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# THE PREPARATION OF SUBSTITUTED 3,4-DIHYDRO-1H-2-BENZOPYRAN-1-ONES FROM THE DIANIONS OF *ORTHO*-TOLUIC ACIDS.

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ABSTRACT: The dianions of *ortho*-toluic and α-phenyl-*ortho*-toluic acids were prepared with lithium diisopropylamide (LDA), condensed with certain aldehydes or ketones, and the resulting intermediates were acid-cyclized to substituted 3,4-dihydro-1H-2-benzopyran-1-ones (dihydroisocoumarins).

In a series of straight-forward and practical synthesis studies, the preparation of the dianions of commercially available and inexpensive *ortho-*, *meta-*, and *para*-toluic acids were reported[1] using lithium diisopropylamide (LDA) for the metalation of the respective carboxylic acid entry compounds. The resulting reactive toluate dianion intermediates were readily condensed at the carbanion center with several types of electrophilic reagents, especially alkylating reagents such as 1-bromobutane. Only two dihydroisocoumarin (3,4-dihydro-1H-benzopyran-1-ones) products were reported (*ca.*, 25-30%) when *o*-toluic acid dianion was condensed/cyclized with benzophenone or *p*-anisaldehyde. Another strong-base multiple anion procedure for the preparation of a dihydroisocoumarin[2] involved two steps starting with the dimetalation of N-methyl-*o*-toluamide,

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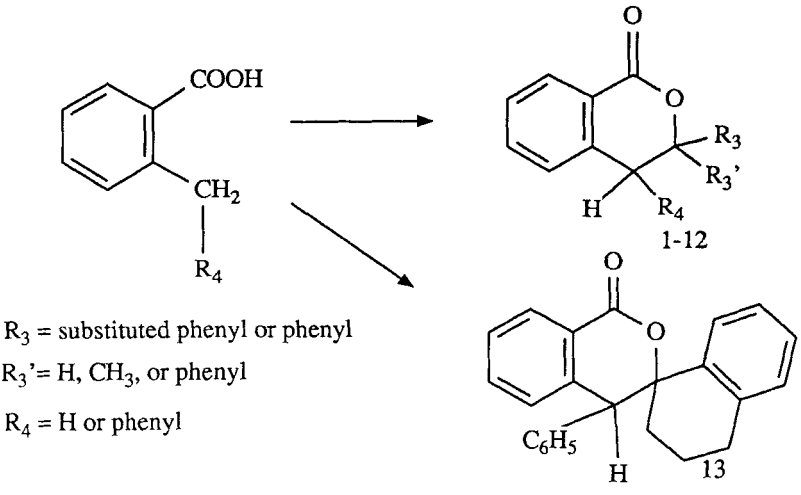
followed by condensation of the resulting dianion intermediate with benzophenone to afford a δ-hydroxyamide condensation product, which in a separate step was thermally- or acid-cyclized to the dihydroisocoumarin in good yield. This lithiation/ condensation/cyclization has been utilized by others [3-5] for the preparation of additional dihydroisocoumarins, and related *o*-toluate ester anions have been utilized for the preparation of compounds containing dihydro-isocoumarins[6]. Other related syntheses have been developed [7-13], and the stereochemistry of certain 3,4-disubstituted dihydroisocoumarins has been reported[14]. Also, new dihydroisocoumarins are continuously being prepared and studied for their potential biological activity[15].

Our attention has been directed to the dilithiation of *o*-toluic acids, and the possible aldol-type condensations of these dianion intermediates with aldehydes and ketones to afford either δ-hydroxy-*o*-toluic acids, or substituted dihydro-isocoumarins. In several of our recent multiple anion studies[16], we have observed that the success of completing aldol-type condensations depends upon the following: [1] the entry compound used; [2] the method of multiple anion formation (*e.g.*, base, solvent); [3] the aldehyde or ketone used; [4] the condensation time of the multiple anion intermediate with a particular carbonyl compound; and [5] the rapidity of acid neutralization of the solution containing the basic condensation precyclization intermediate. We were also interested in conveniently preparing enough new dihydroisocoumarins for biological testing, with emphasis on their potential as insecticides, herbicides, fungicides, bactericides, and plant growth stimulators[17].

The entry compounds we used during this investigation were *o*-toluic and α-phenyl-*o*-toluic acids, which were metalated with lithium diisopropylamide (LDA) (acid:LDA - 1:2, or 1:3 for dihydroisocoumarin **11**), followed by

condensation with certain aldehydes or ketones (*e.g.*, benzophenone, 2-aminobenzophenone, 4-methoxyacetophenone, 3,4-dichlorobenzaldehyde), rapid neutralization and cyclization with hydrochloric acid, and after work-up, recrystallization of heterocyclic products from routine solvents. In a typical experiment, 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 0.042 mol. (0.063 mol. for **11**) of *n*-butyllithium, which was followed by an equivalent amount (0.042 mol. or 0.063 mol. for **11**) of diisopropylamine dissolved in 35-45 mL of dry tetrahydrofuran (THF) [fast dropwise rate - 5 min.]. The resulting solution of LDA was stirred for 20 min., and then the toluic acid (0.020 mol.), dissolved in 45-50 mL of THF, was added from the addition funnel during a 5 min. period. The purple solution was stirred (0°, $N_2$) for 60 min., which was followed by the addition of 0.021 mol. of aldehyde or ketone dissolved in 40-50 mL of dry THF. The fast dropwise addition of the electrophilic reagent (5 min.) was followed by condensation times that varied for the type of aldehyde or ketone. Generally[18], ketones such as benzophenone (unsubstituted aromatic ketone) required a 15-20 min. condensation time; aldehydes such as 3,4,5-trimethoxybenzaldehyde or ketones such as 4-methoxyacetophenone (moderate electron donating group in 4-position) required a 60-75 min. condensation time; and 2-aminobenzophenone (strong electron donating group in 2-position) or 2-hydroxyacetophenone (as lithiated 2-hydroxy-acetophenone...and strong electron donating group) required a 2 hr. condensation time. At the conclusion of the condensation period, the solution was poured into 100-125 mL of 3N hydrochloric acid (inverse neutralization), returned to the round-bottomed flask, and the two-phase mixture was stirred and heated under reflux for 30 min. The hot mixture was then poured into a large flask (2 L)

containing ice (*ca.*, 500 g.), which was followed by ether (*ca.*, 100 mL), neutralization with solid sodium bicarbonate, extraction with ether (2 x 75 mL), and evaporation of the combined organic solvents/extracts. The solid or oil that resulted was taken up in alcohol and recrystallized (see footnote of Table - next page).




$R_3$ = substituted phenyl or phenyl

$R_3$'= H, $CH_3$, or phenyl

$R_4$ = H or phenyl

The melting point of dihydroisocoumarin **1** , mp 142-44°, prepared by this strong-base procedure, had good agreement with the reported value (Lit.[1] mp, 144-45°). Diastereomeric dihydroisocoumarins **4** (1:1) had a tight melting point range, and diastereomeric dihydroisocoumarins **12** (1:4) had a broad melting point range, which did not remain constant upon repeated recrystallization. The mixture (1:4) gave satisfactory combustion analysis results[19]. All dihydroisocoumarins **1-13** were characterized by absorption spectra[20] with support from combustion analysis[19] (for **2-13** C, H, and C, H, N for **5**). Only dihydroisocoumarin **1** is a single stereoisomer, dihydroisocoumarins **2** and **5** would be expected to be

TABLE - 3,4-Dihydro-1H-2-Benzopyran-1-ones[a,b]

[Dihydroisocoumarins]

| Compd. No. | $R_3/R_3'$ | $R_4$ | Mol. Formula[a] | %Yield/Mp °C[c] |
|---|---|---|---|---|
| **1** | $C_6H_5/C_6H_5$ | H | $C_{21}H_{16}O_2$[d] | 60/142-44 |
| **2** | $C_6H_5/C_6H_5$ | $C_6H_5$ | $C_{27}H_{20}O_2$[e] | 30/266-68 |
| **3** | $4\text{-}ClC_6H_4/C_6H_5$ | $C_6H_5$ | $C_{27}H_{19}ClO_2$[f] | 89/213-15 |
| **4** | $3,4\text{-}(Cl)_2C_6H_3/H$ | $C_6H_5$ | $C_{21}H_{14}Cl_2O_2$[e] | 44/198-200[g] |
| **5** | $2\text{-}H_2NC_6H_4/C_6H_5$ | H | $C_{21}H_{17}NO_2$[d] | 67/211-215 |
| **6** | $2,3,4\text{-}(CH_3O)_3C_6H_2/H$ | $C_6H_5$ | $C_{24}H_{22}O_5$[d] | 25/189-91 |
| **7** | $3,4,5\text{-}(CH_3O)_3C_6H_2/H$ | $C_6H_5$ | $C_{24}H_{22}O_5$[d] | 47/168-69 |
| **8** | $3,4\text{-}(CH_3O)_2C_6H_3/H$ | $C_6H_5$ | $C_{23}H_{20}O_4$[d] | 63/150-51 |
| **9** | $4\text{-}CH_3OC_6H_4/CH_3$ | $C_6H_5$ | $C_{23}H_{20}O_3$[d] | 44/180-82 |
| **10** | $4\text{-}ClC_6H_4/CH_3$ | $C_6H_5$ | $C_{22}H_{17}ClO_2$[d] | 55/149-51 |
| **11** | $2\text{-}HOC_6H_4/CH_3$ | $C_6H_5$ | $C_{22}H_{18}O_3$[d,h] | 50/188-90 |
| **12** | $3,4\text{-}(CH_3O)_2C_6H_3/CH_3$ | $C_6H_5$ | $C_{24}H_{22}O_4$[e] | 45/162-94[i] |
| **13** | $CH_2C_6H_4CH_2CH_2$[j] | $C_6H_5$ | $C_{24}H_{20}O_2$[f] | 48/ 150-54 |

[a]Combustion analysis data for C, H,and N (for **5**), see ref. 19. [b]IR and $^1H$ NMR data, see ref. 20. [c]Melting points were obtained in a Mel Temp melting point apparatus in open capillary tubes and are uncorrected. [d]Recryst. from ethanol. [e]Recryst. from benzene/ethanol. [f]Recryst. from methanol. [g]1:1 mixture of diastereomers. [h]$C_{22}H_{18}O_3.1/2\ CH_3CH_2OH$, solvated product, see ref. 19 and 20. [i]1:4 mixture of diastereomers. [j]Illustration on previous page.

enantiomeric mixtures, and other products would be enantiomeric and diasteromeric mixtures. The infrared spectra of all heterocyclic products displayed a lactone carbonyl absorption between 1684 (solvated product **11**) and 1734 $cm^{-1}$.

Usually the products displayed two carboxyl absorptions or a carboxyl absorption with a shoulder. $^1$H NMR spectra were useful in determining if mixtures of diastereomers of other products had resulted. The spectra indicated that a single diastereomer occurred or predominated (>90%) in products **6-11** and **13**, whereas mixtures of diasteroisomers were observed in products **4** (1:1) and **12** (1:4). $^1$H NMR spectra for the following displayed singlets for $C_4$-H, δ ppm: **1** (3.85), **2** (5.10), **3** (5.10), **9** (4.35), **10** (4.35), **11** (5.68), and **12** (4.32 and 4.68; ratio of diastereomers, 4:1), and **13** (4.87). Due to solubility difficulties, the methylene signal for **5** was displayed as either a broad singlet (4.05) [$CF_3COOH$/DMSO-$d_6$] or a poorly displayed doublet (3.79) [DMSO-$d_6$][21]. Coupling constants, J = 4 cps, were assigned to doublets[14] for *cis* diastereomer for $C_3$-$C_4$ protons, δ ppm: **4** (4.42 and 5.93), **6** (4.50 and 6.17), **7** (4.32 and 5.87), and **8** (4.25 and 5.84); *trans* doublet, J = 12 cps, δ ppm (4.42 and 5.62) was also displayed in dihydroisocoumarin **4**.

The yields of dihydroisocoumarins **1-13** ranged from 25-89%, which indicates that the general experimental procedure is satisfactory for the expedient preparation of gram quantities of desired products; but it may not necessarily represent the optimum conditions for the preparation of an individual compound. The fact that the toluic acids are relatively inexpensive and commercially available, and that they can be utilized directly for the preparation of dihydro-isocoumarin products is an attractive feature of this synthetic procedure. Several additional points are presented: (1) dihydroisocoumarins **9-12**[22] resulted from the condensation of the toluic acid dianion with substituted acetophenones, and in the past, we have experienced only limited success or no success from the condensation of other polyanions with aliphatic ketones, especially acetophenones; also, dihydroisocoumarin **13** resulted from condensation of toluate dianion with

1-tetralone; (2) dihydroisocoumarins **5** and **11** resulted from the condensation of the carbanion of the carboxylate dianion where the carbonyl carbon of electrophiles has diminished reactivity, resulting from the location of an electron donating potential of an *o*-amino group (for **5**) or an *o*-phenoxide group (for **11**)[18]; and (3) the preparation of dihydroisocoumarins **3, 4,** and **6-12** have the potential of affording mixtures of diastereomers, which was observed ($^1$H NMR) in **4** and **12**, while **3**, **6-11**, and **13** were predominantly or exclusively a single diastereomer. The latter compounds indicate a high degree of stereoselectivity for the syntheses presented using straight-forward entry compounds, base, and solvents.

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18. Unsubstituted and halogenated ketones or aldehydes for **1-4**, 15-20 min.; for ketones with amino or phenoxide groups for **5** and **11,** 2 hours were required because the *o*-amino or *o*-phenoxide ion is in a resonance deactivation position to the electrophilic carbonyl carbon; the methoxy groups for **6-9** and **12** are in a resonance position; but they are somewhat less deactivating than phenoxide and required a condensation time of 1-1.25 hr.; the ketone for the preparation of **10** required condensation time of 1 hr. possibly because it was 4-chloroacetophenone; and the ketone, α-tetralone, for the preparation of **13** required 1 hr.
19. Microanalyses for C, H, (and N for **5**) were obtained from Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Whitehouse, NJ 08888 and Robertson Laboratory, Inc., 29 Samson Ave., Madison, NJ 07940 [Compd. No. from Table]. Calcd. for **2**: C, 86.14; H, 5.36. Found: C, 86.08; H, 5.22. Calcd. for **3**: C, 78.92; H, 4.66. Found: C, 78.84; H, 4.66. Calcd. for **4**: C, 68.31; H, 3.82. Found: C, 68.08; H, 3.68. Calcd. for **5**: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.73; H, 5.57; N, 4.32. Calcd. for **6**: C, 73.83; H, 5.86. Found: C, 73.79; H, 5.56. Calcd. for **7**: C, 73.83; H, 5.86. Found: C, 73.76; H, 5.54. Calcd. for **8**: C, 76.65; H, 5.59. Found: C, 76.49; H, 5.53. Calcd. for **9**: C, 80.21; H, 5.85. Found: C, 79.81; H, 5.68. Calcd. for **10**: C, 75.75; H, 4.91. Found: C, 75.53; H, 4.76. Calcd. for **11**: C, 78.17; H, 5.99. Found: C, 78.55; H, 5.79. Calcd. for **12**: C, 76.99; H, 5.92. Found: C, 76.91; H, 5.81. Calcd. for **13**: C, 84.68; H, 5.92. Found: C, 84.52; H, 5.90.
20. Infrared spectra (Nujol) were obtained from a Mattson Polaris FT-Infrared Spectrometer. $^1$H nmr were obtained from a Varian Associates, EM 360L Nuclear Magnetic Resonance Spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane (TMS) standard. **1**, IR: 1700 and 1718 cm$^{-1}$ (C=O); NMR ($CDCl_3$): 3.85 (s, -$CH_2$-) and

7.12-7.72 and 8.08-8.32 (m, ArH); **2**, IR: 1720 $cm^{-1}$ (sh)(C=O); NMR ($CDCl_3$): 5.10 (s, -CH-), and 6.58-8.18 (m, ArH); **3**, IR: 1724 $cm^{-1}$ (sh) (C=O); NMR ($CDCl_3$): 5.10 (s, -CH-), and 6.60-8.20 (m, ArH and $NH_2$); **4**, IR: 1706 and 1717 $cm^{-1}$ (C=O); NMR ($CDCl_3$/DMSO-$d_6$, several drops): 4.36 (d, -CH-, J = 3 cps), 4.42 (s, -CH-, J = 12 cps), 5.62 (d, -CH-, J = 12 cps), and 5.93 (s, -CH-, J = 3 cps), and 6.55-7.78 and 8.12-8.55 (m, ArH); **5**, IR: 1700 $cm^{-1}$ (sh) (C=O), 3368 and 3489 $cm^{-1}$ ($NH_2$); NMR (solubility difficulties) ($CDCl_3$/DMSO-$d_6$): 3.79 (d, -$CH_2$-) and 6.40-8.27 (m, ArH and $NH_2$); (DMSO-$d_6$/$CF_3COOH$): 4.05 (s, broad, -$CH_2$-); (DMSO-$d_6$): 3.89 (d, -$CH_2$-); **6**, IR: 1734 $cm^{-1}$ (sh) (C=O); NMR ($CDCl_3$): 4.50 (d, -CH-, J = 4 cps), 6.17 (d, -CH-, J = 4 cps), and 6.43-7.77 and 8.27-8.53 (m, ArH); **7**, IR: 1717 $cm^{-1}$ (sh) (C=O); NMR ($CDCl_3$): 3.65 (s, $OCH_3$), 3.98 (s, $OCH_3$), 4.32 (d, -CH-, J = 4 cps), 5.87 (d, -CH-, J = 4 cps), and 6.57-7.75 and 8.27-8.50 (m, ArH); **8**, IR: 1721 $cm^{-1}$ (sh) (C=O); NMR ($CDCl_3$): 3.52 (s, $OCH_3$), 4.02 (s, $OCH_3$), 4.25 (d, -CH-, J = 4 cps), 5.84 (d, -CH-, J = 4 cps), 6.20-7.70 and 8.20-8.45 (m, ArH); **9**, IR: 1700 and 1713 $cm^{-1}$ (C=O); NMR ($CDCl_3$): 1.82 (s, $CH_3$), 3.73 (s, $OCH_3$), 4.35 (s, -CH-), and 6.47-7.63 and 8.23-8.45; **10**, IR: 1713 $^{-1}$ (sh) (C=O); NMR ($CDCl_3$): 1.85 (s, $CH_3$), 4.35 (s, -CH-), and 6.63-7.62, and 8.22-8.42 (m, ArH); **11**, IR: 3207 and 3400 $cm^{-1}$ (broad, OH) and 1684 $cm^{-1}$ (sh) (C=O); NMR ($CDCl_3$/DMSO-$d_6$): 1.18 (t, $CH_3$), 1.53 (s, $CH_3$), 3.67 (q, -$OCH_2$-), 5.68 (s, -CH-), 6.53-7.47, and 8.02-8.28 (m, ArH); **12**, IR: 1715 $cm^{-1}$ (C=O); NMR ($CDCl_3$): 1.47 (80%) and 1.85(20%) (s, $CH_3$), 3.65 (s, $OCH_3$), 3.83 (s, $OCH_3$), 4.32 (80%) and 4.68 (20%) (s, -CH-), and 6.63-7.67 and 8.27-8.48 (m, ArH); **13**, IR: 1700 $cm^{-1}$ (sh) (C=O); NMR ($CDCl_3$): 1.55-3.03 (m, -$CH_2CH_2CH_2$-), 4.87 (s, -CH-), and 7.02-7.67 and 8.18-8.43 (m, ArH).

21. We attribute the differences in observed chemical shifts resulting from a protonated and an unprotonated 2-anilino nitrogen in the 3-position.

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