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An efficient synthesis of isothiazolidines via sulfonium ylides formed by the reaction of thietanes and nitrene

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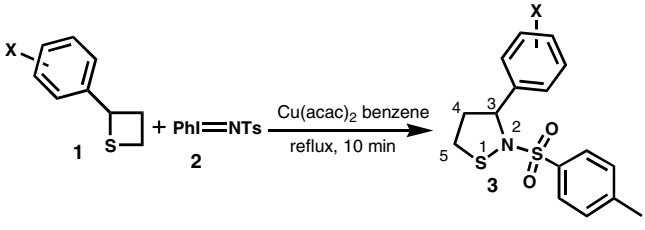
Abstract—An efficient synthesis of isothiazolidines in good yields is described.

The synthetic potential of sulfonium ylides has received considerable attention in recent years. Asymmetric epoxidation[1] and cyclopropanation reactions[2] are among the important reactions mediated by sulfonium ylides. The [1,2]-sigmatropic rearrangement of sulfonium ylides, generated in situ by the reaction of metallocarbenes with sulfides, is also a topic of current interest.[3,4] Much of the work on sulfonium ylides, however, has involved carbon–sulfur ylides. In contrast, sulfur–nitrogen ylides have received only scant attention. Recently we have shown that sulfonium ylides derived from thietanes and electrophilic carbenes undergo easy rearrangement to afford tetrahydrothiophenes.[5] In view of the efficient and diastereoselective ring expansion observed in this case, it was of interest to examine the reaction of thietanes with a nitrene from the vantage point of its potential utility in the synthesis of thiazolidines,[6] which constitute an integral part of several therapeutic agents. It may be noted that except for an isolated report on the thermal rearrangement of sulfimides, there has not been any work in this area.[7] Herein we report the preliminary results of our studies constituting a stereoselective synthesis of isothiazolidine derivatives presumably by the [1,2]-rearrangement of the ylides (sulfimides) formed by the reaction between thietanes and a nitrene.

In our initial experiment, we treated 2-(4-chlorophenyl)thietane[8] **1a** in benzene with (*N*-(*p*-tolylsulfonyl)-imino)phenyliodinane in the presence of a catalytic amount of Cu(II) acetylacetonate. An easy reaction occurred to afford isothiazolidine **3a**[9] in 67% yield (Scheme 1). To our surprise, only a single isomer was obtained. The product was characterized by spectroscopic methods. In the IR spectrum of **3a**, the sulfonyl group exhibited absorptions at 1345 and 1159 cm^{-1}. In the ^1H NMR spectrum, resonance signals due to the C-4 methylene protons appeared as multiplets centered at δ 2.15 and 2.30. The methylene protons at C-5 displayed their signals as multiplets centered at δ 2.63 and 2.85. The benzylic proton signal was discernible at δ 5.18 as an overlapping double doublet. The reaction was found to be general for various 2-aryl substituted thietanes and the results are summarized below.[10] The regioselective formation of **3** by rearrangement of the ylide derived from thietane **1** and nitrene is noteworthy. This selectivity, however, is expected since the reaction is a formal [1,2]-benzylic rearrangement. Such regioselectivity is precedented in the rearrangement of an oxonium ylide derived from 2-phenyl oxetane and methoxycarbonyl carbene.[11]



1a	X = *p*-Cl		**3a**	X = *p*-Cl 67%
1b	X = H		**3b**	X = H 63%
1c	X = *p*-F		**3c**	X = *p*-F 60%
1d	X = *m*-Cl		**3d**	X = *m*-Cl 56%

Scheme 1.

Keywords: Nitrene; Thietane; Sulfonium ylide; Isothiazolidine.
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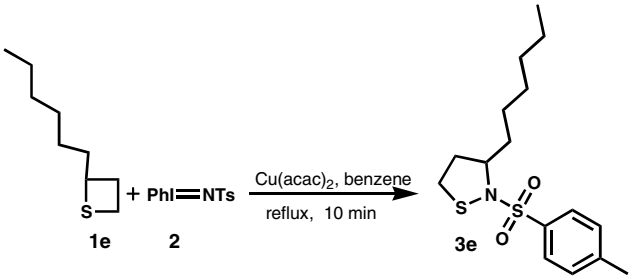


Scheme 2.

A similar reactivity was observed when 2-hexylthietane **1e** was treated with PhI=NTs in benzene in the presence of a catalytic amount of Cu(II) acetylacetonate, the product **3e** being obtained in 54% yield (Scheme 2).

Subsequently we investigated the reaction of the nitrenoid generated from PhI=NTs and $Cu(acac)_2$ with diastereomeric mixtures of 2,4-bis-(aryl)thietanes **4a–d**. As expected, the reaction afforded isothiazolidines **5a–d** in good yields (Scheme 3).[12] The IR spectrum of **5a** showed sulfonyl absorptions at 1345 and 1159 cm^{-1}. In the ^1H NMR spectrum, the benzylic protons on C-3 and C-5 displayed their signals at δ 5.21 and δ 3.89, respectively. In the ^1H NMR spectrum, the C-4 methylene protons appeared as two separate multiplets centered at δ 2.43 and δ 2.87. In the ^{13}C NMR spectrum, benzylic carbons C-3 and C-5 resonated at δ 68.3 and δ 55.0, respectively. Conclusive evidence for the stereochemistry of **5a** was obtained by ^1H NOE difference spectroscopic studies (Fig. 1). The product was assigned cis stereochemistry since selective separate irradiations of H_a and H_d produced enhancement in the signal corresponding to H_c. The selectivity observed in the reaction can be attributed to the preferential attack of the *cis* thietane by the nitrene.

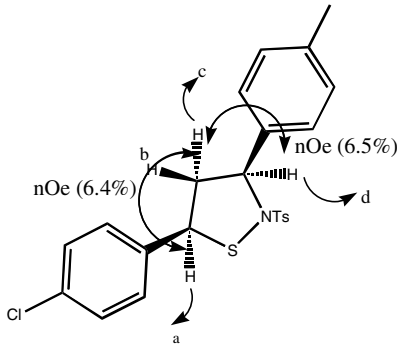
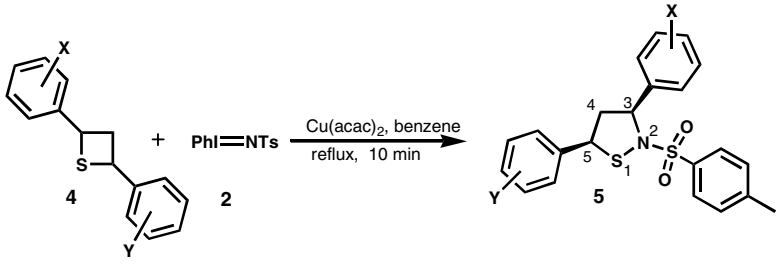


Figure 1. NOE correlations for **5a**.

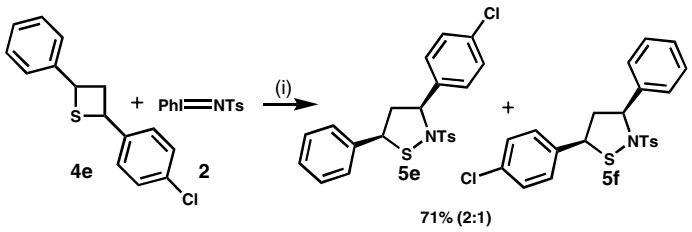
2-(4-Chlorophenyl)-4-phenylthietane **4e** on reaction with (*N*-(*p*-tolylsulfonyl)imino)phenyliodinane in the presence of a catalytic amount of Cu(II) afforded isothiazolidines **5e** and **5f** in 71% yield as an inseparable mixture in the ratio 2:1 (Scheme 4).

A mechanistic rationale for the reaction of thietanes with a nitrene leading to isothiazolidines can be illustrated along the following lines. Of the cis:trans diastereomeric mixture of thietanes, the cis isomer selectively reacts with the nitrenoid to form the intermediate (sulfimide).[13] The [1,2]-rearrangement of the latter results in the stereoselective formation of the product (Scheme 5).

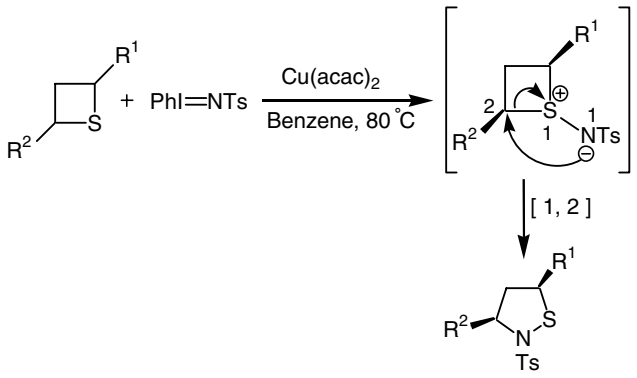


4a	X = *p*-CH_3, Y = *p*-Cl		**5a**	X = *p*-CH_3, Y = *p*-Cl	76%
4b	X = Y = H		**5b**	X = Y = H	73%
4c	X = Y = *p*-Cl		**5c**	X = Y = *p*-Cl	72%
4d	X = Y = *m*-Cl		**5d**	X = Y = *m*-Cl	75%

Scheme 3.



Scheme 4. Reagents: (i) $Cu(acac)_2$, benzene, reflux, 10 min.



Scheme 5.

In conclusion, we have uncovered an easy synthesis of substituted isothiazolidines, which may be of interest both from mechanistic and synthetic standpoints.

Acknowledgments

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7. It is worthy of note that there is an isolated report on the synthesis of thiazolidines by the reaction of thietanes with aniline and *tert*-butyl hypochlorite. See: Claus, P. K.; Jäger, E. *Monatsh. Chem.* **1985**, *116*, 1153–1164.
8. The diastereomeric mixture of thietanes used in our investigations was obtained from the corresponding 1,3-dibromide and sodium sulfide nonahydrate. The ratio of diastereomers in the case of **4d** has been determined by HPLC analysis. 1,3-Dibromides in turn were prepared following the literature procedure. (a) Smith, D. J. H.; Lancaster, M. *Synthesis* **1982**, 582–583; (b) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2001**, *42*, 5793–5796.
9. Typical experimental procedure and data for compound **3a**: 2-(4-chlorophenyl)thietane **1a** (100 mg, 0.54 mmol), PhI=NTs (41 mg, 0.108 mmol), and 2 mol % of $Cu(acac)_2$ in 2 mL of dry benzene was refluxed under argon for 10 min. The solvent was then removed under vacuum. The residue when subjected to chromatography on a silica column using 95:5 hexane–ethyl acetate afforded 87 mg of unreacted **1a**. Further elution using 90:10 hexane–ethyl acetate solvent mixture afforded 26 mg of **3a** (67%) as a white crystalline solid. Compound **3a**: mp 94–96 °C: IR (KBr) ν_{max}: 1681, 1572, 1451, 1345, 1159, 1091, 901 cm^{-1}; ^1H NMR (300 MHz $CDCl_3/CCl_4$, v/v, 3:1): 2.10–2.19 (m, 1H, CH_2), 2.26–2.34 (m, 1H, CH_2), 2.47 (s, 3H, CH_3), 2.60–2.66 (m, 1H, SCH_2), 2.81–2.88 (m, 1H, SCH_2), 5.18 (uneven triplet, 1H, NC*H*Ar), 7.26–7.35 (m, 6H, Ar*H*,), 7.88 (d, 2H, Ar*H*, $J = 8.1$ Hz). ^{13}C NMR (60 MHz $CDCl_3/CCl_4$, v/v, 3:1): 21.7, 35.1, 37.6, 66.7, 127.7, 128.6, 128.7, 128.9, 129.7, 138.7, 144.5. HRMS (EI): *m/z* calcd for $C_{16}H_{16}ClNO_2S_2$ [M^+]: 353.0304. Found: 353.0387. Expecting an increase in the yield of **3a** this experiment was repeated with **1a** (100 mg, 0.666 mmol), PhI=NTs (249 mg, 0.666 mmol), and 2 mol % of $Cu(acac)_2$ under the same reaction conditions. However, the yield of **3a** remained unchanged and toluenesulfonamide resulting from hydrolysis of the iodonium ylide was obtained.
10. The yields are reported on the basis of the nitrene precursor used.
11. Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* **1966**, *22*, 3393–3401.
12. Typical experimental procedure and data for compound **5a**: The diastereomeric mixture of 2-(4-chlorophenyl)-4-(4-methylphenyl)thietane **4a** (100 mg, 0.365 mmol), PhI=NTs (31 mg, 0.083 mmol), and 2 mol % of $Cu(acac)_2$ in 2 mL dry benzene was refluxed under argon for 10 min. The solvent was then removed under vacuum. The residue on chromatographic separation on silica gel using 95:5 hexane–ethyl acetate afforded 82 mg of the unreacted thietane **4a**. Further elution using 90:10 hexane–ethyl acetate afforded 26 mg of **5a** (76%) as a white crystalline solid. Compound **5a**: mp 124–126 °C; IR (KBr) ν_{max}: 1645, 1491, 1406, 1345, 1159, 1084, 1001, 936, 821 cm^{-1}; ^1H NMR (300 MHz $CDCl_3/CCl_4$, v/v, 3:1): 2.36 (s, 3H, ArCH_3), 2.43–2.47 (m, 1H, CH_2), 2.50 (s, 3H, CH_3), 2.82–2.91 (m, 1H, CH_2), 3.89 (dd, 1H, SC*H*Ar, $J = 6$Hz, $J = 10.6$ Hz), 5.21 (t, 1H, C*H*Ar, $J = 7.5$ Hz), 7.19 (d, 2H, Ar*H*, $J = 8.4$ Hz), 7.19–7.40 (m, 8H, Ar*H*), 7.94 (d, 2H, Ar*H*, $J = 8.2$ Hz); ^{13}C NMR (60 MHz $CDCl_3/CCl_4$, v/v, 3:1): 21.2, 21.8, 48.8, 55.0, 68.3, 126.1, 128.7, 129.0, 129.2, 129.7, 133.1, 133.4, 134.2, 137.3, 138.4, 144.5. HRMS (EI): *m/z* calcd for $C_{23}H_{22}ClNO_2S_2$ [M^+]: 444.0103. Found: 443.9886.
13. HPLC analysis of a solution of thietane **4d** in methanol before and after the reaction was carried out. The cis:trans ratios of **4d** before and after the reaction were 1.9:1 and 0.5:1, respectively. Thus it was clear that only the cis isomer reacts. Experiments with varying amounts of PhI=NTs for a fixed amount of **4d** revealed that the yield is invariable. When the reaction time and temperature were varied, poor yields of the product **5d** resulted. We assume that there is an inherent kinetic selectivity for the cis isomer over the trans isomer.