A New Preparation of Substituted 4*H*-1-Benzothiopyran-4-ones from C(α),*N*-Benzoylhydrazones or C(α),*N*-Carboalkoxyhydrazones and Methyl Thiosalicylate

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C(α),*N*-Benzoylhydrazones or C(α),*N*-carboalkoxyhydrazones were dilithiated with excess lithium diisopropylamide, and the dianion-type intermediates were condensed with lithiated methyl thiosalicylate, followed by cyclization/hydrolysis to substituted 4*H*-1-benzothiopyran-4-ones (thioflavones/thiochromones).

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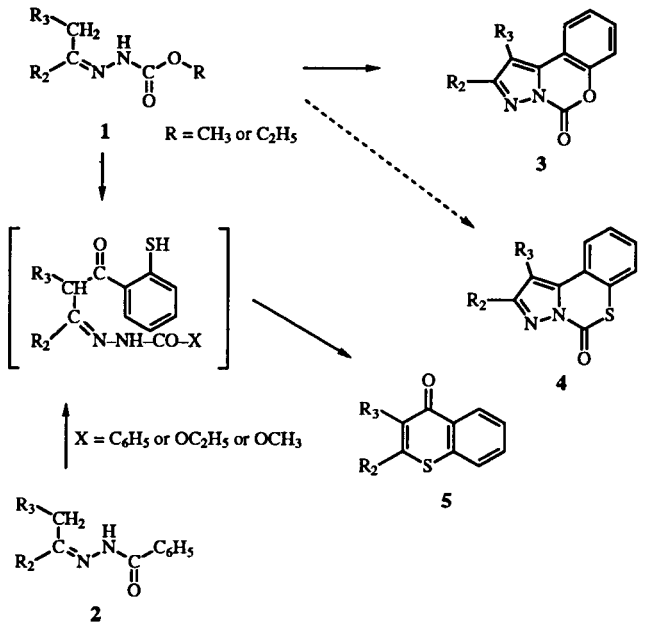
Thioflavones/thiochromones, 4*H*-1-benzothiopyran-4-ones, are known for their usefulness in organic syntheses and other studies [1] in addition to their potential for biological activity [2]. A favored method of preparation of these materials is the condensation/cyclization of thiophenols and β-ketoesters [3]; however, there is a continued interest in their preparation by other methods [4]. In this report, we describe a new and unexpected method for their preparation which has synthetic value.

Earlier investigations [5] with dilithiated C(α),*N*-carboalkoxyhydrazones **1** or C(α),*N*-benzoylhydrazones **2** [6] involved the treatment of these reactive intermediates with electrophilic reagents that included ketones, carboxylic acid anhydrides, or aromatic esters. In the case of the condensations with esters or amino-ketones, the intermediates were cyclized following treatment with dilute acid to substituted 1*H*-pyrazoles [5d], or they were cyclized after hydrolysis (hydrazones→ketones) to quinolines [6]. When salicylate esters were used for the condensation/cyclization, the resulting *N*-carboalkoxypyrazole underwent a second cyclization to afford substituted 5*H*-pyrazolo[1,5-*c*][1,3]benzoxazin-5-ones **3** [5a-c]. Since the latter compounds are a relatively new type of fused-ring heterocycle [7], an initially proposed extension of this reaction type was to substitute methyl thiosalicylate for the methyl salicylate esters previously used, because the condensation/cyclization offered the potential for preparing an even lesser known type of fused-ring heterocycle, 5*H*-pyrazolo[1,5-*c*][1,3]benzothiazin-5-ones **4** [8].

During this investigation, C(α),*N*-carboalkoxyhydrazones **1** or C(α),*N*-benzoylhydrazones **2** were dilithiated with excess lithium diisopropylamide, followed by a Claisen-type condensation with lithiated methyl thiosalicylate to give C-acylated intermediates that underwent hydrolysis/cyclodehydration [9] of the carboalkoxyhydrazone or benzoylhydrazone to the substituted 4*H*-1-benzothiopyran-4-ones **5a-i** instead of the originally anticipated pyrazolobenzothiazinones **4**.



The substituted benzothiopyranones **5a-i** prepared during this investigation are listed in the Table. The yields ranged from 48-94%, and each compound was readily purified by recrystallization with ethanol/water. Thioflavones **5f** and **5g** have been prepared by traditional methods [10], and the melting points obtained for these materials prepared agreed very well with the literature reports. Each compound was also characterized by absorption spectra, and new compounds, **5a-e**, **h**, and **i**, also had additional support from combustion analyis for C and H. The infrared spectra for each compound displayed intense carbonyl absorptions from 1614-1629 cm^{-1}, which were distinguishable from intense aromatic absorptions observed at approximately 1600 cm^{-1}, and are confirmed by similar data obtained by others [10a,b]. The ^1H nmr spectra of **5a-i** displayed aromatic and other pendant group absorptions. In three cases, C_3-H were clearly observed as singlets and distinguishable from aromatic

absorptions from δ 7.15-7.37 ppm in **5a**, **f**, and **g**. Characteristic aromatic absorptions were noted from δ 6.95-8.32 ppm, with a second clearly noted downfield multiplet (1H) for C_5-H centered at δ 8.56-9.00 ppm. The C_2-benzyl methylene protons in thiochromone **5c** were noted at δ 3.80 ppm, and methoxy protons in thioflavones **5b**, **f**, and **h** were displayed as singlets at approximately δ 4.00 ppm.

While the condensation of an anion type substrate with another anion type substrate may at first appear to be impractical, condensations of this type have been established by us [6b,11] and others [12]. The formation of the thioflavones **5a**, **b**, **d-i** and thiochromone **5c** instead of the pyrazolobenzothiazinones **4** might be attributed to the differences in the nucleophilicity of the thiophenyl sulfur in comparison to that of the nitrogen bonded to the carbonyl carbon. Either the thiophenoxide attacked the imine carbon in the basic medium, or more probably the thiophenol attacked the same imine carbon in acidic medium which, followed by hydrolysis, resulted in the substituted benzothiopyranones **5a-i** [13].

During the early stages of this investigation, we did isolate impure pyrazolobenzothiazinones **4** when 4-fluoroacetophenone and 4-methoxyacetophenone carboethoxyhydrazones were used. The developed procedure used a longer condensation time and ensured that good stirring always occurred during reflux of the biphasic mixture (see Experimental). The same situation does not have the potential of happening when benzoylhydrazones are used instead. In spite of the preference for benzoylhydrazone entry compounds, the utilization of 4-fluoroacetophenone carboethoxyhydrazone gave a better yield of product **5e**, 73% in comparison to 20%. Based upon the results reported here, a preference for a benzoylhydrazone over a carboalkoxyhydrazone cannot be stated.

The yields of products reported vary from 48-94%, and they may not be optimal for a particular compound, but the current general procedure readily affords multi-gram quantities of pure heterocyclic products resulting from recrystallization from routine solvents, which are sufficient amounts for spectral characterization, biological testing, and other uses. The experimental procedure is straightfor-

Table

4H-1-Benzothiopyran-4-ones

No.	R_2	R_3	Mol. Formula	%Yield/ MP,°C [a]	Elemental *Anal* Calcd./Found C	H	IR, cm^{-1} (C=O)
5a	4-BrC_6H_4	H	$C_{15}H_9BrOS$	48 [b,c] 160-163	56.80 56.45	2.86 2.98	1629 [m]
5b	3,4-$(CH_3O)_2$-C_6H_3	H	$C_{17}H_{14}O_3S$	54 [d] 145-148	68.43 68.05	4.73 4.79	1614 [n]
5c	$C_6H_5CH_2$	C_6H_5	$C_{22}H_{16}OS$	65 [b,e] 164-165	80.46 80.25	4.91 4.80	1614 [o]
5d	2-Naphthyl	H	$C_{19}H_{12}OS$	72 [b,f] 202-203	79.14 78.90	4.19 4.23	1619 [p]
5e	4-FC_6H_4	H	$C_{15}H_9FOS$	73 [d,g] 155-157	70.30 69.95	3.54 3.57	1617 [q]
5f	4-$CH_3OC_6H_4$	H	$C_{16}H_{12}O_2S$	84 [h] 126-127 [i]	----	----	1622 [r]
5g	4-ClC_6H_4	H	$C_{15}H_9ClOS$	82 [j] 161-165 [k]	----	----	1629 [s]
5h	3-CH_3O-C_6H_4	H	$C_{16}H_{12}O_2S$	94 [l] 125-126	71.62 71.33	4.51 4.67	1620 [t]
5i	4-HOC_6H_4	H	$C_{15}H_{10}O_2S$	66 [b] 291-294	70.85 71.03	3.96 3.82	1618 [u]

[a] All compounds were recrystallized from ethanol/water. [b] Benzoylhydrazone used. [c] Yield (36%) with carboethoxyhydrazone. [d] Carboethoxyhydrazone used. [e] Yield (40%) with carboethoxyhydrazone. [f] Yield (35%) with carbomethoxyhydrazone. [g] Yield (20%) with benzoylhydrazone. [h] Yield (61%) with carboethoxyhydrazone. [i] Lit. mp 126-127°; ref [10a]. [j] Yield (36%) with carboethoxyhydrazone. [k] Lit. mp 163-165°, ref [10e]. [l] Yield (33%) with carbomethoxycarbazone. [m] ^1H nmr (deuteriochloroform): δ 7.37 (*s*, 1H, C_3-H), 7.63-8.35 (m, 7H, ArH), and 8.60-8.90 (m, ArH 1H). [n] ^1H nmr (deuteriochloroform): δ 4.05 and 4.08 (*s*, $ArOCH_3$, 6H), 7.23-7.95 (m, C_3-H and ArH, 7H), and 8.53-8.96 (m, ArH, 1H). [o] ^1H nmr (deuteriochloroform): δ 3.80 (s, $ArCH_2$, 2H), 7.15-8.18 (m, ArH, 13H), and 8.53-8.88 (m, ArH, 1H). [p] ^1H nmr (deuteriochloroform/trifluoroacetic acid): δ 7.05-8.58 (m, C_3-H and ArH, 11H), and 8.78-9.00 (m, ArH, 1H). [q] ^1H nmr (deuteriochloroform): δ 7.16- 8.13 (m, C_3-H and ArH, 8H), and 8.43-8.90 (m, ArH, 1H). [r] ^1H nmr (deuteriochloroform): δ 3.92 (*s*, $ArOCH_3$, 3H), 7.15 (s, C_3-H, 1H), 7.02-8.32 (m, ArH, 7H), and 8.50-8.83 (m, ArH, 1H). [s] ^1H nmr (deuteriochloroform): 7.37 (*s*, C_3-H, 1H), 7.58-8.05 (m, ArH, 7H) and 8.63-8.93 (m, ArH, 1H). [t] ^1H nmr (deuteriochloroform): δ 3.98 (*s*, $ArOCH_3$, 3H), 7.33-8.07 (m, C_3-H and ArH, 8H), and 8.63-9.03 (m, ArH, 1H). [u] ^1H nmr (dimethyl sulfoxide-d_6): δ 6.95-8.25 (m, C_3-H and ArH, 8H), 8.45-8.68 (m, ArH, 1H); ^1H nmr (trifluoroacetic acid): δ 9.63 (*s*, OH, 1H exchange with deuterium oxide).

ward so that someone not necessarily familiar with strong base procedures can be successful with the reactions.

EXPERIMENTAL

Melting points were obtained with a Mel-Temp 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 EM-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.

General Procedure for Preparation of 4*H*-Benzothiopyran-4-ones **5a-i**.

In a typical reaction sequence, lithium diisopropylamide (0.064 mole) was prepared by the addition of 40 ml of 1.6 *M* *n*-butyllithium (0.064 mole) to a three neck round-bottomed flask equipped with a nitrogen inlet tube, a side-arm addition funnel, and a stir bar. The flask was cooled in an ice bath and 6.46 g (0.064 mole) of diisopropylamine, dissolved in 25-30 ml of dry tetrahydrofuran (sodium/benzophenone) (0°, nitrogen), was added from the funnel at a fast dropwise rate during 5 minutes. The solution was stirred for an additional 15-20 minutes, and then treated *via* the addition funnel with a C(α),*N*-benzoylhydrazone or C(α),*N*-carboalkoxyhydrazone (0.015 mole) dissolved in 35-45 ml of tetrahydrofuran. After 45-60 minutes lithiation, 2.74 g (0.0158 mole) of methyl thiosalicylate, dissolved in 25-35 ml of tetrahydrofuran, was added to the dilithiated intermediate, and the solution was stirred for 3 hours (0°, nitrogen). Finally, 100 ml of 3*N* hydrochloric acid was added, and the two-phase mixture was stirred and heated under reflux for approximately one hour. At the end of this period, the mixture was poured into a large flask containing ice (*ca.*, 100 g) followed by 100 ml of solvent grade ether or tetrahydrofuran. The mixture was then neutralized with solid sodium bicarbonate and the layers separated. The aqueous layer was extracted with ether or tetrahydrofuran (2 x 75 ml), and the organic fractions were combined, evaporated, and recrystallized.

General Procedure for the Preparation of C(α),*N*-Carboalkoxyhydrazones or C(α),*N*-Benzoylhydrazones.

The entry compounds were prepared [14] by heating under reflux a solution of 0.05 mole of ketone, 0.0525 mole of ethyl or methyl carbazate, or benzoylhydrazine, 100-125 ml of ethanol or methanol, and approximately 1 ml of glacial acetic acid. After 1.5 hours, the solution was concentrated to 50-60 ml, crystallization usually occurred, and this material after filtration and drying was generally pure enough to use directly. Pure samples for new compounds were recrystallized once from ethanol, ethanol/water, or methanol/water.

Benzoic Acid, [1-(3-Methoxyphenyl)ethylidene]hydrazide.

The 3-methoxyacetophenone benzoylhydrazone was obtained in 76% yield (ethanol) from the reaction of 3-methoxyacetophenone with benzoylhydrazine, mp 145-147°; ir (paraffin oil): 3279, 1658 (sh) and 1643 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.38 (s, CH_3, 3H), 3.88 (s, $ArOCH_3$, 3H), and 6.90-8.90 (m, ArH, 9H).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.71; H, 6.19; N, 10.49.

Benzoic Acid, (1,3-Diphenyl-2-propylidene)hydrazide.

The 1,3-diphenylacetone benzoylhydrazone was prepared in 88% yield (ethanol) by the reaction of 1,3-diphenylacetone with benzoylhydrazine, mp 142-145°; ir (paraffin oil): 3284 and 1652 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.53 (s, 2H, $-CH_2-$), 3.77 (s, 2H, $-CH_2-$), 7.00-7.82 and 8.36-9.38 (m, 15H, ArH).

Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.21; H, 6.10;N, 8.47.

Hydrazinecarboxylic Acid, [1-(4-Fluorophenyl)ethylidene]-, Ethyl Ester.

The 4-fluoroacetophenone carboethoxyhydrazone was prepared in 88% yield (ethanol/water) by the condensation of 4-fluoroacetophenone with ethyl carbazate, mp 129-132°; ir (paraffin oil): 3184, 1730 and 1705 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.46 (q, 2H, OCH_2), and 7.10-7.60 and 7.78-8.58 (m, 4H, ArH).

Anal. Calcd. for $C_{11}H_{13}FN_2O_2$: C, 58.92; H, 5.84; N, 12.49. Found: C, 59.17; H, 5.85; N, 12.62.

Hydrazinecarboxylic Acid, (1,3-Diphenyl-2-propylidene)-, Ethyl Ester.

The 1,3-diphenylacetone carboethoxyhydrazone was prepared in 68% yield (ethanol/water) by the condensation of 1,3-diphenylacetone with ethyl carbazate; mp 90-92°; ir (paraffin oil), 3202 (sh) and 1722 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, CH_3, 3H), 3.56 (s, $-CH_2-$, 2H), 3.77 (s, $-CH_2-$, 2H), 4.35 (q, CH_2O-, 2H), and 7.10-7.67 (m, ArH, 10H).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.96; H, 6.82; N, 9.42.

Hydrazinecarboxylic Acid, [1-(3-Methoxyphenyl)ethylidene]-, Methyl Ester.

The 3-methoxyacetophenone carbomethoxyhydrazone was prepared in 87% yield (methanol/water) by the condensation of 3-methoxyacetophenone with methyl carbazate; mp 94-97°; ir (paraffin oil): 3250 and 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3), 3.93 and 3.97 (s, 6H, CH_3O), 6.93-7.62 (m, 4H, ArH) and 8.63 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.66; H, 6.17; N, 12.53.

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[13] If the cyclization route involving the nitrogen were to have taken preference, this nitrogen would have participated in making the pyrazole ring by formation of a nitrogen-carbon bond (N_1 to C_5) with the *ortho*-ketone functional group originally part of the thiosalicylate ester. Once the pyrazole formed, the second cyclization involving the thiophenol and the carboalkoxy group would have resulted in the formation of the fused-ring pyrazolobenzothiazinones **4**. Under the reaction conditions reported here, this did not occur.

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