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Chemo- and regio-selective synthesis of functionalized 3(2*H*)-furanones by the first cyclization reactions of 1,3-bis(trimethylsiloxy)buta-1,3-dienes with α-chlorocarboxylic acid chlorides

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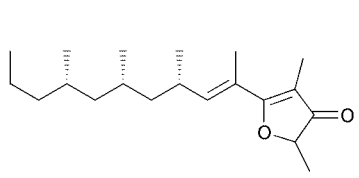
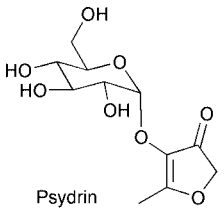
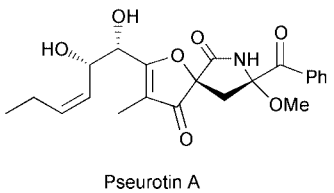
Reaction of 1,3-bis(trimethylsiloxy)buta-1,3-dienes with α-chlorocarboxylic acid chlorides resulted in chemo- and regio-selective formation of 6-chloro-3,5-dioxoesters which were regioselectively converted into functionalized 3(2*H*)-furanones.

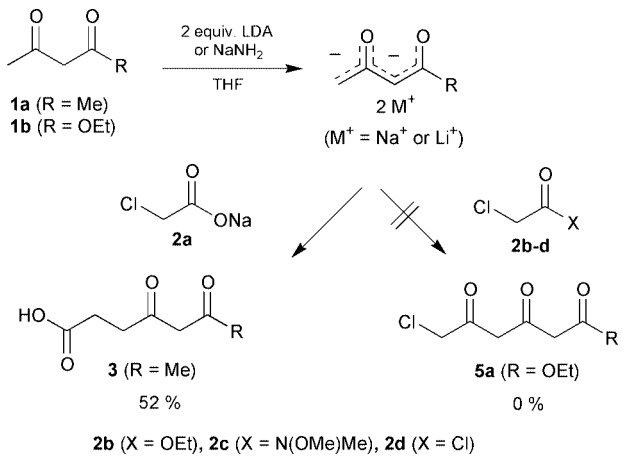
Domino and consecutive reactions are of great interest in organic chemistry since they enable the rapid assembly of complex products in a one-pot process.[1] Surprisingly, despite the simplicity of the idea, only few domino and consecutive reactions of 1,3-dianions[2] with 1,2-dielectrophiles have been reported so far.[3] Several drawbacks are possible for these reactions: on the one hand, dianions are highly reactive compounds which can react both as a nucleophile and a base; on the other hand, 1,2-dielectrophiles often represent rather labile compounds. Therefore, previous attention in dianion chemistry has been mainly focused on reactions with monofunctional electrophiles after which the resultant monoanion is simply quenched with water following the initial reaction. We have recently reported the first domino reactions of 1,3-dianion synthons with oxalic acid dielectrophiles to give γ-alkylidene-butenolides.[4,5] Herein, to the best of our knowledge, we report the first cyclization reactions of 1,3-dianion synthons with α-chlorocarboxylic acid chlorides. These reactions provide a convenient, chemo- and regio-selective access to a variety of functionalized 3(2*H*)-furanones. A large number of natural products and pharmacologically important compounds belong to the group of 3(2*H*)-furanones: prominent examples include polyketides from *siphonaria pectinata*,[6a] the antitumor active trachyspic acid,[6b] antiallergic 4,5-dihydro-4-oxo-2-amino-3-furancarboxylic acids,[6c] the mutagenic furaneols,[6d] pseurotin A,[6e] the antitumor active sesquiterpenes eremantholide A-C,[6f] lychnophorolide A,[6g] ciliarin,[6h] and the recently reported metabolite longianone.[6i,j]





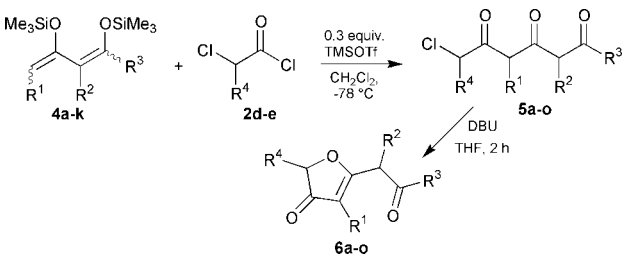


A variety of products are, in principle, possible in the reaction of 1,3-dicarbonyl dianions with α-chloroacetic acid derivatives. Both the initial attack of the dianion onto the dielectrophile and the subsequent cyclization can proceed with different chemo- and regio-selectivities. Reaction of the disodium salt of acetylacetone **1a** with the sodium salt of chloroacetic acid **2a** was reported to give 4,6-dioxoheptanoic acid **3** by attack of the terminal carbon of the dianion onto the carbon attached to the chlorine atom.[7] Unfortunately, our first attempts to induce a chemoselective attack of 1,3-dicarbonyl dianions onto the carbonyl group of chloroacetic acid derivatives in order to prepare the ester **5a** were unsuccessful: reaction of the dianion of ethyl acetoacetate **1b** with ethyl chloroacetate **2b**, *N*-methyl-*N*-methoxy-chloroacetic acid amide **2c** or chloroacetyl chloride **2d** resulted in formation of complex mixtures only (Scheme 1).



Scheme 1

In order to overcome these problems, we decided to study the Lewis-acid catalyzed reaction of 1,3-bis-(trimethylsiloxy)buta-1,3-dienes, synthons of 1,3-dicarbonyl dianions,[8] with chloroacetyl chloride **2d**. Our initial attempts to realize this concept were unsuccessful. Reaction of **2d** with the diene **4a** in the presence of stoichiometric amounts of $BF_3{\cdot}OEt_2$ or $TiCl_4$ resulted in formation of complex mixtures. Much to our satisfaction, the use of catalytic amounts of TMSOTf resulted in chemo- and regio-selective formation of the desired 6-chloro-3,5-dioxoester **5a** (Scheme 2).† Optimal yields (up to 71%) were obtained when the reaction was started at −78 °C and slowly warmed to ambient during 12 h. Treatment of **5a** with base resulted in regioselective cyclization[9] *via* the oxygen atom



Scheme 2

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to give the 3(2*H*)-furanone **6a**.† The use of KOBu^t resulted in the formation of a complex mixture from which **6a** could be isolated in only 23% yield. Eventually, we found that optimal yields (up to 91%) were obtained when 2 equivalents of DBU were used as the base. It is noteworthy that isolation of **5a** was not necessary: the crude product of **5a** could be directly transformed into **6a** which was isolated in 65% overall yield (from **4a**).

In order to study the preparative scope of the new methodology for the synthesis of 3(2*H*)-furanones the substituents of the 1,3-bis(trimethylsiloxy)-1,3-dienes were systematically varied (Table 1). Reaction of chloroacetyl chloride **2d** with the diene derived from methyl acetoacetate and subsequent cyclization afforded the 3(2*H*)-furanone **6b** in 70% overall yield. Reaction of **2d** with 1,3-bis(trimethylsiloxy)-1,3-dienes **4c**–**g**, containing methyl, ethyl, butyl, benzyl, and allyl groups, respectively at the terminal carbon atom, afforded the 4-alkyl-3(2*H*)-furanones **6c**–**g** in good yields and with very good chemo- and regio-selectivities.

Table 1

6	R^1	R^2	R^3	R^4	Yield[a] (%)
a	H	H	OEt	H	65
b	H	H	OMe	H	70
c	Me	H	OMe	H	54
d	Et	H	OEt	H	53
e	Bu	H	OEt	H	40
f	Bn	H	OEt	H	38
g	Allyl	H	OEt	H	54
h	OMe	H	OMe	H	56
i	H	Me	OEt	H	54
j	H	Et	OEt	H	50
k	$CH_2CH_2CH_2$		OEt	H	34
l	H	H	OEt	Me	56
m	Me	H	OMe	Me	40
n	Et	H	OEt	Me	32
o	$CH_2CH_2CH_2$		OEt	Me	26

[a] Isolated yields of **6a**–**o** over two steps from **4a**–**k** and **2d**–**e**.

A variety of naturally occuring 3(2*H*)-furanones contain an oxygen atom at carbon C-4.[10] The synthesis of 3(2*H*)-furanone **6h**, containing a methoxy group at carbon C-4, was therefore of special interest. Dianions cannot be used for the synthesis of **6h** since, besides the severe selectivity problems discussed above, dianions of methyl 4-methoxyacetoacetate and related substrates cannot be generated. This is presumably due to the fact that the dianion is destabilized by lone pair–lone pair interactions and by the π-donor effect of the oxygen atom.[11] Much to our satisfaction, reaction of **2d** with 4-methoxy-1,3-bis(trimethylsiloxy)-1,3-diene **4h**[12] afforded the 4-methoxy-3(2*H*)-furanone **6h** in good yield and with very good chemo- and regio-selectivity. Starting with the 1,3-bis(trimethylsiloxy)-1,3-dienes **4i**–**j**, which are substituted at the central carbon atoms, the 3(2*H*)-furanones **6i**,**j** were isolated in good yields. Reaction of **2d** with the cyclic diene **4k**, which is derived from ethyl cyclohexanone-2-carboxylate, afforded the interesting bicyclic 3(2*H*)-furanone **6k** in good yield.

Variation of the substituents of the dielectrophile was then studied. Reaction of diene **4a** with 2-chloropropionyl chloride **2e** afforded the 6-chloro-3,5-dioxoester **5l** which was transformed into the 2-methyl-3(2*H*)-furanone **6l**. Reaction of 2-chloropropionyl chloride with the methyl- and ethyl-substituted dienes **4b** and **4c** afforded the 2-methyl-3(2*H*)-furanones **6m** and **6n** in good yields and with very good chemo- and regioselectivities, respectively. Reaction of **2e** with the diene derived from ethyl cyclohexanone-2-carboxylate afforded the bicyclic 2-methyl-3(2*H*)-furanone **6o** as a 1:1 mixture of diastereomers.

In conclusion, we have developed a new approach for the synthesis of a wide range of functionalized 3(2*H*)-furanones which are of pharmacological relevance and of interest for the synthesis of natural products.

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Notes and references

† *General procedure* for the preparation of **6a**–**o**: to a CH_2Cl_2 solution (70 ml) of **2d** (5.5 mmol, 0.62 g) and of **4a** (5.5 mmol, 1.5 g) was added TMSOTf (1.65 mmol, 0.35 g) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 12 h. After stirring for 2 h at 20 °C a saturated solution of $NaHCO_3$ was added, the organic layer was separated and the aqueous layer was repeatedly extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered and the solvent of the filtrate was removed *in vacuo*. The residue was purified by column chromatography [silica gel, ether–petroleum (bp 40–70 °C)] to give **5a** as a colourless oil (805 mg, 71%). To a THF solution (5 ml) of **5a** (0.64 mmol, 122 mg) was added DBU (1.28 mmol, 195 mg). After stirring for 2.5 h, glacial acetic acid (0.4 ml) was added. The solvent was removed *in vacuo* and the residue was purified by chromatography to give **6a** as a colourless oil (100 mg, 91%): δ_H($CDCl_3$, 250 MHz): 1.22 (t, 8 Hz, 3 H, CH_3), 3.55 (s, 2 H, CH_2), 4.18 (q, 8 Hz, 2 H, OCH_2CH_3), 4.48 (s, 2 H, OCH_2), 5.66 (s, 1 H, CH). δ_C($CDCl_3$, 62.5 MHz): 13.79, 36.46, 61.57, 75.10, 106.13, 166.39, 185.95, 202.15. MS (70 eV) *m*/*z* 170 (M^+, 20). Anal. Calc. for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.35; H, 6.08%. All new compounds gave satisfactory spectroscopic and analytical and/or high resolution mass data.

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