Synthesis of 6-Substituted 4-Hydroxy-2-pyrones from Aldehydes by Addition of an Acetoacetate Equivalent, Dess–Martin Oxidation and Subsequent Cyclization

Thorsten Bach,* Stefan Kirsch

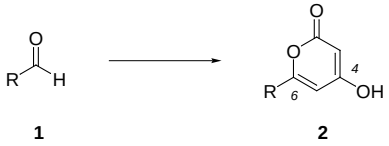
Lehrstuhl für Organische Chemie I, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany
Fax +49(89)28913315; E-mail: thorsten.bach@ch.tum.de

Received 20 August 2001

Abstract: A three step procedure for the synthesis of 6-substituted 4-hydroxy-2-pyrones **2** from aldehydes **1** is described. An acetoacetate equivalent **3** was added to the corresponding aldehyde (10 examples) in a vinylogous Mukaiyama aldol addition (72–99%). The intermediate alcohols **4** were oxidized to the ketones **5** using the Dess–Martin method (67%–quant.). A final thermal cyclization of compounds **5** yielded the title compounds **2** (61–92%; 40–85% overall).

Key words: aldehydes, heterocycles, oxidations, pyrones, ring closure

The conversion of aldehydes **1** to biologically relevant 6-substituted 4-hydroxy-2-pyrones **2**[1,2] generally requires three steps (Scheme 1): Oxidation, C–C bond formation and cyclization. Whereas the C–C bond formation step has obviously to occur prior to cyclization, the oxidation step can occur at any stage of the sequence. An initial oxidation to a carboxylic acid requires further transformations of the acid into an acylating agent, i.e. an acid chloride,[3] an ester,[4] or an amide.[4c,5] A final oxidation, i.e. the conversion of a dihydropyrone to a pyrone, requires drastic conditions[6] which may not be compatible with sensitive substrates.

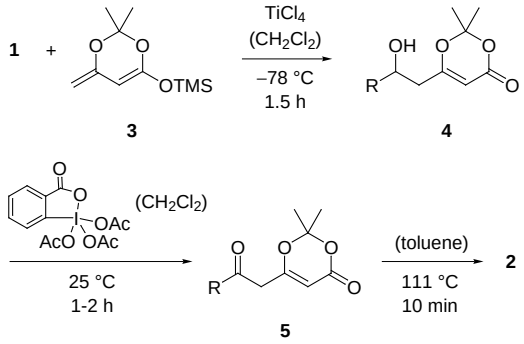


1 **2**

Scheme 1

In light of these facts, the most direct approach for the desired conversion appears to be an oxidation after C-C bond formation and prior to cyclization. A literature search surprisingly revealed that there is only limited precedence for this strategy. The intermediate α,γ-unsubstituted δ-hydroxy-β-ketocarboxylates are prone to a retro-aldol fragmentation and have so far only been oxidized under acidic conditions.[7] In the following communication we present a synthetic sequence which gives general access to the title compounds from aldehydes by three high yielding, mild conversions: Carbonyl addition of an acetoacetate equivalent, Dess–Martin oxidation and thermal cyclization.

The addition of the easily available ketene acetal **3**[8] to various aldehydes **1** proceeded readily employing $TiCl_4$ (1.1 equiv) as the Lewis acid (Scheme 2).[8,9] Only 1.7 equivalents of the reagent were required to ensure complete conversion.[10] The yields of isolated products were high for a broad range of substrates (Table). The oxidation step turned out to be more subtle and required some optimization. We found that the Dess–Martin conditions[11] were ideally suited for the desired conversion of alcohol **4** to the cyclization precursor **5**.[12] The choice of the protected 1,3-dicarbonyl building block **3** was crucial to the success of the oxidation. As briefly mentioned above, all attempts to oxidize unprotected δ-hydroxy-β-ketocarboxylates remained unsuccessful in our hands. In the oxidation step stoichiometric amounts (1.3 equiv) of the reagent were sufficient for a complete conversion. In several instances the oxidation product was not isolated (entries 1, 2, 7, and 10) but was directly converted further to the pyrone **2** by the known[3b,13] thermal cyclization reaction[14] of 6-(2-oxoalkyl)-1,3-dioxin-4-ones.[15] An overview of the reactions we have conducted so far is provided in Scheme 2 and in the Table.[16]



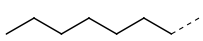
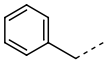
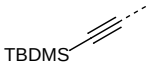
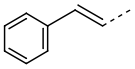
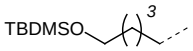
Scheme 2

In general, each reaction step is fairly independent on the choice of substrates. Variations of the reaction conditions have not yet been examined to a large extent. In the case of silyl ether **1j**, the reaction time for the conversion **1j** → **4j** had to be shortened in order to avoid extensive desilylation (entry 10). It is remarkable that even the sensitive

Synlett 2001, No. 12, 30 11 2001. Article Identifier:
1437-2096,E;2001,0,12,1974,1976,ftx,en;G17701ST.pdf.

ISSN 0936-5214

Table Yields for the Three Individual Steps in the Conversion of Aldehydes **1a–j** to the Corresponding 4-Hydroxy-2-pyrones **2a–j**

Entry	R---	#	Yield **4** [%][a]	Yield **5** [%][b]	Yield **2** [%][c]
1		**a**	85	quant.[d]	75
2		**b**	72	quant.[d]	92
3		**c**	82	98	73
4		**d**	76	99	67
5		**e**	85	83	74
6		**f**	90	95	81
7		**g**	98	quant.[d]	87
8		**h**	99	90	72
9		**i**	99	67	61
10		**j**	78[e]	95[d]	92

[a] 1.7 Equiv **3**, 1.1 equiv $TiCl_4$; yield of isolated product after chromatography.[10]
[b] 1.3 Equiv periodinane; yield of isolated product after chromatography.[12]
[c] Yield of isolated product after chromatography or recrystallization.[15]
[d] Yield of crude product.
[e] 2 Equiv **3**, reaction time: 25 min.

furan ring withstands both the oxidation and the ring closure conditions fairly well (entry 9) although the yields achieved in these steps are lower than for the other substrates. The total yield for the conversion **1i** → **2i** amounted to 40% whereas an overall yield of > 50% was obtained in the other nine examples.

The further methylation of 4-hydroxypyrones is well precedented.[17] We have used a standard methylation procedure (Me_2SO_4, K_2CO_3 in acetone, 91% yield) to convert the product **2g** into 5,6-dehydrokavain, a naturally occurring pyrone.[18] Further applications of the presented methodology in the context of more complex syntheses are currently under way in our laboratories and will be reported in due course.

Acknowledgement

This work was supported by the Bayer AG (Wuppertal) and by the Fonds der Chemischen Industrie. We would like to thank Olaf Akkermann for skillful technical assistance.

References

(1) General reviews: (a) Moreno-Mañas, M.; Pleixats, R. *Adv. Heterocycl. Chem.* **1992**, *53*, 1. (b) Moreno-Mañas, M.; Pleixats, R. *Heterocycles* **1994**, *37*, 585.
(2) HIV-protease inhibition: (a) Aristoff, P. A. *Drugs Fut.* **1998**, *23*, 995. (b) Romines, K. R.; Chrusciel, R. A. *Curr. Med. Chem.* **1995**, *2*, 825.
(3) (a) Chan, T. H.; Brownbridge, P. *Can. J. Chem.* **1983**, *61*, 688. (b) Sato, M.; Sakaki, J.-I.; Sugita, Y.; Yasuda, S.; Sakoda, H.; Kaneko, C. *Tetrahedron* **1991**, *47*, 5689.
(4) (a) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343. (b) Harris, T. M.; Harris, C. M.; Oster, T. A.; Brown, L. E. Jr.; Lee, J. Y.-C. *J. Am. Chem. Soc.* **1988**, *110*, 6180. (c) Yamaguchi, M.; Shibato, K.; Nakashima, H.; Minami, T. *Tetrahedron* **1988**, *44*, 4767. (d) Krohn, K.; Roemer, E.; Top, M. *Liebigs Ann.* **1996**, 271.
(5) (a) Yamaguchi, M.; Shibato, K.; Hirao, I. *Chem. Lett.* **1985**, 1145. (b) Lygo, B. *Tetrahedron* **1995**, *51*, 12859. (c) Hiyama, T.; Reddy, G. B.; Minami, T.; Hanamoto, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 350.
(6) (a) Abramson, H. N.; Wormser, H. C. *J. Heterocycl. Chem.* **1981**, *18*, 363. (b) Poulton, G. A.; Cyr, T. D. *Can. J. Chem.* **1982**, *60*, 2821.
(7) Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M. *Org. Lett.* **2001**, *3*, 251.
(8) (a) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91. (b) Sugita, Y.; Sakaki, J.-I.; Sato, M.; Kaneko, C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2855.
(9) (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435. (b) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.
(10) Representative procedure for the conversion **1** → **4**: At –78 °C, a solution of ketene acetal **3** (4.25 mmol, 910 mg) in CH_2Cl_2 (10 mL) was added dropwise to a solution of crotonaldehyde **1f** (2.5 mmol, 175 mg) and $TiCl_4$ (2.7 mmol, 512 mg) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for another 1.5 h at –78 °C and was subsequently quenched with sat. aq $NaHCO_3$ (10 mL). The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the crude product as a pale yellow oil. Purification by flash chromatography on silica with pentane/EtOAc (80/20) as eluent gave alcohol **4f**[9b] (477 mg, 2.25 mmol, 90%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.64 (s, 3 H), 1.65 (s, 3 H), 1.66 (dd, *J* = 1.4 Hz, *J* = 6.4 Hz, 3 H), 2.04 (s, br, 1 H), 2.32–2.47 (m, 2 H), 4.32 (pseudo q, *J* ≅ 7.0 Hz, 1 H), 5.27 (s, 1 H), 5.47 (ddq, *J* = 1.4 Hz, *J* = 7.0 Hz, *J* = 15.3 Hz, 1 H), 5.72 (ddq, *J* = 0.9 Hz, *J* = 6.4 Hz, *J* = 15.3 Hz, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.6, 24.8, 25.3, 41.5, 69.7, 95.1, 106.6, 128.2, 132.3, 161.1, 168.6.
(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Boeckman, R. B. Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **1999**, *77*, 141.
(12) Representative procedure for the conversion **4** → **5**: Dess–Martin periodinane (1.5 mmol, 640 mg) was added as a solid to a solution of compound **4f** (1.12 mmol, 238 mg) in 5 mL of CH_2Cl_2. The resulting mixture was stirred for 90 min at r.t.

The mixture was diluted with 30 mL of ether and 6 mL of a sat. aq $NaHCO_3$-solution containing 5% sodium thiosulfate was added. After stirring for 20 min, the clear organic layer was separated. The organics were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography on silica with pentane–EtOAc (80:20) to yield compound **5f** (197 mg, 1.1 mmol, 95%) as a colorless liquid which was taken directly into the cyclization step.[15] ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.65 (s, 6 H), 1.89 (dd, *J* = 1.5 Hz, *J* = 6.7 Hz, 3 H), 3.41 (s, 2 H), 5.30 (s, 1 H), 6.12 (dq, *J* = 1.5 Hz, *J* = 15.7 Hz, 1 H), 6.88 (dq, *J* = 6.7 Hz, *J* = 15.7 Hz, 1 H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.3, 24.9, 44.5, 96.6, 107.1, 130.8, 145.4, 160.7, 164.9, 192.3.

(13) For a related thermal cyclization, see: Lokot, I. P.; Pashkovsky, F. S.; Lakhvich, F. A. *Tetrahedron* **1999**, *55*, 4783.

(14) For references on the DBU-mediated cyclization of β,δ-diketocarboxylates, see: (a) Oppolzer, W.; Moretti, R.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4713. (b) Marquet, J.; Moreno-Mañas, M.; Prat, M. *Tetrahedron Lett.* **1989**, *30*, 3105. (c) Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1996**, *37*, 2997. (d) Smith, A. B. III.; Kinsho, T. *Tetrahedron Lett.* **1996**, *37*, 6461.

(15) Representative procedure for the conversion **5** → **2**: A toluene (5 mL) solution of compound **5f** (0.79 mmol, 166 mg) was added within 5 min to refluxing toluene (20 mL). After additional 10 min at reflux, the mixture was allowed to cool to r.t. The precipitated solid was collected and recrystallized from pentane/CH_2Cl_2 to give 97 mg (0.64 mmol, 81%) of pyrone **2f** as a crystalline solid. Mp (decomp.): 190 °C (ref.[19]: 191–194 °C). ^{1}H NMR (250 MHz, d^6-DMSO): δ = 1.89 (d, *J* = 7.0 Hz, 3 H), 5.30 (d, *J* = 1.5 Hz, 1 H), 6.05 (d, *J* = 1.5 Hz, 1 H), 6.21 (d, *J* = 15.5 Hz, 1 H), 6.53 (dq, *J* = 7.0 Hz, *J* = 15.5 Hz, 1 H), 11.69 (s, br, 1H). ^{13}C NMR (62.9 MHz, d_6-DMSO): δ = 18.4, 89.7, 100.1, 123.7, 134.0, 159.3, 163.3, 170.7. Anal. Calcd for $C_8H_8O_3$ (152.15): C, 63.15; H, 5.30. Found: C, 62.97; H, 5.25.

(16) (a) Literature references to those compounds in the table which have been previously prepared: **2a**: ref.[13]; **2f**: ref.[19]. (b) **2g**: Resplandy, A. *Bull. Soc. Chim. Fr.* **1965**, 525. (c) **2h** see ref.[3b,4b] and: Butt, M. A.; Elvidge, J. A. *J. Chem. Soc.* **1963**, 4483. (d) **4f**, **4g**, **4i**: ref.[9b]; **4h**: ref.[8b,9b]; **5h**: ref.[3b].

(17) Bu'Lock, J. D.; Smith, H. G. *J. Chem. Soc.* **1960**, 502.

(18) (a) Adityachaudhyvy, N.; Das, A. K.; Daskanungo, P. *Indian J. Chem.* **1976**, *14B*, 909. (b) Ichino, K.; Tanaka, H.; Ito, K. *Tetrahedron* **1988**, *44*, 3251. (c) Ali, M. S.; Tezuka, Y.; Awale, S.; Banskota, A. H.; Shigtoshi, S. *J. Nat. Prod.* **2001**, *64*, 289.

(19) Kato, K.; Hirata, Y.; Yamamura, S. *J. Chem. Soc. C* **1969**, 1997.