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Tetrahedron Letters 46 (2005) 5285–5287
Tetrahedron Letters

One-pot synthesis of *ortho*-hydroxycinnamate esters

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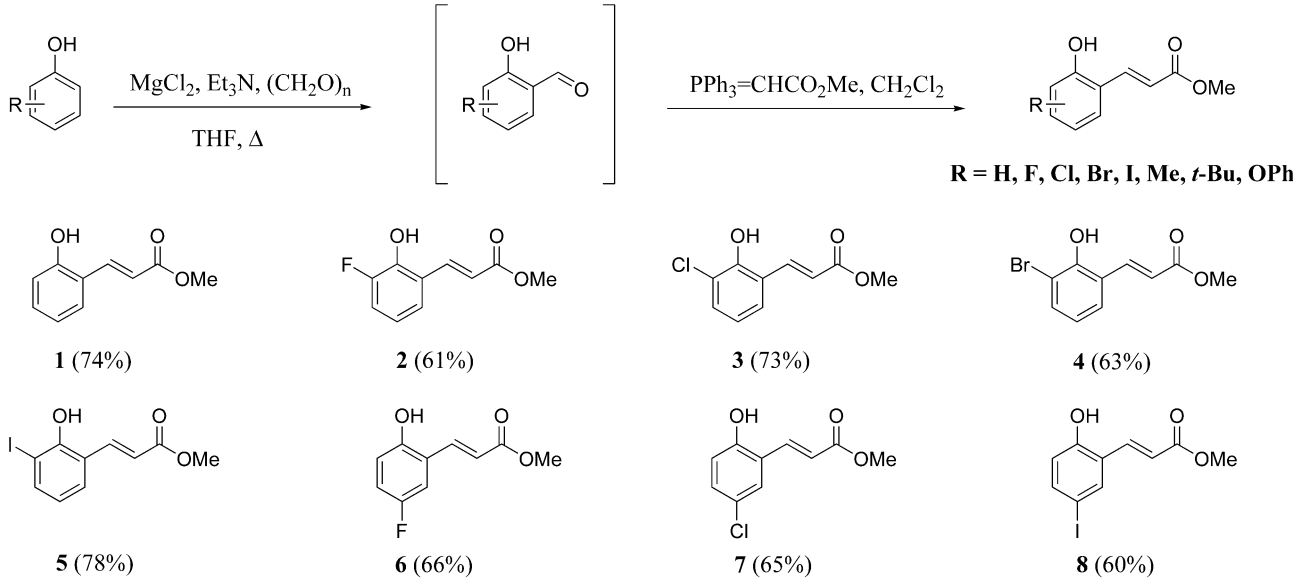
Received 3 May 2005; revised 30 May 2005; accepted 8 June 2005
Available online 27 June 2005

Abstract—Phenols are converted to salicylaldehydes with paraformaldehyde, $MgCl_2$–Et_3N in THF, and subsequent treatment with methyl (triphenylphosphoranylidene)acetate gave the corresponding methyl *ortho*-hydroxycinnamate derivatives. The sequence is conveniently carried out as a one-pot procedure.

Cinnamic acids and their derivatives are useful intermediates for the synthesis of heterocyclic compounds.[1] The Perkin reaction, the most common procedure for the preparation of cinnamic acids, utilizes the corresponding aldehydes, acetic anhydride and anhydrous sodium or potassium acetate; esterification of the acid with an alcohol affords the corresponding cinnamate esters.[2] However, the Perkin reaction is often hampered by low yields,[3] especially for the preparation of *ortho*-hydroxycinnamate esters from salicylaldehydes.[4] Hence, efforts



Scheme 1.

Keywords: *ortho*-Hydroxycinnamate esters; ortho-Formylation of phenols.
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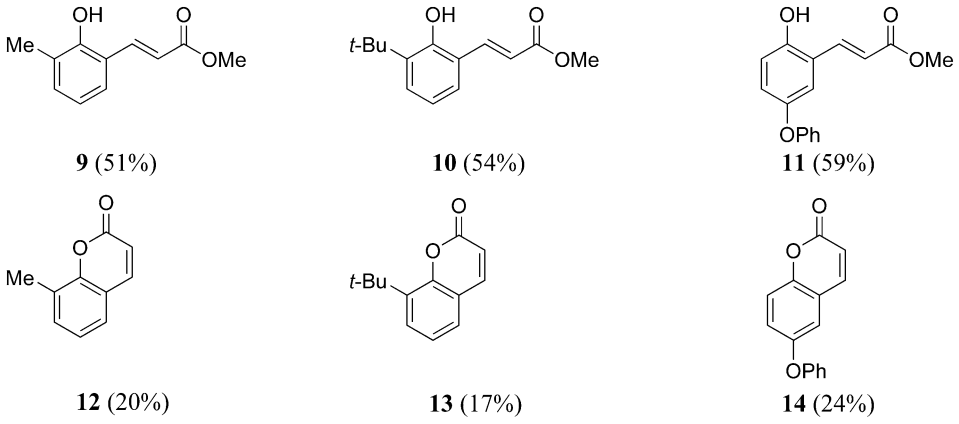
doi:10.1016/j.tetlet.2005.06.017



Scheme 2.

to develop simple and efficient procedures for their synthesis are desirable.

We have recently described a facile procedure for the selective ortho-formylation of phenols to salicylaldehydes that involves heating a mixture of the phenol, anhydrous $MgCl_2$, triethylamine and paraformaldehyde under reflux in acetonitrile or THF. For alkyl and halogen substituted phenols excellent yields of salicylaldehydes were obtained.[5] The salicylaldehydes can, without isolation, be converted to salen ligands[6] and the corresponding catechols.[7] A similar one-pot procedure seemed feasible for the preparation of *ortho*-hydroxycinnamate esters.

Accordingly, to a THF solution of the formylation reaction, a solution of methyl (triphenylphosphoranylidene)acetate in CH_2Cl_2 was added. After stirring for 4–8 h at ambient temperature, the reactions were complete and the products were purified by column chromatography (Scheme 1). Physical and spectral data were in accordance with those previously reported for the known compounds **1** and **7**.[8a] New compounds were characterized on the basis of spectral data.[9] The (*E*)-configuration of the products was established by ^1H NMR spectroscopy. The reactions were carried out with both 2- and 4-substituted phenols as starting materials and the yields ranged from 60% to 78% and were not optimized. In the case of alkyl, that is R = Me, *t*-Bu and phenoxy-substituted phenols, the reaction mixtures were heated for 2–10 h at gentle reflux. The product methyl *ortho*-hydroxycinnamates **9**,[8b] **10**[8b] and **11**[9] were accompanied by minor amounts of the corresponding coumarins **12**,[8c] **13**,[9] and **14**,[9] respectively (Scheme 2).

In conclusion, using this simple one-pot procedure, *ortho*-hydroxycinnamates are available from the respective phenols in considerably better overall yields than those previously reported.

Acknowledgements

The Research Council of Norway is gratefully acknowledged for a scholarship to H.F.A.

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9. General procedure for compounds **1**–**8**: To a stirred solution of the phenol (2 mmol) in dry THF (20 ml), anhydrous magnesium chloride (0.38 g, 4 mmol), triethylamine (0.40 g, 4 mmol) and paraformaldehyde (0.18 g, 6 mmol) were added. The reaction mixture was heated to reflux under an argon atmosphere, and the reaction was monitored by TLC (EtOAc/hexane 1:1). After complete consumption of the phenol, a solution of methyl (triphenylphosphoranylidene)acetate (0.80 g, 2.4 mmol) in CH_2Cl_2 (10 ml) was dropwise added at ambient temperature, and the reaction was monitored by TLC (EtOAc/hexane 1:1). After complete consumption of the salicylaldehyde, 1 N HCl (20 ml) was added and the reaction mixture was extracted with Et_2O (2×20 ml), the combined organics dried ($MgSO_4$) and the product purified by flash chromatography (SiO_2, EtOAc/hexane 1:20). For compounds **9**–**11**, the general procedure was employed except heating for 2–10 h was required for complete consumption of aldehydes. Spectral data of the new compounds: methyl (*E*)-3-(3-fluoro-2-hydroxyphenyl)acrylate (**2**): white solid; mp 116–

118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 5.80 (br s, 1H), 6.61 (d, J = 16.2 Hz, 1H), 6.85 (m, 1H), 7.11 (m, 1H), 7.50 (m, 1H), 7.90 (d, J = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 143.6, 139.3, 124.9, 124.8, 120.6, 120.2, 117.0, 116.7, 52.1; HRMS calcd for $C_{10}H_9FO_3$ (M^+): 196.0536, found: 196.0527. Methyl (*E*)-3-(3-chloro-2-hydroxyphenyl)acrylate (**3**): white solid; mp 120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 6.10 (br s, 1H), 6.56 (d, J = 16.2 Hz, 1H), 6.85 (t, J = 7.8 Hz, 1H), 7.30–7.40 (m, 2H), 7.90 (d, J = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 150.3, 139.2, 130.2, 127.8, 122.8, 121.0, 120.8, 119.8, 51.7; HRMS calcd for $C_{10}H_9ClO_3$ (M^+): 212.0240, found: 212.0238; Methyl (*E*)-3-(3-bromo-2-hydroxyphenyl)acrylate (**4**): white solid; mp 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 6.00 (br s, 1H), 6.56 (d, J = 16.2, Hz, 1H), 6.80 (t, J = 7.9 Hz, 1H), 7.40 (dd, J = 7.9, 1.2 Hz, 1H), 7.45 (dd, J = 7.9, 1.4 Hz, 1H), 7.90 (d, J = 16.2, Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 151.5, 139.8, 133.7, 129.0, 123.2, 122.0, 120.3, 111.9, 52.1; HRMS calcd for $C_{10}H_9BrO_3$ (M^+): 255.9735, found: 255.9732. Methyl (*E*)-3-(2-hydroxy-3-iodophenyl)acrylate (**5**): white solid; mp 108–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3H), 5.90 (br s, 1H), 6.56 (d, J = 16.2 Hz, 1H), 6.71 (t, J = 7.8 Hz, 1H), 7.45 (dd, J = 7.8, 1.2 Hz, 1H), 7.65 (dd, J = 7.8, 1.5 Hz, 1H), 7.90 (d, J = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 153.8, 140.3, 140.2, 129.9, 122.9, 122.5, 120.1, 88.1, 52.2; HRMS calcd for $C_{10}H_9IO_3$ (M^+): 303.9596, found: 303.9606. Methyl (*E*)-3-(5-fluoro-2-hydroxyphenyl)acrylate (**6**): white solid; mp 121–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 6.50 (br s, 1H), 6.55 (d, J = 16.2 Hz, 1H), 6.80 (m, 1H), 6.95 (m, 1H), 7.15 (dd, J = 9.1, 3.0 Hz, 1H), 7.95 (d, J = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 151.7, 139.9, 119.4, 118.6, 118.3, 117.8, 114.9, 114.6, 52.3; HRMS calcd for $C_{10}H_9FO_3$ (M^+): 196.0536, found: 196.0534. Methyl (*E*)-3-(2-hydroxy-5-iodophenyl)acrylate (**8**): white solid; mp 163–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 6.52 (br s, 1H), 6.55 (d, J = 16.1 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 7.50 (dd, J = 8.5, 2.1 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 155.3, 140.1, 139.4, 137.8, 124.6, 119.5, 118.9, 82.9, 52.3; HRMS calcd for $C_{10}H_9IO_3$ (M^+): 303.9596, found: 303.9599. Methyl (*E*)-3-(3-*tert*-butyl-2-hydroxyphenyl)-acrylate (**10**): white solid; mp 101–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9H), 3.85 (s, 3H), 6.25 (br s, 1H), 6.48 (d, J = 15.8 Hz, 1H), 6.89 (t, J = 7.7 Hz, 1H), 7.33 (m, 2H), 8.20 (d, J = 15.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 154.2, 140.8, 137.8, 129.6, 126.2, 123.0, 120.9, 118.9, 52.3, 34.9, 30.2; HRMS calcd for $C_{14}H_{18}O_3$ (M^+): 234.1256, found: 234.1255. Methyl (*E*)-3-(2-hydroxy-5-phenoxyphenyl)acrylate (**11**): white solid; mp 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H), 6.58 (d, J = 16.2 Hz, 1H), 6.65 (br s, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.95 (m, 3H), 7.10 (m, 1H), 7.20 (d, J = 2.8 Hz, 1H), 7.30–7.40 (m, 2H), 8.05 (d, J = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 158.5, 152.0, 150.5, 140.5, 130.1, 123,5, 122.9, 119.8, 119.3, 118.9, 118.1, 117.9, 52.3; HRMS calcd for $C_{16}H_{14}O_4$ (M^+): 270.0892, found: 270.0888. 8-*tert*-Butyl-2*H*-chromen-2-one (**13**): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 9H), 6.42 (d, J = 9.5 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.50 (dd, J = 7.7, 1.6 Hz, 1H), 7.54 (dd, J = 7.7, 1.6 Hz, 1H), 7.72 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 153.1, 144.8, 138.5, 129.8, 126.7, 124.4, 119.6, 119.3, 35.4, 30.3; HRMS calcd for $C_{13}H_{14}O_2$ (M^+): 202.0994, found: 202.0993. 6-Phenoxy-2*H*-chromen-2-one (**14**): white solid; mp 119–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.41 (d, J = 9.5 Hz, 1H), 7.00 (m, 2H), 7.07 (d, J = 2.8 Hz, 1H), 7.12–7.20 (m, 2H), 7.30–7.40 (m, 3H), 7.61 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 157.3, 154.1, 150.3, 143.3, 130.4 (2 × c), 124.3, 123.4, 119.9 (2 × c), 119.3, 118.6, 117.8, 116.8; HRMS calcd for $C_{15}H_{10}O_3$ (M^+): 238.0630, found: 238.0628.