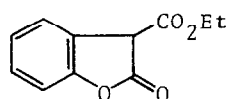SYNTHESIS OF BENZOFURAN-2-ONE DERIVATIVES BY COPPER(I)-PROMOTED COUPLING

REACTIONS OF o-BROMOPHENOL WITH ACTIVE METHYLENE COMPOUNDS

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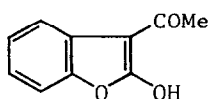
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Summary: Treatment of o-bromophenoxide anion with sodium salts of active
methylene compounds in the presence of copper(I) bromide in dioxane afforded
benzofuran-2-one derivatives. The phenoxide group of o- and p-bromophenol
activates the coupling reaction.

Substitution reactions in non-activated aromatic halides have recently been
utilized as a convenient synthetic tool for carbon-carbon bond formation in aro-
matic system due to the development of metal-catalyzed and $S_{RN}1$ reactions.[1,2]
We have reported that the coupling reactions of aryl halides with sodium diethyl
malonate proceed smoothly in dioxane in the presence of copper(I) salts.[3] As an
attempt to synthesize heterocyclic compounds we wish to report herein on the cop-
per(I)-promoted coupling reaction of bromophenols with sodium salts of diethyl
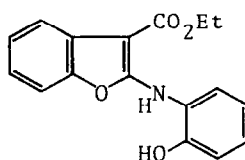malonate, ethyl acetoacetate, and ethyl cyanoacetate.

A mixture of o-bromophenol (10 mM) and diethyl malonate (12 mM) in dioxane
was treated with NaH (22 mM) and CuBr (12 mM) successively. After the resulting
yellow mixture was stirred for 5 hr at 70°C under nitrogen atmosphere, 3-carbo-
ethoxybenzofuran-2-one[4] (1) was obtained in 93% yield on the basis of the con-
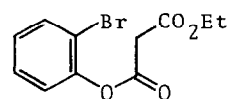verted o-bromophenol. 2-Hydroxy-3-acetylbenzofuran[5] (2) and 2-o-hydroxyanilino-
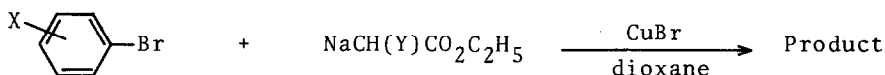

(1)   (2)   (3)   (4)

Table 1.

$$X \text{—} \langle \text{aryl} \rangle \text{—Br} \quad + \quad NaCH(Y)CO_2C_2H_5 \quad \xrightarrow[\text{dioxane}]{\text{CuBr}} \quad Product$$

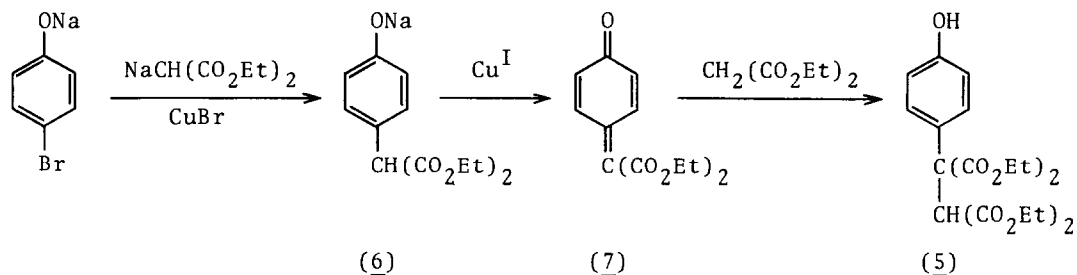| X	Y	Temp. (°C)	Time (hr)	Product	Conversion[a]	Yield[b]
o-OH	$CO_2C_2H_5$	70	5	(1)	8	31
o-ONa	$CO_2C_2H_5$	70	5	(1)	85	93
o-ONa	$COCH_3$	80	5	(2)	-	15[c]
o-ONa	CN	80	5	(3)	-	34[c]
o-OCH_3	$CO_2C_2H_5$	100	5	d)	55	89
p-ONa	$CO_2C_2H_5$	70	3	(5)	70	97
p-OCH_3	$CO_2C_2H_5$	100	5	e)	45	40

a) Mol-% based on the charged aryl halide (GLC analysis). b) Product yield based on the converted aryl halide (GLC analysis). c) Isolation yield. d) o-Methoxyphenyl malonic acid diethyl ester. e) p-Methoxyphenyl malonic acid diethyl ester.

3-carboethoxybenzofuran[6] (3) were isolated in 15% and 34% yield respectively, when ethyl acetoacetate and ethyl cyanoacetate were allowed to react under similar reaction conditions. The formation of (3) is explainable in terms of the initial substitution by ethyl cyanoacetate followed by the intramolecular attack of phenoxide anion to the cyano group, the resulting imide anion replacing brom anion from the second o-bromophenoxide. When o-bromophenol (10 mM) was treated with sodium diethyl malonate (12 mM) and CuBr (12 mM), acid-base equilibrium should occur and we obtained (1) in only 2% yield with 92% recovery of o-bromophenol under the same reaction conditions as above. Because the treatment of the mixed diester of malonic acid (4) with each equivalent of NaH and CuBr has failed to afford (1), we have concluded that the o-bromophenoxide undergoes substitution by active methylene compound initially and lactonization occurs subsequently.

When a mixture of sodium p-bromophenoxide (10 mM), sodium diethyl malonate (20 mM), and CuBr (20 mM) in dioxane was stirred at 70°C for 3 hr, metallic copper was deposited quantitatively and p-1,1,2,2-tetracarboethoxyethylphenol[7] (5) was formed effectively. The compound (5) is reasonably considered to be generated via a series of reactions as shown in Scheme 1. That is, the initially

formed sodium salt of p-hydroxyphenyl malonic acid diethyl ester (<u>6</u>) is oxidized by copper(I) ion to p-quinone methide (<u>7</u>) to which diethyl malonate adds in a Michael reaction.

SCHEME 1.

$$\underset{\text{Br}}{\overset{\text{ONa}}{\bigcirc}} \xrightarrow[\text{CuBr}]{\text{NaCH(CO}_2\text{Et})_2} \underset{\text{CH(CO}_2\text{Et})_2}{\overset{\text{ONa}}{\bigcirc}} \xrightarrow{\text{Cu}^{\text{I}}} \underset{\text{C(CO}_2\text{Et})_2}{\overset{\text{O}}{\bigcirc}} \xrightarrow{\text{CH}_2\text{(CO}_2\text{Et})_2} \underset{\substack{\text{C(CO}_2\text{Et})_2 \\ \text{CH(CO}_2\text{Et})_2}}{\overset{\text{OH}}{\bigcirc}}$$

(<u>6</u>) (<u>7</u>) (<u>5</u>)

We have found the tendency that the more slowly react aryl halides substituted with the more strongly electron-donating group in the case of the copper(I)-promoted arylation of diethyl malonate.[3] It is noteworthy that o- and p-bromophenoxide react effectively under much milder reaction conditions than o- and p-bromoanisole do in spite of the accumulation of negative charge at the reaction center (see Table 1.). Copper(I) malonate generated in situ is responsible for the activation of aromatic carbon-halogen bonds through electron transfer from copper(I), as generally noted in the reactions of organocopper(I) species.[8] Since we have confirmed that addition of an equivalent of sodium phenoxide to a reaction mixture of sodium diethyl malonate, phenyl bromide, and CuBr in dioxane does not cause a considerable rate enhancement, it is unlikely that the coordination of phenoxide may augment the reactivity of copper(I) malonate with respect to intermolecular electron transfer to aryl halides. However, complexation of bromophenoxide to copper(I) malonate seems to facilitate intramolecular metal-to-ligand electron transfer even if the carbon-halogen bond is so far remote from the copper(I) ion as in the case of p-bromophenoxide.

In conclusion, copper(I)-promoted coupling reaction of o-bromophenol with active methylene compounds can serve as a convenient tool for new class of benzofuran-2-one derivatives which are not accessible directly by known methods.[9]

References and Notes

1) R. Noyori, in "Transition Metal Organometallics in Organic Synthesis," H. Alper Ed., vol. 1, p.83. Academic Press, New York (1976).

2) J. F. Bunnett, Acc. Chem. Res., 11, 413 (1978).

3) J. Setsune, K. Matsukawa, H. Wakemoto, and T. Kitao, Chem. Lett., 367 (1981).

4) B.p. 180°C/7 mmHg; IR 1840, 1830, 1810 cm^{-1} (C=O); ^{1}H-NMR(CDCl$_3$) δ ~7.10 (m, 4H, Ar-H), 4.45(s, 1H, CH), 4.18(q, 2H, CH$_2$), 1.29(t, 3H, CH$_3$).

5) M.p. 137°C; IR 1730, 1710 cm^{-1} (C=O); ^{1}H-NMR(CDCl$_3$) δ ~7.10(m, 4H, Ar-H), 2.41(s, 3H, CH$_3$).

6) M.p. 183°C; IR 3400, 3350 cm^{-1} (O-H, N-H), 1660, 1625 cm^{-1} (C=O); ^{1}H-NMR (CDCl$_3$ + d$_6$-DMSO) δ ~9.50(bs, 1H, NH), 7.83(m, 1H, Ar-H), 7.65(m, 1H, Ar-H), 7.34(s, 1H, OH), 7.25 ~ 6.84(m, 6H, Ar-H), 4.37(q, 2H, CH$_2$), 1.44(t, 3H, CH$_3$).

7) B.p. 230°C/1 mmHg; IR 3410 cm^{-1} (O-H), 1730 cm^{-1} (C=O); ^{1}H-NMR(CDCl$_3$) δ 6.50(A$_2$B$_2$, 4H, Ar-H), 6.16(s, 1H, OH), 4.14(s, 1H, CH), 3.98, 3.88(q, 8H, CH$_2$), 1.10, 1.06(t, 12H, CH$_3$); ^{13}C-NMR(CDCl$_3$) ppm 168.9, 167.5(CO), 155.8, 129.1, 126.0, 114.9(C$_6$H$_4$), 63.3(C), 62.3, 61.7(CH$_2$), 57.0(CH), 13.6(CH$_3$).

8) J. K. Kochi, "Organometallic Mechanism and Catalysis," p.176. Academic Press, New York (1978).

9) P. Cagniant and D. Cagniant, Adv. Heterocyclic Chem., 18, 337 (1975), and references therein.