Effect of Calcium Reagents on Aldol Reactions of Phenolic Enolates with Aldehydes in Alcohol

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Organic reactions that occur in aqueous media have received growing attention recently and in general eliminate the constraints of inert atmosphere and anhydrous conditions.[1−4] Many organic compounds, however, exhibit only sparing solubility in water. It has been reported that divalent and trivalent metal reagents such as $Ca(OH)_2$, $CaCl_2$/KOH, or $SmCl_3$/KOH play an important role in the aldol reaction of unprotected ketoses with formaldehyde in water or alcohol.[5,6] Herein we report the aldol-type reaction of phenolic enolates derived from methyl 2,4-dihydroxybenzoate (**1**) and its analogs with not only water-soluble aldehydes but also hydrophobic aldehydes in methanol (Scheme 1). This reaction was accomplished using alkaline earth metal reagents such as $Ca(OH)_2$, $CaCl_2$/KOH, or $BaCl_2$/KOH instead of alkaline metal reagents such as KOH or LiCl/KOH.

Table 1 shows the results of several aldol reactions, referred to as runs 1−13. The reaction of water-soluble formaldehyde with the phenolic enolate of **1** in aqueous KOH produced a 3-hydroxymethylated derivative **2a** (Table 1, run 1). In contrast, the reaction of hydrophobic benzaldehyde in aqueous KOH hardly proceeded (Table 1, run 4). In run 5 (Table 1), methanol was used as the solvent instead of water in order to dissolve both the aldehyde and substrate. Nevertheless, the reaction using KOH in methanol failed to give the desired adduct. We found that a similar reaction using the reagents $CaCl_2$/KOH dissolved in methanol produced a 63% yield of the adduct **2b** in run 11 (Table 1, quantitative yield is based on consumption of **1**).[7] A comparison of runs 2 and 3 (Table 1) shows a similar effect of $CaCl_2$ on the reaction of **1** with formaldehyde in methanol. Any other type of products **3**−**5** were not obtained. A regioselective C−C bond formation at the C(3) position of **1** was estimated by ^{1}H NMR analysis of **2a** and **2b**, which showed two doublet signals corresponding to the aromatic protons having an *o*-coupling constant.[8]

Runs 5, 9, and 10 in Table 1 show that the reaction of **1** with benzaldehyde in methanol did not proceed when various alkaline metal reagents were used. The adduct **2b** was obtained using alkaline earth metal salts combined with KOH (Table 1, runs 12 and 13) and alkaline earth metal hydroxides (Table 1, runs 7 and 8) with the exception of $Mg(OH)_2$ (Table 1, run 6), which hardly dissolved in methanol. Among the various reagents investigated in Table 1, $CaCl_2$/KOH (run 12) gave the best result. The effectiveness of the divalent metal reagents mentioned above is attributed to their ability as Lewis acids to activate the carbonyl group of the aldehyde. Coordination of the carbonyl group of the aldehyde to the metal cation of the phenolic enolate possibly brought both molecules close enough to react.

A comparison of run 12 in Table 1 with runs 1 and 2 in Table 2 demonstrated that this reaction was not affected by the character of carbonyl substituents of resorcinol derivatives, while resorcinol itself failed to give the corresponding adduct. Interestingly, treatment of a mixture of 2,4-dihydroxybenzaldehyde (**8**) and benzaldehyde with $CaCl_2$/KOH did not afford the homocoupling product of **8** but afforded the cross-coupling product **9**. The electrophilic reactivity of the carbonyl group in **8** might be decreased by the anionic charge of the aromatic part of the compound. On the analogy of the regioselective C−C bond formation at the C(3) position of benzoate

Scheme 1

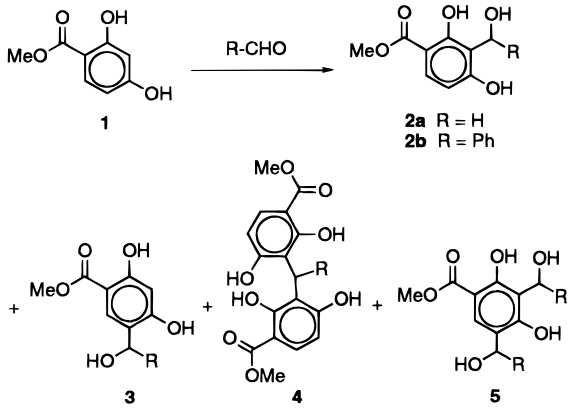

Table 1. Reaction of Methyl 2,4-Dihydroxybenzoate with Formaldehyde or Benzaldehyde[a]

run	RCHO	solvent	reagent (mmol)	product	yield[b] (%)
1[c]	HCHO	H_2O	KOH (0.2)	**2a**	86 (100)
2[c]	HCHO	MeOH	KOH (0.2)	**2a**	0[d]
3	HCHO	MeOH	$CaCl_2$/KOH (0.4/0.4)	**2a**	84 (94)
4	PhCHO	H_2O	KOH (0.4)	**2b**	6 (100)
5	PhCHO	MeOH	KOH (0.4)	**2b**	0[d]
6	PhCHO	MeOH	$Mg(OH)_2$ (0.4)	**2b**	0[e]
7	PhCHO	MeOH	$Ca(OH)_2$ (0.4)	**2b**	63 (94)
8	PhCHO	MeOH	$Ba(OH)_2$ (0.4)	**2b**	65 (100)
9	PhCHO	MeOH	LiCl/KOH (0.4/0.4)	**2b**	0[d]
10	PhCHO	MeOH	NaCl/KOH (0.4/0.4)	**2b**	0[d]
11	PhCHO	MeOH	$CaCl_2$/KOH (0.4/0.4)	**2b**	63 (100)
12	PhCHO	MeOH	$CaCl_2$/KOH (0.4/0.8)	**2b**	73 (100)
13	PhCHO	MeOH	$BaCl_2$/KOH (0.4/0.8)	**2b**	64 (99)

[a] RCHO, 0.72 mmol; **1**, 0.60 mmol; solvent, 2 mL; 0 °C, 24 h. [b] Isolated yield. Yields are based on the consumption of **1** when shown in parentheses. [c] Reaction time, 18 h. [d] Recovery of **1**, 100%. [e] Recovery of **1**, 91%.

(1) For reviews, see: (a) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (c) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741.

(2) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481.

(3) (a) Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 6674. (b) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256.

(4) Denis, C.; Laignel, B.; Plusquellec, D.; Le Marouille, J.-Y.; Botrel, A. *Tetrahedron Lett.* **1996**, *37*, 53.

(5) Shigemasa, Y.; Yokoyama, K.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* **1994**, *35*, 1263.

(6) Saimoto, H.; Yatani, S.; Sashiwa, H.; Shigemasa, Y. *Tetrahedron Lett.* **1995**, *36*, 937.

(7) A typical procedure is as follows: benzaldehyde (76 mg, 0.72 mmol) and **1** (101 mg, 0.60 mmol) were treated with $CaCl_2 \cdot 2H_2O$ (59 mg, 0.4 mmol) in 0.4 M KOH methanol solution (2 mL) for 24 h at 0 °C. After acidification with 1 M HCl, extractive workup followed by purification by preparative TLC (benzene−EtOAc 10:1, developed twice) afforded **2b** (131 mg) along with **1** (27 mg).

(8) Different regioselectivity in the reaction of resorcinols with aldehydes and formation of resins: (a) Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046. (b) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305. (c) Konishi, H.; Ohata, K.; Morikawa, O.; Kobayashi, K. *J. Chem. Soc., Chem. Commun.* **1995**, 309. (d) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, Great Britain, 1989; and references cited therein.

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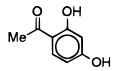
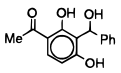
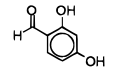
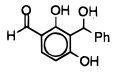
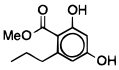
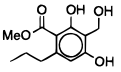
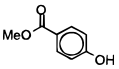
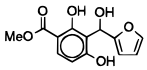
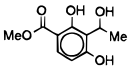
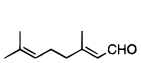
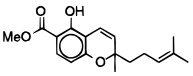
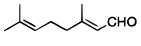
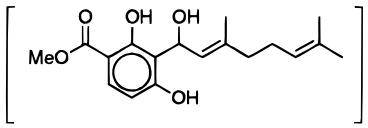
Table 2. Reaction of Resorcinol Derivatives with Various Aldehydes in Methanol[a]

run	substrate	R-CHO	reagent (mmol)	time (d)	yield of product (%)[b]
1	 **6**	Ph-CHO	$CaCl_2$/KOH 0.4/0.8	1	 **7** 70 (100)
2	 **8**	Ph-CHO	$CaCl_2$/KOH 0.4/0.8	1	 **9** 77 (100)
3	 **10**	HCHO	$CaCl_2$/KOH 0.4/0.4	1	 **11** 67 (71)
4	 **12**	Ph-CHO	$CaCl_2$/KOH 0.4/0.8	1	0[c]
5	 **13**	Ph-CHO	$CaCl_2$/KOH 0.4/0.8	1	0[d]
6	**1** 		$CaCl_2$/KOH 0.4/0.4	1	 **14** 59
7	**1**	Me-CHO	$CaCl_2$/KOH 0.4/0.8	2.7	 **15** 26 (72)
8	**1** 		$Ca(OH)_2$ 0.4	7	 **17** 31 (72)
9[e]	**10** 		$Ca(OH)_2$ 0.2	4	**18** 20 (65)

[a] RCHO, 0.72 mmol; substrate, 0.60 mmol; MeOH, 2mL; 0 °C. [b] Isolated yield. Yields are based on the consumption of the substrate when shown in parentheses. [c] Recovery of **12**, 98%. [d] Recovery of **13**, 91%. [e] Citral, 0.29 mmol; **10**, 0.24 mmol; EtOH, 1 mL; 20 °C.

1, the aldol-type reaction of phenolic enolate of benzoate **10**[9] having a substituent at the C(6) position might be performed at the C(3) position (Table 2, run 3). However, benzoates **12** and **13**, having only one hydroxyl group, did not produce any addition products as shown in runs 4 and 5 (Table 2). Therefore, activation of the C(3) position requires the presence of both *o*- and *p*-hydroxyl groups.

Runs 6−8 in Table 2 demonstrated the reaction with various aldehydes. An aliphatic aldehyde, acetaldehyde, was transformed into the corresponding adduct **15** relatively slowly. In the case of an α,β-unsaturated aldehyde, citral (Table 2, run 8), the aldol-type reaction with the phenolic enolate of **1** followed by cyclization of the intermediate **16** led to benzopyran **17**.[10] TLC analysis revealed that the successive cyclization partly proceeded after an acidic workup. The regioselectivity of the cyclization was confirmed by the ^{1}H NMR analysis of **17**, in which a singlet peak corresponding to the remaining *o*-hydroxyl proton was observed at 11.14 ppm. This selectivity is explained by the deactivation of the *o*-hydroxyl group by an intramolecular hydrogen bonding with the neighboring carbonyl group.



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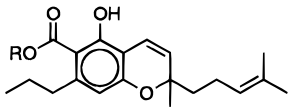

18 R = Me
Cannabichromevarinic acid (**19**) R = H

This sequence was successfully applied to the one-pot synthesis of methyl cannabichromevarinate **18** (Table 2, run 9).[10,11] Similar to the transformation of **1** into **17**, the C−C bond formation between **10** and citral was supposed to be performed at the C(3) position of **10**. Selective incorporation of the *p*-hydroxyl group of **10** into the newly formed pyran ring was estimated by the ^{1}H NMR analysis as mentioned above. The regioselectivity of these processes was also confirmed since the spectral data of synthetic **18** was identical to those reported.[12,13] Hydrolysis of **18** by 1.5 M NaOH in a 1:1 mixture of water and methanol at 45 °C for 2 days produced a naturally occurring cannabinoid, *dl*-cannabichromevarinic acid (**19**),[12,14] in a 42% yield.

In conclusion, the aldol-type reaction of phenolic enolates of 2,4-dihydroxybenzoate derivatives with aldehydes in methanol is achieved using divalent metal reagents such as $Ca(OH)_2$ and $CaCl_2$/KOH. This sequence is successfully applied to the synthesis of *dl*-cannabichromevarinic acid.

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Supporting Information Available: Experimental procedures and characterization data (5 pages).

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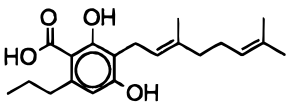
(9) Mori, K.; Kamada, A.; Mori, H. *Liebigs Ann. Chem.* **1989**, 303.
(10) In the case of α,β-unsaturated aldehydes, small amounts of side products of type **4** were formed.

(11) Leading references of the synthesis of naturally occurring 2*H*-chromenes: (a) Cardillo, G.; Cricchio, R.; Merlini, L. *Tetrahedron* **1968**, *24*, 4825. (b) Crombie, L.; Crombie, W. M. L.; Forbes, R.; Whitaker, A. *J. Chem. Res., Miniprint* **1977**, 1301. (c) Mohamed, S. E. N.; Thomas, P.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 431. (d) Iyer, M. R.; Trivedi, G. K. *J. Nat. Prod.* **1993**, *56*, 268. (e) Yamaguchi, S.; Shouji, N.; Kuroda, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 305.
(12) Shoyama, Y.; Hirano, H.; Makino, H.; Umekita, N.; Nishioka, I. *Chem. Pharm. Bull.* **1977**, *25*, 2306.
(13) Different regioselectivity was reported on the reaction of 5-methylresorcinol with cinnamaldehyde: Sartori, G.; Casiraghi, G.; Bolzoni, L.; Casnati, G. *J. Org. Chem.* **1979**, *44*, 803.
(14) Previously **19** was prepared from **20**: Shoyama, Y.; Hirano, H.; Nishioka, I. *J. Labelled Compd. Radiopharm.* **1978**, *14*, 835.



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