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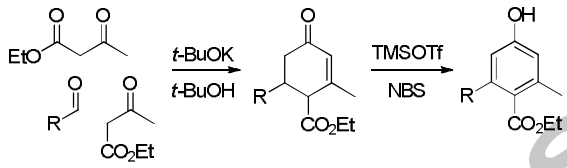

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Efficient preparation method of 4-hydroxybenzoic esters – oxidation of substituted Hagemman's ester

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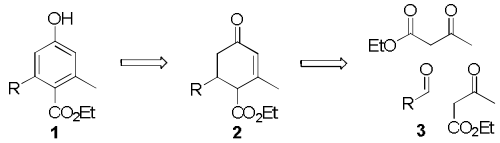
ABSTRACT

A practical two-step synthetic method of diversely R-substituted 4-hydroxybenzoic esters, which may have wide applications in household chemicals and polymeric materials, was developed by 2:1 coupling between ethyl acetoacetate and aldehydes (RCHO) in *t*-BuOK/*t*-BuOH, followed by oxidative aromatization of the resulting Hagemman's esters. Application of the condition using stoichiometric NBS and catalytic TMS·OTf efficiently induced oxidation of the Hagemman's esters to produce 4-hydroxybenzoic esters.

Being found as natural products showing antimicrobial activity[1] as well as major components of lignin,[2] 4-hydroxybenzoic acids and their esters (parabens) have been widely used as food preservatives,[3] monomers for poly(phenylene oxide)s (PPO),[4] and intermediates of pesticides and antiseptics.[5] The electron donating and withdrawing substituents at *para*-position do not allow easy preparation of the parent compound either from phenols or from benzoic acids. Instead, aromatization or oxidation of properly substituted precursors would lead to the desired compounds.[6] It was thus envisioned that the ester of 4-hydroxybenzoic acids could be synthesized by oxidation of the corresponding Hagemman's esters, which might be obtained by the 2:1 coupling and annulation of acetoacetate and various aldehydes (Scheme 1).

In principle, diversely R-substituted hindered Hagemman's esters can be prepared by the selection of the group R in aldehydes.[7] There are a couple of oxidation methods of Hagemman's esters reported in the literature so far, one by air oxidation using expensive metal catalysts like Pt and Pd or base at high temperature,[8] and the other by troublesome Br_2 in CS_2.[9] In an effort to synthesize carotenoids with improved biological activity, we need to develop a practical synthetic method of diversely R-substituted 4-hydroxybenzoic esters as the terminal ring structure.[10] Because a condition using *N*-bromosuccinimide (NBS) with catalytic trimethylsilyl triflormethanesulfonate (TMS·OTf) has been a superior procedure to that of α-bromination of carbonyl compounds using Br_2,[11] oxidation of Hagemman's ester using this condition would be a perfect repertoire for the synthesis of 4-hydroxybenzoic esters. We herein report the details of the two-step protocol for the efficient synthesis of R-substituted 4-hydroxybenzoic esters from readily available simple acyclic compounds.



Scheme 1. Practical disconnection to the R-substituted 4-hydroxybenzoic esters

We have reported the synthesis of ethyl 2,6-dimethyl-4-oxocyclohex-2-ene-1-carboxylate (**2a**) by 2:1 coupling of ethyl acetoacetate and acetaldehyde with catalytic *t*-BuOK in *t*-BuOH (Scheme 2, R = CH_3).[12] The initial 1:1 coupling produces the condensation product **4** (R = CH_3), with which the second coupling of ethyl acetoacetate gives symmetrical diketo-diester **A** (R = CH_3). Aldol reaction between the two carbonyl groups, followed by intramolecular esterification of the resulting hydroxyl group with the opposite ester generates bicyclic lactone **B** (R = CH_3), which may undergo decarboxylation to provide **2a**. The use of *t*-BuOH (playing with higher pK_a) is important in controlling the reaction pathway towards **B**, instead of aldol condensation leading to the isomeric ester at lower pK_a (e.g. EtOH).[12]

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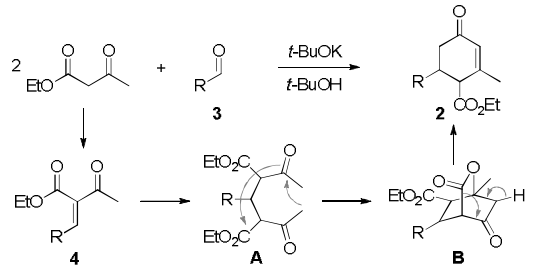
The utility of this reaction sequence was demonstrated for the synthesis of diversely R-substituted Hagemman's esters **2** (Table 1). Two equivalents of ethyl acetoacetate were coupled with various aliphatic aldehydes **3** in *t*-BuOK/*t*-BuOH at 80 °C for 12 h to give the corresponding Hagemman's esters in 73–95% yields (Entries 1–5).[13] Steric hindrance of R seemed to prevent easy formation of bicyclic lactone **B**. No product **2** was obtained from 2,2-dimethylpropanal (R = *t*-Bu, entry 6). It is interesting to note that ethyl 2-oxoacetate also produced 3-methylcyclohex-2-en-1-one with 4,5-diester substitutions in 65% yield (Entry 7). Aromatic aldehydes required higher temperature (110 °C) and longer reaction time (24 h) to produce reasonable yields (43–80%) of Hagemman's esters **2**, presumably as the same reason of steric hindrance (Entries 8–17). 2-Furfural gave the higher yield and naphthalene-2-carbaldehyde gave the lower. There seemed to be some correlations between the electronic nature of R and the yield of **2**: the withdrawer to higher yield.



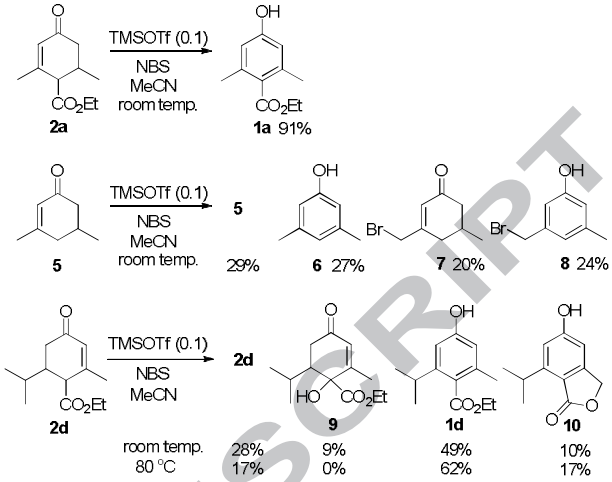
Scheme 2. Mechanism for the synthesis of Hagemman's ester **2** by 2:1 coupling between ethyl acetoacetate and aldehyde **3**.

Table 1. The yield of Hagemman's esters **2** according to the reaction in Scheme 2.[a]

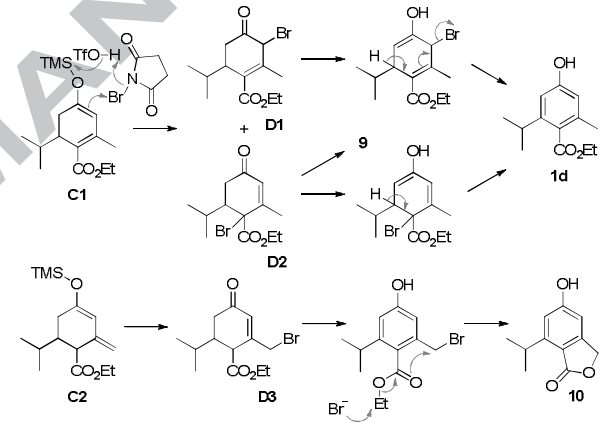
Entry	R	Yield **2** (%)	Entry	R	Yield **2** (%)
1	Me	95	10	*p*-MeC_6H_4	55
2	Et	88	11	*p*-$MeSC_6H_4$	43
3	*n*-Pr	74	12	*p*-$MeOC_6H_4$	40
4	*i*-Pr	93	13	*p*-NCC_6H_4	57
5	*s*-Bu	73	14	*p*-$NO_2C_6H_4$	63
6	*t*-Bu	0	15	*p*-BrC_6H_4	58
7	CO_2Et	65	16	*p*-ClC_6H_4	68
8	2-furanyl	80	17	2-naphtyl	46
9	Ph	53			

[a] Reaction conditions: heated at 80 °C for 12 h (aliphatic aldehyde: Entries 1–7) or heated at 110 °C for 24 h (aromatic aldehyde: Entries 8–17) with 0.15 equiv. of *t*-BuOK in *t*-BuOH.

Oxidation of Hagemman's ester **2a** with NBS and a catalytic (10 mol%) TMS·OTf worked very well in MeCN as expected. Ethyl 2,6-dimethyl-4-hydroxybenzoate (**1a**) was obtained in 91% yield at 25 °C for 12 h (Scheme 3).[14] It was speculated that the presence of an ester group at 4-position was crucial for facile oxidation to phenol through the ring bromination as the initial step. 3,5-Dimethylcyclohex-2-en-1-one (**5**) produced the corresponding phenol **6** only in 27% yield under the above condition (Scheme 3). The side chain bromination became the major pathway to yield compounds **7** (20%) and **8** (24%). In the case of sterically hindered Hagemman's ester **2d**, the desired phenol **1d** was obtained in 49% yield at room temperature along with 28% of **2d** (unreacted starting material), 9% of **9** (hydrolysis of the ring bromination at 4-position), and 10% of **10** (lactonization of the side chain bromination). The yield of **1d** was increased to 62% at 80 ºC at the expense of **9** and some of the unreacted starting material. The formation of lactone **10** was also increased at this temperature (17%).



Scheme 3. Investigation of the oxidation of cyclohex-2-en-1-ones by NBS/TMS·OTf according to the substituent (electronic and steric) effect.



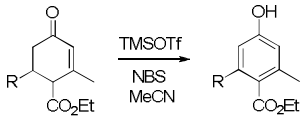
Scheme 4. The mechanism of the oxidation using NBS/TMS·OTf was elucidated for hindered Hagemman's ester **2d**.

The mechanism of the oxidation using NBS and catalytic TMS·OTf was proposed for the hindered Hagemman's ester **2d** based on the above experimental results (Scheme 4). Presence of the 4-carbethoxy group allows the major formation of silyl dienol ether **C1** with TMS·OTf. Bromination with NBS at α-position produces **D1**, which may undergo dehydrobromination and tautomerization to give the desired phenol **1d**. Bromination at γ-position initially produces **D2**, which provides either **9** at room temperature upon hydrolysis or **1d** at 80 °C upon dehydrobromination and tautomerization. Steric hindrance between the substituent groups may allow the formation of the silyl dienol ether **C2** from the side chain (as minor). Bromination at α-position would eventually lead to the desired phenol **1d** (not illustrated), on the other hand, the formation of phenol **10** can be ascribed to γ-bromination, followed by lactonization with the ethyl ester and oxidation of cyclohexenone. The yield of lactone **10** was increased at higher temperature. TMS·OTf was used as a catalyst for bromination because it could be regenerated during the bromination step, as was illustrated for **C1** (Scheme 4).

Generality of the above oxidation using NBS/TMS·OTf was demonstrated in Table 2 for the Hagemman's esters, synthesized in Table 1. The oxidation of hindered Hagemman's ester **2** requires higher temperature (80 °C) for acceptable yields of 4-hydroxybenzoic esters **1** except the case of simple 4-carbethoxy-3,5-dimethylcyclohex-2-en-1-one (**2a**), in which ambient temperature is enough to give 91% of the desired product **1a**. Catalyst TMS·OTf was used in 10 mol% with a stoichiometric amount of NBS.

Similar yields (57–65%) of 4-hydroxybenzoic esters **1** were obtained for alkyl substituent of R, irrespective of the degree of substitution (entries 2–5). It is also noteworthy that the phenol with 3,4-diester group can be obtained in 39% yield by this way (entry 6). 4-Hydroxybenzoic esters **1** with an aryl substituent of R were also obtained in reasonable yields (45–73%, entries 7–16). It is advantageous to have an electron-withdrawing substituent in the aromatic group of R (e.g. CN, entry 12) in producing higher yields of 4-hydroxybenzoic esters **1** presumably due to competing bromination on the electron-rich aromatic ring (e.g. MeO, entry 11).[11]

Table 2. Oxidation of Hagemman's esters **2** by NBS/TMS·OTf to 4-hydroxybenzoic esters **1**.[a]



2 **1**

Entry	R	Yield **1** (%)	Entry	R	Yield **1** (%)
1	Me	91	9	*p*-MeC_6H_4	65
2	Et	65	10	*p*-$MeSC_6H_4$	61
3	*n*-Pr	59	11	*p*-$MeOC_6H_4$	51
4	*i*-Pr	62	12	*p*-NCC_6H_4	73
5	*s*-Bu	57	13	*p*-$NO_2C_6H_4$	66
6	CO_2Et	39	14	*p*-BrC_6H_4	53
7	2-furanyl	45	15	*p*-ClC_6H_4	56
8	Ph	50	16	2-naphtyl	50

[a] Reaction conditions: stirred at 25 °C for 12 h (Entry 1) or heated at 80 °C for 6 h (Entry 2–16) with 0.10 equiv. of TMS·OTf and 1 equiv. of NBS.

In summary, a practical two-step synthetic procedure for 4-hydroxybenzoic esters **1** was developed by 2:1 coupling between ethyl acetoacetate and various aldehyde (RCHO), followed by efficient oxidation of the resulting Hagemman's esters **2**. We extended the facile 2:1 coupling of ethyl acetoacetate and various aldehydes (R-CHO) including aromatic ones under *t*-BuOK/*t*-BuOH condition to produce hindered Hagemman's esters with various substitution patterns. The condition utilizing stoichiometric NBS and catalytic TMS·OTf was successfully applied to the oxidation of the above Hagemman's esters for efficient construction of medicinally and industrially useful 4-hydroxybenzoic esters **1**.

Acknowledgments

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13. Representative experimental procedure for **2a**: To a stirred solution of ethyl acetoacetate (10.40 g, 79.91 mmol) and acetaldehyde (1.76 g, 39.95 mmol) in *t*-BuOH (50 mL) was added *t*-BuOK (0.67 g, 5.99 mmol). The mixture was heated at 80 °C for 12 h. Most of solvent was removed under reduced pressure, and the crude product was dissolved in EtOAc, which was washed with 1 M HCl and with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give cyclohexenone **2a** (7.45 g, 37.96 mmol) in 95% yield as yellow liquid (a 2.4:1 mixture of stereoisomers). Data for **2a**: R_f = 0.26 (1:4 EtOAc/hexane); ^{1}H NMR (major, $CDCl_3$) δ 1.08 (d, *J* = 6.4 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 2.98 (s, 3H), 2.04–2.64 (m, 3H), 3.02 (d, *J* = 7.6 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 5.97 (br s, 1H) ppm; ^{13}C-NMR ($CDCl_3$) δ 14.2, 19.8, 22.7, 32.8, 43.1, 54.5, 61.3, 128.0, 156.0, 171.9, 198.2 ppm.
14. Representative experimental procedure for **1a**: To a stirred solution of cyclohexenone **2a** (11.30 g, 57.60 mmol) in MeCN (50 mL) were added *N*-bromosuccinimide (10.25 g, 57.60 mmol) and TMS·OTf (1.28 g, 5.76 mmol, 10 mol%). The mixture was stirred at room temperature for 12 h under argon atmosphere, diluted with EtOAc, washed with 1 M HCl, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product (16.02 g) as reddish yellow oil. The crude product was purified by SiO_2 flash column chromatography (eluent 25–45% EtOAc/hexane gradient) to give pure phenol **1a** (10.18 g, 52.42 mmol) in 91% yield as yellow oil. Data for **1a**: R_f = 0.23 (1:4 EtOAc/hexane); ^{1}H-NMR ($CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 2.25 (s, 6H), 4.35 (q, *J* = 7.2 Hz, 2H), 6.45 (s, 2H) ppm; ^{13}C-NMR ($CDCl_3$) δ 13.9, 19.8, 61.0, 114.5, 125.2, 137.4, 156.8, 171.0 ppm; IR (KBr) 3381, 2978, 2933, 1715, 1655, 1610, 1592, 1461, 1446, 1368, 1256, 1159, 1088, 1029, 854, 783, 716, 637, 604 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0947.

Highlights.

- Hagemman's esters were prepared by coupling between acetoacetate and aldehydes.
- Coupling, cyclization, and decarboxylation proceeded in one opt using *t*-BuOK/*t*-BuOH.
- 4-Hydroxybenzoic esters were synthesized by oxidation of Hagemman's esters.
- Bromination condition using NBS/TMS·OTf induced oxidation of Hagemman's esters.