Synthesis of 5-Substituted 4,4-Disubstituted 2-Cyclohexen-1-ones by Electro-Generated Base Promoted Michael Addition of 4,4-Disubstituted 2,5-Cyclohexadien-1-ones

Sigeru TORII*, Naoya HAYASHI, and Manabu KUROBOSHI

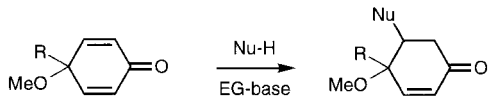
Dept. of Applied Chem., Faculty of Engin., Okayama Universitiy, Tsushima-naka 3-1-1, Okayama 700, JAPAN

Fax 81-86-255-3424 e-Mail: toriiken@cc.okayama-u.ac.jp

Received 31 March 1998

Abstract: 5-Substituted 4,4-dialkoxy-2-cyclohexen-1-ones were electro-synthesized from 4,4-disubstituted 2,5-cyclohexadien-1-ones, which were obtained from 1,4-dialkoxybenzene derivatives by electrolysis, by electro-generated base (EG-base)-promoted Michael addition with CH_2E_2 (E = CO_2R, COMe) in moderate to almost quantitative yield. The cyclohexenone derivatives were found to be a good precursor of benzofuranone derivatives through acid-promoted intramolecular lactonization.

A strategy for the synthesis of poly-oxy-functionalized benzene derivatives involves an aromatic/non-aromatic/aromatic conversion sequence. 4,4-Dialkoxy-2,5-cyclohexadienone **1** is one of the most valuable non-aromatic intermediate for this purpose. Although Parker[1] reported Michael addition of **1** with several activated methylene compounds with chemical bases such as NaOMe/MeOH, this procedure is not reproducible mainly due to retro-Michael addition (*vide infra*). We found that EG-base promotes this conjugate addition very smoothly to afford 5-substituted 4,4-dialkoxy-2-cyclohexenone **2** in high yield with good reproducibility. In this paper are described the experimental details of EG-base promoted Michael addition with **1**.[2]



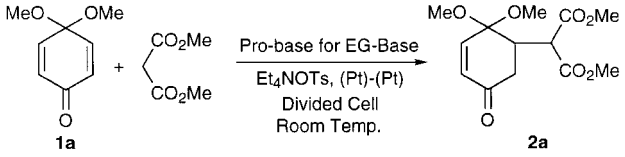
1 **2**

The Michael addition of **1** under electrolysis was carried out as follows (Table 1, Entry 2): In a divided cell were fitted platinum electrodes (1 x 1.5 cm^2) and stirring bars. In the cathodic room were added substrate (1 mmol), dimethyl malonate (1 mmol), azobenzene (0.04 mmol) as a pro-base of EG-Base, Et_4NOTs (0.46 mmol), and CH_3CN (4 mL) as a solvent, and in the anodic room were added a CH_3CN (4 mL) solution of Et_4NOTs (0.46 mmol). These mixtures were electrolyzed for 9 h at the constant current of 0.33 mA/cm^2 (0.17 F/mol) under vigorous stirring before the mixture was stirred for 13 h at room temperature without passing electricity. The results were summarized in Table 1. As a pro-base, azobenzene was found to be a best choice to give the Michael adduct **2a** quantitatively (Entry 2): 2-pyrrolidone (Entry 5), *o*-nitrotoluene (Entry 6), 4-methylimidazole (Entry 7), and benzaldehyde oxime (Entry 8) gave **2a** in only moderate yields. Without pro-base, **2a** was also obtained in 79% yield after rather longer reaction time (24 h). And also chemical base such as NaOMe/MeOH resulted in affording **2a** in moderate yield (Entry 1).

Solvents also affected the product yield (Entries 2, 3): A combination of acetonitrile and Et_4NOTs gave the best results. In all cases, only the desired product and starting material were obtained, no by-products being detected.

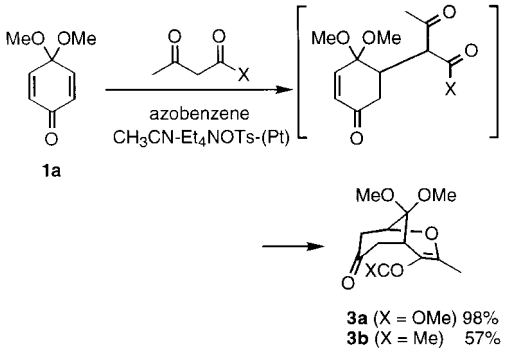
When methyl acetoacetate and acetylacetone were used as active methylene compounds, the second intramolecular Michael addition occurred to give bicyclic compounds **3a** and **3b** in quantitative and 57% yields, respectively, while no simple Michael adducts were detected.[4] Ethyl cyanoacetate and malononitrile also reacted with **1a** to give the corresponding Michael adducts in 13 and 20% yield. 4-Allyloxy-4-methoxy-2,5-cyclohexadien-1-one **1b** also reacted with dimethyl malonate under electrolysis conditions using azobenzene as a pro-base to give the corresponding Michael adducts **2b** in 76% yields as a mixture of diastereomers. This Michael addition is concluded to be strongly affected by the structure of both Michael acceptor **1** and active methylene compounds.

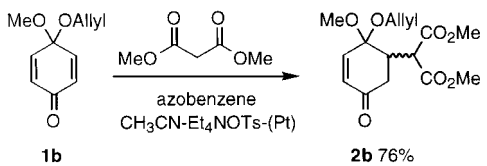
Table 1. EG-base Promoted Michael Addition of Dimethyl Malonate to **1a**



entry	Probase/mmol		Solvent/mL	anode	cathode	Time /h	Yield[a] /%
1[b]	NaOMe	0.2	MeOH	(6)		25	56
2	Azobenzene	0.04	CH_3CN	4	4	9[c]	93
3	Azobenzene	0.04	DMF	12	12	18	55
4	non		CH_3CN	4	4	24	79
5	2-Pyrrolidone	0.04	CH_3CN	8	8	2.5	54
6	*o*-Nitrotoluene	0.4	DMF	4	4	24	68
7	4-Methylimidazole	0.4	CH_3CN	8	8	13	53
8	Benzaldehyde oxime	0.07	CH_3CN	8	8	16	47

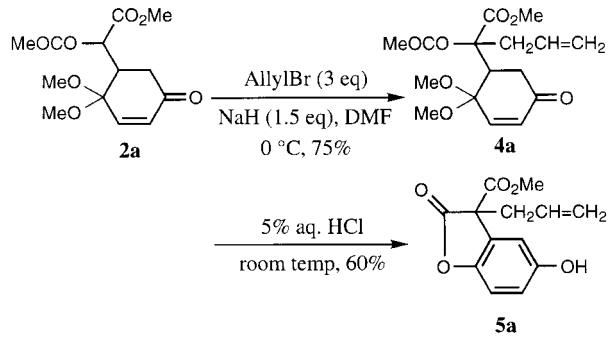
[a]Yields referred to the isolated products. [b]Without electrolysis. [c]After electrolysis, the reaction mixture was stirred for 13 h





Allylation of **2a** with AllylBr/NaH in DMF at 0 °C gave **4a** in 75% yield. Acid-catalyzed deprotection of acetal moiety followed by

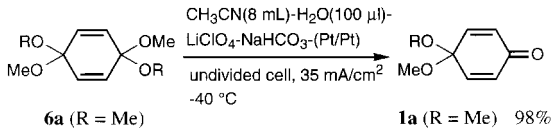
lactonization gave 5-hydroxybenzofuran-2-one derivatives **5a** in 60% yield.



Further investigation to apply this methodology to synthesize valuable compounds such as melatonin is now undergoing in our laboratories.

References and Notes

1. Parker, K. A.; Kang, S.-A. *J. Org. Chem.* **1980**, *45*, 1218.
2. EG-acid promoted partial hydrolysis of 3,3,6,6-tetraalkoxycyclohexadiene derivatives **6**, prepared by electro-oxidation of 1,4-dialkoxybenzenes in an MeOH-KOH(1%)-(Pt/Pt) system,[4] proceeds in an MeCN/H_2O(trace)-$LiClO_4$/$NaHCO_3$-(Pt/Pt) system with constant current density (35 mA/cm^2) at -40 °C to give the products **1a** and **1b** in 98% and 80% yields, respectively.



6a (R = Me) **1a** (R = Me) 98%
6b (R = allyl) **1b** (R = allyl) 80%

3. Parker[1] pointed out that *C,O*-double Michael adduct **3a** was obtained by use of EtONa/EtOH, whereas *C,C*-double adduct was afforded when NaH/THF was used.
4. Nilsson, A.; Palmquist, U.; Pettersson, T.; Ronlán, A. *J. Chem. Soc., Perkin Trans. I.* **1978**, 708.