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A Simple and Effective Method for the Reduction of Acyl Substituted Heterocyclic 1,3-Dicarbonyl Compounds to Alkyl Derivatives by Zinc - Acetic Acid - Hydrochloric Acid

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Abstract: 3-Acyl-4-hydroxy-2(1H)-quinolones (**1a-k**) were reduced in good yields (66-97%) to 3-alkyl-4-hydroxy-2(1H)-quinolinones (**2a-k**) using zinc powder (particle size <45 μm) in acetic acid/hydrochloric acid. This method could be transformed to 3-acetyl-4-hydroxy-coumarin (**1l**), 3-acetyl-4-hydroxy-2-pyranone (**3a**) and 3-acetyl-4-hydroxy-2(1H)-pyridinone (**3b**), which yielded the 3-ethyl derivatives **2l**, **4a** and **4b**, respectively.

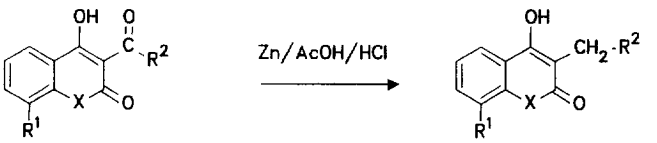
Many heterocyclic 1,3-dicarbonyl compounds possessing alkyl substituents at the electronegative 2-position show interesting biological properties (e.g. some 3-alkyl-4-hydroxy-2-quinolones are contents of bacteria[1]). There are mainly three approaches known in the literature leading to these alkyl derivatives. One reaction type is the cyclocondensation of 1,2- or 1,3-dinucleophiles with alkyl substituted 1,3-dielectrophiles such as malonates[2] having an alkyl substituent at the active methylene site.
In the case of less reactive dinucleophiles, this reaction needs an expensive preparation of reactive malonates[3] used as starting material. A second approach starts from unsubstituted 1,3-dicarbonyl heterocycles and involves an alkylation step. This reaction procedure has the disadvantage of giving also O-alkyl- and C,C-dialkyl derivatives as byproducts, which have to be separated from the desired C-monoalkylation product[4].

*Dedicated to Professor Hans Suschitzky on the occasion of his 80th birthday

A third entry to this class of compounds is the reduction of the corresponding acyl derivatives, which are in many cases available in good yields. There are a few literature procedures that bear some resemblance to the method presented here, using either expensive or complicated reduction methods such as catalytic hydrogenation on platinum metal or sodium cyanoborohydride as reduction agent[5].

Recent publications using either zinc powder as reduction agent for acyl pyrroles[6] or the Clemmensen reduction method with zinc and mercury chloride for acyl thiophenes[7], prompts us to report a simple and inexpensive reduction method developed in our laboratory using a special kind of zinc powder (Merck no. 1.08789, particle size <45 μm) in acetic acid/hydrochloric acid as reduction system for 2-acyl derivatives of heterocyclic 1,3-dicarbonyl systems, which afforded the corresponding 2-alkyl-1,3-dicarbonylsystems in good yields. Experiments with other kinds of zinc powder showed that the yields decreased drastically. Using our preparation procedure, it was not necessary to work with amalgamated zinc. On the contrary, we obtained lower yields and impure products when using the Clemmensen reduction method for the systems described below.

We obtained 3-alkyl-4-hydroxy-2(1H)-quinolones **2a-k** by reduction of 3-acyl-4-hydroxy-2(1H)-quinolones **1a-k** by repeatedly addition of small portions of zinc powder in a solution of ethanol and glacial acetic acid, containing a little amount of hydrochloric acid in order to keep zinc salts in solution formed during the reaction.



1a–l **2a–l**

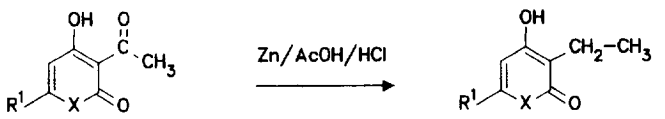
R–Key: see Table 1 and 2

The starting acylquinolones **1a-k** could easily be prepared from 3-unsubstituted 4-hydroxy-2(1H)-quinolones and substituted malonates in a 2-step reaction sequence without formation of isomeric O-acyl derivatives.[8]

Good results were obtained too with 3-acetyl-4-hydroxycoumarin (**1l**), which could be reduced to the 3-ethyl derivative **2l**. This method has many advantages compared with the methods known from literature either using the inconvenient method via diphenyl ethylmalonate[9] or adapting the reaction pathway via diethyl ethylmalonate[2] which leads to rather low yields.

Similar effects were observed when 3-acyl-4-hydroxy-2(1H)-pyrones such as **3a** (dehydracetic acid) or 3-acyl-4-hydroxy-2(1H)-pyridones such as **3b** were reduced with zinc. Also in these cases, the 3-alkyl derivatives **4** could be isolated in good yields.

Whereas pyrones of type **4a** were reported to be only obtained in rather complex multistep syntheses, either by removal of the acetyl group of compounds of type **3a** followed by alkylation[10], or by cyclocondensation of chlorocarbonylketenes with aldehydes and ketones (in some cases even a further activation step via enol ethers was necessary)[11], or by alkylation of 3,5-dioxohexanoate copper complexes followed by basic cyclization[12], we could obtain it in one step from commercial available 3-acetyl-4-hydroxy-2(1H)-pyrone **3a** (dehydracetic acid) by reduction.



3a,b **4a,b**

3,4	R^1	X
a	Me	O
b	Ph	N–Ph

The pyridone **4b** is reported[13] to be obtained from acetophenone anil by reaction with bis-(2,4,6-trichlorophenyl) ethylmalonate in good yields, but using a rather expensive and time consuming method, so that the reaction pathway via the reduction of the 3-acetyl-pyridone **3a** offers some advantages.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes. ^{1}H-NMR spectra (200 MHz) were recorded on a Varian Gemini 200 instrument. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent for NMR spectra was DMSO-d_6 unless otherwise stated. Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer in potassium bromides pellets. Elemental analyses were performed on a Carlo Erba 1106 C,H,N automatic analyzer. All reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel F-254 (Merck) plates using uv light (254 and 366 nm) for detection.

3-Acyl-4-hydroxy-2(1H)-quinolones (**1a-g**) *and 2-Acyl-1-hydroxy-6,7-dihydro-5H-benzo[ij]quinolizin-3-ones* (**1h-k**) *and 3-Acetyl-4-hydroxy-coumarin* (**1l**).

The synthesis of acetyl-quinolones **1a-d** and 2-Acyl-1-hydroxy-6,7-dihydro-5H-benzo[ij]quinolizin-3-ones **1h-k** was performed using the procedure of ref.[8], for 3-benzoyl-quinolones **1e-g** the procedure of ref.[15] was used, and the acetylcoumarin **1l** was synthesized according to ref.[16].

Table 1. Experimental and Spectroscopic Data of 3-Alkyl-4-hydroxy-2(1H)-quinolones **2a-g**

Cpd. No.[a]	X	R^1	R^2	yield %	mp (°C) solvent	IR (cm^{-1}) ^{1}H-NMR (δ ppm)
2a	N-Me	H	CH_3	75	180-182	(ref.[17]: 184)
2b	N-Me	H	C_3H_7	76	180-181	(ref.[17]: 182)
2c	N-Me	H	C_5H_{11}	71	139-140 ethanol	2920 w, 1630 s, 1600 s,
2d	N-Me	H	CH_2Ph	97	217-219 ethanol	2920 w, 1630 s, 1605 s 2.85 (q, J= 7 Hz, 2 CH_2), 3.6 (s, N-CH_3), 7.1-7.5 (m, 8 ArH), 8.0 (dd, J= 7+1.5 Hz, 5-H).
2e	N-Me	H	Ph	72	214-16 ethanol	(ref.[9]: 219-220°)
2f	N-Me	H	4-Me-Ph	79	226-30 ethanol	1645 s, 1600 m, 1550 s 2.24 (s, CH_3), 3.60 (s, N-CH_3), 3.98 (s, CH_2), 7.0-7.34 (m, 5 ArH), 7.45-7.65 (m, 2 ArH), 8.04 (dd, J= 1.5+7 Hz, 5-H), 10.38 (s, OH).
2g	N-Me	H	4-MeO-Ph	76	185-188 ethanol	1640 m, 1610 s, 1570 s 3.60 (s, N-CH_3), 3.70 (s, OCH_3), 3.93 (s, CH_2), 6.82 (d, J= 9 Hz, 2 ArH), 7.16-7.32 (m, 3 ArH), 7.44-7.67 (m, 2 ArH), 8.04 (dd, J= 1.5+7 Hz, 5-H), 10.40 (s, OH).

[a] Analyses agree within ±0.4% of the theoretical values

General Procedure for the Reduction to 3-Alkyl-4-hydroxy-2(1H)-quinolones (**2a-g**), *2-Alkyl-1-hydroxy-6,7-dihydro-5H-benzo[ij]quinolizin-3-ones* (**2h-k**) *and 3-Ethyl-4-hydroxycoumarin* (**2l**).

The corresponding acyl derivative **1a-l** (0.01 mol) is dissolved in a mixture of ethanol (50 ml), glacial acetic acid (25 ml) and conc. hydrochloric acid (1.0 ml). The mixture is heated to 80 °C and under stirring zinc powder (10.0 g, Merck no. 1.08789, particle size <45 μm) is added in small portions (each about 0.5 g). The overall time of the zinc addition is about 2.5 h. When the addition is finished, the mixture is heated under reflux for 5 min and filtered still hot from excess of zinc. The filtrate is concentrated i.vac. to dryness and then water (50 ml) is added. Then hydrochloric acid is added until pH = 1-2. The resulting precipitate is filtered by suction and washed with cold water (20 ml). Experimental and spectroscopic data see Table 1 and 2.

Table 2. Chemical Data of 2-Alkyl-1-hydroxy-6,7-dihydro-5H-benzo[ij]quinolizin-3-ones **2h-k** and 3-Alkyl-4-hydroxycoumarin **2l**

Cpd. No.[a]	X	R^1	R^2	yield %	mp (°C) solvent	IR (cm^{-1}) ^{1}H-NMR (δ ppm)
2h	N-$(CH_2)_3$-		CH_3	83	294-295 ethanol	2960 m, 1640 s, 1600 m 1.1 (t, J= 7 Hz, CH_3), 1.6- 2.1 (m, CH_2), 2.6-3.0 (m, Ar-CH_2), 3.0-3.5 (q, J= 7 Hz, Et-CH_2), 3.85 (t, J= 7 Hz, N-CH_2), 5.8 (s, OH), 6.9-7.4 (m, 2 ArH), 7.65 (dd, J= 1.5 + 7 Hz, 10-H).
2i	N-$(CH_2)_3$-		C_3H_7	66	164-65 (ref.[17]: 163)	
2j	N-$(CH_2)_3$-		C_5H_{11}	75	136-137 ethanol	2920 m, 1625 m, 1600 m 0.75-1.0, 1.1-1.55, 3.2-3.55, 3.9-4.2 (m, 13 H), 1.8-2.3, 2.3-2.8, 2.8-3.1 (m, 3 CH_2), 7.0-7.4 (m, 2 ArH.), 7.85 (dd, J= 7 + 1.5 Hz, 10-H).
2k	N-$(CH_2)_3$-		CH_2Ph	66	171-173 ethanol	2940 s, 1630 s, 1600 s,
2l	O	H	Et	78	153 (ref.[18]: 154) ethanol	

[a] Analyses agree within ±0.4% of the theoretical values

3-Ethyl-4-hydroxy-6-methyl-pyran-2-one (**4a**). From 7.6 g g (0.45 mmol) 3-acetyl-4-hydroxy-6-methyl-pyran-2-one (**3a**) using the general procedure described for **2**. Yield: 4.58 g (66 %), mp 191 °C (ethanol). Lit. mp: 172 °C[12]. IR: 2310-2880 m, 2750-2450 m, 1715 m, 1630 s, 1560 m. ^{1}H-NMR (DMSO-d_6): δ= 0.96 (t, J = 7 Hz, Ethyl-CH_3), 2.16 (s, CH_3 at C-6), 2.29 (q, J = 7 Hz, CH_2), 6.00 (s, 5-H), 11.1 (s, broad, OH).

3-Ethyl-4-hydroxy-1,6-diphenyl-pyridin-2)1H)-one (**4b**). From 1.0 g (3.3 mmol) 3-acetyl-4-hydroxy-1,6-diphenyl-pyridin-2(1H)-one (**3b**)[14] according to the general procedure described for **2**. Yield: 0.78 g (82%), mp 302-4 °C (ethanol); lit. mp: 305 °C[13, 14b].

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