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One-pot synthesis of 6-aryl-2,3-dihydro-4*H*-pyran-4-ones by cyclocondensation of 1,3-diketone dianions with aldehydes

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ABSTRACT

6-Aryl-2,3-dihydro-4*H*-pyran-4-ones were prepared in one step by cyclocondensation of 1,3-diketone dianions with aldehydes. The use of hydrochloric acid (10%) for the aqueous work-up proved to be very important.

2,3-Dihydro-4*H*-pyran-4-ones are present in many natural products and in a great variety of pharmacologically relevant synthetic molecules.[1] 2,3-Dihydro-4*H*-pyran-4-ones are available by hetero-Diels–Alder reaction of aldehydes with Danishefsky's diene[2] or related electron-rich dienes.[3,4] Denmark and Heemstra recently reported[5] a catalytic asymmetric synthesis of 2,3-dihydro-4*H*-pyran-4-ones by reaction of 1,3-bis(silyloxy)-1,3-butadienes[6] with aldehydes, using Lewis base-activated Lewis acids, and subsequent TFA-catalyzed cyclization. Despite the great utility of all these methods, the use of electron-rich dienes requires a special handling, due to their unstable nature and rapid hydrolysis. The synthesis of the dienes requires two or three steps, depending on the substitution pattern. In addition, they cannot be stored for a long period of time (not even at −20 °C). Other syntheses of 2,3-dihydro-4*H*-pyran-4-ones include, for example, palladium(II)-catalyzed oxidative cyclizations of β-hydroxyenones[7] and reactions of β-ethoxy-α,β-unsaturated lactones.[8] Despite their great utility, these methods have some limitations related to the preparative scope.

Feng and co-workers have reported the synthesis of 2,3-dihydro-4*H*-pyran-4-ones by LDA-mediated reaction of 3-methoxy-2-en-1-ones with aldehydes and subsequent acid-mediated cyclization.[9] This method requires the synthesis of the enone starting materials which is sometimes not straightforward. Xian et al. reported the synthesis of 2,3-dihydro-4*H*-pyran-4-ones by reaction of lithiated dithianes with epoxides and subsequent deprotection, oxidation, and cyclization.[10] Light and Hauser were the first to study the reaction of 1,3-dicarbonyl dianions with aldehydes to give 5-hydroxy-1,3-dicarbonyl compounds and their HCl/MeOH-mediated dehydration or transformation into 2,3-dihydro-4*H*-pyran-4-ones.[11,12] Hassner et al. reported the application of this method on the synthesis of the natural product stegobinone.[13] Miller and co-workers reported the transformation of 5-hydroxy-1,3-diketones into 6-alkyl-2,3-dihydro-4*H*-pyran-4-ones using *para*-toluenesulfonic acid (*p*-TsOH, CH_2Cl_2, 24 h, reflux, Dean–Stark trap, 3 Å MS).[14] It is important to note that the preparative scope of this method is limited to the synthesis of 6-*alkyl*-2,3-dihydro-4*H*-pyran-4-ones (derived from *aliphatic* aldehydes) because of the competing dehydration in the case of aromatic substrates. It is important to note that the reaction of *p*-TsOH with 6-hydroxy-6-phenyl-hexane-2,4-dione (**3**), prepared by condensation of the dianion of acetylacetone (**1a**) with benzaldehyde (**2a**), has been reported[14] to give 6-phenyl-hex-5-ene-2,4-dione (**4**) rather than the desired pyran-4-one **5a** (Scheme 1). The facile formation of **4** is a result of the conjugation of the double bond with the aryl group.

We were interested in a direct and convenient method for the synthesis of 6-*aryl*-2,3-dihydro-4*H*-pyran-4-ones which are, as discussed above, not directly available so far. Therefore, we have reinvestigated the reaction of 1,3-diketone dianions with aldehydes and preliminary results of our efforts are reported herein. We have found that a variety of 6-aryl-2,3-dihydro-4*H*-pyran-4-ones can be successfully prepared in good yields and in only one step by reaction of 1,3-diketone dianions with aromatic aldehydes. Interestingly, it proved to be very important to use hydrochloric acid (10%) for the aqueous work-up.

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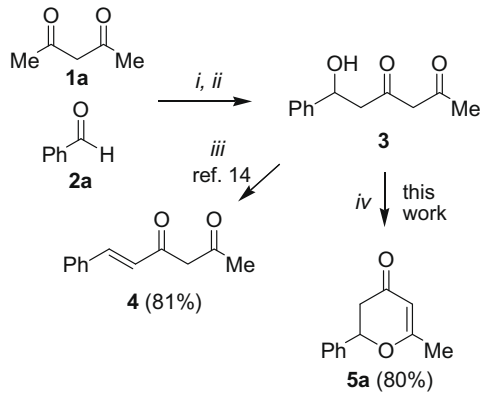
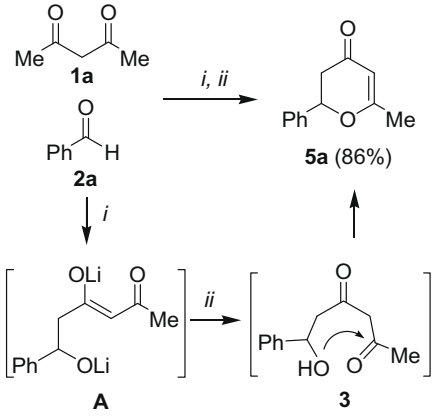


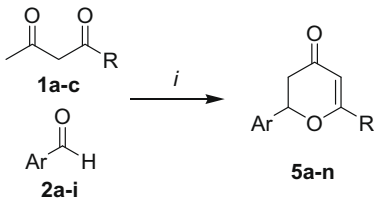
Scheme 1. Dehydration and cyclization of **3**. Reagents and conditions: (i) (1) NaH, THF, 0 °C, 15 min; (2) *n*BuLi, 20 min, 0 °C; (3) **2a**, 15 min, 0 °C; (ii) NH_4Cl (satd); (iii) *p*-TsOH, CH_2Cl_2, 24 h, reflux, Dean–Stark trap, 3 Å MS; (iv) variant A: $FeCl_3{\cdot}6H_2O$, NO_2CH_3, 50 °C, 4 h; variant B: HCl (10%), THF, 15 min, 20 °C, then extraction (EtOAc).

Our starting point was to find suitable conditions for the transformation of **3** into **5a**. The reaction of a nitromethane solution of **3** with catalytic amounts of $FeCl_3{\cdot}6H_2O$ (10 mol %) afforded the desired 6-phenyl-2,3-dihydro-4*H*-pyran-4-one **5a** in high yield (Scheme 1). The same transformation could be induced in high yield by employing hydrochloric acid (10%). This result suggests that $FeCl_3$ reacted as a Lewis or Brønsted acid. Based on these observations, we developed a one-pot protocol for the synthesis of **5a**. We were pleased to find that the reaction of the dianion of acetylacetone (**1a**) (generated by means of 2.5 equiv of LDA) with benzaldehyde (**2a**) (−78→20 °C, 12 h), addition of hydrochloric acid (10%) and, after 15 min, extraction of the mixture with EtOAc afforded the desired pyran-4-one **5a** in 86% yield (Scheme 2).[15]

The formation of **5a** (rather than **4**) can be explained by acid-mediated attack of the hydroxyl group onto the carbonyl group and subsequent elimination of water. The use of an aqueous solution of NH_4Cl, as reported by Miller et al. for the synthesis of **3**,[14] did not result in formation of **5a**. On the other hand, the reaction of **3** with *p*-TsOH gave **4**. This might be explained by the assumption that this elimination is irreversible when *p*-TsOH (CH_2Cl_2, reflux) is used (due to the absence of water) while it is reversible when an aqueous solution of HCl (10%, 20 °C) is employed. On the other hand, Denmark have reported that the cyclization proceeds in high yield when TFA (0.001 equiv in CH_2Cl_2, 0 °C) is used.[5]



Scheme 2. Possible mechanism of the formation of **5a**. Reagents and conditions: (i) (1) LDA (2.5 equiv), THF, 0 °C, 1 h; (2) −78 °C, 1 h; (3) **2a**, −78→20 °C, 12 h; (ii) addition of HCl (10%), 15 min, 20 °C, then extraction (EtOAc).



Scheme 3. Synthesis of **5a–n**. Reagents and conditions: (i) (1) LDA (2.5 equiv), THF, 0 °C, 1 h; (2) −78 °C, **1a–c**, 1 h; (3) **2a–i**, −78→20 °C, 12 h; (ii) addition of HCl (10%), 15 min, 20 °C, then extraction (EtOAc).

While the above-mentioned reaction with *p*-TsOH was carried out under reflux conditions, the reaction with TFA was carried out at 0 °C (16 h). Therefore, the temperature seems to play an important role when an elimination or cyclization reaction occurs. The silica gel chromatography of the products may also play a role to induce a complete transformation of **3** into **5a**.

The reaction of the dianions of acetylacetone (**1a**) and 1,1,1-trifluoropentane-2,4-dione (**1b**) with aldehydes **2a–h** afforded the 6-aryl-2,3-dihydro-4*H*-pyran-4-ones **5a–j** in very good yields (Scheme 3, Table 1). The best yields were obtained for reactions of **1a** with more electron-rich aldehydes. This might be explained by a slightly increased nucleophilicity of the hydroxy group. In the case of 3-nitrobenzaldehyde (**2i**), only the open-chained 5-hydroxy-1,3-diketone (rather than **5k**) was isolated. This can be explained by the decreased nucleophilicity of the hydroxy group of the open-chained product. The reaction of the dianion of benzoylacetone (**1c**) with **2b,c,g** resulted in the formation of **5l–n**. The synthesis of 6-alkyl-2,3-dihydro-4*H*-pyran-4-ones from aliphatic aldehydes also proved to be possible. The novel trifluoromethyl-substituted pyran-4-ones **5i,j** are of special interest, due to the great importance of fluorinated heterocycles in medicinal chemistry.[16]

Table 1
Synthesis of **5a–n**

1	2	5	R	Ar	% (5)[a]
a	**a**	**a**	Me	Ph	86
a	**b**	**b**	Me	4-MeC_6H_4	89
a	**c**	**c**	Me	4-$(MeO)C_6H_4$	84
a	**d**	**d**	Me	3-BrC_6H_4	67
a	**e**	**e**	Me	2,4-$(MeO)_2C_6H_3$	76
a	**f**	**f**	Me	4-$(HO)C_6H_4$	78
a	**g**	**g**	Me	4-PhC_6H_4	80
a	**h**	**h**	Me	2-Furyl	87
b	**a**	**i**	CF_3	Ph	78
b	**b**	**j**	CF_3	4-MeC_6H_4	75
a	**i**	**k**	Me	3-$(NO_2)C_6H_4$	0[b]
c	**b**	**l**	Ph	4-MeC_6H_4	79
c	**c**	**m**	Ph	4-$(MeO)C_6H_4$	73
c	**g**	**n**	Ph	4-PhC_6H_4	78

[a] Isolated yields.
[b] The open-chained product was isolated in 75% yield.

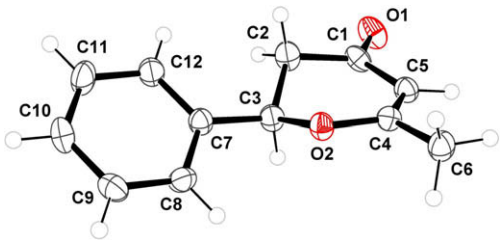


Figure 1. Ortep plot of **5a** (50% probability level).

The structures of all products were established by spectroscopic methods. The structure of **5a** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[17]

In conclusion, a variety of 6-aryl-2,3-dihydro-4*H*-pyran-4-ones were prepared in one step by cyclocondensation of 1,3-diketone dianions with aldehydes and subsequent work-up using hydrochloric acid (10%). We currently study the preparative scope and synthetic applications of the methodology reported.

Acknowledgment

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15. *Typical procedure: synthesis of 2-methyl-6-phenyl-2,3-dihydro-4H-pyran-4-one* (**5a**). A THF Solution of LDA (25.0 mmol) was prepared by addition of *n*BuLi (10 mL, 25.0 mmol, 2.5 M solution in hexanes) to a THF solution (30 mL) of diisopropylamine (2.52 g, 25.0 mmol) at 0 °C. After stirring for 1 h, the solution was cooled to −78 °C and 2,4-pentadion (1.00 g, 10.0 mmol) was added. After stirring for 1 h at −78 °C, benzaldehyde (1.06 g, 10.0 mmol) was added and the solution was allowed to warm to 20 °C within 24 h. Hydrochloric acid (10%, 25 mL) was added and the mixture was allowed to stand for 15 min. Ethyl acetate (25 mL) was added. The organic and aqueous layers were separated and the latter was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/ethyl acetate = 2:1) to give **5a** as a colorless crystalline solid (1.63 g, 87%), mp 45–48 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.98 (s, 3H, CH_3), 2.47–2.55 (dd, $1H_A$, J = 3.2, 16.7 Hz), 2.66–2.79 (dd, $1H_B$, J = 14.0, 16.7 Hz), 5.27–5.34 (dd, 1H, CH, J = 3.2, 14.5 Hz), 5.36 (s, 1H, CH), 7.28–7.33 (m, 5H, Ph). ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.1(CH_3), 42.4 (CH_2), 80.8, 105.2 (CH), 126.1, 128.8 (CH_{Ar}), 138.1, 174.3, 192.3 (C). IR (KBr): ν 3062, 3033, 2962, 2918 (w), 1661, 1603, 1392, 1327 (s), 1237, 1179, 1023 (m), 999 (s), 950, 808 (m), 755, 696 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) 188 (M^+, 2), 170 (8), 155 (6), 145 (36), 104 (100), 91 (2), 78 (16), 77 (12). HRMS (ESI-TOF): calcd for $C_{12}H_{13}O_2$ $[M+H]^+$: 189.09101; found: 189.09077.
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17. CCDC 719665 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Center, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.