Selective reduction of the acyl group in cyclic α-acyl-β-dicarbonyl compounds with sodium cyanoborohydride. Efficient synthesis of cyclic α-alkyl-β-dicarbonyl compounds

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Efficient synthesis of cyclic α-alkyl-β-dicarbonyl compounds of the cyclopentane, cyclohexane, tetronic acid, and α-pyrone series from the corresponding cyclic α-acyl-β-dicarbonyl compounds under the action of $NaBH_3(CN)$ in a THF—HCl system is described.

Key words: cyclic α-acyl-β-dicarbonyl compounds, sodium cyanoborohydride, selective reduction, cyclic α-alkyl-β-dicarbonyl compounds.

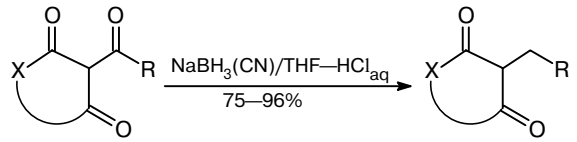
2-Alkylcyclopentane-1,3-diones, 2-alkylcyclohexane-1,3-diones, 3-alkyltetronic acids, and 3-alkyl-3,4-dihydro-2*H*-pyran-2,4-diones are widely used in the synthesis of natural compounds and their biologically active analogs.[1—4]

We have previously proposed a method for the preparation of 2-alkylcycloalkane-1,3-diones and their heterocyclic analogs by the selective reduction of the acyl group in the corresponding α-acyl derivatives of β-dicarbonyl compounds under the action of Et_3SiH in CF_3COOH in the presence of catalytic amounts of $BF_3 \cdot Et_2O$ [5] or $LiClO_4$ [6,7] (ionic hydrogenation). This method makes it possible to synthesize the target α-alkyl-β-dicarbonyl compounds in 66—98% yield from accessible 2-acylcyclopentane-1,3-diones, 2-acylcyclohexane-1,3-diones, 3-acyltetronic acids, and 3-acyl-3,4-dihydro-2*H*-pyran-2,4-diones. In the case of arylmethylideneacyl derivatives of cyclic β-didicarbonyl compounds, the conjugated double bond is reduced along with the carbonyl group.[6] The double bonds of the furan ring in the furfurylideneacyl derivatives are also reduced.[5,7]

In 1980, the chemoselective reduction was described of the carbonyl group of the acyl substituent in acyl derivatives of the Meldrum acid, barbituric acids, 4-hydroxycoumarins, and dehydroacetic acid by $NaBH_3(CN)$ in AcOH to form the corresponding alkyl derivatives in high yields.[8]

We showed for particular examples that this procedure can also be applied to compounds of the cyclohexane, cyclopentane, and tetronic acid series (**1**) to form α-alkyl-β-dicarbonyl compounds (**2**). However, the method is experimentally inconvenient because of difficulties associated with the isolation of the products from the reaction mixtures containing AcOH, which decreases noticeably their yields.

We found that a mixture of approximately equal volumes of THF and 2*M* aqueous HCl is the most convenient medium for this reaction. In this system, tricarbonyl compounds **1** are reduced chemoselectively to form products **2** in 75—96% yield (Table 1). In the case of arylmethylideneacyl derivatives, the whole enone fragment undergoes reduction, as in the ionic hydrogenation. However, the reduction of furfurylideneacyl derivatives is more selective and results in rather unstable (2-furyl)alkyl derivatives even when a large excess of a reducing agent is used. The work-up of the reaction mixtures according to the proposed modification is markedly simplified and allows more complete extraction of the reaction products.



1a—g **2a—g**

Thus, reduction by sodium cyanoborohydride in the THF—HCl system is a preparatively convenient method for the selective transformation of cyclic α-acyl-β-dicarbonyl compounds of the cyclopentane, cyclohexane, tetronic acids, and α-pyrone series into the corresponding α-alkyl-β-diketones. In combination with ionic hydrogenation, this procedure allows the flexible transformation of furfurylideneacyl derivatives into compounds with different degrees of saturation of the furfurylideneacyl fragment.

Experimental

Melting points were measured on a Boetius heating stage. ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer (200.13 MHz) in $CDCl_3$ using Me_4Si as an internal stan-

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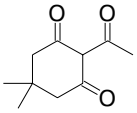
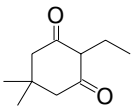
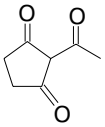
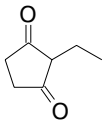
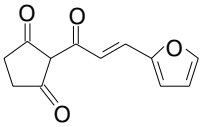
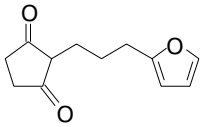
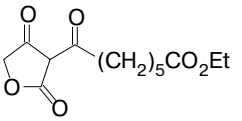
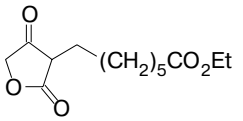
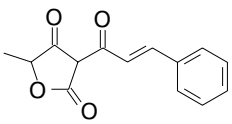
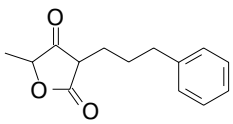
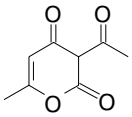
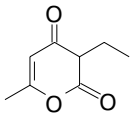
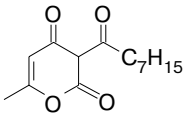
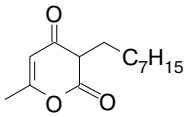
Table 1. Reduction of compounds **1a—g** by $NaBH_3(CN)$ in the THF—2*M* HCl system

Starting tricarbonyl compound	mol. $NaBH_3(CN)$/ 1 mole of substrate	Product	M.p./°C (Lit.)	Yield (%)
 **(1a)**	2.5	 **(2a)**	152—154 (152—153)[5]	80
 **(1b)**	2.5	 **(2b)**	174—177 (173—177)[5] (177—178)[9]	75
 **(1c)**	3.5	 **(2c)**	Decomp.	90
 **(1d)**	2.5	 **(2d)**	45—47	94
 **(1e)**	3.5	 **(2e)**	Oil	96
 **(1f)**	2.5	 **(2f)**	186—187 (185—187)[8]	89
 **(1g)**	2.5	 **(2g)**	100—102 (100—102)[10]	93

dard. IR spectra were recorded on a UR-20 instrument in thin film or KBr pellets.

Reduction of cyclic α-acyl-β-dicarbonyl compounds by $NaBH_3(CN)$ in the THF—2*M* HCl system. 2*M* aqueous HCl (5 mL) was added with stirring to a solution of a tricarbonyl compound (1 mmol) in THF (6 mL). In some cases, partial precipitation of the starting compounds occurred. $NaBH_3(CN)$ (2.5—3.5 mol) was added portionwise with stirring to the solution (or suspension) that formed (see Table 1). The reaction mixture was stirred until the reaction was complete (TLC monitoring). At the end of the reaction, the mixture usually separates into two liquid layers containing no precipitate. After separation of the organic phase, the aqueous phase was extracted with diethyl ether or chloroform. The combined extracts were dried with Na_2SO_4. The solvent was evaporated, and the reaction products (**2c—e,g**) were purified by column chromatography on silica gel. Poorly soluble crystalline compounds **2a,b,f** were isolated from the aqueous phase after removal of THF *in vacuo*. For complete extraction, the aqueous phase was extracted with chloroform. The combined fractions of the β-dicarbonyl compounds from the aqueous phase and chloroform extracts were finally purified by recrystallization.

2-[3-(2-Furyl)propyl]cyclopentane-1,3-dione (2c). ^{1}H NMR, δ: 1.78 (quint, 2 H, $-CH_2-C\underline{H}_2-CH_2$, J = 7.5 Hz); 2.26 (t, 2 H, $-C\underline{H}_2-(CH_2)_2$-furyl, J = 7.5 Hz); 2.56 (s, 4 H, CH_2CO); 2.61 (t, 2 H, $-(CH_2)_2C\underline{H}_2$-furyl, J = 7.5 Hz); 5.98 (d, 1 H, Fur, J = 2.5 Hz); 6.24 (m, 1 H, Fur); 7.26 (d, 1 H, Fur, J = 2.5 Hz); 9.36 (br.s, 1 H, —OH of enol). IR (KBr), ν/cm^{-1}: 1370 (br, max), 1440, 1460, 1565, 1600 (fl), 2060—2810 (br). Found (%): C, 69.77; H, 6.71. $C_{12}H_{14}O_3$. Calculated (%): C, 69.88; H, 6.84.

3-(6-Ethoxycarbonylhexyl)tetrahydrofuran-2,4-dione (2d). ^{1}H NMR, δ: 1.27 (t, 3 H, $-CO_2CH_2C\underline{H}_3$, J = 7.0 Hz); 1.32 (m, 4 H); 1.49 (quint, 2 H, $-CH_2-$, J = 7.5 Hz); 1.60 (quint, 2 H, $-CH_2-$, J = 7.2 Hz); 2.20 (t, 2 H, $-CH_2-$, J = 7.5 Hz); 2.31 (t, 2 H, $-C\underline{H}_2CO_2Et$, J = 7.2 Hz); 4.12 (q, 2 H, $-CO_2C\underline{H}_2CH_3$, J = 7.0 Hz); 4.64 (s, 2 H, OCH_2CO). IR (KBr), ν/cm^{-1}: 1410, 1455, 1650 (br), 1740, 2720 (br).

Found (%): C, 60.81; H, 7.70. $C_{13}H_{20}O_5$. Calculated (%): C, 60.92; H, 7.87.

5-Methyl-3-(3-phenylpropyl)tetrahydrofuran-2,4-dione (2e). ^{1}H NMR, δ: 1.47 (d, 3 H, CH_3, J = 7.0 Hz); 1.82 (quint, 2 H, $—CH_2—C\underline{H}_2—CH_2Ph$, J = 7.5 Hz); 2.27 (t, 2 H, $—C\underline{H}_2(CH_2)_2Ph$, J = 7.5 Hz); 2.62 (t, 2 H, $—CH_2Ph$, J = 7.5 Hz); 4.79 (q, 1 H, CH—, J = 7.0 Hz); 7.07—7.42 (m, 5 H arom.). IR (film), ν/cm^{-1}: 1350, 1405, 1460, 1660 (br, max), 1725, 2730 (br). Found (%): C, 72.26; H, 6.82. $C_{14}H_{16}O_3$. Calculated (%): C, 72.39; H, 6.94.

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