Chinese Chemical Letters Vol. 11, No. 2, pp. 109–110, 2000

Synthesis of *Z* and *E*-(2',5'-dimethoxyphenyl)-methylene-butyrolactones

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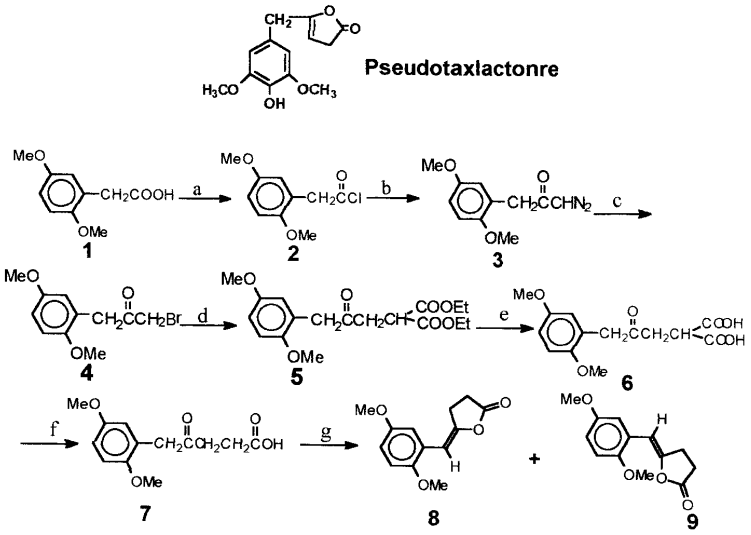
Abstract: A pair of *Z* and *E* isomers of cyclization of γ-ketoacid **7**, which was prepared in six steps from 2,5-dimethoxyphenyl acetic acid **1**, gave a pair of *Z*(20%) and *E* (4%) isomers of (2,5-dimethoxyphenyl)-methylene-butyrolactones

Keywords: Butyrolactone, γ-keto-acid, lactonization, ferric sulfate hydrate.

Pseudotaxlactone was isolated by Zhang[1] from Taxaceae plant *pseudotaxus chienii* (Cheng) Cheng. It's structure was tentatively assigned as 5-(4'-hydroxy-3',5'-dimethoxy)-phenylmethyl-3H-furanolactine (I). In order to ascertain the structure of Pseudotaxlactone (I), we report our study of a model synthesis .

Scheme



Reagents and conditions: a) Oxalyl chloride, CH_2Cl_2, r.t., 6hr; b)Diazomethane, Et_2O, 0°C; c) 40%HBr, Et_2O, 80.6%(a to c); d) NaH, $CH_2(COOCH_2CH_3)_2$, DMF, r.t. 1.5hr, 57.8% ; e) 1N KOH, 70°C, 2hr.; f) Pyridine, 110°C, 1.5hr, 72%(e and f);g) $Fe_2(SO_4)_3 \bullet xH_2O$, Benzene, reflux 9hr.;

20%(*Z*,**9**), 4%(*E*,**8**).

The intermediate **7** was synthesized using 2,5-dimethoxy-phenyl acetic acid as a starting material. However, cyclization reaction gave *Z*-(2,5-dimethoxy-phenyl)-methylene-butyrolactone **9** (20%) and *E*-(2,5-dimethoxy-phenyl)-methylene-butyrolactone **8** (4%), instead of the desired counterpart with endocyclic unsaturation. The reaction of the α-bromoketone **4** with the sodium salt of malonate was unsuccessful under the general conditions using absolute ethyl alcohol, ethyl ether, benzene and acetone, respectively as solvent. Only when DMF was used as solvent, did reaction proceed satisfactorily, After hydrolysis and decarboxylation, 5-(2', 5'-dimethoxy)-phenyl-4-oxo-pentanoic acid **7** was obtained.

The general method for the cyclization of γ-keto-acid is to distil or to reflux γ-ketoacid **7** in acetic anhydride. However, we found that these two methods were not applicable to compound **7.** Since $Fe_2(SO_4)_3 \bullet xH_2O$ has been used as a catalyst in the cyclization of δ-keto-acid, by azeotropic distillation with xylene, we used the same method with benzene as solvent and achieved lactonization of γ-keto-acid **7**

The less polar compound (*Z*,**9**,R_f=0.5/ developing twice in petroleum ether /ethyl acetate=5:1) displays a weaker carbonyl stretching vibration band at 1811cm$^-$ IR(%T=59%). The ^{1}HNMR spectra gave a signal at δ5.97ppm(t,1H) corresponding to the olefinic proton. The more polar compound (*E*, **8**, R_f=0.44/ developing twice in Petroleum ether /ethyl acetate=5:1) showed a stronger vibration absorption of the carbonyl at 1805 cm$^-$(%T=37%) in IR and the proton signal of alkene hydrogen is at δ6.5ppm(t,1H).

We thus conclud that the two compounds are a pair of isomers, with the former being *Z* (**9**) and the latter *E* (**8**).

References and Notes

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4. Intermediate **7**: mp:94-97 ℃, yield 72%, R_f=0. 29{petroleum ether(60-90℃)/ethyl acetate=3:1, HOAc 1 d). IR(KBr, cm^{-1}): 1716(C=O), 1500, 1053, 950(C-O). MS(m/z, %, EI): 252 (M^+, 95), 235(14), 207(10), 151(100). ^{1}H-NMR (300MHz): δ ppm ($CDCl_3$), 9. 5-8. 5(1H, -OH, D_2O exchange), 6. 79-6. 69(m, 3H, Ar), 3. 75(d s, 6H, 2-MeO), 3. 67(s, 2H, Ar-CH_2-CO-), 2. 73(t, J=6. 3, 2H, -CO-CH_2-), 2. 60(t, J=6. 3, 2H, -CH_2-COOH)
   The less polar compound(Z, **9**, R_f=0. 5) :IR(KBr, cm^{-1}):1811(C=O) and 1676(C=C); MS(m/z, %, EI): 234(M^+, 40), 163(30), 149(5); ^{1}H-NMR (300MHz), δ ppm ($CDCl_3$) :6. 87(s, 2H, Ar), 6. 73 (d, J=3, 1H, Ar), 5. 97(t, J=1. 5, 1H, Ar-CH=C), 3. 82(d s, 6H, 2MeO-), 3. 08(d t, J=5. 1, J=1. 5, 2H, CH=C-CH_2-), 2. 7(t, J=5. 1, 2H, -CH_2-COO-).
7. The more polar compound (E, **8**, R_f=0. 44): . IR(KBr, cm^{-1}):1805(C=O) and 1674(C=C); MS (m/z, %, EI): 234(M^+, 40), 163(40), 149(35);^{1}H-NMR(300MHz), δ ppm ($CDCl_3$) : 6. 75 (m, 3H, Ar), 6. 5(t, J=1. 5, 1H, Ar-CH=C), 3. 8(d s, 6H, 2MeO-), 3. 1(d t, J=5. 1, J=1. 5, 2H, CH=C-CH_2-) and 2. 72(d t, J=5. 1, 2H, -CH_2-COO-).

Received 6 September 1999