An Efficient Synthesis of Alkyl Substituted Cyclic 1,3-Diones

Felix S. Pashkovsky,* Igor P. Lokot, Fedor A. Lakhvich

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevicha str. 5/2, 220141 Minsk, Republic of Belarus
Fax 00375 (17) 2637132; E-mail: evk@ns.iboch.ac.by

Received 22 May 2001

Abstract: An efficient method for the synthesis of cyclic α-alkyl β-dicarbonyl compounds of cyclopentane, cyclohexane, tetronic acid and α-pyrone series is described. The method consists of the selective transformation of the corresponding cyclic β,β'-tricarbonyl compounds by $NaBH_3CN$ in a mixture of THF and 2N aqueous HCl.

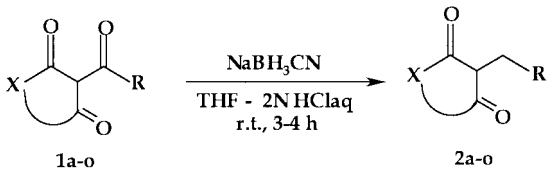
Key words: cyclic β,β'-triones, sodium cyanoborohydride, selective reduction, cyclic α-alkyl β-diones

2-Alkyl cycloalkane-1,3-diones as well as 3-alkyltetronic acids, and 3-alkyl-3,4-dihydro-2H-pyran-2,4-diones have found a widespread application in the synthesis of natural and structurally related compounds.[1] Earlier we have developed a method for obtaining 2-alkyl cycloalkane-1,3-diones and their heterocyclic analogs starting from the readily available 2-acylcyclohexane-1,3-diones, 2-acylcyclopentane-1,3-diones, 3-acyltetronic acids, and 3-acyl-3,4-dihydro-2H-pyran-2,4-diones.[2] The method consists of the regioselective hydrogenolysis of the carbonyl function at the side chain of the latter compounds under the action of Et_3SiH in CF_3CO_2H in the presence of catalytic amounts of $BF_3{\cdot}OEt_2$ or $LiClO_4$ (ionic hydrogenation).[3] The yields of the target β-dicarbonyl compounds were in the range of 66-98%. In the case of arylidene acyl derivatives of cyclic β-dicarbonyl compounds saturation of conjugated double bond of arylidene acyl fragment occurs along with hydrogenolysis of the carbonyl function. Additionally, in furylidene acyl derivatives reduction of the furan ring takes place.

In the course of our investigations directed towards the synthesis of natural products we searched for alternative methods for selective reduction of cyclic β,β'-triones. In view of the similar mechanistic aspects of the carbonyl function reductions by $NaBH_3CN$ in acidic medium[4] to those of reductions by organosilanes, we focused our attention on the use of $NaBH_3CN$ for our synthetic purpose. It should be noted that $NaBH_3CN$ has received extensive application in organic reductions as versatile and remarkably selective reagent.[5]

Two decades ago Nutaitis et al.[6] have demonstrated that treatment of acyl derivatives of Meldrum's acid, 5-acylbarbituric acids as well as dehydroacetic acid and 3-acyl-4-hydroxycoumarins with 2 equivalents of $NaBH_3CN$ in AcOH led to hydrogenolysis of the carbonyl group of the acyl substituent to give the corresponding alkyl derivatives in excellent yields. Kende et al. successfully applied this protocol for selective reduction of some acyl coumarines and acyl pyrimidine triones.[7] Therefore, it was of interest to extend the scope of the method by Nutaitis et al. to β,β'-tricarbonyl compounds of the cyclohexane, cyclopentane and tetronic acid series. However, in our hands attempted application of this protocol to some β,β'-triones **1** showed that although the reduction proceeded regioselectively at the side chain the yields of the corresponding α-alkyl-β-dicarbonyl compounds **2** in general were remarkably lower as compared with the method of ionic hydrogenation. Probably, this is due to incomplete crystallization of the reaction products from dilute aqueous solutions of AcOH during work-up of the reaction mixtures. Another reason may be the drastic conditions during removal of high boiling acidic solvent in the case of the formation of oily materials.

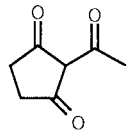
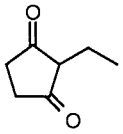
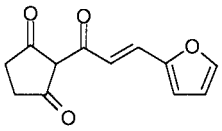
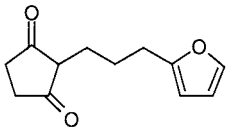
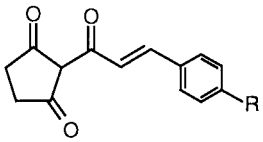
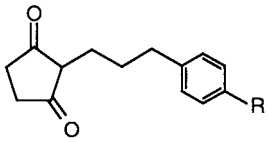
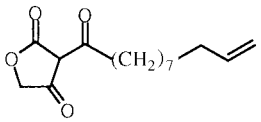
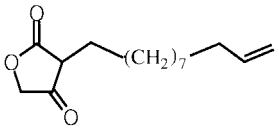
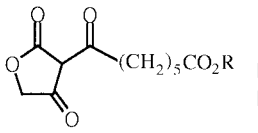
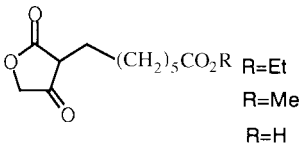
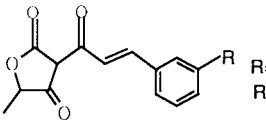
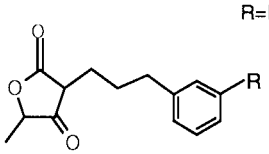
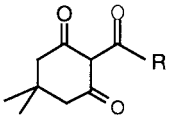
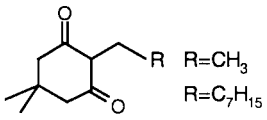
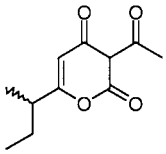
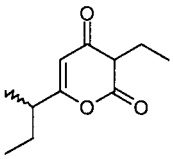
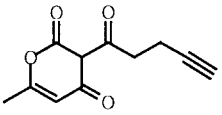
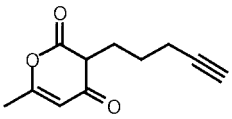
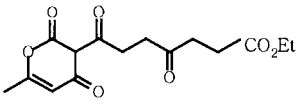
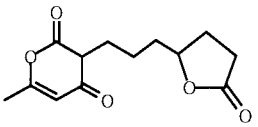
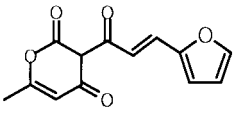
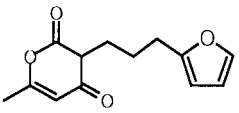
In the present communication we wish to report an efficient method for the selective reduction of cyclic β,β'-triones of cyclohexane, cyclopentane, tetronic acid and α-pyrone series. As a result of our research efforts it has been established that the use of approximately equal volumes of THF and 2 N aqueous HCl instead of organic acid improved considerably the yields (comparable with those when Et_3SiH/CF_3CO_2H was employed) of the $NaBH_3CN$ reduction of **1** to β-dicarbonyl compounds **2** (75-96%).[8] The excess of reducing agent does not cause further reduction of the cyclic β-dicarbonyl system in the products formed.



1a-o **2a-o**

Experimental results are summarized in the Table. Nonconjugated double bonds without branching at the ethylene carbon[9] (entry 4), triple bonds (entry 9) and ester groups (entry 5) in the side chain are tolerant to reduction. Hydrolysis of the ethyl ester was not observed and the target 3-(6-ethoxycarbonyl) tetronic acid **2f** was isolated in 94% yield. In the case of the methyl ester the main component in the reaction mixture was 3-carboxyhexyl tetronic acid **2g** (R = H). Nonconjugated ketones were reduced to give the corresponding hydroxy derivatives. Thus, for example, reduction of **1n** led to lactone **2n** arising from the transformation of the C-4 oxo-function into a hydroxy group followed by intramolecular re-esterification in acidic medium (entry 10).

Table Reduction of cyclic β,β'-tricarbonyl compounds **1a-o** by sodium cyanoborohydride in THF-2 N aq HCl

Entry	β,β'-Tricarbonyl compound[10]		$NaBH_3CN$ (equiv.)	Product[a]		Yield[b] (%)
1		**1a**	2.5		**2a**	75(53)[c]
2		**1b**	3.5		**2b**	90
3	 R=CH_3 R=NO_2	**1c** **1d**	3.5 3.5	 R=CH_3 R=NO_2	**2c** **2d**	87 83(79)[c]
4		**1e**	2.5		**2e**	89
5	 R=Et R=Me	**1f** **1g**	2.5 2.5	 R=Et R=Me R=H	**2f** **2g**	94(68)[c] 37 60
6	 R=H R=OCH_3	**1h** **1i**	3.5 3.5	 R=H R=OCH_3	**2h** **2i**	96(65)[c] 95
7	 R=CH_3 R=C_7H_{15}	**1j** **1k**	2.5 2.5	 R=CH_3 R=C_7H_{15}	**2j** **2k**	80(51)[c] 92(68)[c]
8		**1l**	2.5		**2l**	93
				rac-Germicidin[11]		
9		**1m**	2.5		**2m**	87(69)[c]
10	 CO_2Et	**1n**	3.5		**2n**	77
11		**1o**	3.5		**2o**	79

[a]All new compounds gave satisfactory analytical and/ or spectral data.[8] [b]Isolated yields. [c]The yields when $NaBH_3CN$/acetic acid was used for reduction.

Similar to the method of ionic hydrogenation in arylidene acyl derivatives of cyclic β-dicarbonyl compounds reduction of the enone fragment of the arylidene acyl substituent takes place. The nature of substituents on the aromatic ring (compounds **1c,d,i**) does not interfere with the reduction.

Surprisingly, we found that reduction of furylidene acyl derivatives **1b,o** by $NaBH_3CN$ under these conditions proceeded more selectively as compared to the method using Et_3SiH/CF_3CO_2H to furnish 2-furylalkyl derivatives **2b,o** (entries 2,11) even when a large excess of the reducing agent was employed.

The proposed method offers an advantage over the protocol by Nutaitis et al. in terms of simple separation of the reaction products. Thus, the work-up of the reaction mixture is reduced to removal of THF in vacuo followed by crystallization of the target β-dicarbonyl compounds from the aqueous solution of inorganic components. More complete isolation can be achieved by extraction from the water phase with organic solvents. Oily materials can be isolated by extraction without evaporation of THF.

It should be noted that in contrast to ionic hydrogenations where water-free conditions are essential, the presence of water in the sodium borohydride reduction does not cause any interference.

In conclusion, the reduction by $NaBH_3CN$ in THF - aqueous HCl is a simple and versatile method for selective transformation of cyclic β,β'-tricarbonyl compounds of cyclopentane, cyclohexane, tetronic acid and α-pyrone series to the corresponding cyclic α-alkyl-β-dicarbonyl derivatives. By using Et_3SiH and $NaBH_3CN$ furylidene acyl β-dicarbonyl compounds can be converted to derivatives with different extent of saturation of the furylidene acyl fragment.

Acknowledgement

Financial support provided by INTAS (grant 97-0084) and the Belorussian Foundation for Basic Research (grant X98-143) is greatly appreciated.

References and Notes

(1) Akhrem, A.A.;Titov, Yu.A. *Total Synthesis of Steroids;* Nauka: Moscow, 1967; p322; Szantay, Cs.; Novak, L. *Synthesis of prostaglandins;* Academiai Kiado: Budapest, 1978; p267; Damon, R.E.; Luo, T.; Schlessinger, R.H. *Tetrahedron Lett.* **1976**, 2749; Nishide, K.; Aramata, A.; Kamanaka, T.; Node, M. *Heterocycles* **1993,** *36*, 2237.

(2) Akhrem, A.A.; Lakhvich, F.A.; Liss, L.G.; Khripach, V.A.; Filchenkov, N.A.; Koziniets, V.A.; Pashkovsky, F.S. *Doklady Acad. Nauk SSSR* **1990**, *311*, 1381; Lakhvich, F.A.; Pashkovsky, F.S.; Liss, L.G. *J.Org.Chem. Russia* **1992,** *28*, 1626; *Chem. Abstr.* **1993**, *119*, 49087z; Pashkovsky, F.S.; Lokot, I.P.; Lakhvich, F.A. *Vesti Acad. Navuk Belarusi, ser. khim. navuk* **1993,** 81.

(3) For ionic hydrogenation reactions, see: Kursanov, D.N.; Parnes, Z.N.; Bassova, G.I.; Loim, N.M.; Zdanovich, V.I. *Tetrahedron* **1967**, *23*, 2235; Carey, F.A.; Tremper, H.S. *J. Am. Chem. Soc.* **1968**, *90*, 2578; Fry, J.L.; Orfanopoulos, M.; Adlington, M.G.; Dittman, W.R.; Silverman, S.B.Jr. *J.Org.Chem.* **1978**, *43*, 374; Olah, G.A.; Arvanaghi, M.; Ohannesian, L. *Synthesis* **1986**, 770 and references cited in refs. 2 and 9.

(4) Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(5) For reviews on borohydride reductions, see: Lane, C.F. *Aldrichimica Acta* **1975**, *8*, 3; Lane, C.F. *Synthesis* **1975**, 135; Gribble, G.W. *Chem. Soc. Rev.* **1998**, *27*, 395.

(6) Nutaitis, C.F.; Schultz, R.A.; Obaza, J.; Smith, F.X. *J.Org.Chem.* **1980**, *45*, 4606.

(7) Kende, A.S.; Koch, K.; Smith, C.A. *J. Am. Chem. Soc.* **1988**, *110*, 2210.

(8) *General experimental procedure*: To a stirred solution of 1 mmol of cyclic β,β'-tricarbonyl compounds in 6 mL of THF 5 mL of 2 N aq HCl was added. In some cases partial precipitation of the reagents took place. To the resulting solution (or suspension) $NaBH_3CN$ (see Table) was added portionwise. On addition of the reducing agent the dissolution of precipitated starting materials was observed and in most cases formation of two separate phases took place. The reaction mixture was stirred until reduction was complete (TLC-monitoring). After separation of the organic layer the desired β-dicarbonyl compounds obtained were extracted from the water phase with Et_2O or $CHCl_3$. The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuo the crude products were purified by column chromatography on silica gel. In the case of hardly soluble products, THF was evaporated under reduced pressure. After cooling of the water phase the crystalline materials were filtered off, washed with cold water and dried in air. The products were purified by recrystallization.
Representative examples: **2b** (entry 2) : mp dec., ^{1}H NMR (200 MHz, $CDCl_3$,): δ 1.78 (2H, quint, J = 7.5 Hz,-CH_2-CH_2-CH_2furyl), 2.26 (2H, t, J = 7.5 Hz,-CH_2-$(CH_2)_2$furyl), 2.56 (4H, s, $2CH_2$ carbocyclic), 2.61 (2H, t, J = 7.5 Hz, -CH_2furyl), 5.98 (1H furan, d, J = 2.5 Hz), 6.24 (1H furan, m), 7.26 (1H furan, d, J = 2.5 Hz), 9.36 (1H, broad, -OH enolic). IR (KBr): ν 1370 (br, max), 1440, 1460, 1565, 1600 (sh), 2060-2810 (br) (cm^{-1}). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.77; H, 6.77.
2e (entry 4): mp 80-82 °C (from diethyl ether), ^{1}H NMR (200 MHz, $CDCl_3$,): δ 1.10-1.57 (14H, m, $7CH_2$), 2.04 (2H, q, J = 6.5 Hz, -CH_2CH=CH_2), 2.20 (2H, t, J = 7.5 Hz, -$CH_2(CH_2)_7$-CH=CH_2), 4.68 (2H, s, -OCH_2- heterocyclic), 4.88-5.08 (2H, m, -CH=CH_2), 5.82 (1H, ddt, J = 17.5, 10.0, 6.5 Hz, -CH=CH_2). IR (KBr): ν 1400, 1440, 1600 (br, max), 1645 (sh), 1710, 2680 (br) (cm^{-1}). MS (m/z): 252 (M^+). *Anal.* Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.44.
2h (entry 6): pale yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (3H, d, J = 7.0 Hz, CH_3), 1.82 (2H, quint, J = 7.5 Hz, -CH_2-CH_2-CH_2Ph), 2.27 (2H, t, J = 7.5 Hz, -CH_2-$(CH_2)_2$Ph), 2.62 (2H, t, J = 7.5 Hz, -CH_2Ph,), 4.79 (1H, q, J = 7.0 Hz, >CH- heterocyclic), 7.07-7.42 (5H aromatic, m). IR (film): ν 1350, 1405, 1460, 1660 (br, max), 1725, 2730 (br) (cm^{-1}). MS (m/z): 232 (M^+). *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.29; H, 6.89.
2m (entry 9): mp 147-148 °C (from ethyl acetate), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78 (2H, quint, J = 7.0 Hz, -CH_2CH_2C≡CH), 2.04 (1H, t, J = 2.5 Hz, -C≡CH), 2.24 (5H, m, CH_3+-CH_2C≡CH), 2.58 (2H, t, J = 7.0 Hz, -$CH_2(CH_2)_2C$≡CH), 6.10 (1H heterocyclic, s), 9.02 (1H, broad, -OH enolic). IR (KBr): ν 1415 (max), 1590, 1640, 1680, 2660 (br), 3085 (br), 3310 (cm^{-1}). MS (m/z): 192 (M^+). *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.59; H, 6.21.

(9) During ionic hydrogenation with silane hydrides in CF_3CO_2H, reduction of the double bond in alkenes or cycloalkenes occurs only in the case when branching at the ethylene carbon is present, i.e. when the tertiary carbocation is formed in acidic medium: Kursanov, D.N.; Parnes, Z.N.; Lojm, N.M. *Synthesis* **1974**, 633.

(10) Initial β,β'-triones **(1a,j)** were synthesized according to the protocol: Merenyi, F., Nilsson, M. *Acta Chem. Scand.* **1963**, *17*, 1801. Furylidene- and arylidene acyl derivatives **(1b-d,h,i,o)** were obtained as a result of Claisen-Schmidt condensation of the readily available 2-acetylcyclopentane-1,3-dione, 3-acetyltetronic acids and dehydroacetic acid with furfural or aromatic aldehydes, see ref.2. β,β'-Tricarbonyl compounds **(1e-g,k,m,n)** were synthesized according to the protocol described in: Nomura, K.; Hori, K.; Arai, M.; Yoshii, E. *Chem.Pharm.Bull.* **1986**, *34*, 5188 and ref. 2.

(11) Germicidin, an autoregulative germination inhibitor of *Streptomyces viridochromogenes* NRRl B-1551. Isolation, biological properties and structure elucidation: Petersen, F.; Zahner, H.; Metzger, J.W.; Freund, S.; Hummel, R.-P. *J. Antibiot.* **1993**, *46*, 1126. Synthesis of *rac*-germicidin and spectroscopic data: Lokot, I.P.; Pashkovsky, F.S.; Lakhvich, F.A. *Mendeleev Commun.* **1999**, 22; Lokot, I.P.; Pashkovsky, F.S.; Lakhvich, F.A. *Tetrahedron* **1999**, *55*, 4783.

Article Identifier:
1437-2096,E;2001,0,09,1391,1394,ftx,en;G09401ST.pdf