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Letter

Substituted Benzothietes: Synthesis and a Quantum Chemical Investigation of Their Cycloreversion Properties

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ABSTRACT: A flexible synthesis for highly substituted benzothietes that does not require flash-vacuum pyrolysis was developed. This allows for the use of a number of functional groups and nonvaporizable molecules. Highly stabilized derivatives were isolated. The molecular orbital properties of various benzothietes were evaluated by density functional methods. The mechanism of the cycloreversion of the four-membered ring was compared to that of the oxygen-containing analogues.

enzothietes consist of a thietane annelated to a benzene. B As heteroatom analogues of benzocyclobutanes, they can undergo electrocyclic ring-opening reactions leading to a dearomatized six-membered ring system. The oxygen counterparts of benzothietes are well-known in their ring-opened form as o-quinone methides. Commonly, they are generated in situ and immediately further transformed. Today, o-quinone methides are widely employed in the synthesis of a variety of oxygen-containing aromatic compounds, including complex natural products.¹⁻³ They can be accessed by various strategies such as oxidation, internal elimination, and transition metal catalysis; however, benzothietes have been studied only to a small extent, and literature reports of their use in organic synthesis are rare. This fact is certainly rooted in the lack of convenient and reliable methods for the synthesis of benzothietes and their precursors. Once in hand, they show a remarkable range of reactivity.⁴ The procedures are tedious, with the exception of a few carbene-based methods, and the methods of Okuma and Kobayashi allow for an only limited number of different substituents on the four-membered ring.^{5,6} Older methods rely on either flash-vacuum pyrolysis or highenergy ultraviolet (UV) irradiation (e.g., by Schweig,⁷ Aron,⁸ Meier,⁹ Boekelheide,¹⁰ Katritzky,¹¹ and Plomp¹²). Scheme 1 provides an overview of the most important procedures.

Flash-vacuum pyrolysis is unsuitable if the starting material cannot be evaporated or if it decomposes under harsh conditions. Okuma's procedure enables the synthesis of stable benzothietes that are sterically and electronically shielded; however, only highly sterically hindered thioketones can be employed. Upon scaling up the reaction, we found a steep decrease in the yield. The addition of arynes to bisaromatic or less hindered thioketones exclusively produces xanthenes.¹³

Lacking a method that allows the convenient synthesis of a range of benzothietes, we tested the applicability of *o*-quinone methide strategies to their S analogues, but the unique properties of sulfur limit the number of adaptable strategies. For example, thiols cannot be used along with oxidizing agents, whereas thiosilyl moieties undergo Brook rearrangement or lead to S_EAr-type side reactions. The only viable method was a variation of the procedure reported by Pettus that uses an elegant rearrangement—elimination sequence.^{14,15}

The reaction conditions from 1 to 2 were optimized starting from various protecting groups (Table 1). All precursors were synthesized from the corresponding thiols according to known procedures (see the Supporting Information). The best results among the carbonate-based protecting groups were obtained using the electron-rich, mildly shielding p-MeO-phenyl oxycarbonyl group (entry 2) and Cbz (entry 3) moiety. The remaining groups (entries 4-7) either provided little regioselectivity or were unstable under the reaction conditions. Boc protection, analogous to the original method of Pettus,¹⁵ is not applicable. The tert-butyl thiocarbonate releases CO₂ in the presence of catalytic amounts of magnesium salt, forming the corresponding tert-butyl thioether. Optimum conditions were achieved using an N,N-dimethylcarbamate group (entry 1). The reaction was further optimized with regard to stoichiometry, duration, and temperature. The choice of

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Scheme 1. Existing Methods for the Preparation of Benzothietes (top) and Our Novel Method (bottom)



Table 1. Optimization of Reaction Conditions

	1a-g	H PhMgCl	Ph S 2	
entry	compound	protecting group	time	yield ^a (%)
1 ^b	1a	-C(O)NMe ₂	10 min	34
2 ^b	1b	-C(O)O(PMP)	2 h	20
3 ^b	1c	-Cbz	15 h	19
4 ^b	1d	-Alloc	10 min	16
5 ^b	1e	-C(O)OMe	15 h	15
6 ^b	1f	-Troc	15 h	15
7 ⁶	1g	-C(O)OPh	2 h	14
8 ^c	1a	-C(O)NMe ₂	45 min	75

^aDetermined by GC-MS measurement, undecane standard, measured at 10, 45, 120, 360, and 900 min, respective maximum shown. ^bWith 0.2 mmol of thiosalicylic aldehyde, 0.4 mmol of PhMgCl (2.0 M in THF), 0.2 mmol/min, THF (5 mL), -60 °C. ^cWith 0.2 mmol of thiosalicylic aldehyde, 0.3 mmol of PhMgCl (2.0 M in THF), 0.2 mmol/min, THF (5 mL), -20 °C, triple flash column chromatography of the starting material.

solvent had an immense effect. Coordinating ethers (DME, THF, and dioxane) perform the best. Less polar solvents do not dissolve the starting material at low temperatures. Various metal–organic species were tested. Phenyllithium provided little conversion. Normant and Gilman cuprates show no reaction, even at room temperature. Additives did not improve the yield.

The product's stability depends on the electronic and steric properties of the electrophilic carbon. Bisaryl-substituted benzothietes and those prepared from aldehydes are stable in solution but decompose upon purification. Acetophenonederived benzothietes formed only in trace amounts. Derivatives that carry a strongly shielding *tert*-butyl group on the benzylic carbon were isolated by common purification methods (flash column chromatography on silica gel). Except for **9e**, secondary or primary carbons next to the benzylic carbon were not tolerated (Scheme 2); however, compound **9e** is the first benzothiete that bears a secondary carbon atom adjacent to the benzylic position.





11a (61%,5.0 h, 25 °C) **11b** (77%, 3.0 h, 25 °C)

"Reactions were performed on a 0.2 mmol scale (thiol) using 3 equiv of Grignard reagent at -20 °C. The reaction mixture was stirred for 30 min at -20 °C and then warmed to the indicated temperature. **9a-g** were prepared from **5**, **10a** and **10b** from **6**, and **11a** and **11b** from 7. For the large scale, see the Supporting Information.

All products were synthesized from pivalophenones 5-7. The use of benzophenones (e.g., 4 and 8) gave only trace amounts of the corresponding products, surprisingly even upon treatment with *tert*-butyl magnesium halides. None of the products show signs of decomposition upon purification and can be stored for months in a freezer. To the best of our knowledge, compounds **9g**, **10b**, and **11b** are the first examples of heterocycle-bearing benzothietes. We see a clear advantage in our two-component reaction over the existing procedures. The use of Grignard reagents allows for straightforward late stage modification in comparison to existing methods. Of course, their usage sets a limit on functional group tolerance.

We were able to crystallize compound **10b** (see section 3 of the Supporting Information); to the best of our knowledge, this is the first crystal structure of a benzothiete. The crystals contain two independent molecules, in both of which the thienyl group is disordered over two orientations, but this disorder was successfully refined. The benzene ring is neither distorted nor dearomatized; the carbon–sulfur bond lengths pubs.acs.org/OrgLett



Figure 1. Molecular structures of compound **10b** in the solid state (50% ellipsoid probability). Only the major positions of the disordered thienyl rings are shown. Bond lengths (angstroms) and angles (degrees) in the two independent molecules: S1–C4, 1.771(1), 1.771(1); S1–C8, 1.927(1), 1.919(1); C4–S1–C8, 74.80(4), 75.07(5).

Scheme 3. Proposed Mechanism



and angles are within the conventional ranges for carbon– sulfur single bonds (Figure 1). The X-ray structure establishes that the benzothiete does not possess any *o*-quinone-like properties.

We assume a mechanism analogous to the formation of *o*-quinone methides as proposed by Pettus (Scheme 3).¹⁵ The thiocarbamate is sufficiently deactivated to provide absolute regioselectivity for the Grignard attack.

To predict the stability of benzothietes and the effect of substituents and to explain the differences compared to o-quinone methides, a computational study was conducted. We investigated the thermodynamics of the thermal ring opening of the monoarylated benzothiete with several representative substituents in electronic key positions (Figure 2). The BMK (Boese–Martin for kinetics) functional was employed for these studies and gives reliable results for the dissociation of C–S bonds.¹⁶

The transition state for the thermal ring opening, connecting the benzothietane to the product structure, is composed of a single imaginary frequency at which the C–S bond breaks. Both the thermodynamics and the barrier height of the reaction were dependent on the substituents; consequently, we evaluated a wide range of substituents.

To approximate the reaction coordinates, linear transits were performed in which the C–S bond was systematically lengthened. These calculations provided results in excellent agreement with transition states and intrinsic reaction coordinates at reduced computational costs (see Figure S3



Figure 2. Two-dimensional Hammett plots of monoarylated benzothietes: (top) activation energy $\Delta_A U$ and (bottom) reaction energy $\Delta_R U$. Energy differences calculated from bond length scans. Numerical values in section 4.2.10 of the Supporting Information. BMK 6-311+g(d,p) (with dispersion).

for an exact energy diagram from IRCs). Because the change in entropy of the molecule upon ring opening is negligible, the differences in total energies ΔU of the respective process are a good estimate for the change in Gibbs energy ΔG (for $\Delta_R S \approx$ 0, $\Delta_R U \approx \Delta_R G \approx \Delta_R H$; for $\Delta_A S \approx 0$, $\Delta_A U \approx \Delta_A G \approx \Delta_A H$).

The substituent para to the benzylic carbon (R_{phenyl}; Hammett constant, $\sigma_{\rm phenyl}$) has a strong influence on the activation energy $\Delta_A \hat{U}$ and the total reaction energy $\Delta_B U$. Electron-withdrawing groups para to the benzylic carbon significantly stabilize the HOMO, which is strongly correlated with an increase in $\Delta_{\rm R} U$ (section 4.2.11 of the Supporting Information). As a result, the energy required for the cleavage of the C-S bond and the related activation energy increase steeply. The electron-withdrawing functional groups para to the chalcogen (R_{benzo} ; Hammett constant, σ_{benzo}) similarly stabilize the cleaved system and reduce the activation and reaction energy necessary for the ring opening; however, this dependence of the reaction energy on the electronic properties of the benzo substituent is only weakly correlated, which indicates that the stabilization of the benzylic carbon is far more important to the total energy than the substituent effects on the electronegative sulfur. For $\Delta_A U$, this was substantiated by a mathematical separation of the effects of R_{phenyl} and R_{benzo} after a Young-Jencks-Yukawa-Tsuno analysis provided only unsatisfying results; no σ scale sufficiently depicted our reaction (section 4.2.12 of the Supporting Information).¹⁷ For fixed functional groups R_{benzo}, the effect of different substituents $R_{\mbox{\scriptsize phenyl}}$ can be linearized in a Hammet–Brown model [for all substituents, $R^2 > 0.98$ (section 4.2.11 of the Supporting Information)].¹⁸ The resulting ρ values are approximately affinely dependent on $\sigma_{m,benzo}$ ($R^2 = 0.85$).

For the $R_{phenyl} = NMe_2$ substituent, when the other substituent is varied from methoxy ($\sigma = -0.27$) to nitro ($\sigma = 0.78$), $\Delta_R U$ exhibits the expected behavior. However, with Hammett constants lower than that of the methoxy group, we observe a sudden drop in the reaction energy $\Delta_R U$, which suggests an orbital effect that exceeds simple charge effects, as the net charge on the sulfur is not correlated with $\Delta_R U$.

The HOMO of the dimethylamino-bearing and isopropoxybearing ($R_{benzo} = NMe_2$ and OiPr, respectively) benzothiete possesses an additional node, indicating that these strongly electron-donating groups additionally stabilize the benzylic *meta* position; this effect outweighs the decrease in the HOMO energy. The opposite effect can be observed in the $R_{phenyl} =$ NO_2 row of the reaction energy $\Delta_R U$. The energy increases again as we pass $R_{benzo} = Br$ ($\sigma = -0.23$) en route to even electron-poorer substituents.

Benzothietes, in contrast to *o*-quinone methides, are more stable in their closed-ring form, even though C–S bonds are typically ~20 kcal/mol weaker than C–O bonds because of the higher valence shell ionization energy of sulfur.¹⁹ As an example, the H-substituted monoarylated benzothiete is favored by 16.8 kcal/mol over the open form. In contrast, the monoarylated *o*-quinone methide is favored over the benzoxetane by 10.4 kcal/mol. A computational homodesmic (HD2) reaction scheme was employed to estimate the difference in ring strain (section 4.2.22 of the Supporting Information).²⁰ The S derivative releases approximately 10.5 kcal/mol of ring strain, accounting for nearly 50% of the energetic difference.

To investigate this thermodynamic peculiarity, we first calculated the intrinsic reaction coordinate for the ringopening reaction of the phenyl benzothiete and phenyl *o*quinone methide.²¹ The comparable qualitative structure of the MO-IRC plots indicates that the elemental cycloreversion mechanism of the heteroatom-bearing four-membered rings is similar. As one can clearly see from the plots (Figure 3), the E–C antibonding LUMO decreases in energy as the E–C



Figure 3. MO-IRC plot of the ring opening of phenyl benzothiete to phenyl *o*-thioquinone methide (top) and phenyl benzoxetane to phenyl *o*-quinone methide (bottom) (HOMO-3 to LUMO+3). BMK/6-311+g(d,p) (with dispersion).

bond is lengthened and finally broken by internal electron transfer. However, the molecular orbitals show that the relative contributions of O versus S are very different in the LUMOs. The S contributions in the HOMO and LUMO vary from 50% and 43% in the closed form to 40% and 21% in the open form. The analogous O contributions range from 18% and 2% to 12% and 9%, which indicates significantly less oxygen character in these frontier molecular orbitals. These values indicate a substantially more covalent C-S interaction in the benzothiete compared to C-O in the benzoxetane, which is consistent with the observed thermodynamic preference. We expect that this observation is general with regard to benzothietes; substituent effects alone are not likely to be strong enough to overcome covalency differences between E-C bonds, which are dependent primarily on the valence shell ionization energy of the chalcogen.

In summary, we have developed a versatile two-component reaction to synthesize benzothietes from Grignard reagents and S-protected thiosalicylic ketones and aldehydes that does not rely on flash-vacuum pyrolysis or high-intensity irradiation. We have studied the bonding properties in benzothietes and compared them to the related, well-established *o*-quinone methides. Our findings indicate that for sulfur the closed-ring form is preferred (as also demonstrated by X-ray crystallography) because of ring strain effects and its lower electronegativity and consequently higher valence shell ionization energy, leading to significantly enhanced covalency.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01261.

Detailed experimental procedures, analytical data, ¹H and ¹³C NMR spectra of all new compounds, and computational results, including Cartesian coordinates (PDF)

Accession Codes

CCDC 1993935 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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