Tetrahedron Letters, Vol. 34, No. 6, pp. 947-950, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

INTRAMOLECULAR DIELS-ALDER REACTIONS OF 2*H*-THIOPYRANS

Dale E. Ward* and Thomas E. Nixey

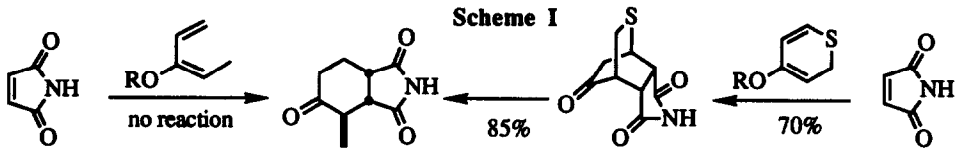
Department of Chemistry, University of Saskatchewan,
Saskatoon, CANADA S7N 0W0

Key Words: intramolecular Diels-Alder, 2H-thiopyran diene, cis-diene

Abstract: *Intramolecular Diels-Alder reactions of a series of substrates with 4-triisopropylsilyloxy-2H-thiopyran as the diene and a dienophile attached to each of the four possible positions by a three carbon tether were examined.*

A significant limitation of the Diels-Alder reaction is the poor reactivity associated with *cis*-dienes.[1] Recently, we have investigated a strategy involving the use of 2*H*-thiopyrans as functional equivalents to *cis*-dienes.[2] The Diels-Alder adducts from reactions of 2*H*-thiopyrans with dienophiles are, after desulfurization, synthetically equivalent to adducts derived (in principle) from unreactive *cis*-dienes (Scheme I).[2a] Reactions of 2*H*-thiopyrans bearing activating substituent(s) with reactive dienophiles (e.g.maleic anhydride, maleimide) give predominantly *endo* adducts in good yield.[2b] With less reactive dienophiles (e.g acrylate, crotonate) reactions are slower and thermal decomposition of the diene competes effectively with cycloaddition.[2b] Lewis acid mediated reaction at lower temperatures is often satisfactory in these cases.[2c,2d]

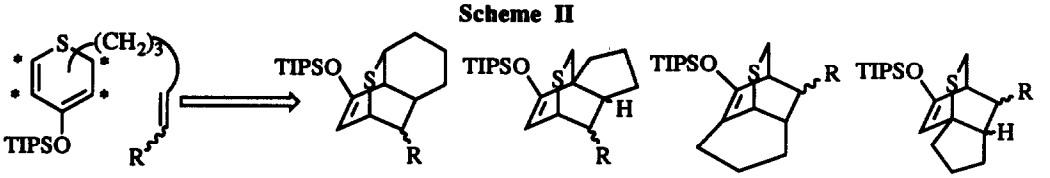
Scheme I



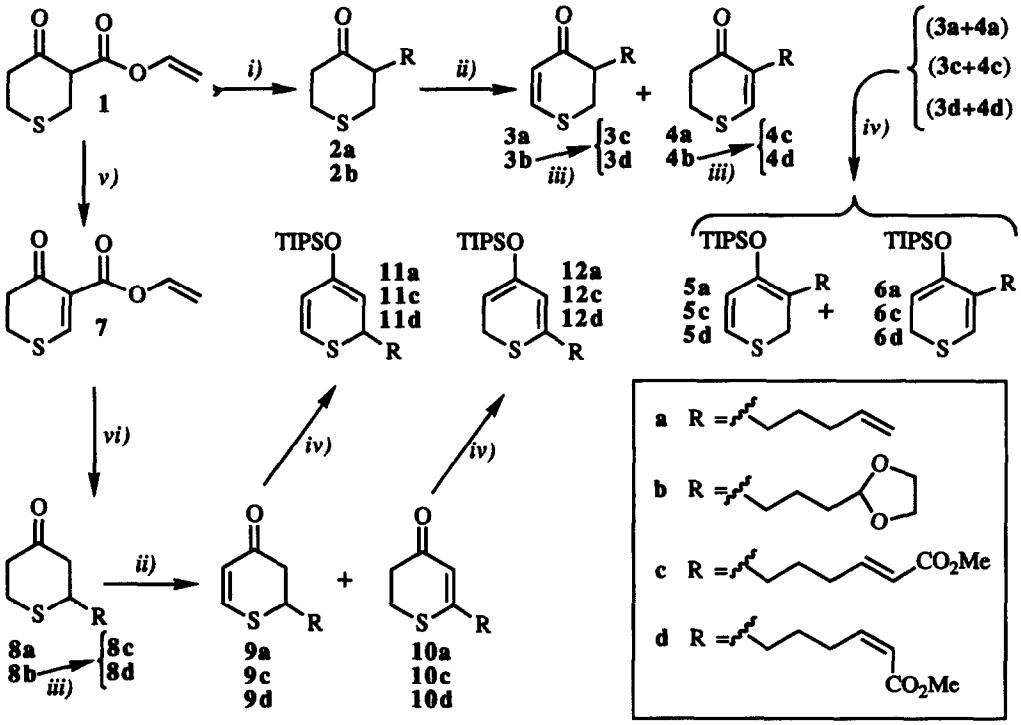
The intramolecular Diels-Alder (IMDA) reaction has emerged as a powerful synthetic method for the stereoselective construction of polycylic ring systems in a single step.[3] The poor reactivity of *cis*-substituted dienes limits the scope of the IMDA reaction, although not as severely as in the intermolecular counterpart. Relatively few examples of IMDA reactions[3] involve (*Z*)-dienes[4] or *cis*-substituted dienes[5] which are conformationally mobile (i.e. capable of s-*cis* and s-*trans* conformers). The reduced reactivity of *cis*-dienes compared to their *trans* isomers[6] can preclude IMDA reaction[3f] in favor of a competitive pathway(s).[5a,5b] The feasibility of using 2*H*-thiopyrans as dienes in IMDA reactions to address this limitation has been examined.

The reactivity of a series of substrates with 4-triisopropylsilyloxy-2*H*-thiopyran as the reactive diene and the dienophile attached to each of the four possible positions by a three carbon tether was examined (Scheme II).

Scheme II



Scheme III[a]

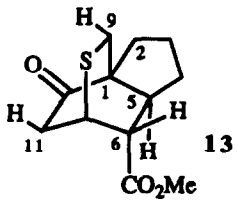


[a] Reaction Conditions: *i)* 1. NaH, NaI, RBr, acetone;[7,8] 2. $(Ph_3P)_4Pd(0)$, morpholine, THF;[7] *ii)* NCS, pyridine, CH_2Cl_2;[9] *iii)* 1. $HClO_4$(aq), acetone; 2. $MeO_2CCH{=}PPh_3$, MeOH;[10] *iv)* TIPSOTf, Et_3N, CH_2Cl_2;[2] *v)* MnO_2; *vi)* 1. RMgBr, CuI·Me_2S;[9b,11] 2. $(Ph_3P)_4Pd(C)$, morpholine, THF;[7]

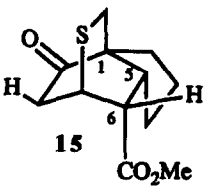
The desired compounds were readily prepared from the known[7] β-ketoester **1** according to Scheme III. Alkylation of the enolate with 5-bromopentene[12] or with the ethylene acetal of 4-bromobutanal[13] followed by decarboxylation and generation of the enone gave inseparable 1:1 mixtures of **3a** and **4a**, and **3b** and **4b**, respectively (20-30% overall, unoptimized). The mixture of **3b** and **4b** was hydrolyzed and treated with $MeO_2CCH{=}PPh_3$ in MeOH[10] to give a separable 5:3 mixture of *trans* esters (**3c** and **4c**; 1:1) and *cis* esters (**3d** and **4d**; 1:1), respectively (60%). Alternatively, Cu mediated conjugate addition[9b,11] of the Grignard reagents derived from the above alkyl halides to **7** followed by decarboxylation gave **8a** and **8b**, respectively (40-50%, unoptimized). Olefination of **8b** as above gave a 2:1 mixture of **8c** and **8d** (75%). Treatment of 8a, 8c, or 8d with NCS gave, in each case, a separable 1:2 mixture of **9** and **10** (75-90%, unoptimized).

Treatment of the enones **9a**, **10a**, and the 1:1 mixture of **3a** and **4a** with TIPSOTf[2] gave the trienes **11a**, **12a**, and a mixture of **5a** and **6a**, respectively (quantitative). Solutions of the above trienes in toluene-d_8 were heated in sealed tubes for several days at up to 200 °C. IMDA products were not detected; only products of decomposition (oxidation, desilylation)[2] of the dienes were observed.

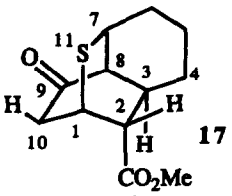
The activated trienes **11c**, **11d**, **12c**, **12d**, **5c** + **6c** (1:1 mixture), and **5d** + **6d** (1:1 mixture) were similarly prepared from the corresponding enones (Scheme III). The results of IMDA reaction of these trienes under various conditions are summarized in Table 1.



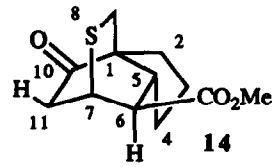
13



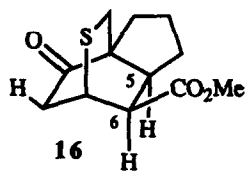
15



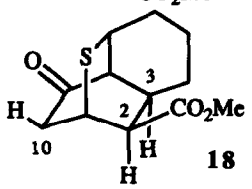
17



14



16



18

Table 1. IMDA reactions of 4-triisopropylsilyloxy-2*H*-thiopyrans with activated dienophiles.

Triene	Conditions[a]	Products[b]	Triene	Conditions[a]	Products[b]
5c+6c (1:1)	Thermal 140 °C, 4 d	**13** (55%) **14** (43%)	**5d+6d** (1:1)	Thermal 140 °C, 4 d	**15** (70%) **16** (10%)
	TIPSOTf 2 h	**13** (44%) **14** (42%)		TIPSOTf 24 h	**13** (44%) **14** (43%)
	$EtAlCl_2$ 3 min.	**13** (38%) **14** (34%)		$EtAlCl_2$ 3 min.	**13** (34%) **14** (27%) **15** (30%)
6c	Thermal 140 °C, 4 d	---			**16** (trace)
11c	Thermal 175 °C, 17 h	**17** (86%)	**11d**	Thermal 175 °C, 17 h	**17** (30%) **18** (33%)
	TIPSOTf 13 h	**17** (17%)	**12c**	Thermal 175 °C	---
	$EtAlCl_2$ 7h	**17** (34%)	**12d**	Thermal 175 °C	---

[a] Thermal: C_6D_6 solution containing BHT (0.15 equiv.), sealed tube; $EtAlCl_2$:).4 equiv. in C_6D_6 solution; TIPSOTf: (2 equivalents) with Et_3N (4 equiv.) in CH_2Cl_2. [b] Isolated yield after hydrolysis ($HF_{(aq)}$, CH_3CN).

Diels-Alder[14] products[15] were obtained in good yield with **5c**, **5d**, **11c**, and **11d** under thermal and Lewis acid mediated conditions. The lower reactivity of **6c**,[16] **12c**, and **12d** would be expected since IMDA reaction enforces an unfavorable regiochemistry in these systems. Interestingly, the stereoselectivity in the reaction of **5c** is independent of the reaction conditions and is lower than **5d**.[3a,3e] Reactions of **6d** indicate that dienophile isomerization competes effectively with cyclization under Lewis acid mediated reactions. As expected,[3a,3e] a single isomer results from cylcization of **11c**. Reaction of **11d** is slower than **11c** and some isomerization of the dienophile occurs.

In conclusion, IMDA reactions of 2*H*-thiopyrans have been shown to be feasible. Few examples of cyclization of analogous (i.e. without sulfur) acyclic compounds have been reported.[3,4,5] Further work aimed at improving the stereoselectivity of this process and application of the strategy to the synthesis of hydrindan and decalin systems is underway.

Acknowledgement: Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

REFERENCES AND FOOTNOTES

1. (a) Martin, J. G.; Hill, R. K. *Chem. Rev.*,**1961**, *61*, 537. (b) Sauer, J. *Angew. Chem., Int. Ed. Engl.*,**1967**, *6*, 17.
2. (a) Ward, D. E.; Zoghaib, W. M.; Rhee, C. K.; Gai, Y. *Tetrahedron Lett.*, **1990**, *31*, 845. (b) Ward, D. E.; Gai, Y.; Zoghaib, W. M. *Can. J. Chem.*, **1991**, *69*, 1487. (c) Ward, D. E.; Gai, Y. *Tetrahedron Lett.*, **1992**, *33*, 1851. (d) Ward, D. E.; Gai, Y. *Can. J. Chem.*, **1992**, *70*, 0000.
3. Reviews: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Flemming, I., Ed.; Pergamon: Oxford, **1991**; Vol. 5, Chapter 4.4. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series Volume 8, Pergamon: Oxford, **1990**; p 140. (c) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, **1990**, Vol. 2, p 91. (d) Taschner, M. J. In *Organic Synthesis: Theory and Application*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, **1989**, Vol. 1, p 79. (e) Craig, D. *Chem. Soc. Rev*,. **1987**, *16*, 187. (f) Fallis, A. *Can. J. Chem.*, **1984**, *62*, 183. (g) Ciganek, E. *Org. React.*, **1984**, *32*, 1. (h) Taber, D. F. *Intramolecular Diels-Alder and Ene Reactions*; Springer-Verlag: Berlin, **1984**. (i) Paquette, L A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, **1984**, Vol. 3, Chapter 7. (j) G. Brieger and J.N. Bennett, *Chem. Rev.*, **1980**, *80*, 83. (k) Funk, R; Vollhardt, K. P. C. *Chem. Soc. Rev.*, **1980**, *9*, 41. (l) Oppolzer, W. *Synthesis*, **1978**, 793. (m) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 10. (n) Mehta, G. *J. Chem. Ed.*, **1976**, *53*, 551. (o) Carlson, R.G. *Ann. Rep. Med. Chem.*, **1974**, *9*, 270.
4. See for example: (a) Sodeoka, M.; Yamada, H; Shibasaki, M. *J. Am. Chem. Soc.*, **1990**, *112*, 4906. (b) Chou, S.-S.P.; Wey, S.-J. *J. Org. Chem.*, **1990**, *55*, 1270. (c) Wattanasin, S.; Kathawala, F. G.; Boekman, R. K. *J. Org. Chem.*, **1985**, *50*, 3810. (d) Yoshida, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.*, **1984**, *106*, 1133. (e) Koreeda, M.; Luengo, J. I. *J. Org. Chem.*, **1984**, *49*, 2079. (f) Boeckman, R. K.; Alessi, T. R. *J. Am. Chem. Soc.*, **1982**, *104*, 3216. (g) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.*, **1982**, *104*, 5719. (h) Kuenhe, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.*, **1981**, *46*, 2002. (i) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta*, **1977**, *60*, 48. (j) House, H. O.; Cronin, T. H. *J. Org. Chem.*, **1965**, *30*, 1061.
5. See for example: (a) Borch, R. F.; A. J. Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.*, **1977**, *99*, 1612. (b) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.*, **1983**, *48*, 5170. (c) Jenkins, P. R.; Menear, K. A.; Barraclough, P.; Nobbs, M. S. *J. Chem. Soc., Chem. Commun.*, **1984**, 1423. (d) Magnus, P.; Walker, C.; Jenkins, P. R.; Meanar, K. A. *Tetrahedron Lett.*, **1986**, *27*, 651. (e) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.*, **1987**, *109*, 8115. (f) Corey, E. J.; Jardine, P. D. S.; Rohloff, J. C. *J. Am. Chem. Soc.*, **1988**, *110*, 3672. (g) Nicolaou, K. C.; Li, W. S. *J. Chem. Soc., Chem. Commun.*, **1985**, 421.
6. An often cited report[4j] claims similar IMDA reactivity for the methyl esters of (2*E*, 7*E*)- and (2*E*, 7*Z*)-2,7,9-decatrienoic acid. Interpretation of these results in light of those of Roush (Roush, W.R.; Ko, A.I.; Gillis, H.R. *J. Org. Chem.*, **1980**, *45*, 4264) leads to the conclusion that the 7*E* isomer is considerably more reactive than the 7*Z* isomer. For an example of relative IMDA reactivity of *E* and *Z* dienes see ref. 4f.
7. Casey, G.; Sutherland, A.G.; Taylor, R. J. K.; Urben, P. G. *Synthesis*, **1989**, 767.
8. Matsuyama, H.; Miyazawa, Y.; Takei, Y.; Kobayashi, M. *J. Org. Chem.*, **1987**, *52*, 1703.
9. (a) Chen, C. H.; Reynolds, G. A.; Van Allan, J. H. *J. Org. Chem.*, **1977**, *42*, 2777. (b) Kansal, V. K.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. I*, **1984**, 703.
10. House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.*, **1964**, *29*, 3327.
11. (a) Batten, R. J.; Coyle, J. D.; Taylor, R. J. K.; Vassiliou, S. *J. Chem. Soc., Perkin Trans. I*, **1982**, 1177. (b) Lane, S.; Quick, S. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. I*, **1985**, 893. (c) Casy, G.; Lane, S. Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. I*, **1986**, 1397.
12. Krause, G.A.; Landgrebe, K. *Synthesis*, **1984**, 885.
13. Vedejs,E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem.*, **1979**, *44*, 3230.
14. A sequential Michael reaction mechanism is plausible. We have not detected products corresponding to intramolecular Michael addition of the silyl enol ether with the enoate. See also ref. 2d.
15. The stereochemistry of the adducts **13-18** was readily determined by analysis of the coupling constants in the ^{1}H NMR spectra. For example, the configuration at C-6 in **13-16** was assigned by the presence (**13**, **15**; ca. 2 Hz) or absence (**14**, **16**) of w-coupling between H-6 and H-11.[2b,2d] The relative configuration at C-5 and C-6 was assigned based on the H-5/H-6 coupling constant (5-8 Hz for **13** and **14**; 10-12 Hz for **15** and **16**). Similar arguments apply for the stereochemical assignment of **17** and **18**.
16. Triene **6c** is obtained from **4c** which can be isolated from the hydrolyzed products from IMDA reaction of the inseparable mixture of **5c** and **6c**.

(Received in USA 30 September 1992; accepted 16 November 1992)