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THE PREPARATION OF 2-(2-OXO-2-PHENYLETHYL)BENZOIC ACIDS FROM DILITHIATED *ORTHO*-TOLUIC ACID.

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ABSTRACT: *ortho*-Toluic acid was dimetalated with excess lithium diisopropylamide, and the resulting intermediate was condensed with a variety of aromatic esters to afford new substituted 2-(2-oxo-2-phenylethyl)benzoic acids (*ortho*-phenacylbenzoic acids).

In a series of synthesis studies, the preparation and reactions of dilithiated toluic acids using lithium diisopropylamide (LDA) for the metalation of the acids were reported[1]. The resulting dilithiated toluates were condensed at the carbanion-type center with several types of electrophilic reagents, especially alkylating reagents such as 1-bromobutane. The condensation of these dilithiated intermediates with esters has not been reported, and until recently[2] their condensation with aldehydes and ketones had been limited to the condensation of dilithiated toluates with benzophenone or *p*-methoxybenzaldehyde. *o*-Phenacylbenzoic acids[3] are routinely prepared by a Friedel-Crafts acylation[4] of benzenes and related aromatic compounds with homophthalic anhydrides. This is an intrinsically acidic

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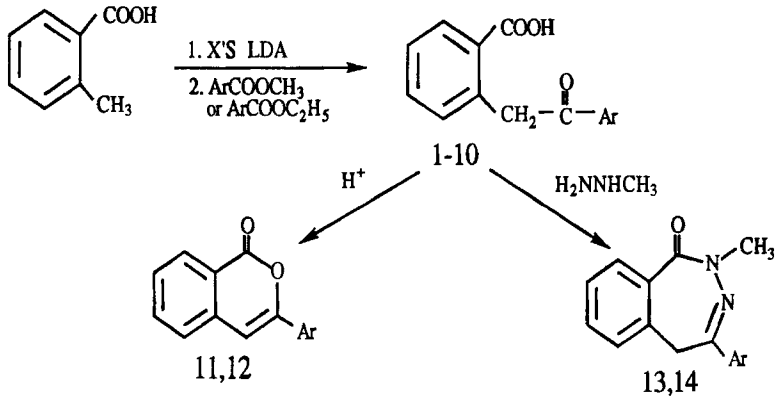
procedure that is subject to the restrictions encountered with Friedel-Craft condensations. Other preparative procedures include ozonolysis of 2-phenyl-3-(acyloxy)-1H-indenes[5a] or the rearrangement/saponification of indenone oxides[5b].

Our attention has been directed to the Claisen-type condensation of the dilithiated *o*-toluic acid with esters to afford *o*-phenacylbenzoic acids, which have the potential for use in the preparation of additional products. We were also interested in conveniently preparing gram quantities of these materials for potential biological testing. In several of our earlier multiple anion studies[6], we have observed that the success of completing Claisen-type condensations depends upon the following: [1] the type of entry compound used; [2] the method of preparation of the multiple anion-type intermediate in an excess of base, such as LDA; [3] the type of ester used; [4] the condensation time of the polymetalated intermediate with a particular ester; and [5] the metalation/condensation temperature.



The entry compound used during this investigation was readily available *o*-toluic acid[7], which was treated with excess LDA, condensed with select esters (acid:LDA:ester - 1:3:1; hydroxybenzoates, acid:LDA:ester - 1:4:1) and followed by neutralization with cold dilute hydrochloric acid. After work-up, *o*-phenacyl-benzoic acids **1-10** were isolated and recrystallized from routine solvents.

o-Phenacylbenzoic acids can undergo further reactions, such as acid cyclization to 1H-2-benzopyran-1-ones (isocoumarins)[3] or treatment with hydrazines to 1-oxo-2,5-dihydro-1H-2,3-benzodiazepines (2,3-benzodiazepin-1-ones)[3]. For example, products **9** and **10** were acid cyclized[8] ($HOAc/H_2SO_4$) to isocoumarins **11** and **12**, and products **2** and **3** were condensed/cyclized with methylhydrazine[9] to 2,3-benzodiazepin-1-ones **13** and **14** (footnote of Table).

o-Phenacylbenzoic acids **2-10** are new along with the representative isocoumarins, (**11** and **12**), and the 2,3-benzodiazepin-1-ones, (**13** and **14**). *o*-Phenacyl- benzoic acid **1** has been previously prepared by traditional procedures[8], and its properties (Table) resulting from this strong-base procedure agreed with the literature. The other new materials were characterized by absorption spectra along with support from combustion analysis (for C, H and N, when applicable). The infrared spectra of the products **1 - 10** displayed carboxy and carbonyl absorptions from 1681 -1726 cm^{-1} (most with shoulders) and each spectrum had the overall characteristic features of carboxylic acids[12]. Proton magnetic resonance for each compound displayed phenacyl methylene absorptions between δ 4.62 - 4.90 ppm (s) and aromatic hydrogens were displayed between δ 6.73 - 8.37 ppm. The absorption at δ 6.56 in **2** and at δ 6.18 in **7** can be reasonably assigned to vinyl hydrogens of the enolic form of this material. The carboxy hydrogens were not usually observed or distinguishable, except in **9** δ 8.68 ppm (s - exchange with D_2O). Pendant group methoxy absorptions in **2, 7, 9,** and **10** were noted δ 3.85 - 3.95 (s) ppm, and the *t*-butyl in **6** was observed at δ 1.37 ppm (s). The characteristic spectra for **11-14** are consistent with their structures[8].

The yields of *o*-phenacylbenzoic acids **1 - 10** ranged from 25-99 %, which indicates that the general experimental procedure is satisfactory for the expedient preparation of 0.5-1.0 gram quantities of the desired products that can be easily purified by recrystallization from routine solvents. The yields reported may not

necessarily represent those obtained under the optimum conditions for the preparation of an individual compound.

Several additional points are noted: (1) The products are prepared from a readily available and inexpensive starting material; (2) a single product[4a] is isolable following crystallization and recrystallization from routine solvents; (3) the products have potential for use in the preparation of other compounds or for the initiation of new studies[8,9]; and (4) the experimental procedure is straightforward so that someone not necessarily familiar with strong-base procedures can be successful with the reactions.

General Experimental Procedure for Preparation of *ortho*-Phenacylbenzoic Acids:

In a typical reaction a three-necked round-bottomed flask equipped with a stir bar, nitrogen inlet tube, and side-armed addition funnel (*e.g.*, 125 mL) was cooled in an ice water bath and charged with 0.063 mol. of *n*-butyllithium (0.084 mol. for hydroxybenzoates). This was followed by the addition of an equivalent amount (0.063 mol. or 0.084 mol. for hydroxybenzoates) of diisopropylamine dissolved in 25 mL of dry tetrahydrofuran (THF, sodium, benzophenone-ketyl) [fast dropwise rate - 5 min.]. The resulting solution of LDA was stirred for 20 min. at which time *o*-toluic acid (0.020 mol.) dissolved in 30-40 mL of THF was added from the addition funnel during a 5 min. period. The resulting purple solution was stirred (0°, N_2) for 60 min. and followed by the addition of 0.021 mol of ester dissolved in 30-40 mL of THF. The fast dropwise addition of this electrophilic reagent (5 min.) was followed by condensation times that varied with the type of ester used. Generally, esters such as methyl benzoate required a 45 min. condensation time and esters such as methyl 4-hydroxybenzoate required a 2 hour condensation time[10]. At the conclusion of the condensation period, the solution was neutralized

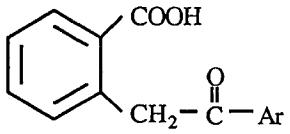


TABLE: 2-(2-Oxo-2-Phenylethyl)-Benzoic Acids/*ortho*-Phenacylbenzoic Acids

Compd. No.	Ar	Mol. Formula[11,12]	%Yield/Mp°C[a]
1	C_6H_5	$C_{15}H_{12}O_3$	25/164-67[b,d]
2	3,5-$(CH_3O)_2C_6H_3$	$C_{17}H_{16}O_5.H_2O$	65/143-45[d,g]
3	2-HOC_6H_4	$C_{15}H_{12}O_4$	99/160-62[d,g]
4	4-HOC_6H_4	$C_{15}H_{12}O_4$	77/211-13[e]
5	3-ClC_6H_4	$C_{15}H_{11}ClO_3$	24/131-34[d]
6	4-$(CH_3)_3CC_6H_4$	$C_{19}H_{20}O_3$	90/161-63[d]
7	3,4-$(CH_3O)_2C_6H_3$	$C_{17}H_{16}O_5$[b]	55/200-02[e]
8	2-HO,5-ClC_6H_3	$C_{15}H_{11}ClO_4$	90/159-61[d]
9	3,4,5-$(CH_3O)_3C_6H_2$	$C_{18}H_{18}O_6$	61/166-68[d,f]
10	2-OCH_3,5-Cl	$C_{16}H_{13}ClO_4.H_2O$	43/170-72[d,e,f]

[a]Melting points were obtained with a Mel Temp melting point apparatus in open capillary tubes and are uncorrected. [b]Lit., mp 163° (see ref. 4a). [c]The potassium salt of this compound has been reported (see ref. 13). [d]Recryst. from ethanol/water. [e]Recryst. from ethanol/benzene. [f]Isocoumarins **11** (from **9**) [$C_{18}H_{16}O_5$, mp 178-81°, 91 % (methanol)] and **12** (from **10**) [$C_{16}H_{11}ClO_3$, mp 148-51°, 83 % (methanol)] were prepared by acid cyclization (see ref. 8). [g]2,3-benzodiazepin- 1-ones **13** (from **2**)[$C_{18}H_{18}N_2O_3$, mp 122-24°, 59 % (ethanol)] and **14** (from **3**)[$C_{16}H_{14}N_2O_2$, mp 229-31°, 38 % (ethanol)] were prepared by condensation with methylhydrazine (see ref. 9).

with 100 mL of 3N hydrochloric acid and ice (*ca.* 50-100 g.) and 50-75 mL of solvent grade ether was added to the solution. After separation of layers, the aqueous phase was treated with 50-100 mL of solvent grade ether, partially neutralized with solid sodium bicarbonate (pH 4-5), and the organic layer was separated. After an additional extraction of the aqueous solution with ether (50 mL), the organic layers were combined and dried ($MgSO_4$). If the crude product had limited solubility, solvent grade THF was used to effect solution. After filtration, the ether solution was evaporated. The solid or oil that resulted was taken up in alcohol and recrystallized (see footnote of Table).

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3. *Chemical Abstracts* currently names these materials as 2-(2-oxo-2-phenylethyl)benzoic acids. Their former reference was α-benzoyl-*o*-toluic acids. Other names used for these compounds have included *o*-phenacylbenzoic acids. We are using the latter designation. In addition, 1H-2-benzopyranon-1-ones are referred to as isocoumarins, and 1-oxo-2,5-dihydro-

1H-2,3-benzodiazepines are referred to as 2,3-benzodiazepin-1-ones in this paper.

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7. *o*-Toluic acid and esters were obtained from Aldrich Chemical Co.
8. *o*-Phenacylbenzoic acid (1.00 gram) was dissolved in hot glacial acetic acid (10-15 mL), and then treated with 5-10 drops of concentrated sulfuric acid. The color of the solution darkened immediately and after 2 minutes of heating and stirring, the solution was poured into a beaker containing approximately 100 g. of ice. After the ice melted, the mixture containing solid material was filtered, and the resulting solid isocoumarin was recrystallized from alcohol or alcohol and water. See also: (a) Allen, C.. H. and VanAllan, J.A., *J. Amer. Chem. Soc.*, **1948**, *70*, 2069. (b) Koelsh, C.F. and LeClaire, C.D., *J. Amer. Chem. Soc.*, **1943**, *65*, 754. (c) Beautement, K. and Clough, J.M. Tetrahedron Lett, 1984, 25, 3025. (d) Brahmbhatt, D.I. and Bhide, B.H., *Indian J. Chem.*, **1984**, *23B*, 889.

9. *o*-Phenacylbenzoic acid (1.00 g.) was mixed with 1.00 g. of methylhydrazine, [5 drops of water] 10-15 mL of 2-ethoxyethanol, and heated under reflux overnight (12 hr. minimum, solution occurred). After evaporation of the 2-ethoxyethanol solvent, the resulting solid was recrystallized from ethanol. See also: (a) Ames, D.A., and Dodds, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 705; (b) Wolbling, H., *Ber.*, **1905**, *38*, 3846. (c) Wolbling, H., *Ber.*, **1905**, 2845. (d) Flammang, M., *C.R. Hebd. Seances Acad. Sci. Ser. C*, **1978**, *286*, 671; *Chem. Abstr.*, **1978**, *89*, 146878b. (e) Flammang, M., and Wermuth, C.G., *Eur. J. Med. Chem.-Chim. Ther.*, **1977**, *12*, 121. (f) Flammang, M. and Wermuth, C.G., *C.R. Hebd. Seances Acad. Sci. Ser. C*, **1980**, *290*, 361; *Chem. Abstr.*, **1980**, *93*, 203556d. (g) Rose, A., and Buu-Hoi, N.P., *J. Chem. Soc.*, **1968**, *C*, 2205. (h) Vorozhtov, N.N., and Petuchkova, A.T., *J. Gen Chem. USSR (Engl. Trans.)*, **1957**, *27*, 2342. (i) Somei, M., Karasawa, Y., Shoda, T., and Kaneko, C., *Chem. Pharm. Bull., Japan.*, **1981**, *29*, 249. (j) Grogan, F., O'Brian, A.E., Philbin, E.M., O'Conner, N.S., Tommoney, R.F., and Wheeler, T.S., *Tetrahedron*, **1958**, *3*, 140. (k) Legrand, L. and Lozac'h, N., *Bull. Soc. Chim. Fr.*, **1970**, 2237 and 2240.
10. The principal electrophilic reagent used in the condensation is monolithiated 2- or 4-hydroxybenzoate.
11. Microanalysis for C, H, and N, when applicable were obtained from Quantitative Technologies, Inc., Box 470, Salem Industrial Park, Whitehouse, NJ 08888 [Compd. No. from Table]. Calcd. for **2**, $C_{17}H_{16}O_5.H_2O$ ($C_{17}H_{18}O_6$): C, 64.14; H, 5.70. Found: C, 64.13; H, 5.65. Calcd. for **3**: C, 70.31; H, 4.72. Found: C, 70.22; H, 4.72. Calcd. for **4**: C, 70.31; H, 4.72. Found: C, 70.18; H, 4.90. Calcd. for **5**: C, 65.58; H, 4.04. Found: C, 65.82; H, 4.27. Calcd. for **6**: C, 77.00; H, 6.80. Found: C, 76.84; H, 6.69. Calcd. for **7**: C, 67.99; H, 5.37. Found: C, 67.74; H, 5.35. Calcd. for **8**: C, 61.98; H, 3.81. Found: C, 62.12; H, 3.75. Calcd. for **9**: C, 65.45; H, 5.49. Found: C, 65.59; H, 5.65. Calcd. for **10**, $C_{16}H_{13}ClO_4.H_2O$ ($C_{16}H_{15}ClO_5$): C, 59.54; H, 4.68. Found: C, 59.51; H, 4.80. Calcd. for **11**: C, 69.22; H, 5.16. Found: C, 68.98; H, 5.17. Calcd. for **12**: C, 67.03; H, 3.87. Found: C, 66.95; H, 3.73. Calcd. for **13**: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.42; H, 5.87; N, 8.96. Calcd. for **14**: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.03; H, 5.19; N, 10.29.

12. Infrared spectra were obtained from a Mattson Polaris FT-Infrared Spectrometer. Each compound **1 - 10** displayed less defined but somewhat characteristic OH absorptions observed for carboxylic acids between 3400 - 3200 and 2700 -2500 cm^{-1}. ^1H nmr for **1** and **4 - 14** were obtained from a Varian Associates, EM-360L and **1** and **3** from a EM-360A Nuclear Magnetic Resonance Spectrometers, and chemical shifts are reported in δ ppm downfield from an internal tetramethylsilane (TMS) standard. [Compd. No.: ir (paraffin oil), cm^{-1}; ^1H nmr (solvent), δ ppm] Compd. **1**: ir, 3150 (broad, OH), 1687 (C=O-O), and 1672 (C=O-CH_2); nmr ($CDCl_3$/DMSO-d_6), 4.86 (s, CH_2-C=O) and 7.20 - 8.37 (m, AH). Compd. **2**: ir, 3509 and 3430 (OH), 1711 (C=O-O), and 1672 (C=O-CH_2); nmr ($CDCl_3$/DMSO-d_6), 3.85 (s, OCH_3), 4.70 (s, CH_2-C=O), 6.58 (s, vinyl), 7.15 - 7.67 (m, ArH), and 8.15 (s broad, OH). Compd. **3**: ir, 3101 (broad, OH), 1693 (C=O-O), and 1682 (C=O-CH_2); nmr (DMSO-d_6), 4.90 (s, CH_2-C=O) and 7.13 - 8.27 (m, ArH). Compd. **4**: ir, 3174 (OH), 1726 (C=O-O), and 1651 (C=O-CH_2); nmr (DMSO-d_6), 4.70 (s, CH_2-C=O) and 6.73 - 8.20 (m, ArH, vinyl - enol, COOH). Compd. **5**: ir, 1689 and 1681 (C=O-O and C=O-CH_2); nmr ($CDCl_3$), 4.63 (s, CH_2-C=O) and 7.10 - 8.27 (m, ArH and COOH). Comp. **6**: ir, 1691 (shoulders, C=O-O and C=O-CH_2); nmr ($CDCl_3$/DMSO-d_6), 1.37 (s, Ar-C(CH_3)$_3$), 4.68 (s, CH_2-C=O_2), and 7.07 - 8.33 (m, ArH and COOH). Compd. **7**: ir, 1674 (shoulders, C=O-O and C=O-CH_2); nmr ($CDCl_3$/DMSO-d_6), 3.87 and 3.90 (s, $ArOCH_3$), 4.70 (s, CH_2-C=O), and 6.18-8.18 (m, ArH, vinyl - enol, COOH). Compd. **8**: ir, 1684 and 1645 (shoulders, C=O-O and C=O-CH_2); nmr ($CDCl_3$/DMSO-d_6), 4.78 (s, CH_2-C=O_2) and 6.83 - 8.30 (m, ArH and COOH). Compd. **9**: ir, 1700 (C=O-O); nmr ($CDCl_3$/DMSO-d_6), 3.92 and 3.95 (s, $ArOCH_3$), 7.40 - 8.33 (m, ArH), and 8.68 (s, COOH - exchange with D_2O). Compd. **10**: ir, 3438 (OH), 1693 (C=O-O), and 1666 (C=O-CH_2); nmr ($CDCl_3$/DMSO-d_6), 3.93 (s, $ArOCH_3$), 4.62 (s, CH_2-C=O), and 6.93 - 8.18 (m, ArH and COOH). Compd. **11**: ir, 1734 (C=O); nmr (DMSO-d_6), 3.92 (s broad, $ArOCH_3$) and 7.23 - 8.42 (m, C_4-H and ArH). Compd. **12**: ir, 1724 (C=O); nmr ($CDCl_3$), 3.95 (s, $ArOCH_3$), and 6.82-8.40 (m, C_4H and ArH). Compd. **13**: ir, 1644 (C=O-N); nmr ($CDCl_3$), 3.65 (s, N-CH_3), 3.85 (s, $ArOCH_3$), 3.95 (s, -CH_2-), and 6.51 -

8.18 (m, ArH). Compd. **14**: ir, 1635 (C=O-N); nmr (DMSO-d_6), 3.55 (s, N-CH_3), 4.22 (s, -CH_2-), and 6.77 - 8.05 (m, ArH).

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