Pergamon

Tetrahedron Letters 42 (2001) 597–600

TETRAHEDRON LETTERS

Reaction of aryl-2-hydroxypropenoic derivatives with boron tribromide

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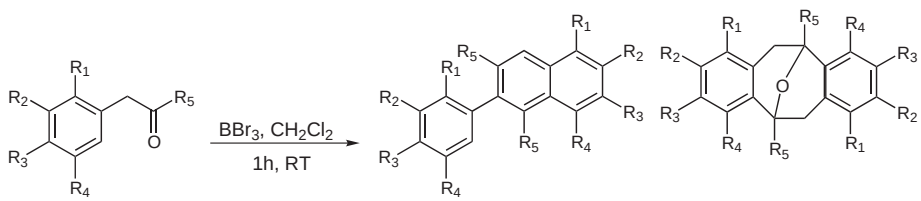
Received 24 May 2000; accepted 7 November 2000

Abstract—(*Z*)-Mono, di or trimethoxyphenyl-2-hydroxypropenoic acids **1a–d** gave mixtures of (*E*) and (*Z*) mono, di or trihydroxyphenyl-2-hydroxypropenoic acids **2a–d** when treated with boron tribromide. The isomerisation proceeds during the work-up and depends on the duration of the hydrolysis and the number of oxygens on the aromatic ring. When the aromatic ring was substituted with a methoxy group at the *ortho* position, a cyclisation occurs, and 3-hydroxycoumarins **3** and benzofuran-2-carboxylic acids **4** can be obtained. 3-Hydroxycoumarin **3a** can also be obtained almost quantitatively from the reaction of methyl 3-(2-methoxyphenyl)-2,3-epoxypropanoate with boron tribromide.

As part of our studies on the synthesis of new biologically active polyhydroxylated compounds, we have developed a new convenient synthesis of polyhydroxylated 2-phenylnaphthalenes in a one-pot procedure from mono or dimethoxyphenylacetones[1,2] (Scheme 1).

The extension of this reaction to arylethanals has revealed remarkable aspects of product differentiation,[3] i.e. formation of 2-phenylnaphthalene from phenylethanal and epoxydibenzo[*a*,*e*]cyclooctenes from activated arylethanals. In order to evaluate the influence of R_5, we turned to the synthesis of aryl-2-hydroxypropenoic acids **1** where the aryl group was substituted by one, two or three methoxy groups. We herein report the reaction of **1** with boron tribromide. The results are given in Table 1.

1a–d were obtained mainly in the *Z*-enol form (95% *Z*-enol, 5% keto and 0% *E*-enol calculated from the ^{1}H NMR spectrum). **1a–d** reacted with boron tribromide to give mixtures of (*E*) and (*Z*) mono, di or trihydroxyphenyl-2-hydroxypropenoic acid. When the hydrolysis duration was fixed at 1 hour, the *E*/*Z* ratio increased with the number of methoxy groups on the aromatic ring. Varying the hydrolysis time in the case of **1b** and **1c**, led to changes in the *E*/*Z* ratio. Pure **2b(*E*)** and **2c(*E*)** may be obtained by prolonging hydrolysis time (24 h, not optimised). As a control, pure **2c(*Z*)** obtained by the method of Wong et al.[4] when treated in a solution of boric acid and hydrogen bromide was totally isomerised into the *E* isomer. In the presence of boric acid alone, **2c(*Z*)** did not isomerise. The exact role of boric and hydrogen bromide is under investigation.



Scheme 1.

Keywords: boron and derivatives; isomerisation; benzofurans; coumarins.

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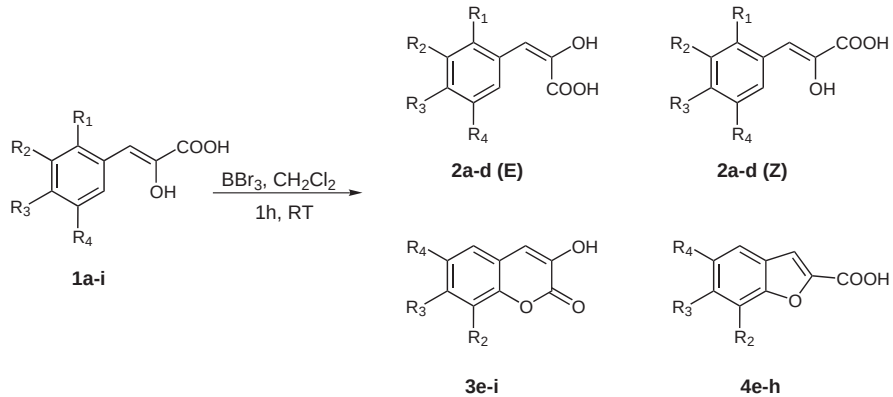
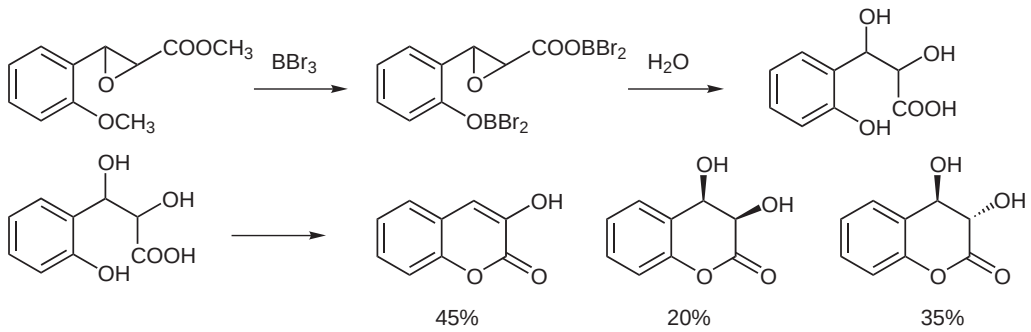
0040-4039/01/$ - see front matter
PII: S0040-4039(00)02011-6

Table 1. Reaction of **1** with BBr_3 in CH_2Cl_2



Starting material	R_1	R_2	R_3	R_4	Products	R_2	R_3	R_4	Yield[a] in products %	% ***E***[b] or yield in **3**	% ***Z***[b] or yield in **4**
1a(Z)	H	H	H	H	**2a**	H	H	H	71	0	100
1b(Z)	H	H	OCH_3	H	**2b**	H	OH	H	91	33[5]	67
1c(Z)	H	OCH_3	OCH_3	H	**2c**	OH	OH	H	63	67[5]	33
1d(Z)	H	OCH_3	OCH_3	OCH_3	**2d**	OH	OH	OH	74	100[5]	0
1e	OCH_3	H	H	H	**3e** or **4e**	H	H	H	90[c]	15[6]	15[11]
1f	OCH_3	OCH_3	H	H	**3f** or **4f**	OH	H	H	75	12[7]	17[12]
1g	OCH_3	H	OCH_3	H	**3g** or **4g**	H	OH	H	81[c]	10[8]	19[12]
1h	OCH_3	H	H	OCH_3	**3h** or **4h**	H	H	OH	73[c]	11[9]	16[13]
1i	OCH_3	H	OCH_3	OCH_3	**3i**	H	OH	OH	–	8[10]	–

[a] Yields are given in crude mixtures except for **2a(*Z*)** and **2d(*E*)**.
[b] Yields in pure products. (Percentages in **2a–d(*Z*)** and **2a–d(*E*)** were calculated from the ^1H NMR spectra of the crude products. The hydrolysis time was fixed at 1 hour).
[c] ^1H NMR spectra of the crude products indicated that **3e–h** and **4e–h** are approximately in a 3/2 ratio.



Scheme 2.

The isomerisation was favoured by the presence of electron-rich groups and the *Z* form was totally converted into the *E* form when three methoxy groups substitute the phenyl ring. These results are in accordance with the kinetic data of phenylpyruvate tautomerase.[14] Curiously, (*E*)-phenyl-2-hydroxypropenoic acids substituted on the aromatic ring by hydroxyl groups have never been described to our knowledge. The availability of the *E* form of 2-hydroxyphenylpropenoic acids would be of great interest in the study of phenylpyruvate tautomerase.

Since 2-methylbenzofurans[2] and coumarins[15] have previously been obtained by the treatment of 2-methoxyarylacetones and 2-methoxycinnamic acids respectively with boron tribromide, a series of 2-methoxyarylpyruvic acids has also been prepared. **1e–i** were obtained using the usual procedure[4] as variable mixtures of *Z*-enol and keto forms with some detectable *E*-enol form. As expected, 3-hydroxycoumarins **3** and benzofuran-2-carboxylic acids **4** were obtained when **1e–h** were treated with boron tribromide. The ratio **3/4** calculated from the ^{1}H NMR spectra of the crude products was estimated as 3/2 which indicated that the cyclisation and the isomerisation have similar kinetic parameters. Since **4** was the more polar product, its purification was easier than that of **3** and its yield in pure product was generally higher. In order to control that the tautomeric form of the starting material has no fundamental importance in the results (yields and proportions in **3** and **4**) **1e(*Z*)** and a sample where the keto form represents about 75% were treated separately with boron tribromide. The yields in pure **3e** and **4e** are not significantly different. The reaction of **1i** with boron tribromide gave **3i** as the sole isolated product, **4i** was never detected even in the crude reaction product. The low yield in this case was due to purification problems since **3i** is very sensitive to air oxidation. In connection with our interest for salvianolic acid family[16,17] and particularly salvianolic acid K and sagecoumarin,[18] we prepared methyl 3-(2-methoxyphenyl)-2,3-epoxypropanoate **5**[19] and treated it with boron tribromide. Compound **5** gave a mixture of *cis* (20%) and *trans* (35%) 3,4-dihydro-3,4-dihydroxycoumarins and 3-hydroxycoumarin (45%) in 93% yield. By heating to reflux and prolonging the hydrolysis, 3-hydroxycoumarin **3e** was obtained almost quantitatively. Since **5** was synthesised only as the *trans* isomer, we supposed that the epoxide ring was first opened and the cyclisation occurred secondly (Scheme 2).

Acknowledgements

This work was supported by grants from the Centre National de la Recherche Scientifique (CNRS) and the Région Nord-Pas-de-Calais.

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5. **2b(*E*)** and **2b(*Z*)** were easily separated during work-up since **2b(*E*)** was soluble in water and was extracted with diethyl ether whereas **2b(*Z*)** was totally insoluble in water and dichloromethane. **2c(*E*)** was obtained by prolonging the hydrolysis time (24 h) and was crystallised in water. **2b(*E*)**: mp = 160°C; ^{1}H NMR (DMSO-6*d*): 5.70 (br s, 3H), 6.05 (s, 1H), 6.74 (d, 2H, ^3J = 8.45 Hz), 7.58 (d, 2H, ^3J = 8.45 Hz); ^{13}C NMR (DMSO-6*d*): 108.6 (C), 120.6 (CH), 131.2 (C), 135.5 (CH), 147.7 (C), 161.8 (CH), 173.2 (C); MS (60 eV): *m*/*z* 180 (17), 134 (30), 107 (100), 77 (45); **2c(*E*)**: mp = 190°C; ^{1}H NMR (DMSO-6*d*): 5.85 (br s, 4H), 5.96 (s, 1H), 6.67 (d, 1H, ^3J = 8.4 Hz), 6.89 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.9 Hz), 7.36 (d, 1H, ^4J = 1.9 Hz); ^{13}C NMR (DMSO-6*d*): 103.9 (C), 115.6 (CH), 115.7 (CH), 121.2 (CH), 126.3 (C), 142.3 (C), 145.0 (C), 145.03 (CH), 168.1 (C); MS (60 eV): *m*/*z* 196 (45), 150 (43), 123 (100), 77 (31); **2d(*E*)**: mp = 270°C; ^{1}H NMR (DMSO-6*d*): 5.85 (s, 1H), 6.10 (br s, 5H), 6.73 (s, 2H); ^{13}C NMR (DMSO-6*d*): 109.4 (C), 113.4 (CH), 130.4 (C), 138.3 (C), 147.6 (C), 150.9 (CH), 173.3 (C); MS (60 eV): *m*/*z* 212 (1), 140 (4), 110 (7), 108 (10), 96 (58), 94 (100).
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10. **3i**: mp = 273–4°C; ^{1}H (DMSO-6*d*): 6.70 (s, 1H), 6.81 (s, 1 H), 6.99 (s, 1H), 9.19 (br s, 1H), 9.67 (br s, 1H), 10.21 (br s, 1H). All the signals broadened and the signal at 6.70 ppm shifted to downfield due to the formation of a radical species which can be easily detected by ESR spectroscopy. Its paramagnetic properties are currently under investigations and will be published in due course.
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