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SYNTHESIS OF PHENOLS BY POLYKETIDE CONDENSATION AND AN EFFICIENT SYNTHESIS OF 3,5-DIOXOALKANOATES FROM AMIDES

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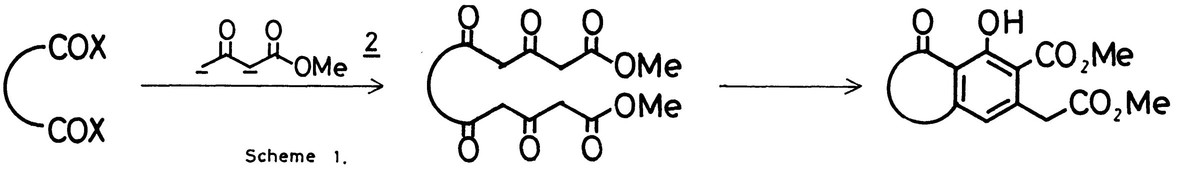
Several phenols were synthesized from dimethyl β,β',δ,δ'-tetraoxoalkanedioates, which were prepared by the condensation of methyl acetoacetate dianion with N,N,N',N'-tetramethylalkanediamides in the presence of $BF_3 \cdot OEt_2$.

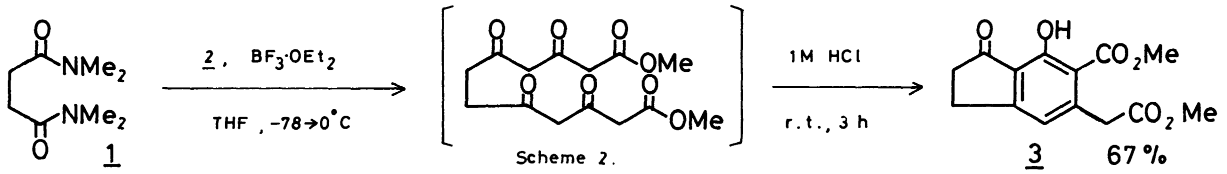
Polyketides are one of important intermediates in the biosynthesis of natural products, and various aromatic compounds including anthraquinones and tetracyclines are considered to be produced by the intramolecular condensation of these substances. Various β-polycarbonyls have been chemically prepared and subjected to the cyclization.$^{1)}$ However, little is still known on the chemical property of these linear compounds. We have continued investigation of the synthesis and the cyclization of β-polycarbonyls, and our initial results concerning the formation of bicyclic phenols are now described.

At first, we planned to synthesize dimethyl tetraoxoalkanoates by the dual condensation of alkanedioic acid derivatives with methyl acetoacetate dianion (Scheme 1). Thus, dimethyl succinate was reacted with the lithium sodium dianion of methyl acetoacetate (2) according to the Weiler's procedures.$^{2)}$ The result was unsatisfactory, and low yield of monoacyalted product was obtained.



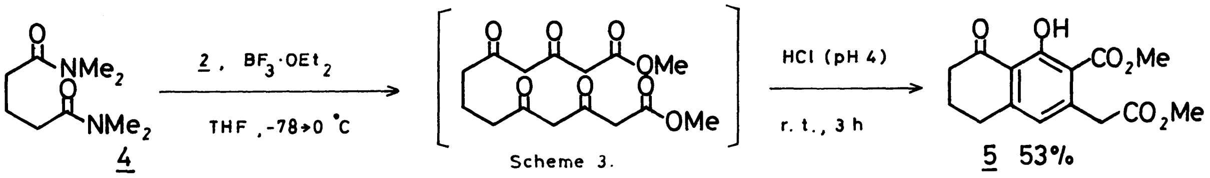
Scheme 1.

As it was previously found in our laboratory that, in the presence of $BF_3 \cdot OEt_2$, tertiary amides reacted with lithium acetylides effectively to give acetylenic ketones,$^{3)}$ we performed the above acylation in the presence of the Lewis acid. To a THF solution of N,N,N',N'-tetramethylsuccinamide (1) and a 2-fold molar excess of $BF_3 \cdot OEt_2$ was added a 6-fold molar excess of dianion 2 in THF at -78 °C. The reaction temperature was raised to 0 °C over 2 h, and the mixture was treated with 1M HCl for 3 h at room temperature. The acylation and intramolecular dehydration occurred during these procedures, and 7-hydroxy-6-methoxycarbonyl-5-methoxycarbonylmethyl-1-indanone (3) was isolated in 67% yield (Scheme 2). Mp 129-131 °C (ether-hexane). ^1H-NMR ($CDCl_3$) δ 2.5-2.8 (2H,m), 3.0-3.2 (2H,m), 3.69 (3H,s), 3.85 (2H,s), 3.92 (3H,s), 6.81 (1H,s), 10.91 (1H,s). IR (KBr) 1740, 1700, 1610 cm^{-1}. Exact mass calcd for $C_{14}H_{14}O_6$: 278.0789. Found: 278.0763.



Scheme 2.

N,N,N',N'-Tetramethylglutaramide (4) was also subjected to this dual condensation,[4)] and the expected 8-hydroxy-6-methoxycarbonyl-7-methoxycarbonylmethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (5) was obtained in 53% yield. Mp 92.5-93 °C (ether). ^{1}H-NMR ($CDCl_3$) δ 1.9-2.3 (2H,m), 2.60 (2H,t,J=6Hz), 2.83 (2H,t,J=6Hz), 3.70 (5H,s), 3.91 (3H,s), 6.66 (1H,s), 13.04 (1H,s). IR (KBr) 1730, 1715, 1620 cm^{-1}. Exact mass calcd for $C_{15}H_{16}O_6$: 292.0945. Found: 292.0920 (Scheme 3).



Scheme 3.

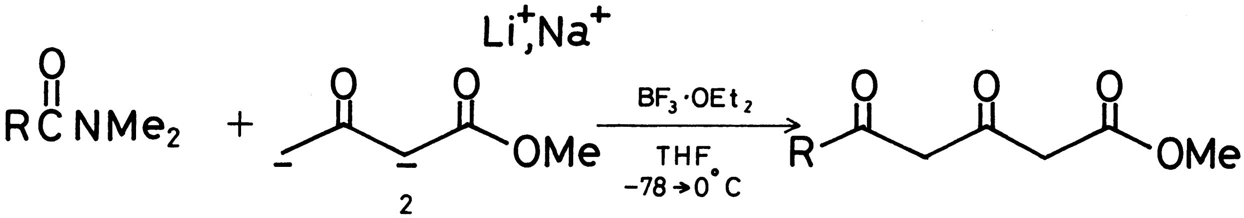
As the BF_3-assisted condensation of N,N-dimethylamides with dianion 2 proceeded effectively, the synthesis of various 3,5-dioxoalkanoates was also examined (Scheme 4, Table 1).

A typical procedure is described for the synthesis of methyl 3,5-dioxodecanoate. Under a nitrogen atmosphere, a THF solution (2 mL) of methyl lithiosodioacetoacetate (2.0 mmol) was prepared from methyl acetoacetate (2.0 mmol), sodium hydride (2.0 mmol), and a hexane solution of butyllithium (2.0 mmol) according to the Weiler's procedure.[5)] A THF (2 mL) solution of N,N-dimethylhexanamide (72 mg, 0.5 mmol) and $BF_3\cdot OEt_2$ (0.4 mL) were successively added to it at -78 °C. The temperature was raised to 0 °C over 2 h. The mixture was poured on silica gel (10 g), and allowed to stand overnight. Organic materials were eluted with ethyl acetate, concentrated in vacuo, and chromatographed on silica gel (ethyl acetate : hexane = 1:3) to give methyl 3,5-dioxodecanoate (78 mg, 73%). Bp 100 °C/ 1mm (bath temperature). ^{1}H-NMR ($CDCl_3$) δ 0.91 (3H,t,J=5Hz), 1.0-2.0 (6H,m), 2.1-2.5 (2H,m), 3.31 (2H,s), 3.74 (3H,s), 5.56 (1H,s), 15.0 (1H, brs). IR (neat) 1740, 1600 cm^{-1}. Exact mass calcd for $C_{11}H_{18}O_4$: 214.1204. Found: 214.1204.

In this synthesis, the treatment of the reaction mixture with silica gel prior to the purification is required to obtain reproducible results, and this manipuration would decompose a boron-complex presumably formed during the condensation reaction. The use of the dilithium dianion generated from methyl acetoacetate and 2 equiv. of LDA,[6)] instead of its lithium sodium dianion, did not give the acylation product under the present reaction conditions.

In the absence of $BF_3\cdot OEt_2$, any dioxoalkanoate was not detected after the reaction of 2 with N,N-dimethyldecamide at room temperature for 2 h.[7)]

The previous synthesis[2, 8)] of 3,5-dioxoalkanoates from esters, in some cases, suffered from self-condensation of the dianion or hydrolysis and transesterification of the products. Then, the present process would furnish an



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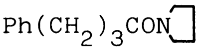
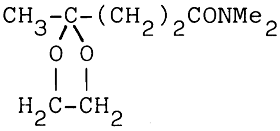
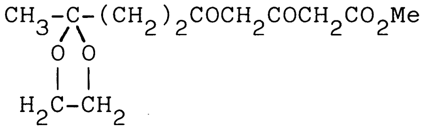
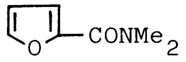
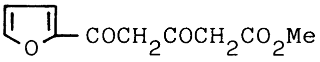
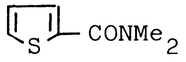
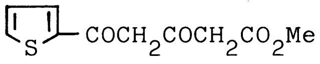
Scheme 4.

Table 1. Synthesis of 3,5-Dioxoalkanoates [a)]

Amides	Products	Yield /%
CH_3CONMe_2	$CH_3COCH_2COCH_2CO_2Me$	77[b)]
$n\text{-}C_5H_{11}CONMe_2$	$n\text{-}C_5H_{11}COCH_2COCH_2CO_2Me$	73
$n\text{-}C_9H_{19}CONMe_2$	$n\text{-}C_9H_{19}COCH_2COCH_2CO_2Me$	74
$Ph(CH_2)_3CONMe_2$	$Ph(CH_2)_3COCH_2COCH_2CO_2Me$	85
 $Ph(CH_2)_3CON$	$Ph(CH_2)_3COCH_2COCH_2CO_2Me$	57
 $CH_3\text{-}\underset{\substack{O\ \ O\\ \mid\ \ \mid\\ H_2C\text{-}CH_2}}{C}\text{-}(CH_2)_2CONMe_2$	 $CH_3\text{-}\underset{\substack{O\ \ O\\ \mid\ \ \mid\\ H_2C\text{-}CH_2}}{C}\text{-}(CH_2)_2COCH_2COCH_2CO_2Me$	62
$PhCONMe_2$	$PhCOCH_2COCH_2CO_2Me$	84
 $CONMe_2$	 $COCH_2COCH_2CO_2Me$	77
 $CONMe_2$	 $COCH_2COCH_2CO_2Me$	86

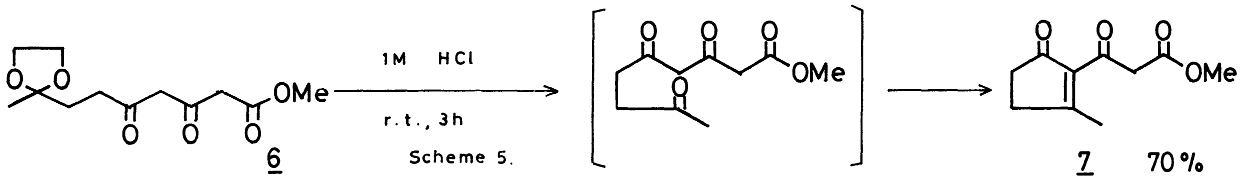
a) The reaction was carried out as described in the typical procedures. And satisfactory spectral data (^{1}H-NMR and IR) and/or elemental compositions by high resolution mass spectroscopy were obtained.

b) The reaction was carried out with 5.0 mmol of an amide and 10.0 mmol of dianion 2.

efficient method for the preparation of 3,5-dioxoalkanoates.

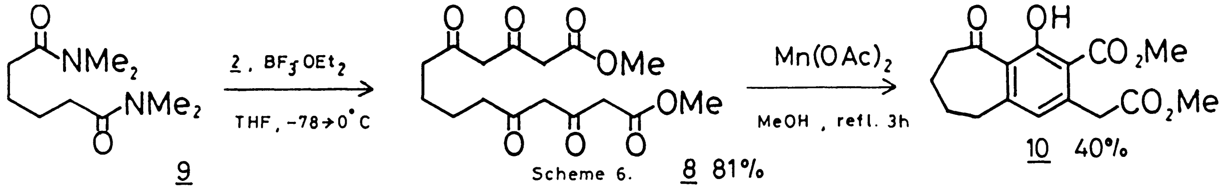
Additional examples of the intramolecular condensation of the isolated 3,5-dioxoalkanoates are also presented. 2-(3,5-Dioxo-6-methoxycarbonylhexyl)-2-methyl-1,3-dioxolane (6), prepared from N,N-dimethyl-4-oxopentanamide ethylene acetal as above, was treated with 1M HCl at room temperature for 4 h. The deprotection and condensation occurred to give 2-(2-methoxycarbonyl-1-oxoethyl)-3-methyl-2-cyclopenten-1-one (7) in 70% yield. This compound was found to be a 4:1 mixture of keto- and enol-tautomers as indicated by ^{1}H- and ^{13}C-NMR studies. Mp 48-50 °C (hexane). ^{1}H-NMR ($CDCl_3$) δ 2.4-2.8 (4H,m), 2.48 (3H,s), 3.27 and 3.76 (3H, s and s), 3.92 (1.6H, s), 5.97 (0.2H,s), 12.21 (0.2H, s). ^{13}C-NMR (CD-

Cl_3) δ 20.2, 32.9, 33.4, 34.9, 35.3, 48.6, 51.3, 52.1, 91.9, 132.3, 136.8, 165.4, 168.4, 181.1, 189.2, 190.9, 204.7, 205.2. IR (neat) 1700, 1630 cm^{-1}. Exact mass calcd for $C_{10}H_{12}O_4$: 196.0735. Found: 196.0747 (Scheme 5).



Scheme 5.

Seven-membered ring formation was also performed using dimethyl 3,5,10,12-tetraoxotetradecanedioate (8), which was prepared from N,N,N',N'-tetramethyladipamide (9). As 8 resisted to the cyclization under acidic conditions, the use of the metal template was examined. The condensation was achieved in the presence of $Mn(OAc)_2 \cdot 4H_2O$ in refluxing methanol, and 1-hydroxy-2-methoxycarbonyl-3-methoxycarbonylmethyl-9-oxo-6,7,8,9-tetrahydro-5H-benzocycloheptene (10) was obtained in 40% yield. Mp 114-116 °C (benzene-hexane). ^1H-NMR ($CDCl_3$) δ 1.6-2.0 (4H,m), 2.6-3.0 (4H,m), 3.79 (5H,s), 3.92 (3H,s), 6.06 (1H,s), 12.90 (1H,s). IR (KBr) 3500, 2900, 1720, 1630, 1610 cm^{-1}. Exact mass calcd for $C_{16}H_{18}O_6$: 306.1103. Found: 306.1112. Other protic solvents such as acetic acid or water also gave 10. Notably, $MnCl_2 \cdot 4H_2O$, $Mn(NO_3)_2 \cdot 6H_2O$, $Mn(acac)_2$, or $Mn(H_2PO_4) \cdot 4H_2O$ in refluxing methanol was not effective at all. To our knowledge, this is the first example of the transition metal-assisted condensation of polyketides (Scheme 6).



Scheme 6.

The synthesis of various β-polycarbonyl compounds utilizing the BF_3-assisted acylation, and studies of their intramolecular condensation is now in progress.

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2) S. N. Huckin and L. Weiler, Tetrahedron Lett., 1972, 2405; Can. J. Chem., 52, 1343 (1974). 3) M. Yamaguchi, T. Waseda, and I. Hirao, Chem. Lett., 1983, 35. 4) A reaction of acetylacetone dianion with diethyl 3-oxoglutarate ethylene acetal is reported; T. M. Harris, A. D. Webb, C. M. Harris, P. J. Wittek, and T. P. Murray, J. Am. Chem. Soc., 98, 6065 (1976). 5) L. Weiler, J. Am. Chem. Soc., 92, 6702 (1970). 6) N. S. Narasimham and R.-K. Ammanamanchi, J. Org. Chem., 48, 3945 (1983). 7) Acetylation of polyanions of polyketones with N-methoxy-N-methylacetoamide is known; T. A. Oster and T. M. Harris, Tetrahedron Lett., 24, 1851 (1983). Acylation of the trianion of 3,5-dioxohexanoate with N,N-dimethylacetamide is also known; A. G. M. Barrett, T. M. Morris, and D. H. R. Barton, J. Chem. Soc., Perkin Trans. 1, 1980, 2272. Cf. T. A. Oster and T. M. Harris, J. Org. Chem., 48, 4307 (1983). 8) T. M. Harris, T. P. Murray, C. M. Harris, and M. Gumulka, J. Chem. Soc., Chem. Commun., 1974, 362; J. S. Hubbard and T. M. Harris, Tetrahedron Lett., 1978, 4601.

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