The Preparation of 4-Oxo-*N*-Aryl-4*H*-1-benzopyran-2-acetamides by the Condensation/Cyclization of Trilithiated Acetoacetanilides with Lithiated Methyl Salicylates

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Several acetoacetanilides were trilithiated in excess lithium diisopropylamide, and the resulting polylithiated intermediates were regioselectively condensed with lithiated methyl salicylates followed by acid cyclization to substituted 4-oxo-*N*-aryl-4*H*-1-benzopyran-2-acetamides (benzopyranone-2-acetamides).

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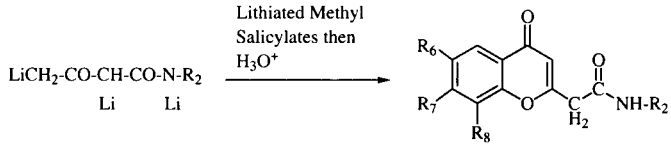
Chromones, 2-alkyl-4*H*-1-benzopyran-4-ones, of all types have a well documented history of usefulness, especially with regard to broad spectrum biological activity and other applications [1,2]. For example, 2-methylchromone has been prepared by traditional Claisen-type condensation/cyclization of 2'-hydroxyacetophenone and ethyl acetate [3,4]. Very few select chromones, benzopyranone-2-acetic acids [5], or their methyl [6] or ethyl esters [7] have been reported. The synthesis of a limited variety of additional substituted benzopyranone-2-acetic acid esters are also known [8]. One account [5] describes a three step process involving the condensation of allene 1,3-dicarboxylic ester and a phenol, followed by a saponification, and an acid cyclization to the benzopyranone-2-acetic acid. Another preparation germane to this study is the select lithiation of 2,6-dimethylchromone [7], followed by condensation with ethyl chloroformate to afford the benzopyranone-2-acetic acid, ethyl ester.

In a preliminary study [9a], we prepared trilithioacetoacetanilide and treated it with select electrophilic reagents in order to make new and potentially useful products taking advantage of the regioselectivity of the polyanion-type intermediate. One part of this study dealt with the feasibility of condensation/cyclization of these intermediates with lithiated salicylate esters, to afford benzopyranone-2-acetamides. The condensation of these anionic-type electrophilic reagents presented a challenge [9b] because of the potential for diminished reactivity of the carboxyl carbon, which is in a resonance position relative to the phenoxide ion portion of the salicylate ester [10].

During this investigation, several commercially available substituted acetoacetanilides, were polylithiated with excess lithium diisopropylamide, followed by regioselective Claisen-type condensation of the resulting polyanion-type intermediate at the terminal methylene carbanion center with the carboxy carbon of several lithiated methyl salicylates. This was followed by a straightforward acid-cyclization with aqueous hydrochloric acid to afford the desired benzopyranone-2-acetamides, **1-16**. Every compound targeted for preparation is new and would be difficult to prepare by traditional synthetic procedures.



1-16

All of the benzopyranone-2-acetamides, **1-16,** were characterized by absorption spectra, with support from combustion analyses for C, H, and N. The infrared spectra displayed carbonyl absorptions between 1651-1697 cm^{-1}, which were attributed to the benzopyranone carbonyl group. The acyclic amide carbonyl was usually distinguishable from the other carbonyl (except **3, 4** and **11**), and they were displayed between 1614-1666 cm^{-1}. In each case an aromatic absorption was also identified at approximately 1600 cm^{-1}. Conspicuous NH amide single absorptions were noted from 3132-3330 cm^{-1}. The ^1H nuclear magnetic resonance singlet absorptions were noted for methylene (CH_2CO), δ 3.86-4.45 ppm with vinyl (for enol) noted as singlets from δ 5.05-5.32 ppm in **9**, **12** and **13**, and pendant group singlet absorptions for $ArCH_3$ in **1, 3, 10**, **14-16** and $ArOCH_3$ in **3, 6, 9**, **11-13** and **16,** were noted at δ 2.22-2.50 ppm and δ 3.73-3.99 ppm, respectively. Another distinguishing feature was the C_3-H, δ 6.20-6.85 ppm, which was usually discernible from aromatic absorptions. The downfield sharp singlet absorption between δ 9.58-10.53 ppm is assigned to NH hydrogens, and they either exchanged with addition of deuterium oxide (**3, 5-7**, and **13**), or this reagent precipitated the compound. An intramolecular hydrogen bond between the amide hydrogens and the oxygen of the benzopyranone ring may explain the location of these chemical shifts.

The yields of benzopyranone-2-acetamides **1-16** ranged from 32-92% (see Table). The expedient preparation of multi-gram quantities of the desired products is especially attractive for amounts needed for biological testing, but it may not necessarily represent the optimum conditions for the preparation of each individual compound. The experimental

Table

4-Oxo-4*H*-1-benzopyran-2-acetamides

No	R_2	R_6	R_7/R_8	Molecular Formula %Yield/Mp,°C	Analyses Calcd./Found C	H	N
1	2-$CH_3C_6H_4$	H	H	$C_{18}H_{15}NO_3$	73.71	5.15	4.78
				92/226-227 [a]	73.35	5.40	4.72
2	4-ClC_6H_4	H	H	$C_{17}H_{12}ClNO_3$	65.08	3.86	4.46
				65/208-210 [b]	65.27	4.19	4.33
3	2-$CH_3OC_6H_4$	H	H	$C_{18}H_{15}NO_4$	69.89	4.89	4.53
				51/201-203 [c]	69.67	5.05	4.37
4	C_6H_5	Cl	H	$C_{17}H_{12}ClNO_3$	65.08	3.86	4.46
				42/226-228[d]	65.12	3.80	4.25
5	2-$CH_3C_6H_4$	Cl	H	$C_{18}H_{14}ClNO_3$	65.96	4.31	4.27
				62/224-226 [e]	65.95	4.26	4.06
6	2-$CH_3OC_6H_4$	Cl	H	$C_{18}H_{14}ClNO_4$	62.89	4.10	4.07
				43/189-191 [f]	62.77	4.00	3.95
7	C_6H_5	I	H	$C_{17}H_{12}INO_3$	50.39	2.99	3.46
				41/250-253 [g]	50.27	3.01	3.36
8	C_6H_5	Br	H	$C_{17}H_{12}BrNO_3$	57.01	3.38	3.91
				61/238-239 [h]	56.81	3.58	3.67
9	2-$CH_3OC_6H_4$	I	H	$C_{18}H_{14}INO_4$	49.68	3.24	3.22
				87/206-207 [i]	49.65	3.31	3.04
10	2-$CH_3C_6H_4$	I	H	$C_{18}H_{14}INO_3$	51.57	3.37	3.34
				51/248-250 [j]	51.87	3.33	3.24
11	2,4-$(CH_3O)_2C_6H_3$	H	H	$C_{19}H_{17}NO_5$	67.25	5.05	4.13
				88/191-193 [k]	67.04	5.16	3.97
12	2,5-$(CH_3O)_2C_6H_3$	H	H	$C_{19}H_{17}NO_5$	67.25	5.05	4.13
				60/144-145 [l]	66.94	5.10	3.94
13	C_6H_5	H	CH_3O (R_8)	$C_{18}H_{15}NO_4$	69.89	4.89	4.53
				38/221-224 [m]	69.73	4.68	4.42
14	2-$CH_3C_6H_4$	Br	H	$C_{18}H_{14}BrNO_3$	58.08	3.79	3.76
				42/224-227 [n]	57.92	3.86	3.56
15	2,5-$(CH_3)_2C_6H_3$	H	H	$C_{19}H_{17}NO_3$	74.26	5.58	4.56
				32/211-212 [o]	73.86	5.57	4.40
16	2,5-$(CH_3)_2C_6H_3$	H	CH_3O (R_7)	$C_{20}H_{19}NO_4$	71.20	5.68	4.15
				40/213-214 [p]	71.17	5.66	4.05

[a] ir: 3269 (NH), 1664 (C=O) and 1655 (C=O) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.25 (s, 3H, $ArCH_3$), 3.91 (s, 2H, CH_2), 6.42 (s, 1H, C_3-H), 7.08-8.09 (m, 8H, ArH), and 9.90 (s, 1H, NH). [b] ir: 3330 (NH), 1687sh (C=O), and 1645 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): δ 4.05 (s, 2H, CH_2), 6.67 (s, 1H, C_3-H), 7.48-8.40 (m, 7H, ArH), 8.70-9.20 (m, 1H, ArH), and 10.36 (s, 1H, NH). [c] ir: 3275 (NH), 1668 (C=O), and 1614 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): δ 3.93 (s, 3H, $ArOCH_3$), 4.42 (s, 2H, CH_2), 6.55 (s, 1H, C_3-H), and 6.66-8.35 (m, 8H, ArH); (dimethyl-d_6 sulfoxide): 9.78 (s, NH, exchange with deuterium oxide). [d] ir: 3132 (NH), 1673 (C=O), and 1618 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/ dimethyl-d_6 sulfoxide): δ 3.96 (s, 2H, CH_2), and 6.83-8.18 (m, 9H, ArH and C_3-H); (dimethyl-d_6 sulfoxide), 10.50 (s, 1H, NH). [e] ir: 3300 (NH), 1664 (C=O) and 1645 (C=O) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.22 (s, 3H, $ArCH_3$), 3.91 (s, 2H, CH_2), 6.53 (s, 1H, C_3-H), 7.10-8.18 (m, 7H, ArH), and 9.84 (s, 1H, NH, exchange with deuterium oxide). [f] ir: 3305 (NH), 1660 (C=O), and 1633 broad (C=O) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.92 (s, 3H, $ArOCH_3$), 4.22 (s, 2H, CH_2), 6.54 (s, 1H, C_3-H), and 7.16-8.02 (m, 7H, ArH); (dimethyl-d_6 sulfoxide), 9.74 (s, 1H, NH, exchange with deuterium oxide). [g] ir: 3325 (NH), 1697 (C=O) and 1639 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform/ dimethyl-d_6 sulfoxide): δ 3.90 (s, 2H, CH_2), 6.53 (s, 1H, C_3-H), and 7.13-8.80 (m, 8H, ArH); (dimethyl-d_6 sulfoxide), 10.50 (s, 1H, NH - exchange with deuterium oxide). [h] ir: 3263 (NH), 1660 (C=O) and 1651 (C=O) with shoulder at 1633 cm^{-1}; ^1H nmr (trifluoroacetic acid/deuteriochloroform): δ 3.92 (s, 2H, CH_2), 6.78 (s, 1H, C_3-H) and 7.10-8.92 (m, 8H, ArH); (dimethyl-d_6 sulfoxide), 10.48 (s, 1H, NH). [i] ir: 3329 (NH), 1664 (C=O), and 1651 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): δ 3.83 (s, 3H, $ArOCH_3$), 3.92 (s, CH_2), 5.32 (s, vinyl), 6.58 (s, 1H, C_3-H), 7.03-8.57 (m, 7H, ArH), and 9.80 (s, 1H, NH). [j] ir: 3259 (NH), 1664 (C=O)and 1651 (C=O) cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 2.37 (s, 3H, $ArCH_3$), 4.45 (s, 2H, CH_2), 6.20 (s, 1H, C_3-H), 7.18-9.02 (m, 7H, ArH), and 10.32 (s, 1H, NH). [k] ir: 3296 (NH), 1651 (C=O) and 1614 (C=O) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.73 (s, 3H, $ArOCH_3$), 3.83 (s, 3H, $ArOCH_3$), 4.37 (s, 2H, CH_2), 6.47 (s, 1H, C_3-H), 7.30-8.30 (m, 7H, ArH), and 9.58 (s, 1H, NH). [l] ir: 3305 (NH), 1687 (C=O), 1666 (sh at 1652) (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.82 (s, 6H, $ArOCH_3$), 3.95 (s, CH_2), 5.12 (s, vinyl), 6.48 (s, 1H, C_3-H), 6.67-8.67 (m, 7H, ArH); (dimethyl-d_6 sulfoxide), 9.72 (s, 1H, NH). [m] ir: 3284 (NH) and 1666 (broad) (C=O) cm^{-1}; ^1H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): δ 3.93 (s, 2H, CH_2), 4.07 (s, 3H, $ArOCH_3$), 5.05 (s, vinyl), 6.47 (s, 1H, C_3-H), and 6.90-7.91, 8.97 (m, 8H, ArH); (dimethyl-d_6 sulfoxide), 10.53 (s, 1H, NH - exchange with deuterium oxide). [n] ir: 3270 (NH), 1666 (C=O) with shoulder at 1643 cm^{-1}; ^1H nmr (trifluoroacetic acid/deuteriochloroform): δ 2.25 (s, 3H, $ArCH_3$), 3.98 (s, 2H, CH_2), 6.85 (s, 1H, C_3-H), 7.20-8.75 (m, 7H, ArH); (dimethyl-d_6 sulfoxide): 9.84 (s, 1H, NH). [o] ir: 3249 (NH), 1662 (C=O) and 1645 (C=O) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.17 (s, 3H, $ArCH_3$), 2.26 (s, 3H, $ArCH_3$), 3.86 (s, 2H, CH_2), 6.40 (s, 1H, C_3-H), 6.91-8.08 (m, 7H, ArH), and 9.68 (s, 1H, NH). [p] ir: 3246 (NH), 1660 (C=O) and 1651 (C=O) (sh) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.22 (s, 3H, $ArCH_3$) and 2.50 (s, 3H, $ArCH_3$), 3.99 (s, 3H, $ArOCH_3$), 4.19 (s, 2H, CH_2), 6.49 (s, 1H, C_3-H), 6.92-7.88 (m, 6H, ArH), and 9.72 (s, 1H, NH).

procedure is also general and straightforward so that it is reproducible by someone not necessarily familiar with strong-base preparative techniques and procedures, and the experimental set-up does not require elaborate apparatus (see Experimental).

EXPERIMENTAL

Melting points were obtained with a Mel-Temp II melting point apparatus in open capillary tubes and are uncorrected. Fourier Transform infrared spectra were obtained on a Nicolet Impact 410 or Mattson Polaris FT-IR. Proton magnetic resonance spectra were obtained with a Varian Associates 360L nuclear magnetic resonance spectrometer, and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888. The tetrahydrofuran was distilled from sodium (benzophenone ketyl) prior to use, and chemicals were obtained from Aldrich Chemical Co. and Pfaltz and Bauer, Inc.

General Experimental Procedure for Preparing 4-Oxo-*N*-aryl-4*H*-1-benzopyran-2-acetamides **1-16.**

In a typical experiment, the acetoacetanilide was added to excess lithium diisopropylamide, followed by the salicylate ester (β-ketoamide:base:ester, 1:5:1), and then acid-cyclization to the product.

The lithium diisopropylamide was prepared by adding 5.36 g (0.0525 mole) of diisopropylamine, dissolved in 45-55 ml of dry tetrahydrofuran, to 33 ml (0.0525 mole) of *n*-butyllithium (1.6*M*) (nitrogen, 0°). After 20 minutes, 0.0100 mole of an acetoacetanilide, dissolved in 35-45 ml of dry tetrahydrofuran, was added at a fast dropwise rate (5 minutes). After stirring at 0° for 3 hours, 0.0105 mole of salicylate ester, dissolved in 25-35 ml of dry tetrahydrofuran, was added at a fast dropwise rate (5 minutes), and the resulting mixture was stirred at 0° for an additional 2 hours. The mixture was quenched by addition of 100 ml of 3*N* hydrochloric acid, and the resulting two-phase mixture was stirred and heated under reflux for 1 hour. The mixture was then poured into a large flask (1 liter) containing ice (*ca.*, 100 g), and after adding solvent grade ether (*ca.*, 100 ml), it was neutralized with solid sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with ether or tetrahydrofuran (2 x 75 ml), and the ether extracts were combined and evaporated. The resulting solid or oil was recrystallized from alcohol.

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