A New One-Pot Synthesis of 2-Quaternary 1,3-Diketones

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Abstract: A facile one-pot synthesis of 1,3-diketones with stereogenic quaternary center at C-2 has been developed on the basis of an oxidative-rearrangement of a series of tertiary α-hydroxy epoxides on treatment with pyridinium chlorochromate (PCC). A possible mechanism is also discussed.

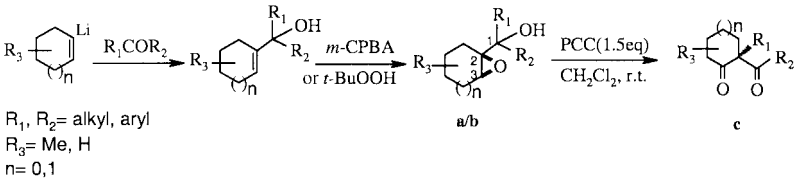
Key words: 1,3-diketones, quaternary carbon, pyridinium chlorochromate, tertiary α-hydroxy epoxides, oxidative rearrangement

1,3-Diketones with quaternary C-2 are strongly required building blocks in organic synthesis due to the fact that many important organic compounds incorporate this kind of key structural units, or similar "2-quaternary 3-hydroxy ketone"[1] or "2-quaternary 1,3-diol"[2] units such as the biologically active taxol[3] and epothilone,[4] and various chiral ligands used for preparing asymmetric catalysts.[5] Although several synthetic procedures for 2-quaternary 1,3-diketones have been developed,[6] they generally involve two or more reaction steps. In connection with our recent investigation on the diastereo-recognizable reaction of tertiary α-hydroxy epoxides with Cr(VI) reagents,[7] we found interestingly that a few α-hydroxy epoxides bearing aromatic groups at C-1 could undergo a carbon-to-carbon 1,2-migration and the successive oxidation of the hydroxy group with pyridinium chlorochromate (PCC) in a one-pot reaction. This observation reminded us to expand this reaction and develop a new one-pot procedure for the preparation of 2-quaternary 1,3-diketones. The major distinct features of this method involve: 1) the easy construction of a stereogenic quaternary carbon center that is generally difficult to access in organic synthesis; 2) the convenient experimental procedure; 3) the mild reaction condition and the inexpensive reagent; 4) the more important synthetic value is that two C-1 epimers of the tertiary α-hydroxy epoxides could afford a single diastereoisomerically pure 2-quaternary 1,3-diketone; and 5) the diastereo-differentiation between two C-1 epimers in some examples. Herein, we present our experimental results, a few of which have been mentioned in our previous report.[7]

In consideration of their wide presence in organic compounds, we selected here mainly the α-hydroxy epoxide substrates with the cyclohexyl and cyclopentyl units for investigation, which were prepared from the corresponding racemic α-hydroxy alkenes by epoxidation with *m*-CPBA or *t*-BuOOH/VO(acac)$_2$.[8] The rearrangement-oxidation was carried out in a typical procedure (see experimental section) with 1.5 equivalents of PCC in CH_2Cl_2 solution at room temperature, as shown in Scheme 1. The obtained results are listed in Table 1, from which we can see that all examples afforded the 2-quaternary 1,3-diketones in moderate to excellent yields.

Interestingly, entries 1–3, in which the sterically hindering methyl group is situated at the six-membered ring of the substrate pairs, showed the diastereo-recognizable activity. Thus, the PCC reagent reacted selectively with the isomers **1b**,**2b** and **3a** to form the 2-quaternary 1,3-diketones **1c**,**2c** and **3c**, respectively, while the isomers **1a**,**2a** and **3b** were recovered in yields of 42%, 40% and 25% and with de values of 75%, 66% and 96%, respectively. In contrast, entries 4 and 6–9, in which all the substrates possess a pair of C-1 epimers, gave only products **4c** and **6c**–**9c**, respectively. We were not able to isolate other isomeric products, or recover any enriched C-1 epimers of the substrates in these examples. This fact is of great use in organic synthesis.[7]

By further inspection of the results in Table 1, we can see that the product yields were dependent, to some extent, upon the property of migratory group or the substrate



Scheme 1

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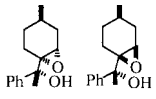
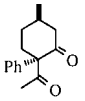
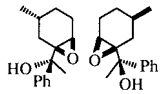
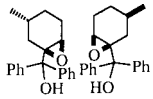
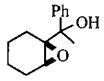
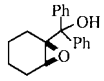
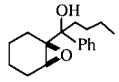
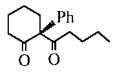
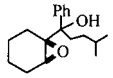
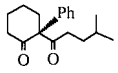
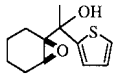
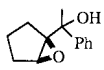
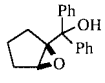
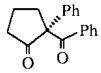
structures. For example in entries 4–7, all substrates incorporated similarly the 'cyclohexene oxide' units and gave high yields (91–99%) of the 2-quaternary 1,3-diketones **4c**–**7c**. Whereas entry 8, which involved the migration of 2′-thiophenyl group, afforded only 67% of **8c**. In entries 9 and 10, the substrates possess similarly the 'cyclopentene oxide' units and gave only moderate yields of **9c** and **10c**. At this stage, however, we were not clear about the details of relationship between the product yields and the migratory aptitude of groups or the substrate structures.

Generally, the oxidation with Cr(VI) reagents involves complex processes, some of which are proposed only on the basis of deduction.[9] For this rearrangement-oxidation reaction here reported, we presume that, in entries 4–10, this reaction may involve two steps: 1) the tertiary α-hydroxy epoxide **a**/**b** rearranged to form the intramolecular rearrangement product (β-hydroxy ketone) via migration

Table 1 Preparation of 2-Quternary 1,3-Diketones[a,b]

Entry	Substrate	*syn*/*anti* Ratio	Reaction Time	Product	Yield (%)
1	 **1a/1b**	63:37	10 h	 **1c**	84
2	 **2a/2b**	56:44	25 h	 **2c**	71
3	 **3a/3b**	69:31	25 h	 **3c**	98
4	 **4a/4b**	70:30	18 h	 **4c**	94
5	 **5a**	–	24 h	 **5c**	99
6	 **6a/6b**	79:21	4 h	 **6c**	91
7	 **7a/7b**	99:1	24 h	 **7c**	93
8	 **8a/8b**	80:20	25 h	 **8c**	67
9	 **9a/9b**	80:20	5 d	 **9c**	61
10	 **10a**	–	48 h	 **10c**	77

[a] Structures of all products were determined by ^{1}H and ^{13}C NMR and MS. Isomer ratios were measured with ^{1}H NMR and/or GC, and the stereochemistry was determined using 2D NMR techniques.
[b] The yields of entries 1–3 refer to single starting isomers **1b**,**2b** and **3a**

of aryl group; and 2) after transfer of the hydride and electron between Cr(VI) reagent and rearrangement product, a final product **c** (2-quaternary 1,3-diketone) was formed in a one-pot reaction. To assign a possible reaction mechanism, we conducted supporting experiments. It is well known that PCC has a slightly acidic character,[10] so in the present reaction we used PCC in combination with NaOAc, which acted as a buffer to avoid the effect of the acidic character of PCC on this reaction. As a result, we found that the reaction worked very slowly. For example, in entry 4, treatment of **4a**/**4b** with PCC/NaOAc (1:1) for 24 hours afforded only a small amount of product **4c**, and most of the substrates **4a**/**4b** did not react. This fact shows that sufficiently acidic character is essential for acceleration of this reaction and there seems to be a possibility that the rearrangement reaction may be prompted by acid. Consequently, we treated **4a**/**4b** (50 mg) in CH_2Cl_2 (5 mL) with concentratedd HCl (0.02 mL) at room temperature and found that in less than 30 minutes **4a**/**4b** disappeared completely to give the rearrangement product (β-hydroxy ketone). After that, we added PCC (1.5 equiv) to the reaction mixture above, which was stirred for further 12 hours to afford the 2-quaternary 1,3-diketone **4c** in high yield. But **4a**/**4b** did not react at all with the basic PDC (pyridinium dichromate).[11] These facts indicate that this one-pot reaction may first undergo rearrangement prompted by acid and PCC simply oxidized the rearrangement products to afford 2-quaternary 1,3-diketones.

In addition, from entries 1–3 we selected **1a**/**1b** for further investigations. We treated **1a**/**1b** (50 mg) in CH_2Cl_2 (5 mL) with concentrated HCl (0.02 mL) at room temperature, and in less than 1 hour **1a**/**1b** disappeared completely to afford the rearrangement product (β-hydroxy ketone). However, it did not show diastereo-recognizable activity at all and we were not able to recover any enriched C-1 epimer **1a** or **1b**. These experimental results indicated that the reaction mechanism for entries 1–3 may be different from that for entries 4–10. So we presumed that it first involves the coordination of Cr(VI) of PCC with C-1 OH and epoxy oxygen, which promoted the ring opening of the epoxide, as shown in Scheme 2. Concomitantly, an *anti* 1,2-migration of R_3 led to the formation of stereogenic C-2 quaternary carbon center and C-1 carbonyl. Then the 2-quternary 1,3-diketone was formed through oxidation of the hydroxy group by Cr(VI) of PCC. As for the diastereo-recognization of this reaction in entries 1−3, we thought it would be effected by the sterically hindering methyl situated at the six-membered ring in substrates **1a**/**b**–**3a**/**b**, as shown in the chair conformations in the Figure.

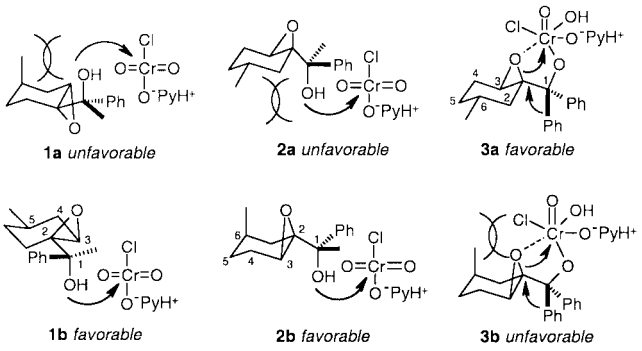


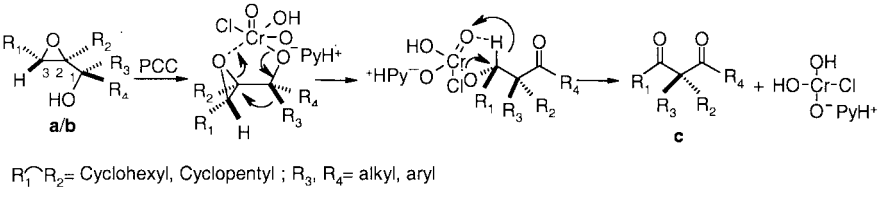
Figure Favorable and unfavorable chair conformations of **1a**–**3a** and **1b**–**3b** for oxidation with PCC

For entries 1 and 2, the controlling step of the reaction would be, first the coordination of Cr(VI) of PCC with C-1 OH, hence the isomers **1b** and **2b**, in which the C-5 Me (**1b**) or C-6 Me (**2b**) and C-1 located at different sides of the cyclohexane plane are more reactive than **1a** and **2a**, in which the C-5 Me (**1a**) or C-6 Me (**2a**) and C-1 are located at the same side of the cyclohexane plane (see Figure). While in entry 3, the two big phenyl groups attached to C-1 prevent Cr(VI) of PCC from approaching to C-1 OH. So the controlling step in entry 3 would be, first the coordination of Cr(VI) of PCC with epoxy oxygen, and thus the isomer **3a** is more reactive than **3b** for the same reason as above.

In conclusion, we have successfully developed a new synthetic method for 2-quaternary 1,3-diketones and further examination of its scope and applications are in progress.

Reaction of Tertiary α-Hydroxy Epoxides 1–10 with PCC; General Procedure

To a stirred solution of tertiary α-hydroxy epoxide **a**/**b** (0.47 mmol) in CH_2Cl_2 (15 mL) was added PCC (0.71 mmol). The reaction mixture was stirred at r.t. until the reactants disappeared completely (TLC monitoring), then diluted with Et_2O (15 mL) and stirred for further 5 min. The black reaction mixture was passed through a neutral Al_2O_3 column, eluting with Et_2O (20 mL). The obtained overall fractions were concentrated under reduced pressure and the crude product was chromatographed on silica gel eluting with petroleum ether (bp 60−90 °C)/EtOAc (10:0→10:3) to afford pure 1,3-diketones **c**. The ^1H, ^{13}C NMR and mass spectral data of all products are listed in Table 2.



Scheme 2

Table 2 Spectral Data of 2-Quaternary 1,3-Diketones[a,b]

Product	^{1}H NMR δ, *J* (Hz)	^{13}C NMR δ	MS *m/z* (%)
1c	0.83 (d, *J* = 6.4, 3 H), 1.15 (m, 1 H), 1.66 (m, 1 H), 1.90 (s, 3 H), 2.31 (m, 4 H), 2.56 (m, 1 H), 7.13–7.35 (m, 5 H)	21.8, 28.5, 29.4, 31.8, 35.7, 48.7, 70.6, 127.8 (3 C), 129.2 (2 C), 137.0, 206.6, 210.5	230 (M^+, <1), 188 (100), 146 (22), 117 (20), 115 (15), 103 (18), 97 (13), 91 (43), 84 (18), 77 (17) (HRMS: [M^+] calcd for $C_{15}H_{18}O_2$, 230.1307; found, 230.1314)
2c	0.93 (d, *J* = 6.4, 3 H), 1.36–2.66 (m, 10 H), 7.14–7.41 (m, 5 H)	21.2, 27.1, 28.7, 35.9, 40.0, 41.1, 70.8, 127.7–129.3 (5 C), 137.6, 206.5, 211.4	230 (M^+, <1), 188 (100), 173 (15), 146 (43), 118 (27), 115 (13), 103 (16), 97 (3), 91 (21), 77 (15), 43 (16) (HRMS: [M^+] calcd for $C_{15}H_{18}O_2$, 230.1307; found, 230.1320)
3c	1.05 (d, *J* = 6.3, 3 H), 1.64–2.80 (m, 7 H), 7.23–7.51 (m, 10 H)	21.3, 27.2, 34.9, 40.3, 43.4, 70.6, 127.2–131.1 (10 C), 137.4, 137.8, 200.7, 210.8	292 (M^+, 6), 129 (1), 128 (1), 115 (2), 105 (100), 103 (3), 91 (5), 89 (2), 77(21) (HRMS: [M^+] calcd for $C_{20}H_{20}O_2$, 292.1463; found, 292.1466)
4c	1.63 (m, 2 H), 1.78 (m, 2 H), 1.92 (s, 3 H), 2.43 (m, 3 H), 2.56 (m, 1 H), 7.11–7.34 (m, 5 H)	21.4, 27.6, 33.6 (2 C), 40.9, 71.7, 127.8, 127.9 (2 C), 129.0 (2 C), 136.7, 206.7, 209.7	216 (M^+, <1), 197 (0.2), 174 (100), 156 (6), 146 (19), 115 (20), 91 (60), 77 (17), 43 (32) (HRMS: [M^+] calcd for $C_{14}H_{16}O_2$ + Na, 239.1043; found, 239.1039)
5c	1.67 (m, 3 H), 1.96 (m, 1 H), 2.15 (m, 1 H), 2.47 (m, 2 H), 2.83 (m, 1 H), 7.16–7.48 (m, 10 H)	22.3, 27.6, 37.9, 42.0, 71.1, 127.5–132.4 (10 C), 136.4, 138.0, 200.1, 207.9	278 (M^+, 6), 165 (1), 149 (2), 105 (100), 77 (19), 51 (3) (HRMS: [M^+] calcd for $C_{19}H_{18}O_2$ + H, 279.1380; found, 279.1378)
6c	0.68 (t, *J* = 7.3, 3 H), 1.02–1.07 (m, 1 H), 1.34 (m, 1 H), 1.62–1.66 (m, 3 H), 1.76–1.80 (m, 3 H), 2.08–2.11 (m, 1 H), 2.26–2.58 (m, 5 H), 7.11–7.33 (m, 5 H)	14.0, 21.5, 22.0, 26.1, 27.7, 33.7, 39.5, 41.1, 71.8, 127.7, 128.0 (2 C), 128.9 (2 C), 136.9, 209.0, 209.9	258 (M^+, 0.2), 211 (0.1), 176 (1), 174 (100), 146 (5), 91 (7), 77 (2), 63 (0.6) (HRMS: [M^+] calcd for $C_{17}H_{22}O_2$ + H, 259.1693; found, 259.1696)
7c	0.63, 0.65 (2 d, *J* = 6.7, 2 × 3 H), 1.12 (m, 1 H), 1.27 (m, 1 H), 1.62 (m, 3 H), 1.79 (m, 2 H), 2.08 (m, 1 H), 2.30 (m, 1 H), 2.44 (m, 3 H), 2.56 (m, 1 H), 7.12–7.34 (m, 5 H)	21.5, 22.1, 22.3, 27.3, 27.7, 32.9, 33.7, 37.8, 41.0, 71.6, 127.7, 128.0 (2 C), 128.9 (2 C), 136.8, 209.2, 210.0	272 (M^+, 2), 257 (0.2), 211 (0.2), 174 (100), 156 (3), 115 (8), 91 (16), 84 (20), 77 (5), 55 (3), 43 (8) (HRMS: calcd for $C_{18}H_{24}O_2$ + Na, 295.1669; found, 295.1667)
8c	1.85 (m, 4 H), 2.06 (s, 3 H), 2.24 (m, 1 H), 2.46 (m, 1 H), 2.67 (m, 1 H), 2.76 (m, 1 H), 6.69 (m, 1 H), 7.03 (m, 1 H), 7.35 (m, 1 H)	21.8, 26.8, 27.0, 36.3, 40.7, 68.9, 126.1,127.0 (2 C), 140.5, 204.6, 207.3	222 (M^+, <1), 180 (100), 151 (17), 134 (1), 123 (25), 97 (19), 65 (3), 43 (13) (HRMS: [M^+] calcd for $C_{12}H_{14}O_2S$ + Na: 245.0607, found, 245.0611)
9c	1.81–1.96 (m, 2 H), 1.97 (s, 3 H), 2.29 (m, 1 H), 2.39 (m, 2 H), 2.88 (m, 1 H), 7.26–7.40 (m, 5 H)	19.6, 26.7, 34.6, 39.2, 73.1, 127.9 (2 C), 128.3, 129.7 (2 C), 139.1, 204.1, 214.0	160 (M^+–42, 100), 159 (26), 131 (5), 117 (15), 91 (12), 77 (13), 63 (4), 43 (16) (HRMS: [M^+] calcd for ($C_{13}H_{14}O_2$ + Na, 225.0886, found, 225.0882)
10c	1.87–1.94 (m,1 H), 2.03–2.07 (m, 1 H), 2.35–2.45 (m, 2 H), 2.75–2.81 (m, 1 H), 2.85–2.90 (m, 1 H), 7.26–7.69 (m, 10 H)	19.8, 35.4, 38.3, 71.2, 128.1–133.4 (10 C), 135.6, 139.0, 198.3, 212.4	264 (M^+, 4), 219 (0.3), 181 (2), 165 (2), 128 (2), 105 (100), 77 (25), 51 (5) (HRMS: [M^+] calcd for $C_{18}H_{16}O_2$ + Na, 287.1043, found, 287.1047)

[a] The NMR spectra were measured on Bruker AM-400 MHz spectrometer using $CDCl_3$ as solvent and TMS as standard.
[b] The mass spectral data for all products were measured as GC-MS (EI: 70eV). The HRMS for **1c**–**3c** were recorded on VG ZAB-HS spectrometer using FAB mode, and those for **4c**–**10c** on Bruker Daltonics APEX II spectrometer using ESI positive mode.

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