.

The reaction of the vicinal dianion **2a** derived from **1a** by employing LDA (2 equiv.) in THF at −78°C for 1 h with benzaldehyde (1 equiv.) at −78°C for 2 h followed by quenching the reaction mixture with glacial acetic acid at the same temperature provided the crude adduct **3a**. Without purification, this was treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene for 2 h to afford the expected dihydrofuran **4a**[6] in 71% yield as a mixture of *cis*- and *trans*-isomers together with γ-butyrolactone **5a** (13% yield). *cis*-**4a** was obtained in 59% yield as the major isomer after chromatography on silica gel. Under the standard conditions, the vicinal dianions **2a**–**c** reacted with aromatic aldehydes to give moderate yields of the desired dihydrofurans **4a**–**k** as mixtures of *cis*- and *trans*-isomers together with 5–15% yields of the corresponding γ-butyrolactones **5**. In all cases, the *cis*-isomers were obtained as the major isomers, and in most cases could be isolated pure by chromatography as summarized in Table 1. The relative *cis* and *trans* stereochemistries of compounds **4** were established by the coupling constants between H-2 and H-3 (J_{cis}= 10.9–11.0 Hz and J_{trans}=6.8–7.1 Hz) and the results of NOE experiments.[7]

Having succeeded in preparing in one-step the dihydrofurans **4** possessing aryl substituents, we further illustrated the synthetic utility of our method by the preparation of 2,5-diaryl-3,4-dicarboethoxyfurans, which are important precursors for syntheses of lignans[2g,h,8] and 2,4-diaryl substituted 3,7-dioxabicyclo[3.3.0]octanes **9**. Thus, conversion of *cis*-**4** into furan **6** could be achieved smoothly by dehydrogenation employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene for 5 h.[9] Furans **6a**–**f** were obtained in good yields (Table 2). Dehydrogenation of *trans*-**4** was found to proceed slower than *cis*-**4** under the standard conditions. Thus, when a mixture of *cis*- and *trans*-**4b** was treated with DDQ in benzene under reflux for 5 h, the *cis*-isomer **4b** was completely converted into furan **6b**, while the *trans*-isomer **4b** was still present in the mixture as shown by thin-layer chromatography. The reaction was complete after refluxing for 20 h and **6b** was obtained in 92%

Table 1. Preparation of 2,3-dihydrofurans **4**

Entry	1	Electrophile	Ar^1	Ar^2	% Yields[a]				
					4	*cis*-**4**	*trans*-**4**	*cis*-**4**+*trans*-**4** (*cis*:*trans*)	**5**[b]
1	**1a**	Benzaldehyde	Ph	Ph	**4a**	59	12	–	13
2	**1a**	Piperonal	Ph	Piperonyl	**4b**	41	10	–	5
3	**1a**	4-Methoxybenzaldehyde	Ph	4-MeOPh	**4c**	50	13	–	11
4	**1a**	Isobutyraldehyde	Ph	*i*-Pr	**4d**	–	–	63 (66:34)	–[c]
5	**1b**	Benzaldehyde	Piperonyl	Ph	**4e**	41	7	–	7
6	**1b**	Piperonal	Piperonyl	Piperonyl	**4f**	26	–	13 (80:20)	8
7	**1b**	4-Methoxybenzaldehyde	Piperonyl	4-MeOPh	**4g**	30	–	11 (74:26)	10
8	**1b**	Isobutyraldehyde	Piperonyl	*i*-Pr	**4h**	–	–	55 (67:33)	–[c]
9	**1c**	Benzaldehyde	4-MeOPh	Ph	**4i**	53	–[c]	–	15
10	**1c**	Piperonal	4-MeOPh	Piperonyl	**4j**	39	11	-	11
11	**1c**	4-Methoxybenzaldehyde	4-MeOPh	4-MeOPh	**4k**	37	–[c]	-	13

[a] Isolated yields. All compounds were fully characterized by IR, MS, 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra as well as by elemental analyses or HRMS.

[b] Contained mainly the 3,4-*trans*-4,5-*cis*-isomer.

[c] Could not be isolated.

Table 2. Preparation of compounds **6**–**9**

cis-**4**	Ar^1	Ar^2	% Yields[a]			
			6	**7**	**8**	**9**
cis-**4a**	Ph	Ph	**6a**, 85	**7a**, 85	**8a**, 83	**9a**, 70
cis-**4b**	Ph	Piperonyl	**6b**, 95	**7b**, 86	**8b**, 89	**9b**, 82
cis-**4c**	Ph	4-MeOPh	**6c**, 90	**7c**, 88	**8c**, 82	**9c**, 75
cis-**4e**	Piperonyl	Ph	**6b**, 93	–[b]	–[b]	–[b]
cis-**4f**	Piperonyl	Piperonyl	**6d**, 94	**7d**, 86	**8d**, 80	**9d**, 74
cis-**4i**	4-MeOPh	Ph	**6c**, 96	–[b]	–[b]	–[b]
cis-**4j**	4-MeOPh	Piperonyl	**6e**, 95	**7e**, 89	**8e**, 84	**9e**, 75
cis-**4k**	4-MeOPh	4-MeOPh	**6f**, 93	**7f**, 83	**8f**, 82	**9f**, 76

[a] Isolated yields. All compounds were fully characterized by IR, MS, 300 MHz ^1H and 75 MHz ^{13}C NMR spectra as well as by elemental analyses or HRMS.

[b] The reactions were not performed.

yield. On the other hand, tetrahydrofurotetrahydrofurans **9** were prepared in good overall yields by a simple three-step synthesis starting from *cis*-dihydrofurans **4**. Catalytic hydrogenation (10% Pd on C) of *cis*-**4a** in ethyl acetate at rt afforded a good yield (85%) of the all-*cis*-**7a** as the sole isomer. Reduction of **7a** with $LiAlH_4$ in THF at rt for 30 min gave **8a** in 83% yield after chromatography on silica gel. Treatment of **8a** with *p*-toluenesulfonyl chloride in pyridine[10] at rt overnight furnished the expected tetrahydrofurotetrahydrofuran **9a** in 70% yield. The ^1H and ^{13}C NMR data of **9a** were consistent with reported values.[11] Thus, the formation of **9a** as the sole product and in good yield confirmed the all-*cis*-stereochemistry in **7a**. Under the same reaction sequence and conditions, tetrahydrofurotetrahydrofurans **7b**–**f** were prepared in good yields from *cis*-2,3-dihydrofurans **4b**, **4c**, **4f**, **4j** and **4k**, respectively.

In summary, our results demonstrate that the vicinal dianions derived from diethyl α-aroylsuccinates react with aldehydes regioselectively at the β-carbon to provide a mixture of *cis*- and *trans*-2,3-dihydrofurans as the major products along with γ-butyrolactones. This method provides an easy entry to 2,5-diaryl substituted dihydrofurans, of which both aryl groups can be varied by using appropriate α-aroylsuccinic esters and aromatic aldehydes. Furthermore, *cis*-2,3-dihydrofurans have been proved to be very useful for the preparation of 2,5-diaryl-3,4-dicarboethoxyfurans and diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes.

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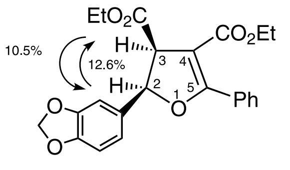
7. NOE experiments for *cis*-**4b** and *trans*-**4b** were carried out. The results are as shown below. Upon irradiation of H-2 and H-3, *cis*-**4b** showed the NOE effects of H-3 (12.6%) and H-2 (10.5%), but displayed no enhancements in case of *trans*-**4b**.



cis-**4b**

The coupling constants J_{cis} of compounds **4** are larger than J_{trans}.[4f]

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