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It Is "Thiazolidene-2-imine" and Not Imidazole-2-thione as the Reaction Product of 1-Benzoyl-3-phenylthiourea with Br_2/Enolizable Ketone†

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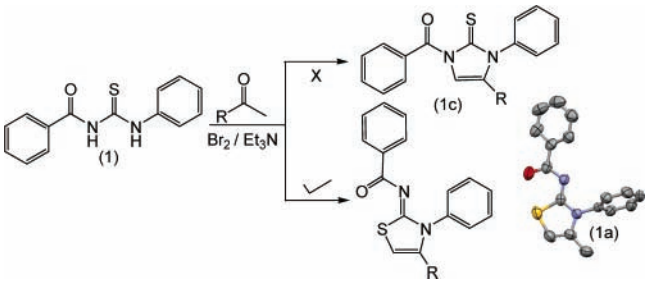
ABSTRACT



The products obtained by the reaction of benzoyl-3-phenylthioureas with bromine and enolizable ketones in the presence of triethylamine are not imidazole-2-thione derivatives as reported (*Org. Lett.* 2003, *5*, 1657−1659) rather they are thiazolidene-2-imine derivatives.

We have been utilizing tetrabutylammonium tribromide for bromination[1] and for various other organic transformations.[2] Recently we have synthesized a ditribromide reagent, 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT), which is superior to all known tribromides because of its stability, higher bromine content per molecule, higher bromination efficiency, selectivity, reduced phase transfer property, and quantitative recovery of the spent reagent.[3] This reagent is an excellent source of bromine capable of brominating varieties of organic substrates and is found to be an excellent catalyst for the acylation of alcohols with various anhydrides.[4] Being a source of bromine we thought to utilize this for the synthesis of imidazole-2-thione derivative following the reported procedure of Zou et al.[5] When 1-benzoyl-3-phenylthiourea (**1**) (1 equiv) was reacted with 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) (0.5 equiv) in acetone (10 mL) in the presence of triethylamine (1 equiv) the product obtained was identical in all respects (m.p, IR, ^{1}HNMR and ^{13}CNMR) with that reported by Zou et al. However, X-ray crystallographic analysis[8−11] of the product revealed an isomeric structure with a completely different skeleton. The product obtained was not an imidazole

† Dedicated with best wishes to Professor Mihir K. Chaudhuri on the occasion of his 60th birthday.

(1) (a) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163. (b) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247.

(2) (a) Roy, R. K.; Bagaria, P.; Naik, S.; Kavala, V.; Patel, B. K. *J. Phys. Chem. A.* **2006**, *110*, 2181. (b) Roy, R. K.; Usha, V.; Patel, B. K.; Hairo, K. *J. Comp. Chem.* **2006**, 773. (c) Kavala, V.; Patel, B. K. *Eur. J. Org. Chem.* **2005**, 441. (d) Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *ARKIVOC* **2006**, 119. (e) Naik, S.; Gopinath, R.; Goswami, M.; Patel, B. K. *Org. Biomol. Chem.* **2004**, 1670. (f) Gopinath, R.; Haque, Sk. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842. (g) Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, *42*, 7679. (h) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177.

(3) (a) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267. (b) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 6556.

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(5) Zeng, R.-S.; Zou, J.-P.; Zhi, S.-J.; Chen, J.; Shen, Q. *Org. Lett.* **2003**, *5*, 1657.

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derivative (**1c**) as reported[5] rather it is 1-benzoyl-3-phenyl-4-methylthiazolidene-2-imine (**1a**) as shown in Figure 1.

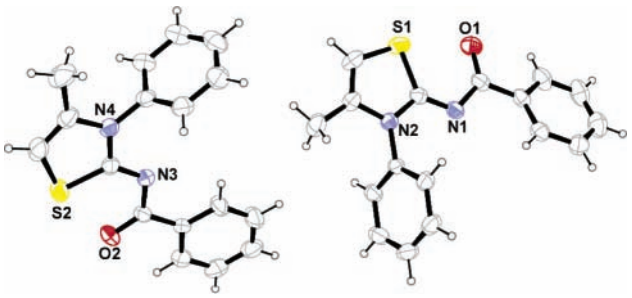


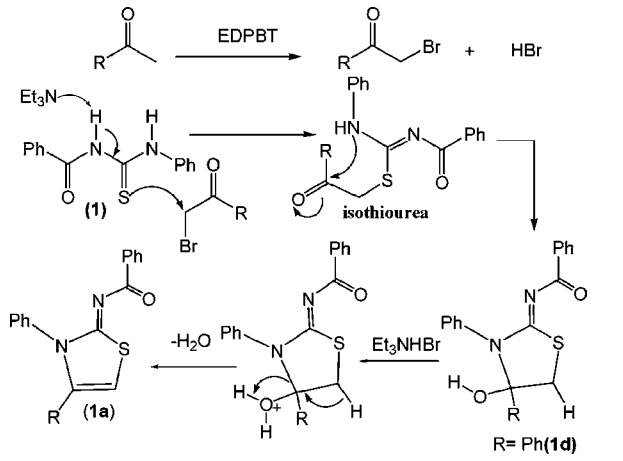
Figure 1. An ORTEP view with the atomic numbering scheme of **1a**.

In our experience of working with organic ammonium tribromides we have never encountered such a drastic change in reactivity/selectivity, after all, tribromides are just an efficient bromine carrier with similar or better reactivity. Thus, there is no reason why the product obtained by Zou et al. using molecular bromine instead of EDPBT should be so much different. This prompted us to repeat the reaction of Zou et al.[5] exactly under their reported conditions using molecular bromine. Comparison of melting point, IR, and ^{1}H and ^{13}CNMR of the sample prepared by us using bromine following the procedure of Zou et al. and using EDPBT was identical. Furthermore, all the spectral, analytical and melting point data obtained were in perfect agreement with those reported by Zou et al.[5]

The structure 1-benzoyl-3-phenyl-4-methylimidazole-2-thione (**1c**) as proposed by Zou et al. and the structure 1-benzoyl-3-phenyl-4-methylthiazolidene-2-imine (**1a**) obtained by us are two isomeric compounds with the same molecular formula ($C_{17}H_{14}N_2OS$) which cannot be differentiated by their elemental composition and HRMS analyses. It is also difficult to differentiate the two compounds based on their ^{1}HNMR, as both have identical ethylenic, methyl, and aromatic protons. The only difference in the structure is the presence of a −C*═S group in **1c** and a −C*═N− group in **1a**. The DEPT spectrum is not of much help in arriving at the correct structure as both structures have identical numbers of CH_3, CH, and C carbon.

Single-crystal X-ray crystallography unequivocally established the structure to be 1-benzoyl-3-phenyl-4-methylthiazolidene-2-imine (**1a**). On the basis of the structure we proposed the following mechanism for the reaction (Scheme 1). Either the ditribromide reagent EDPBT or bromine brominates acetone to bromoacetone. The carbon of the bromomethyl group is attacked by the sulfur of thiourea, which is facilitated due to an abstraction of the NH proton by triethylamine giving an isothiourea intermediate.[6] The NH proton flanked by a carbonyl and a thiocarbonyl moiety is more acidic, hence it is preferentially deprotonated in the presence of the other NH proton. Intramolecular attack of the second NH group of the isothiourea intermediate on the carbonyl group would give 1-benzoyl(4-hydroxy-3,4-diphenylthiazolidine)-2-imine (**1d**)[6] followed by dehydration of the tertiary alcohol leading to the formation of 1-benzoyl-3-phenyl-4-methylthiazolidene-2-imine (**1a**). This mechanism seems resonable since the thiazolidene-2-imine derivative has

Scheme 1. Proposed Mechanism of Formation of **1a**



(6) (a) Murav'eva, K. M.; Shckukina, M. N. *Zh. Obshch. Khim.* **1960**, *30*, 2327. (b) Ruettinger, H. H.; Dehne, H.; Schroth, W. *Pharmazie* **1976**, *31*, 218. (c) 1-Benzoyl(4-hydroxy-3,4-diphenyl-thiazolidine)-2-imine (**1d**): mp 156-157 °C; IR (KBr) υ 3222, 3064, 2927, 1595, 1562, 1474, 1392, 1324, 1210, 1017, 999, 790, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (d, 1H, J = 12.4 Hz), 3.72 (d, 1H, J = 12.4 Hz),7.20 (m, 10H), 7.40 (m, 1H), 7.49 (d, 2H, J = 7.6 Hz), 7.61 (s,1H), 7.85 (d, 2H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 93.4, 126.3, 126.7, 127.7, 127.8, 128.3, 128.9, 131.7, 136.1, 138.5, 141.1, 171.8, 175.2.

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(8) **Crystallographic description of 1a:** crystal dimension (mm) 0.28 × 0.20 × 0.17; $C_{17}H_{14}N_2OS$, M_r = 294.36; triclinic, space group P_1; a = 9.6420(2) Å, b = 9.9530(2) Å, c = 16.2792(3) Å; α = 97.0930(10)°, β = 92.5310(10)°, γ = 97.6890(10)°, V = 1533.44(5) Å;^{3} Z = 4; ρ_{cal} = 1.275 mg/m^3; μ (mm^{-1}) = 0.211; F(000) = 616; reflection collected/unique = 17050/6625; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R1 = 0.0499, wR2 = 0.1175, R indices (all data) R1 = 0.1087, wR2 = 0.1496; goodness of fit = 1.015. **1b**: crystal dimension (mm), 0.28 × 0.20 × 0.15; $C_{22}H_{16}N_2OS$, M_r = 356.43; monoclinic, space group $P2(1)/n$; a = 10.4679(13) Å, b = 15.2299(18) Å, c = 11.7243(14) Å; α = γ = 90°, β = 101.491(9)°, V = 1831.7(4) Å;^{3} Z = 4; ρ_{cal} = 1.293 mg/m^3; μ (mm^{-1}) = 0.189; F(000) = 744; reflection collected/unique = 17704/4573; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R1 = 0.0739, wR2 = 0.1326, R indices (all data) R1 = 0.1827, wR2 = 0.1597; goodness of fit = 1.176. **2a**: crystal dimension (mm), 0.50 × 0.28 × 0.16; $C_{17}H_{13}N_2OSBr$, M_r = 373.26; monoclinic, space group $P2(1)/c$; a = 16.059(2) Å, b = 13.4006(18) Å, c = 7.6695(11) Å; α = γ = 90°, β = 98.6800 (10)°, V = 1631.6(4) Å;^{3} Z = 4; ρ_{cal} = 1.520 mg/m^3; μ (mm^{-1}) = 2.650; F(000) = 752; reflection collected/unique = 15962/3897; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] R1 = 0.0508, wR2 = 0.1215, R indices (all data) R1 = 0.0844, wR2 = 0.1394; goodness of fit = 1.031. **2b**: yield 80%; IR (KBr) υ 3058, 1599, 1559, 1438, 1337, 1280, 1193, 1066, 930, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 7.13 (d, 2H, 7.2 Hz), 7.24 (m, 7H), 7.42 (d, 2H, J = 6.8 Hz), 7.53 (d, 1H, J = 8 Hz), 8.01 (d, 1H, J = 7.6 Hz), 8.23 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.8, 122.3, 128.0, 128.6, 128.8, 129.0, 129.1, 129.7, 130.5, 132.6, 134.4, 137.6, 139.0, 139.4, 170.1, 173.2.

(9) *SMART* V 4.043 Software for the CCD Detector System; Siemens Analytical Instruments Division: Madison, WI, 1995.

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been prepared by the condensation of acyl and arylacyl thioureas with α-haloketones.[6,7] Under basic condition several hydroxy thiazolidine derivatives have been isolated.[6] When we reacted benzoyl thiourea (**1**) (1 equiv) with phenacyl bromide (1 equiv) in the presence of triethylamine (1.5 equiv) in acetonitrile, the corresponding 1-benzoyl(4-hydroxy-3,4-diphenylthiazolidine)-2-imine (**1d**)[6c] derivative precipitated out quantitatively, which could not be converted to its final thiazolidene-2-imine (**1b**) even under reflux condition. However, on addition of 2 equiv of HBr the final thiazolidene-2-imine (**1b**) was obtained in quantative yield at room temperature suggesting an acid-catalyzed elimination of tertiary alcohol. In this reaction the in situ generated HBr serves as an acid for the dehydration of the intermediate tertiary alcohol (**1d**).

We believe that this may not be an isolated example and all the structures reported by Zou et al. are expected to have a thiazolidene-2-imine moiety and not imidazole. To further demonstrate our claim 1-benzoyl-3-phenylthiourea (**1**) was reacted under an identical condition with EDPBT but replacing acetone with acetophenone. The spectral and analytical data of the product obtained (**1b**) were again in perfect agreement with those reported by Zou et al. It may be mentioned here that replacement of bromine with EDPBT also gave the same product. Formation of the thiazolylidene ring was confirmed by single-crystal X-ray diffraction Figure 2.

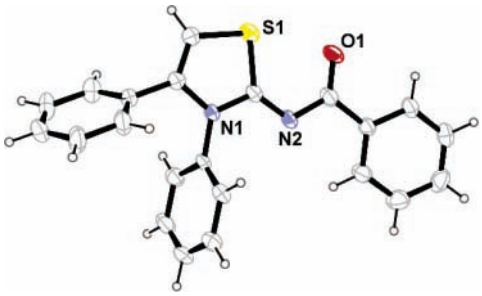

Figure 2. An ORTEP view with the atomic numbering scheme of **1b**.

Thiazolidene-2-imine ring formation is general and not specific to a particular benzoyl thiourea. When 3-bromobenzoyl-3-phenylthiourea (**2**) was reacted under the above conditions separately with acetone and acetophenone both gave corresponding thiazolidene-2-imine derivatives **2a** and **2b**, respectively. The structure of **2a** was again confirmed by crystal X-ray crystallography as shown in Figure 3.

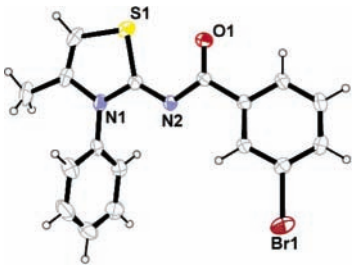

Figure 3. An ORTEP view with the atomic numbering scheme of **2a**.

In conclusion, we have unambiguously proved that the products obtained by the reaction of benzoyl-3-phenylthuioureas with bromine/EDPBT and acetone/enolizable ketone in the presence of triethylamine are thiazolidene-2-imine derivatives not imidazole-2-thione as reported earlier.[5] We also believe that all other structures reported by Zou et al. are expected to have a thiazolidene-2-imine moiety and not imidazole. The wrong structure has led to the proposal of an incorrect reaction mechanism.[5] Further scope of the reaction to other similar substrates is currently under investigation.

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Supporting Information Available: Experimental details and full characterization of compounds: IR, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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