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A New Convenient Synthetic Procedure for 4-Allyl-2,6-Dimethoxyphenol

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A NEW CONVENIENT SYNTHETIC PROCEDURE FOR 4-ALLYL-2,6-DIMETHOXYPHENOL

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ABSTRACT: 4-Allyl-2,6-dimethoxyphenol was synthesized from 4-hydroxy-2,6dimethoxybenzoic acid and allylbromide by condensation under basic condition and by subsequent Claisen rearrangement.

4-Allyl-2,6-dimethoxyphenol (3) is a very important naturally occurring compound, which possesses interesting biological activities¹. It also an important intermediate of sinapyl alcohol, which is involved in lignin biosynthesis and degradation². Several methods of this transformation have been developed in recent years ^{3,4}. As a basic C6-C3 unit, (3) is also the synthetic precursor for many biologically active natural products.

4-Allyl-2,6-dimethoxyphenol has been synthesized from 2,6-dimethoxyphenol and allylbromide in two steps in an overall-yield of 48% as reported in 1961⁵.

In our synthetic studies of syringin, an active component in traditional Chinese medicine, we found that 4-hydroxy-2,6-dimethoxybenzoic acid 6 reacted with allylbromide under basic conditions to produce mainly a mixture of (2) and (3). The compound (2)

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can undergo Claisen rearrangement and decarboxylation resulting into (3)(scheme 1). After the mixture of (2) and (3) was subjected to Claisen rearrangement conditions (at about 200°C), the main product (3) was obtained in a yield of 71%. Compared with the known method⁵, this new procedure is more convenient and practical.

Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. Reaction of 4-hydroxy-3, 5 -dimethoxybenzoic acid with allylbromide

4-Hydroxy-3,5-dimethoxybenzoic acid (1) (5g, 25mmol) was dissolved in a solution of sodium hydroxide (2.3g, 57.5mmol) in water (25ml). Allylbromide (3.4g, 28mmol) was added to this solution and the reaction mixture was heated to 70-80°C under stirring for 2hr. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (50ml×2). The combined organic layers were washed with water (50ml) and dried over Na₂SO₄. After removal of solvent, distillation under reduced pressure gave 2g (yield: 40%) of 4-allyl-2,6-dimethoxyphenol (3) ,obtained as a colourless liquid. I.R. v_{max} (cm⁻¹) : 3520, 3080, 1620, 1520,1460, etc. NMR (CDCl₃) $\delta_{H^{\circ}}$: 6.40 (2H, s), 5.72-6.14(1H, m), 5.00-5.24 (2H, m), 3.82 (6H, s), 3.30(2H, d). The data are in agreement with literature⁷.

The remaining aqueous layer of the reaction was acidified with 10% HCl and extracted with ethyl acetate(50ml×2). The combined organic layers were dried over Na₂SO₄ and then distilled under reduced pressure. The residue was purified by chromatography on a silica gel column (eluted with 4:1 petroleum ether-ethyl acetate +1% HOAc), 2.2g (yield: 36.6%) of 4-(2-propenoxy)-3,5-dimethoxybenzoic acid 2 obtained as a white solid, m.p.108-110°C. Ms(EI) m/e: 238(M+), 223, 197(100%), 169, 141, 93, 77, etc. I.R. $v^{\text{KBr}}_{\text{max}}$ (cm⁻¹): 2940, 1680, 1585, 1500, 1420, etc. NMR (DCCl₃) δ_{H} : 10.45(1H, D-exchangeable), 7.32(2H, s) , 5.88-6.30(1H, m), 5.10-5.38(2H, m), 4.56(2H, d). (Found: C, 60.57%; H, 5.80%. C₁₂H₁₄O₅ requires C, 60.50%; H, 5.88%).

Claisen reaction of 2

2 (2g) was heated at 200°C in the nitrogen atmosphere for 2hr. Distillation under reduced pressure gave 0.8 g (yield: 48.6%) of 3. TLC analysis indicated that it was a pure liquid and had the same Rf value as a standard sample.

Synthetic procedure for 3

4-Hydroxy-3,5-dimethoxybenzoic acid (1) (15g, 75.8mmol) was dissolved in a solution of sodium hydroxide (7.3g, 183mmol) in water (66ml). Allylbromide (11.2g, 92.7mmol) was added ito this solution and the reaction mixture was heated to 70-80°C under stirring for 6 hr. After cooling to room temperature, ethyl acetate (100ml) was added. The reaction mixture was acidified to pH 2-3 with 10% HCl. The aqueous layer was extracted with ethyl acetate (100ml) once again. The combined organic layers were washed with water (100ml×2) and dried over Na₂SO₄. The solvent was removed under

reduced pressure. The residue was protected in a nitrogen atmosphere and kept at 190-200°C for 2.5hr. Then distilled in vacuum at 148-150°C/5mmHg, 10.5g, yield: 71%.

References and notes

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- 6. 3,4,5-trimethoxybenzoic acid (50g) was stirred in 800ml H₂SO₄ at room temperature for 50 hr. 4-hydroxy -2,6-dimethoxybenzoic acid (40g, 86%) was obtained,
 210, 21000

m.p.210- 212°C.

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