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ORIGINAL PAPER

Synthesis and Crystal Structure Determination of 3-Phenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one

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Abstract A new type of substituted benzothiopyranone, 3-phenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one, has been prepared by the condensation-acid cyclization of polylithiated phenylacetic acid phenylhydrazide with lithiated methyl thiosalicylate. Absorption spectra, especially ^{13}C NMR, provided good indication of its structure, which was conclusively established with X-ray crystal structure analysis. In comparison to the few benzothiopyran X-ray reports documented, the benzothiopyranone ring of the molecule was found to be essentially planar, with the 3-phenyl ring nearly perpendicular to the benzothiopyranone fused-ring system. Crystals of $C_{21}H_{16}N_2OS$ are orthorhombic, $P2_12_12_1$, $a = 10.140(4)$ Å, $b = 10.432(4)$ Å, $c = 16.228(7)$ Å, $Z = 4$, $V = 1717(1)$ Å^3, $R_1 = 0.0267$ and $wR_2 = 0.0725$ for reflections with $I > 2\sigma(I)$. The molecular packing in the crystal is the result of N–H···O hydrogen bonding.

Keywords Phenylhydrazino-benzothiopyranone synthesis · X-ray analysis

Introduction

In comparison to benzopyranones, benzothiopyranones (BTP-4-ones or BTP-2-ones) have received minimal study (Fig. 1). BTP-4-ones (R_2 = H, alkyl, other; R_3 = aryl) have been studied for their synthetic approaches such placing substituted aryl moieties in the 3-position of the thiopyranone ring by condensation *via* diazonium salts, or by select oxidation of dihydrobenzothiopyranones [1–5], for their use in other syntheses such as select oxidation of the ring sulfur to sulfone or sulfoxides [6, 7], for their spectrophotometric determination study of basicity [8, 9], for their biological potential in medicine (e.g., aromatase inhibition in select cancer studies) [10, 11], and for theoretical studies (e.g., Hückel MO and LCAO calculations) [12, 13]. Two somewhat related benzothiopyranones have received limited X-ray structural analysis [14–16], while other BTP-4-ones (R_3 = Ar) have not.

Strong-base monoanion and multiple anion syntheses from this laboratory have resulted in several benzothiopyranone preparations: BTP-2-one **4** and BTP-4-ones **6** and **8** (Scheme 1). They involved a Claisen type condensation-acid cyclization of lithiated methyl thiosalicylate **2** with a variety of reactive but selective lithiated nucleophiles **3**, **5**, or **7**, where the condensation occurred at the carboalkoxy carbon atom of **2**. For example, (1) lithiated ethyl propionate **3** was condensed-cyclized with lithiated thiosalicylate **2** to afford BTP-2-one **4** [17]; (2) trilithiated acetoacetanilide **5** was condensed-cyclized with **2** to give BTP-4-one **6** [18]; (3) dilithiated carbomethoxyhydrazones **7** were condensed-cyclized with **2** to afford BTP-4-ones **8** [19]. Each of these studies was straightforward, and structure confirmation was made from absorption spectra, comparison of melting points with a known compound in a few instances, and a reaction path described with a straightforward mechanism. This was evident in the third project cited for BTP-4-ones **8** [19], where carbomethoxyhydrazine, initially part of the carbomethoxyhydrazones functional group were displaced by the sulfur of the thiophenol of a

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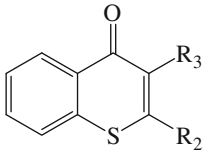
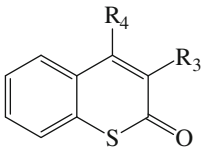


4*H*-1-benzothiopyran-4-ones
abbreviation, BTP-4-ones



2*H*-1-benzothiopyran-2-ones
abbreviation, BTP-2-ones

Fig. 1 Benzothiopyranones

C-acylated intermediate, not isolated, to form BTP-4-ones **8** instead of thiophenol-pyrazole (not illustrated).

While an X-ray crystal structural analysis would have been an attractive addition in each of the projects illustrated in **4**, **6**, and **8** cited, they were not essential for absolute structural verification.

An earlier strong base preparation of 3*H*-pyrazol-3-ones **12** (Scheme 2) resulted from the condensation–cyclization of polylithiated phenylacetic acid phenylhydrazides **10** (from **9**) with aromatic esters including lithiated methyl salicylate, but the condensation–cyclization of lithiated thiosalicylate **2** with lithiated hydrazide **10** gave products that were later determined to be BTP-4-ones **13**. Spectral properties of **13** did not correlate with other pyrazolone **12** products [20]. Other potential cyclization products, in addition to BTP-4-ones **13**, include BTP-2-ones **14** (related to **4**) [17], or other pyrazolones **15**.

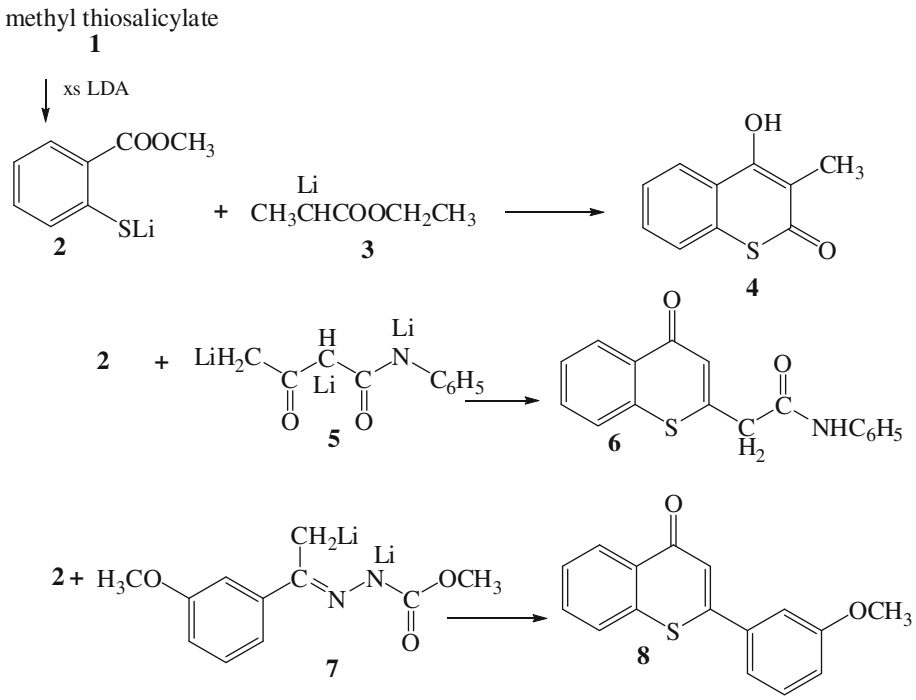
Experimental Section

Materials and Characterization

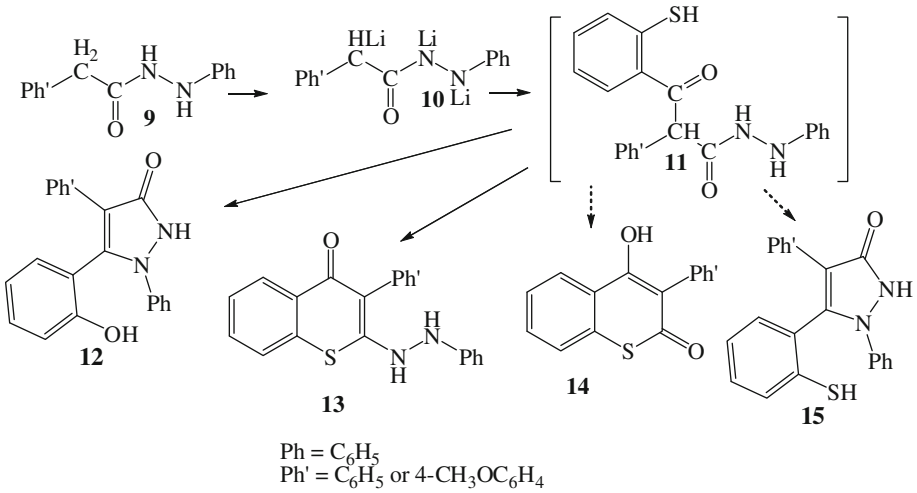
Fourier transform infrared spectra were obtained on a Nicolet Impact 410 FT-IR. Proton and ^{13}C NMR spectra were obtained with a Varian Associates Mercury Oxford 300 MHz nuclear magnetic resonance spectrometer, and chemical shifts were recorded in δ ppm downfield from an internal tetramethylsilane standard. Combustion analyses were performed by Quantitative Technologies, Inc., P.O. Box 470, Salem Industrial Park, Whitehouse, NJ 08888 USA. The tetrahydrofuran (THF) was distilled from sodium (benzophenone ketyl as an indicator of dryness) prior to use, and organic chemicals were obtained from Aldrich Chemical Co.

Entry compounds, phenylacetic acid phenylhydrazides **9**, were prepared from a phenylacetic acid (or 4-methoxyphenylacetic acid for **13a**) condensation with phenylhydrazine [21]. The preparation 3-phenyl-2-(2-phenylhydrazino) -4*H*-1-benzothiopyran-4-one (BTP-4-one) **13** involved the following reagents and procedure. Lithium diisopropylamide (LDA) (0.079 mol) was prepared by the addition of 49 mL of 1.6 *M* *n*-butyllithium in hexanes (0.079 mol) to a three-neck round-bottomed flask (e.g., 500 mL), equipped with a nitrogen inlet tube, a side-arm addition funnel (e.g., 125 mL), and a magnetic stir bar. The flask was cooled in an

Scheme 1 Previous benzothiopyranone (BTP-2-one and BTP-4-one) related investigations



Scheme 2 Reactions: actual and potential products



ice water bath and 8.02 g (0.079 mol) of diisopropylamine, dissolved in 25–30 mL of dry tetrahydrofuran (THF), was added from the addition funnel at a fast drop wise rate during a 5 min period (0 °C, nitrogen). The solution was stirred for an additional 15–20 min, and then rapidly treated *via* a powder funnel, with a slurry of 3.39 g (0.015 mol) of **9** and 50 mL of dry THF. After 2 h of polylithiation, 2.91 g (0.016 mol) of methyl thiosalicylate **1** (97%), dissolved in 25–35 mL of THF was added, during 5 min, to the polylithiated intermediate **10** (Scheme 2), and the solution was stirred and condensed for 2 h. Finally, 100 mL of 3*M* hydrochloric acid was added quickly, and the two-phase mixture was well stirred and heated under reflux for approximately 60 min. At the end of this period, the mixture was poured into a large flask containing ice (*ca.*, 100 g), followed by the addition of 100 mL of solvent grade ether. The mixture was then neutralized with solid sodium bicarbonate, and the liquid layers or solid materials separated. If a solid appeared at this point, the biphasic mixture could be filtered using a large Buchner funnel. The aqueous layer was extracted with ether or THF (2 × 75 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, evaporated, and recrystallized. Yield of **13,** 2.84 g (55%); mp 229–232 °C (ethanol/benzene). IR (KBr) 3456, 1646 and 1599 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm) 6.80–6.84, 7.20–7.70, 8.25–8.28 (m, 14H, ArH), and 8.81 (s broad, 1H); ^{13}C NMR (DMSO-d_6): δ (ppm) 110.1, 112.8, 119.9, 126.4, 126.7, 127.0, 127.6, 128.7, 128.9 [possible isochronous], 130.5, 131.2, 133.2, 135.3, 148.1, 161.7, and 176.2. Anal. calcd. for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13. found: C, 72.98; H, 4.60; N, 7.96. 3-(4-Methoxyphenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one **13a** (R_3 = 4-$CH_3OC_6H_4$) was prepared in 45% yield by the procedure above from the condensation–cyclization of trilithiated 4-methoxyphenylacetic phenylhydrazide **10** and **2** [22].

Single Crystal X-Ray Structure Determination

Colorless crystals of $C_{21}H_{16}N_2OS$ **13** were recrystallized from ethanol/benzene in order to give satisfactory crystals for X-ray determination. Crystal data for X-ray studies were collected at room temperature on a Siemens R3mV diffractometer at Clemson University using the $\omega/2\theta$ scan mode. Details of the data collection are reported in Table 1 [23].

The unit cell dimensions were determined by a least-squares refinement based on the setting angles of 50 carefully centered reflections in the range $31.91° < 2\theta < 44.98°$. Diffraction data were collected for 3068 unique reflections with $-12 < h < 12$, $-12 < k < 0$, and $-19 < l < 0$. A total of 2939 reflections with $I > 2.0\sigma(I)$ were used in the structure determination. Weights based on counting statistics were applied to the data. No correction was made for absorption.

The non-hydrogen atoms were refined anisotropically. The positions for all hydrogen atoms were obtained from difference maps; the hydrogen atoms were refined with isotropic thermal parameters. The final least-squares refinement on F^2 converged with $R_1 = 0.0278$ and $wR_2 = 0.0733$ (all data). The final Fourier map had no hole deeper than −0.169 e $Å^{-3}$ and no peak greater than 0.127 e $Å^{-3}$. Structure solution, refinement, and the calculation of derived results were performed using the *SHELX-97* [24] package of computer programs and the analysis of the crystal packing results was performed using *Mercury* [25]. Neutral atom scattering factors were those of Cromer and Waber [26], and the real and imaginary anomalous dispersion corrections were those of Cromer [27].

Table 1 Crystallographic data, 3-phenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one **13**

CCDC deposit number [23]	689210
Color/shape	Colorless/parallelopiped
Crystal dimensions (mm)	0.44 × 0.56 × 0.82
Formula	$C_{21}H_{16}N_2OS$
Formula mass	344.43
T (°C)	22(1)
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a (Å)	10.140(4)
b (Å)	10.432(4)
c (Å)	16.228(7)
V (Å^3)	1716(1)
Z	4
d_{calc} (g cm^{-3})	1.333
λ (Å)	0.71073
μ (mm^{-1})	0.199
$F(000)$	720
θ range (°)	2.32–25.14
Reflections collected	3542
Independent reflections	3068
Independent reflections $I > 2\sigma(I)$	2939
Max and min transmission	0.9174, 0.8537
Data, restraints, parameters	3068, 0, 290
Final R indices $I > 2\sigma(I)$	$R_1 = 0.0267$, $wR_2 = 0.0725$
R indices all data	$R_1 = 0.0278$, $wR_2 = 0.0733$
Goodness of fit on F^2	1.044
Largest diff peak and hole (e Å^{-3})	0.127, −0.169

Results and Discussion

During the current investigation (Scheme 2) phenylacetic acid phenylhydrazide **7** was trilithiated to **10** with excess LDA followed by condensation with lithiated methyl thiosalicylate **2**, and acid cyclization of *C*-acylated intermediate **11**. Intermediate compound **11** was not isolated, and an acid cyclization with dilute hydrochloric acid (3*M*) was implemented. BTP-4-one **13** (R_2 = NHNHPh, R_3 = Ph), was isolated in 55% yield, and indicative but inconclusive absorption spectra (IR, ^{1}H-NMR and ^{13}C-NMR) plus X-ray crystal analysis confirmed that **13** was an isomer of the originally targeted product, a substituted 3*H*-pyrazol-3-one **12**. It also ruled out the possibility of the product being a 4-hydroxy 2*H*-1-benzothiopyran-2-one **14**.

Additional spectral data was obtained by the preparation of another benzothiopyranone **13a** from 4-methoxyphenylacetic hydrazide **9a**. Its preparation also indicated that the preparation of **13** was not an isolated single result.

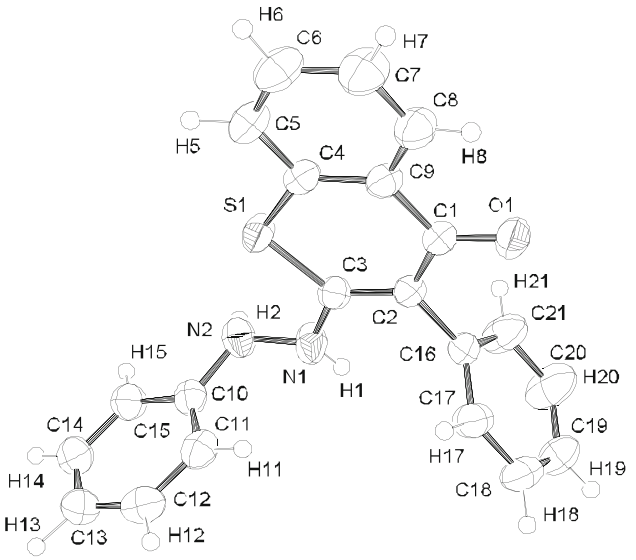


Fig. 2 Thermal ellipsoid plot, 3-phenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one **13** (50% ellipsoids for non-hydrogen atoms)

Table 2 Selected bond distances (Å), bond angles (°), and dihedral angles (°), 3-phenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one **13**

S1–C3	1.731(2)	S1–C4	1.739(2)
O1–C1	1.235(2)	N1–N2	1.387(2)
N1–C3	1.348(2)	N1–H1	0.84(2)
N2–C10	1.402(2)	N2–H2	0.84(2)
C1–C2	1.428(2)	C1–C9	1.477(2)
C2–C3	1.365(2)	C2–C16	1.488(2)
C4–C5	1.397(2)	C4–C9	1.388(2)
C3–S1–C4	101.72(7)	N2–N1–C3	118.7(1)
N1–N2–C10	116.4(2)	O1–C1–C2	121.2(1)
O1–C1–C9	118.8(1)	C2–C1–C9	120.0(1)
C1–C2–C3	124.3(1)	C1–C2–C16	117.6(1)
C3–C2–C16	118.0(1)	S1–C3–N1	112.1(1)
S1–C3–C2	125.9(1)	N1–C3–C2	122.1(1)
S1–C4–C5	115.2(1)	S1–C4–C9	124.9(1)
C1–C9–C8	118.6(1)	C1–C9–C4	123.0(1)
N2–C10–C11	122.5(1)	N2–C10–C15	117.6(2)

The molecular structure of $C_{21}H_{16}N_2OS$ **13** is shown in Fig. 2 and selected bond distances and angles are listed in Table 2. The bond lengths agree with the assignment of the double bond shown in **13** between C2 and C3 and the single bonds shown for C1–C9, C1–C2, C3–S1, and S1–C4.

The least squares best planes representing the fused rings are nearly coplanar with an angle of 3.38° between them. The two phenyl groups are nearly perpendicular to the heterocyclic ring containing S1 with angles of 86.35°

and 88.75° for the rings containing C10 and C16, respectively.

The packing of the molecules in the unit cell results from the formation of N–H···O intermolecular hydrogen bonding between each molecule and two additional molecules. Each O1 forms two hydrogen bonds with a second molecule with bond lengths of 2.128 Å and 2.651 Å for O1···H1–N1 and O1···H2–N2, respectively.

Conclusions

X-ray analysis is important for the conclusive structure determination of 3-phenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one **13**, which unexpectedly resulted from the condensation–cyclization of trilithiated phenylacetic acid phenylhydrazide **10** with lithiated methyl thiosalicylate **2**. The product **13** resulted from an anionic nucleophile **10** and an anionic electrophile **2** condensation, involving the carbanion-type center of the dilithiated phenylhydrazide **10** with the carbomethoxy carbon of the lithiated thiosalicylate **2**, followed by a selective cyclization. It is not an isolated result.

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22. 3-(4-Methoxyphenyl-2-(2-phenylhydrazino)-4*H*-1-benzothiopyran-4-one **13a** mp 178–180 °C (ethanol/benzene). IR 3377 and 3317, and 1658 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.90 (s, 3H, $ArOCH_3$), 6.98–702, 7.25–7.78, 8.53–8.56 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$): δ (ppm) 55.6, 113.0, 124.2, 126.6, 127.5, 127.7, 129.6, 129.8, 131.6, 132.5, 133.1, 133.7, 136.1, 139.9, 152.0, 157.1, 159.9, and 182.5. Anal. calcd. for $C_{22}H_{18}N_2O_2S$: C, 70.57; H, 4.85; N, 7.48. found: C, 70.97; H, 4.37; N, 7.88
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