A Simple Method for the Preparation of New α-Oxoacetic Acid Esters with a Plug Flow Reactor

Fred Hollwedel, Gerhard Koßmehl*

Institut für Organische Chemie, Freie Universität Berlin, Takustraße 3, D-14195 Berlin, Germany
Fax +49(30)8385310

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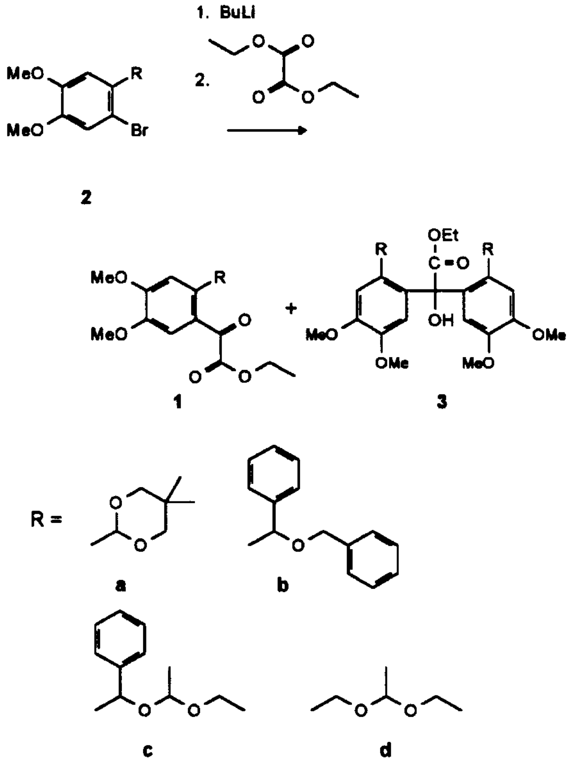
Abstract: The formation of ethyl 2-(2-substituted-4,5-dimethoxyphenyl)-2-oxoacetates in high yield, with negligible byproducts, by reaction of 2-substituted 4,5-dimethoxyphenyl bromides with diethyl oxalate using a plug flow reactor is reported.

Key words: α-oxoacetic acid esters, plug flow reactor, diethyl oxalate

For the preparation of 4-hydroxy-6,7-dimethoxyisochroman-3-ones[1] we needed some α-oxoacetic acid esters **1a–d** of the type shown in the Scheme.



Scheme

For the synthesis of α-oxoacetic acid esters many methods have been published,[2] most of which, however, proved to be unsatisfactory for the preparation of **1**.

The reaction of **2b** with butyllithium and trapping the formed anion with diethyl oxalate gave only a 23% yield of the desired ester **1b** besides 50% of the alcohol **3b** as a double addition product, even if the solution of the anion was injected in diethyl oxalate dissolved in THF. In our system, **2a–d**, we found similar product distribution, if we used dimethyl oxalate, ethyl oxalyl chloride or 2,3-dioxo-1,4-dioxane instead of diethyl oxalate.

This double addition is well known[3] and many workers have tried to suppress it by the use of ethyl oxalyl chloride[4] or ethyl cyanoformate[5] with organocadmium compounds or different solvent mixtures and low temperatures.[6] No reaction of **2b** with magnesium was observed, even if it was activated with iodine, dibromoethane or ultrasound. So we had to use butyllithium for generating the anion. Axiotis[7] described the addition of organolithium compounds to triethoxyacetonitrile to give α-oxoacetic acid esters in high yields. The main drawback is, however, the expense and the low yield of the nitrile from tetraethyl orthocarbonate and acetonitrile.[8]

In order to avoid formation of **3** when using the low-cost diethyl oxalate we constructed a small plug flow reactor out of a 1-mL syringe, a T-junction as mixing chamber and some Teflon tubes as shown in the Figure. The low pressure in the 2-L flask leads to a flow velocity of about 7 mL/s. This prevents the direct contact between anion and **1** and therefore no double addition can take place.

With this procedure we obtained the new α-oxoacetic acid esters **1a–d** in high yields with negligible yields of the side reaction products **3a–d**, as shown in the Table.

This method should also be suitable for generating other oxo esters.

Preparation of the Aryl Bromides:

2-(2-Bromo-4,5-dimethoxyphenyl)-5,5-dimethyl-1,3-dioxane **(2a):**
Out of a solution of 2-bromo-4,5-dimethoxybenzaldehyde (12.2 g, 0.05 mol), 2,2-dimethylpropane-1,3-diol (6.3 g, 0.06 mol) and TsOH (60 mg) in toluene (150 mL), was distilled azeotropically ca. 100 mL of water/toluene over ca. 1 h. The residue was cooled down, diluted with hexane (50 mL) and filtered over a column (5 × 3 cm) fitted with alox "super active". The solvents were evaporated and the oil crystallized from Et_2O/hexane (2:1, 30 mL); yield: 14.0 g (85%); colorless crystals.

Benzyl [(2-Bromo-4,5-dimethoxyphenyl)phenylmethyl] Ether **(2b):**
(2-Bromo-4,5-dimethoxyphenyl)phenylmethanol[9] was protected with benzyl bromide/NaH by conventional methods.[10]

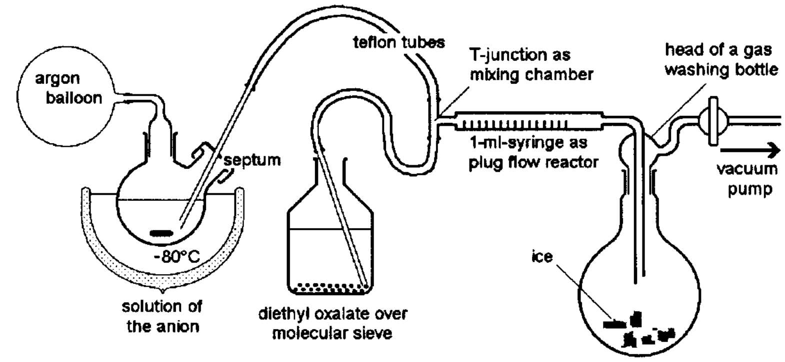
[(2-Bromo-4,5-dimethoxyphenyl)phenylmethyl] 1-Ethoxyethyl Ether **(2c):**
(2-Bromo-4,5-dimethoxyphenyl)phenylmethanol was protected with ethyl vinyl ether/TsOH by conventional methods.[10]

(2-Bromo-4,5-dimethoxyphenylmethyl) 1-Ethoxyethyl Ether **(2d):**
2-Bromo-4,5-dimethoxyphenylmethanol[11] was protected with ethyl vinyl ether/TsOH by conventional methods.

Table. Preparation of α-Oxoacetic Acid Esters via Lithioarenes and Diethyl Oxalate with a Plug Flow Reactor

Product	Yield (%)	mp (°C)	^{1}H NMR (DMSO-d_6 250 MHz) δ, J (Hz)	IR (KBr) υ (cm^{-1})	MS (EI) m/z (%)
1a	83	142[a]	0.74 (s, 3 H, CH_3 ax); 1.03 (s, 3 H, CH_3 eq); 1.28 (t, 3 H, J = 6, $OCH_2C\mathit{H}_3$); 3.58 (q, 4 H, CH_2); 3.76 (s, 3 H, OCH_3); 3.82 (s, 3 H, OCH_3); 4.34 (q, 2 H, J = 6, $OC\mathit{H}_2CH_3$); 5.50 (s, 1H, CH); 7.08 (s, 1H, arom); 7.10 (s, 1H, arom)	1698, 1726	352 (M^+ 8.78), 279; 250; 193 (100)
1b	71	92[a]	1.25 (t, 3 H, J = 5, $OCH_2C\mathit{H}_3$); 3.78 (s, 6 H, OCH_3); 3.82 (s, 6 H, OCH_3), 4.33 (q, 2 H, J = 5, $OC\mathit{H}_2CH_3$); 4.44 (m, 2 H, CH_2); 6.22 (s, 1 H, CH); 7.16 (s, 1 H, arom); 7.30 (m, 11 H, arom)	1669, 1735	434 (M^+ 0.58); 361; 343; 269; 91 (100)
1c	82	oil	1.00 (dt, 3 H, J = 6, $OCH_2C\mathit{H}_3$); 1.22 (m, 6 H, $CHC\mathit{H}_3$ + $COOCH_2C\mathit{H}_3$); 3.38 (m, 2 H, $OC\mathit{H}_2CH_3$); 3.78 (d, 3 H, OCH_3), 3.88 (d, 3 H, OCH_3); 4.34 (q, 2 H, J = 6, $COOC\mathit{H}_2CH_3$); 4.65 (dq, 1 H, $C\mathit{H}CH_3$); 6.52 (ds, 1 H, CH); 7.09 (s, 1 H, arom); 7.16 (s, 1 H, arom); 7.24 (m, 5 H, arom)	1674, 1736	416 (M^+ 0.77); 327; 326; 271 (100); 255; 73
1d	64	oil	1.08 (t, 3 H, J = 6, $OCH_2C\mathit{H}_3$), 1.30 (m, 6H, $CHC\mathit{H}_3$ + $COOCH_2C\mathit{H}_3$); 3.50 (m, 2 H, $OC\mathit{H}_2CH_3$); 3.8 (s, 3H, OCH_3); 3.90 (s, 3 H; OCH_3); 4.36 (q, 2 H, J = 6, $COOC\mathit{H}_2CH_3$); 4.78 (m, 3 H, $C\mathit{H}CH_3$ + CH_2); 7.18 (s, 1H, arom); 7.24 (s, 1 H, arom)	1669, 1734	340 (M^+ 2.09); 268; 251; 195; 73 (100)

[a] Satisfactory microanalyses were obtained: C ± 0.41; H ± 0.08.



Figure

Preparation of α-Oxoacetic Acid Esters 1a–d with the Plug Flow Reactor; General Procedure:

A 2-L round-bottomed flask was filled with ice (ca. 300 g), closed with the head of a gas washing bottle and then connected with the plug flow reactor, as shown in the Figure. In a 250-mL two-necked, round-bottomed flask equipped with an argon balloon and a septum was the aryl bromide **2** (0.05 mol) dissolved in abs THF (50 mL) and cooled to –80 °C. 1.6 M BuLi in hexane (38 mL, 0.06 mol) was added via a syringe and stirred for 5 min keeping the temperature of the solution below 60 °C. Then one of the Teflon tubes with a cannula was put into the bottle containing diethyl oxalate (50 mL, 0.32 mol) and the other was stuck through the septum of the flask. Evacuation was started. The two-necked flask should be empty after ca. 1 min. Just before the flask was empty, abs THF (20 mL) was added through the septum to remove the solution of the aryllithium completely. The two cannulae were pulled out and put into a flask with CH_2Cl_2 (200 mL) for the purpose of cleaning the tubes and the reactor. Then evacuation was stopped, the head of the gas washing bottle removed and the 2-L flask was shaken vigorously. The organic layer was separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$ or $CaCl_2$), (a small amount of Na_2CO_3 was added in the cases of **1c** and **1d**) and then the solvent was evaporated. From the residue, the diethyl oxalate was distilled off on a rotary evaporator at 5 mbar and 60–70 °C water bath temperature. **1a** and **1b** were crystallized from Et_2O; **1c** and **1d** were isolated by column chromatography (hexane/EtOAc 7:3).

The diethyl oxalate contained about 3–4% THF as major impurity and was used a second time without further purification.

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