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Synthesis of *o*-Dimethylene Isoxazole *via* Isoxazole-fused 3-Sulfolene

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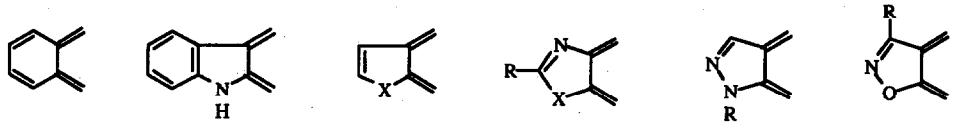
Abstract *Isoxazole-fused 3-sulfolene* **12** *has been synthesized from the readily available starting material* **7** *in three steps. Heating compound* **12** *at 160–180 °C generates o-dimethylene isoxazole* **6b** *which undergoes smooth cycloaddition reactions.*

The generation and synthetic applications of *o*-quinodimethane **1**[1] and indolo-2, 3-quinodimethane **2**[2] have been extensively explored. However, there are only scattered reports on the study of other *o*-dimethylene heterocycles, mostly about the five-membered heterocycles **3**[3], **4**[4], **5**[5], and **6a**[6]. A commonly adopted approach toward the preparation of these reactive compounds involes the flash vacuum pyrolysis of benzoyloxymethyl-bearing heterocycles or similar precursors.[3-6] The limitations of this approach include that a specific precursor is required for each target *o*-dimethylene heterocycle and that the precursors are sometimes not easily accessible. It is perhaps strategically more versatile to prepare *o*-dimethylene heterocycles *via* the corresponding heterocycle-fused 3-sulfolenes. For example, *o*-dimethylene pyrroles[7] (**3**, X = NR), which have not been prepared by other methods, can be easily generated from pyrrolo-3-sulfolenes. Based on similar strategy, furan-,[8] thiophene-,[3f,9] thiazole-[10] and pyrazole-[11]fused 3-sulfolenes have all been demonstrated to be excellent precursors to the corresponding *o*-quinodimethanes. We now report that this approach can be applied to the synthesis of the unsubstituted *o*-dimethylene isoxazole **6b**.

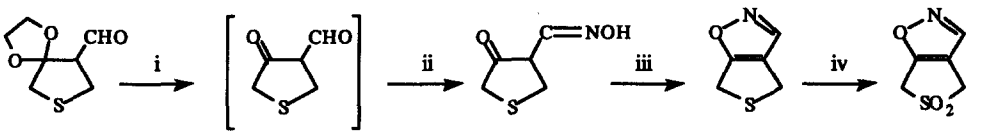


1 **2** **3** **4** **5** **6a** R = Ph; **6b** R = H

The readily available ketal-aldehyde **7**[7] was chosen as the starting material for the synthesis (Scheme I) because it contains a 1, 3-dicarbonyl functionality and a latent 3-sulfolene moiety. Compound **7** was hydrolyzed under acidic conditions to the keto-aldehyde **8** which was not isolated but treated directly with NH_2OH•HCl at room temperature to give **9** (50%) chemoselectively. Because NH_2OH normally reacts with an aldehyde faster than with a ketone,[12] the keto-oxime **10** was not obtained in this reaction. Cyclization of **9** to the isoxazole **11** was achieved by treatment with polyphosphoric acid under

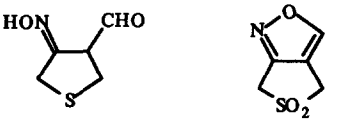
nitrogen. Subsequent oxidation with m-CPBA gave the target molecule **12** in 96% yield.[13] Spectral analyses revealed that the structural isomer **13** was not present.[14]

Scheme I



7 **8** **9** **11** **12**

(i) 20% H_2SO_4, room temp, 3 hr. (ii) NH_2OH•HCl (1.2 eq), room temp, 1 hr, 50% from **7**.
(iii) PPA, 80 °C, N_2, 15 min, 43%. (iv) *m*-chloroperbenzoic acid, CH_2Cl_2, room temp, 30 min, 96%.

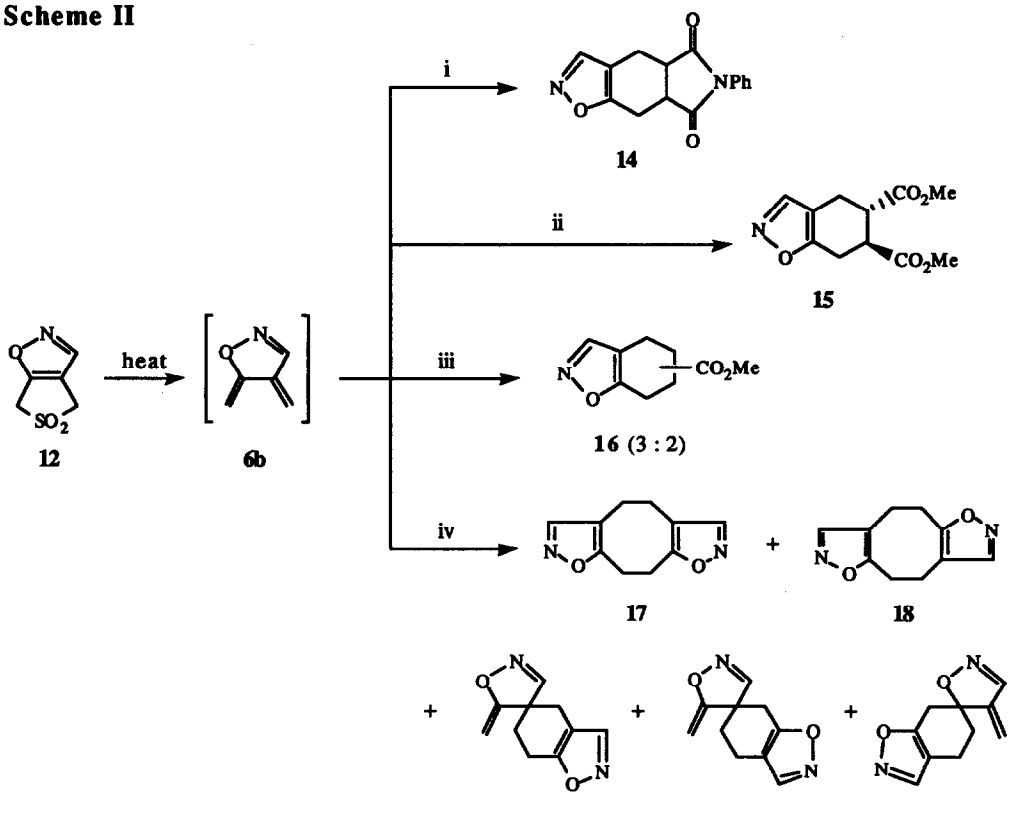


10 **13**

Heating the isoxazole-fused 3-sulfolene **12** in the presence of a suitable dienophile readily produced the [4+2] cycloadduct (Scheme II). This is consistent with that loss of SO_2[15] from **12** occurred in the first place to give the *o*-dimethylene isoxazole **6b** which was then intercepted by the dienophiles. When methyl acrylate, an unsymmetric dienophile, was used in this reaction, a 3 : 2 mixture of isomers of the cycloadduct **16** was produced showing little regioselectivity. When **12** was heated in the absence of a dienophile, the complex dimerization ractions of **6b** produced in low yield a mixture of two [4+4] dimers [**17** (10%), **18** (3%)] and three [4+2] dimers [**19**, **20**, **21** (3% altogether)]. The mode of dimerization of **6b** is quite different from those of other known *o*-dimethylene heterocycles. Only [4+2] dimers were obtained from dimethylene thiophene (**3**, X = S)[3g-j] and thiazole (**4**, X = S, R = H).[10] Whereas only head-to-head [4+4] dimers were formed from dimethylene furan (**3**, X = O),[3b], pyrrole (**3**, X = NSO_2Ph),[7] and oxazole (**4**, X = O, R = H).[4] Furthermore, the dimers of some other *o*-dimethylene heterocycles, such as pyrazole[5,11] analogue, were never observed.

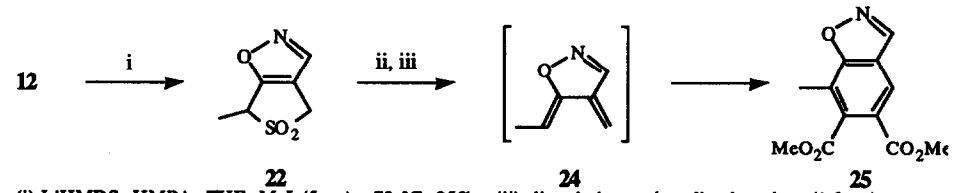
The 3-sulfolene ring of compound **12** not only serves as a masked functionality of *o*-dimethylene, but also is the 1-carbanion equivalent of the *o*-quinodimethane.[16] Thus, the deprotonation of **12** with lithium hexamethyldisilazide (LiHMDS) followed by treatment with excess MeI gave the α-methylated product **22** (Scheme III). Although the yield was only moderate (25%), the alkylation reaction is regioselective that no other methylated isomers were obtained. The structural assignment was confirmed by an unambiguous synthesis of **22** from **23** (eq 1) following the same reaction sequence shown in Scheme I. Compound **22** should serve as the precursor for the substituted *o*-dimethylene isoxazole **24**. Indeed the reaction of compound **22** with dimethyl acetylenedicarboxylate at 180 °C produced a cycloadduct which was directly aromatized with DDQ to give the benzoisoxazole **25** in nearly quantitative yield. This example illustrates the broad synthetic applicability of **12** as the equivalent of *o*-dimethylene isoxazole **6b** because other alkylated derivatives of **6b** should also be preparable from **12**.

Scheme II

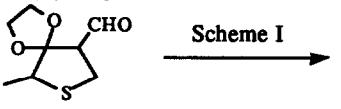


(i) N-phenylmaleimide, 180 °C, $CHCl_3$, 15 min, 73%. (ii) dimethyl fumarate, 180 °C, $CHCl_3$, 15 min, 89%. (iii) methyl acrylate, 160 °C, $CHCl_3$, 30 min, 88%. (iv) 180 °C, $CHCl_3$, 15 min, 16%.

Scheme III



(i) LiHMDS, HMPA, THF, MeI (5 eq), -78 °C, 25%. (ii) dimethyl acetylenedicarboxylate (1.2 eq), toluene, 180 °C, 15 min. (iii) DDQ, 140 °C, 2hr, >99% from **22**.



(eq 1)

In summary, we have described herein the first success of the synthesis of the unsubstituted *o*-dimethylene isoxazole **6b** and its cycloaddition reactions. In addition, one can take advantage of the 3-sulfolene functionality of **12** to prepare the precursors of the alkylated derivatives of **6b** such as **22**.

It should also be noted that compound **7**, containing a 1, 3-dicarbonyl functionality, should be a useful intermediate for the preparation of a number of other heterocycle-fused 3-sulfolenes, the precursors for *o*-dimethylene heterocycles.

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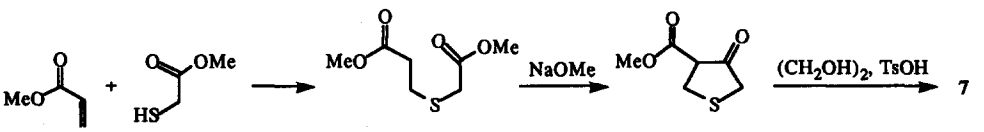
REFERENCES

1. For a recent review, see: Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proc. Int.*, **1991**, *23*, 237.
2. (a) Haber, M.; Pindur, U. *Tetrahedron*, **1991**, *47*, 1925. (b) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acct. Chem. Res.*, **1984**, *17*, 35. (c) Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.*, **1989**, *89*, 1681.
3. (a) Munzel, N.; Schweig, A. *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 471. (b) Chou, C. H.; Trahanovsky, W. S. *J. Am. Chem. Soc.*, **1986**, *108*, 4138. (c) Trahanovsky, W. S.; Cassady, T. J.; Woods,T. L. *J. Am. Chem. Soc.*, **1981**, *103*, 6691. (d) Jullien, J.; Pechine, J. M.; Perez, F.; Piade, J. J. *Tetrahedron Lett.*, **1979**, 3079. (e) Plant, A.; Chadwick, D. J. *Synthesis*, **1990**, 915. (f) Crew, A. P. A.; Jenkins, G.; Storr, R. C.; Yelland, M. *Tetrahedron Lett.*, **1990**, *31*, 1491. (g) van Leusen, A. M.; van den Berg, K. J. *Tetrahedron Lett.*, **1988**, *29*, 2689. (h) Chauhan, P. M. S.; Jenkins, G.; Walker, S. M.; Storr, R. C. *Tetrahedron Lett.*, **1988**, *29*, 117. (i) Chadwick, D. J.; Plant, A. *Tetrahedron Lett.*, **1987**, *28*, 6085. (j) Takeshita, M.; Koike, M.; Mataka, S.; Tashiro, M. *J. Org. Chem.*, **1991**, *56*, 6948.
4. Chauhan, P. M. S.; Crew, A. P. A.; Jenkin, G.; Storr, R. C.; Walker, S. M.; Yelland, M. *Tetrahedron Lett.*, **1990**, *31*, 1487.
5. Mitkidou, S.; Stephanidou-Stephanatou, J. *Tetrahedron Lett.*, **1990**, *31*, 5197.
6. Mitkidou, S.; Stephanidou-Stephanatou, J. *Tetrahedron Lett.*, **1991**, *32*, 4603.
7. Chou, T. S.; Chang, R. C. *J. Chem. Soc., Chem. Commun.*, **1992**, 549. Compound **7** was prepared by the following scheme:



8. Chou, T. S.; Tsai, C. Y. *Heterocycl.*, **1992**, *34*, 663.
9. Chou, T. S.; Tsai, C. Y. *J. Chem. Soc., Chem. Commun.*, **1991**, 1287.
10. Chou, T. S.; Tsai, C. Y. *Tetrahedron Lett.*, **1992**, *33*, 4201.
11. Chaloner, L. M.; Crew, A. P. A.; Storr, R. C.; Yelland, M. *Tetrahedron Lett.*, **1991**, *32*, 7609.
12. Grünanger, O.; Vita-Finzi, P. in *The Chemistry of Heterocyclic Compounds*, Taylor, E. C. Eds., John Wiley and Sons: New York **1990**, *49*, pp 126-129.
13. All new compounds gave satisfactory spectral and analytical data.
14. ^{1}H NMR (200 MHz) for compound **12** (in d_6-acetone) δ 4.36 (s, 2H), 4.56 (s, 2H), 8.62 (s, 1H).
15. (a) Mock, W. L. *J. Am. Chem. Soc.*, **1975**, *97*, 3666. (b) Kellogg, R. M.; Prins, W. L. *J. Org. Chem.*, **1974**, *39*, 2366.
16. Chou, T. S.; Tso, H. H. *Org. Prep. Proc. Int.*, **1989**, *21*, 257.

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