Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 5759–5762

Tetrahedron Letters

The Rh(II) catalyzed reaction of diethyl diazomalonate with thietanes: a facile synthesis of tetrahydrothiophene derivatives via sulfonium ylides

Vijay Nair,[a,*] Smitha M. Nair,[a] Sindhu Mathai,[a] Jürgen Liebscher,[b] Burkhard Ziemer[b] and K. Narsimulu[c]

[a] *Organic Chemistry Division, Regional Research Laboratory, Trivandrum 695 019, India*
[b] *Institute of Chemistry, Humboldt University, D-12489 Berlin, Germany*
[c] *Indian Institute of Chemical Technology, Hyderabad 500007, India*

Received 20 October 2003; revised 26 April 2004; accepted 7 May 2004
Available online 10 June 2004

This paper is dedicated with best wishes to Professor M. V. George, on the occasion of his 75th birthday

Abstract—A facile Rh(II) catalyzed reaction of diethyl diazomalonate with thietanes leading to highly substituted tetrahydrothiophenes along with allyl thioethers is described.

The reaction of electrophilic carbenes with oxetanes leading to oxonium ylides and the 1,2-rearrangement of the latter to afford tetrahydrofuran derivatives has been studied in great detail.[1–3] Surprisingly, however, to our knowledge, the reaction of carbenes with thietanes has received only scant attention.[4,5] In view of the perception that such a reaction would be of value in the synthesis of tetrahydrothiophenes a la the construction of tetrahydrofuran derivatives mentioned above, we have investigated the reaction of diethyl diazomalonate with thietanes, catalyzed by Rh(II). It is worthy of mention that the tetrahydrothiophene moiety is a structural fragment of biologically active compounds such as biotin, biocytin and thiophthalene Lu 5003. The methods available for the synthesis of tetrahydrothiophenes involve trapping thiocarbonyl ylides with suitable dipolarophiles such as electron deficient alkenes,[6] carbonyl compounds[7] as well as the photolysis of diazo compounds bearing sulfur at the β, γ or at δ-positions.[4] The preliminary results of our investigations are presented in this Letter.

Our studies commenced by exposing a solution of a diastereomeric mixture[8] of 2,4-bis(4-chlorophenyl)thietane **1a**, *cis*:*trans* ratio 1:2.2, in benzene to dicarboethoxycarbene, generated by the Rh(II) catalyzed decomposition of diethyl diazomalonate. A slow but facile reaction occurred to afford a diastereomeric mixture of tetrahydrothiophenes **2a** and **3a** along with the allyl thioether **4a** as shown in Scheme 1.

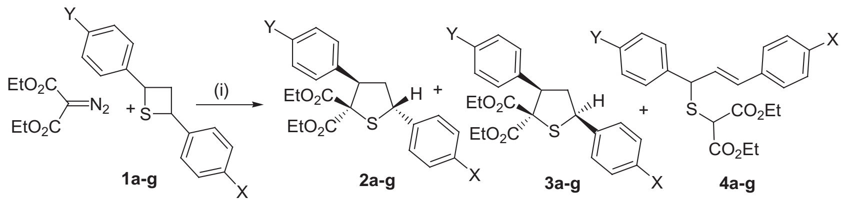
The products[9] were separated by column chromatography and characterized by spectroscopic methods. The IR spectrum of **2a** showed an ester carbonyl absorption at 1745 cm^{-1}. In the ^{1}H NMR spectrum, benzylic protons were present at δ 4.21–4.28 as a multiplet and at 4.7 as a triplet. In the ^{13}C NMR spectrum, the benzylic carbons resonated at 52.65 and 51.16 ppm. The signals due to the ester carbonyls were visible at 169.85 and at 167.57 ppm. Final proof of the structure and stereochemistry of **2a** was obtained by single crystal X-ray analysis, see Figure 1.

The reaction appeared to be general for 2,4-disubstituted thietanes. The tetrahydrothiophene derivatives were obtained in moderate to excellent yields. In the case of thietanes **1d** and **1e**, in addition to the products **2d**, **3d**, **2e** and **3e** small amounts of regioisomeric products arising from the alternative 1,2-rearrangement were

---

* Corresponding author. Tel.: +91-471-490406; fax: +91-471-491712; e-mail: vijaynair_2001@yahoo.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.062



1a	Y = X = Cl	57%	31%	9%
1b	Y = X = H	54%	31%	11%
1c	Y = X = CH_3	50%	24%	18%
1d	Y = Cl, X = H	38%	32%	14%
1e	Y = CH_3, X = H	32%	26%	17%
1f	Y = H, X = NO_2	36%	18%	38%
1g	Y = CH_3, X = Cl	36%	32%	12%

Scheme 1. Reagents and conditions: $Rh_2(OAc)_4$, benzene, reflux, argon.

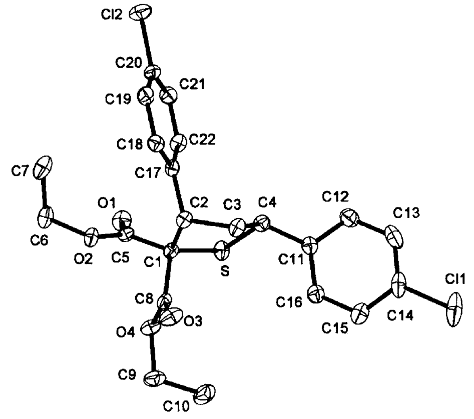


Figure 1. X-ray structure of compound **2a**.

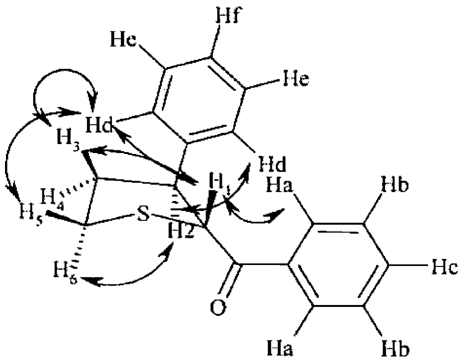


Figure 2. 2-NOE cross-peaks present in the major isomer of **7c**.

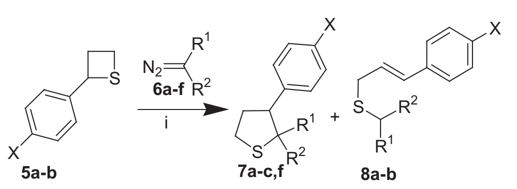
isolated. With thietanes **1f** and **1g**, only single pairs of diastereomeric products **2f**, **3f** and **2g**, **3g** were obtained.

In our subsequent investigations a similar reactivity pattern was observed with 2-substituted thietanes and various diazo compounds and the results are presented in Scheme 2.

As indicated by ^{1}H NMR, **7c** was a mixture of isomers in the ratio 3.2:1. The stereochemistry of the major isomer was assigned by NOE difference spectroscopic studies undertaken in $CDCl_3$ solution at 500 MHz (Fig. 2). The presence of H_1/H_3 NOE cross peaks indicates that they are on the same side of the tetrahydrothiophene ring; H_2/H_6 cross-peaks also support their presence on the same side of thiophene ring. The H_1/H_d, H_3/H_d and H_5/H_d NOE confirmed that the protons H_1, H_3 and H_5 are on the same side of the ring, whereas H_2, H_4 and H_6 are on the other side. The intra-ring vicinal couplings $^3J_{1\text{-}2} = 6.5$ Hz, $^3J_{2\text{-}3} = 9.4$ Hz, $^3J_{2\text{-}4} = 6.1$ Hz, $^3J_{3\text{-}5} = 6.4$ Hz, $^3J_{3\text{-}6} = 9.1$ Hz, $^3J_{4\text{-}5} = 4.4$ Hz and $^3J_{4\text{-}6} = 5.7$ Hz all supports the assigned structure. Thus the major isomer obtained was *trans*.

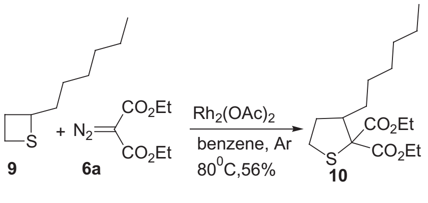
The reaction is also applicable to alkyl substituted thietanes; 2-hexylthiethane **9** furnished tetrahydrothiophene **10** in moderate yield (Scheme 3).

Mechanistically, the reaction can be viewed as occurring by the initial formation of the sulfonium ylide[10,11]

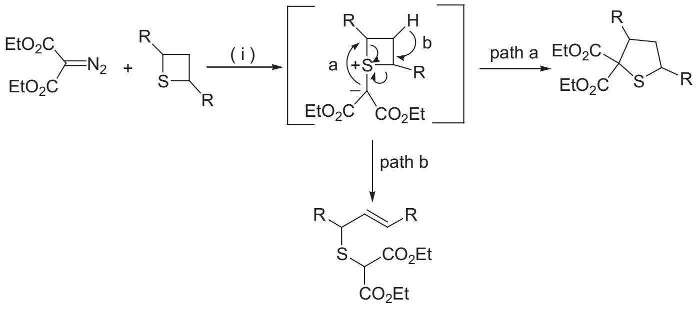


5a X=Cl	**6a** R^1= R^2=CO_2Et	**7a** (65%)	**8a** (9%)
5b X=H	**6a** R^1= R^2=CO_2Et	**7b**^{1} (64%)	**8b** (8%)
5b X=H	**6b** R^1=H R^2=CO_2Et	**7b**^{2} (55%)	0
5b X=H	**6c** R^1=H R^2=COPh	**7c** (60%), [3.2:1]	0
5b X=H	**6d** R^1= R^2=COPh	no reaction	
5b X=H	**6e** R^1= R^2=SO_2Ph	no reaction	
5a X=Cl	**6f** =1,3-Cyclohexanedione	**7f** (48%)	0

Scheme 2. Reagents and conditions: (i) $Rh_2(OAc)_4$ or Cu(II) acetylacetonate, benzene, reflux, argon.



Scheme 3.



Scheme 4.

followed by the Stevens rearrangement (path a). It is reasonable to assume that the open chain compound arises via a fragmentation predicted by the β-elimination process (path b),[2c] Scheme 4.

In conclusion we have uncovered a facile method for the synthesis of highly substituted tetrahydrothiophene derivatives. It is conceivable that this reaction protocol can be extended to the enantioselective synthesis of substituted tetrahydrothiophenes.

Acknowledgements

S.M.N. thanks the CSIR, New Delhi for a research fellowship, Ms. Soumini Mathew for recording NMR spectra and Mrs. S. Viji for elemental analysis.

References and notes

1. For excellent reviews see: (a) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50; (b) Clark, J. S. In *Nitrogen*; Clark, J. S., Ed.; Oxygen and Sulfur Ylide Chemistry: Oxford, 2002; pp 1–98.
2. (a) Katsuki, T.; Ito, K. *Chem. Lett.* **1994**, 1857; (b) Carless, H. A.; Trivedi, H. S. *J. Chem. Soc., Chem. Commun.* **1979**, *1*, 382; (c) Kirmse, W.; Lelgemann, R.; Friedrich, K. *Chem. Ber.* **1991**, *124*, 1853.
3. Masaki, Y.; Itoh, A.; Hirose, Y.; Kashiwagi, H. *Heterocycles* **1994**, *38*, 2165.
4. The photolysis of diazocompounds bearing sulfide groups leading to tetrahydrothiophene derivatives has been postulated to occur via the intermediacy of episulfonium and thietonium ylides (a) Kondo, K.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1972**, *1*, 63; (b) Kondo, K.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1972**, 860.
5. For the isolated example of the reaction of unsubstituted thietane with diethyl diazomalonate in the presence of $CuSO_4$ see: (a) Ando, W.; Yagihara, T.; Tozune, S.; Imai, I.; Suzuki, J.; Toyama, T.; Nakaido, S.; Migita, T. *J. Org. Chem.* **1972**, *37*, 1721; (b) Kondo, K.; Ojima, I. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1490.
6. (a) Achiwa, K.; Imai, N.; Tanaka, M.; Terao, Y. *Tetrahedron Lett.* **1985**, *25*, 3011; (b) Achiwa, K.; Terao, Y.; Hyodo, C.; Aono, M. *Tetrahedron Lett.* **1986**, *34*, 4039; (c) Ohno, M.; Ishida, H. *Tetrahedron Lett.* **1999**, *40*, 1543.
7. Hosomi, A.; Hayashi, S.; Hoaschi, K.; Kohra, S.; Tominaga, Y. *J. Chem. Soc., Chem. Commun.* **1987**, *1*, 1442.
8. The thietanes were prepared from the corresponding 1,3-dibromides following a literature procedure. These were obtained as inseparable diastereomeric mixtures. The ratio of thietanes **1a** and **1b** were found to be *cis*:*trans* 1:2.2 and 1:2.4, respectively. Smith, D. J. H.; Lancaster, M. *Synth. Commun.* **1982**, *1*, 582.
9. All new compounds were fully characterized. Typical experimental procedure and data for compounds **2a**, **3a** and **4a**: A mixture of thietane **1a** (*cis*:*trans* ratio 1:2.2) (0.44 mmol), diethyl diazomalonate (0.487 mmol) and 2 mol% of $Rh_2(OAc)_4$ was refluxed in 5 mL of dry benzene under an argon atmosphere for 16 h. The solvent was then removed under vacuum and the residue after chromatographic separation on silica gel using hexane/ethyl acetate (95:5) gave the tetrahydrothiophene **2a** (57%), **3a** (31%) and the allyl thioether **4a** (9%).
Compound **2a**: Colourless crystalline solid, recrystallized from ethyl acetate/hexane mixture (5:95), mp 84–86 °C; IR (KBr) ν_{max}: 2981, 1745:1574, 1491:1258, 1201:1093, 1041:958, 825, 720, 622, 560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$, v/v, 3:1): 0.87 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 1.31 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 2.60–2.66 (m, 2H, CH_2), 3.67–3.87 (m, 2H, OCH_2CH_3), 4.21–4.28 (m, 3H, ArC*H*, OCH_2CH_3), 4.7 (t, 1H, $J = 7.1$ Hz, SC*H*Ar), 7.13–7.55 (m, 8H, Ar*H*), ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$, v/v, 3:1): 13.48, 13.91, 46.16, 51.16, 52.65, 62.01, 62.19, 70.61, 128.21, 128.51, 128.71, 129.14, 129.44, 133.31, 133.40, 137.35, 167.57, 169.85. Elemental analysis calcd for $C_{22}H_{22}O_4SCl_2$: C, 58.28, H, 4.89, S, 7.07. Found: C, 57.99, H, 4.86, S, 7.44.
Compound **3a**: Pale yellow viscous liquid; IR (neat) ν_{max}: 2887, 1739:1594, 1491:1260, 1115:1050, 927:813, 727, 636, 555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$, v/v, 3:1): 0.83 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 1.16 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 2.45–2.51 (m, 1H, CH_2), 2.80–2.84 (uneven q, 1H, CH_2), 3.54–3.60 (m, 1H, OCH_2CH_3), 3.87–3.93 (m, 1H, OCH_2CH_3), 4.12–4.25 (m, 3H, CH_2C*H*Ar, OCH_2CH_3), 4.61(dd, 1H, $J = 5.2$ Hz, 11.5 Hz, SC*H*Ar), 7.16–7.30 (m, 6H, Ar*H*), 7.81 (d, 2H, $J = 7.2$ Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3/CCl_4$, v/v, 3:1): 13.51, 13.89, 44.74, 50.23, 53.14, 62.05, 62.16, 69.08, 128.27, 128.84, 129.54, 129.97, 133.60, 133.63, 135.42, 138.44, 169.12, 169.78; HRMS (EI): m/z Calcd for $C_{22}H_{22}O_4SCl_2$ [M^+]: 452.0616. Found: 452.0637.
Compound **4a**: Pale yellow viscous liquid; IR (neat) ν_{max}: 2980, 1740:1579, 1491:1253, 1150:1093, 927:82, 725, 627, 508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CCl_4$, v/v, 3:1): 1.19 (m, 6H, OCH_2CH_3) 3.95 (s, 1H, $CH(CO_2Et)_2$), 4.1 (m, 4H, OCH_2CH_3), 4.81 (d, 1H, $J = 8.8$ Hz, SC*H*Ar), 6.29 (dd, 1H, $J = 8.8$ Hz, $J = 15.6$ Hz, C*H*=CHAr), 6.43 (d, 1H, $J = 15.7$ Hz, CH=C*H*Ar), 7.19–7.31 (m, 8H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$–CCl_4, v/v, 3:1): 14.00, 14.03, 51.89, 52.51, 62.13, 62.18, 126.72, 127.88, 128.65, 128.97,

129.48, 131.32, 133.81, 133.84, 134.92, 136.20, 137.82, 139.00, 166.46, 166.72.

10. (a) Porter, M. J.; Ioannou, M.; Saez, F. *Chem. Commun.* **2002**, *1*, 346; (b) Kametani, T.; Kawamuri, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010; (c) Kim, G. C.; Kang, S. W.; Kim, S. N. *Tetrahedron Lett.* **1993**, *34*, 7627.
11. Rainier, H. D.; Tadat, M. H.; Kennedy, A. R. *Org. Lett.* **2001**, *3*, 2407.