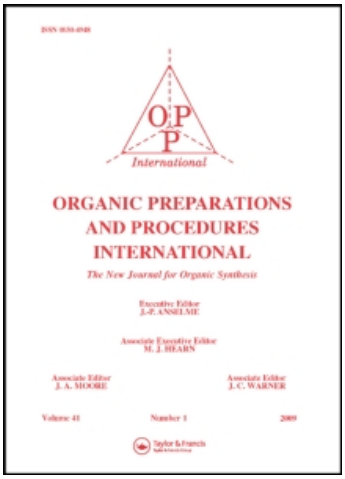

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FRIEDEL-CRAFTS ACYLATION WITH MALONIC ACIDS IN POLYPHOSPHORIC ACID

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FRIEDEL-CRAFTS ACYLATION WITH MALONIC ACIDS IN POLYPHOSPHORIC ACID

Submitted by (04/05/99)

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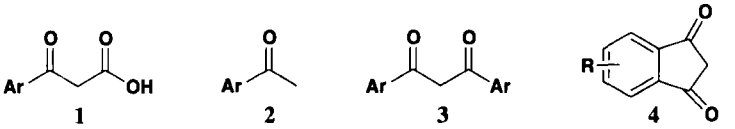
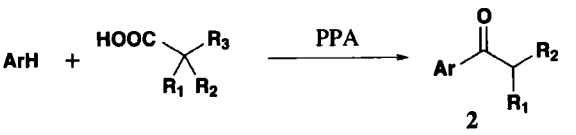
In the course of the synthesis of new heterocyclic derivatives of biological interest,[1] aryloxopropionic acids **1** were required as potential starting materials for new indanones,[2] cyclopentafuranones[3] and cyclopentathiophenones.[4] It is well known[5] that malonyl chloride itself or its derivatives condense under the conditions of the Friedel-Crafts reaction with aromatic rings to give such diverse products as monoketones **2**, diketones **3** or fused indanediones **4**.



Replacement of malonic chloride with sililic malonic anhydride[5] lead to the β-ketoacids, albeit in poor yields. Conversely, the reactivity of malonic acid[6] itself as acylating agent is very poorly documented. We thus decided to investigate the reaction. Since polyphosphoric acid[7] can serve as both solvent and acid catalyst for Friedel-Crafts acylations, our study focused on the acylation of benzene derivatives (toluene, anisole, chlorobenzene and benzoic acid), thiophene derivatives (thiophene, 2-bromothiophene and thiophene 2-carboxylic acid), furan, pyrrole and *N*-phenylpyrrole with malonic, phenylmalonic and diethylmalonic acids. The reactions were carried out in polyphosphoric acid (84% minimum) at 60-80° for 2 h, with a 2:1 ratio of the malonic acid to the aromatic compound. The acylated products **2** were isolated, after hydrolysis by extraction with Et_2O. None of these attempts lead to the β-ketoacids **1**, which underwent decarboxylation in acidic medium.[8]

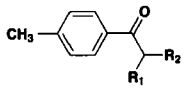
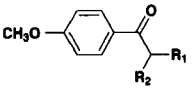
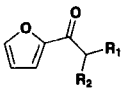
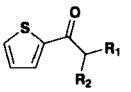
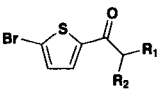
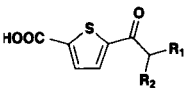
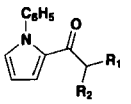
Interest in these compounds as chemical precursors leads us to report this selective method which exhibits increased yields compared to the use of the corresponding disubstituted acetic acids under the same conditions (Table 1) and avoids the use of strongly lacrymatory malonyl chloride derivatives.

In the phenyl substituted series, the best yields (82-92%) were obtained for the rings carrying an electron-donating group (methyl, methoxy). In this case, acylation occurred at the para-position. The absence of ortho-product may be explained as a steric effect of the electrophilic agent. For deactivating substituents such as Cl or CO_2H, the starting material was recovered. Thiophene, 2-bromothiophene, thiophene 2-carboxylic acid, furan underwent selective acylation at the α-position of the ring, whereas pyrrole gave only degraded products and *N*-phenylpyrrole gave only 5% of the acylated product (Table 1).



2

Table 1. Reaction of Aromatic Substrates with Malonic and Acetic Acids (Yields %).

Reactant	Product	R_1=R_2=H	R_3=CO_2H R_1=C_6H_5 R_2=H	R_1=R_2=C_2H_5	R_3=H R_1=H R_2=C_6H_5
Toluene		92[9-10]	90[11]	89[9]	–
Anisole		86[12-14]	83[14]	82[15]	–
Furan		70[16-17]	73[16, 18-19]	68[17]	34
Thiophene		86[17, 20]	90[21-23]	89[17]	41
2-Bromothiophene		93[22]	93[23]	88	41
Thiophene-2-carboxylic acid		10[26]	–	–	–
N-Phenylpyrrole		5	–	–	–

We suggest that the reactive intermediates are the malonic anhydrides which then acylate the aromatic substrates; this is supported by the failure of cyanoacetic acid to effect acylation. No gas evolution was observed nor did acylation occur below 60°.

The use of H_3PO_4 or P_2O_5 instead of polyphosphoric acid always failed to promote acylation. In a similar manner no acylation occured with malonic ester derivatives and cyanoacetic acid. In the same way, the use of these conditions other diacids such as succinic, glutaric and adipic acids as electrophilic agents failed; with $AlCl_3$ the corresponding anhydrides gave the acylated products.

In conclusion, this method of acylation by malonic acid derivatives, which are easily obtained by malonic synthesis,[27] in polyphosphoric acid could be extended to the preparation of aromatic ketones and particularly in furan series which usually give low yields in the Friedel-Crafts reaction.

EXPERIMENTAL SECTION

Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded as KBr pellets. NMR spectra were obtained on a JEOL Lambda 400 spectrometer in $CDCl_3$ solution using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS.

General Procedure.- To the aromatic compound (0.01 mol) were added the malonic acid derivatives (0.02 mol) and 15 mL of polyphosphoric acid (85% minimum). The reaction mixture was heated at 60-80° for 2 h with vigorous stirring. After cooling to rt, 100 mL of cold water was added, and the solution was stirred for 30 min. Extraction with 3x50 mL of diethyl ether, washing with 20 mL of saturated aqueous Na_2CO_3, drying ($MgSO_4$), filtering and evaporating under reduced pressure gave the crude ketone. Distillation under reduced pressure furnished the expected product.

1-(5-Bromothiophen-2-yl)-2-phenylethanone:[21-23] (93%), beige solid, mp. 124°, lit. mp. 124°, IR: 1665 cm^{-1}. ^1H NMR ($CDCl_3$): d = 4.18 (s, 2 H, CH_2), 7.11 (d, J = 4.0 Hz, 1 H, H3-thienyl), 7.27 (m, 5 H, aromatic H), 7,43 (d, J = 4.0 Hz, 1 H, H4-thienyl).

1-(5-Bromo-thiophen-2-yl)-2-ethylbutan-1-one: (88%), yellow oil, bp. 177° (11 Torr). IR: 1645 cm^{-1}. ^1H NMR ($CDCl_3$): d = 0.88 (t, J = 7.4 Hz, 6 H, $2CH_3$), 1.57 (m; 2 H, CH_2), 1.77 (m, 2 H, CH_2), 2.99 (m, 1 H, CH), 7.11 (d, J = 4.1 Hz, 1 H, H3-thienyl), 7.47 (d, J = 4.1 Hz, 1 H, H4-thienyl).

Anal. Calcd for $C_{10}H_{13}BrOS$: C, 45.94; H, 5.03. Found: C, 45.94; H, 5.01

2-Ethyl-1-thiophen-2-yl-butan-1-one:[17] (89%), colorless oil, bp. 139° (11 Torr), lit. bp. 105° (5 Torr), IR: 1636 cm^{-1}. ^1H NMR ($CDCl_3$): d = 0.87 (t, J = 7.3 Hz, 6 H, $2CH_3$), 1.57 (m; 2 H, CH_2), 1.76 (m, 2 H, CH_2), 3.05 (m, 1 H, CH), 7.05 (dd, J = 4.8 Hz and J = 3.6 Hz, 1 H, H4-thienyl), 7.59 (d, J = 4.8 Hz, 1 H, H5-thienyl), 7.76 (d, J = 3.6 Hz, 1 H, H3-thienyl).

2-Ethyl-1-fur-2-yl-butan-1-one:[17] (68%), yellow oil, bp. 92° (11 Torr), lit. bp. 97° (17 Torr), IR: 1642 cm^{-1}. ^1H NMR ($CDCl_3$): d = 0.88 (t, J = 7.4 Hz, 6 H, $2CH_3$), 1.56 (m; 2 H, CH_2), 1.78 (m, 2 H, CH_2), 3.12 (m, 1 H, CH), 6.47 (dd, J = 3.5 Hz and J = 0.4 Hz, 1 H, H4-furyl), 7.12 (d, J = 3.5 Hz, 1 H, H5-furyl), 7.52 (d, J = 0.4 Hz, 1 H, H3-furyl).

2-Ethyl-1-p-tolyl-butan-1-one:[9] (89%), colorless oil, bp. 132° (11 Torr), lit. bp. 129-130° (10 Torr), IR: 1651 cm^{-1}. ^1H NMR ($CDCl_3$): d = 0.86 (t, J = 7.4 Hz, 6 H, $2CH_3$), 1.55 (m; 2 H, CH_2), 1.78 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 3.28 (m, 1 H, CH), 7.25 (d, J = 8.0 Hz, 2 H, H3 and H5-phenyl), 7.87 (d, J = 8.0 Hz, 1 H, H2 and H6-phenyl).

2-Ethyl-1-(4-methoxy-phenyl)-butan-1-one:[15] (82%), colorless oil, bp. 154° (11 Torr), lit. bp. 156° (12 Torr), IR: 1666 cm^{-1}. ^1H NMR ($CDCl_3$): d = 0.86 (t, J = 7.4 Hz, 6 H, $2CH_3$), 1.56 (m; 2 H, CH_2), 1.77 (m, 2 H, CH_2), 3.25 (m, 1 H, CH), 3.87 (s, 3 H, OCH3), 6.94 (d, J = 9.0 Hz, 2 H, H3 and H5-phenyl), 7.96 (d, J = 9.0 Hz, 1 H, H2 and H6-phenyl).

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SYNTHESIS OF NEW TYPES OF LEWIS ACIDS

REARRANGEMENT OF STILBENE OXIDES

Submitted by
(11/09/98)

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Lewis acids have been used as promoters of carbon-carbon bond-forming reactions such as the Friedel-Crafts reaction[1] and oxygenophilic organoaluminum reagents Lewis acids which usually include methylaluminum bisphenoxide type molecules are highly useful for selective carbon-carbon coupling and selective Diels-Alder reaction.[2] A previous described new type of Lewis acid that contains a linked bisphenol moiety[3,4] and that methyl [2,2'-*m*-xylene-α,α'-diyl*bis*(4,6-di-*t*-butylphenoxide)]aluminum and its derivatives also are useful in the protection of some ketones from selective reductions.[3] However, the properties of methyl [2,2'-*o*-xylene-α,α'-diylbis(4,6-di-*t*-butylphenoxide)]aluminum (**4**) were not reported. We now describe four new Lewis acids, which incorporate bisphenols linked by an *o*-xylene-α,α-diyl moiety.

The reaction of 1,2-*bis*(hydroxymethyl)benzene (**2**) with *p*-substituted 2-*t*-butylphenol (**1a-d**) gave ligands **3a-3d** in 36%, 39%,[3] 49%, and 44% yields respectively; upon treatment with trimethyl-