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THE SYNTHESIS OF DIHYDROFURANO[2,3-b]THIOPYRANS, THIEPINS AND THIOPHENES

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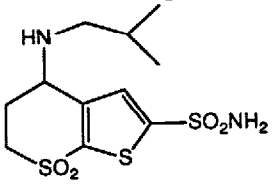
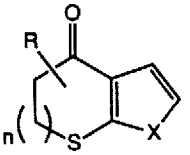
ABSTRACT: An intramolecular Diels-Alder retro Diels-Alder sequence is presented as a route to dihydrofurano[2,3-b]thiopyrans, thiepins, and thiophenes.

Compound **1** (MK-927) is a potent inhibitor of carbonic anhydrase II and when applied topically to the eye is effective at lowering intraocular pressure. Thus **1** is being developed as a potential therapeutic agent in the treatment of glaucoma.[1] Previous reports have described the syntheses of the precursor 5,6-dihydro-4H-4-oxothieno[2,3-b]thiopyran (n = 1) and thiepin (n = 2) ring systems (**2**) via an intramolecular Friedel-Crafts acylation.[2] Because of the interest generated by **1** a general synthesis of the corresponding furano analogs **3** was desired. A search of the literature revealed that the intramolecular Friedel-Crafts approach failed to produce compounds of type **3**.[3] In this paper, we wish to report on a convenient and practical synthesis of compounds of this general structure.

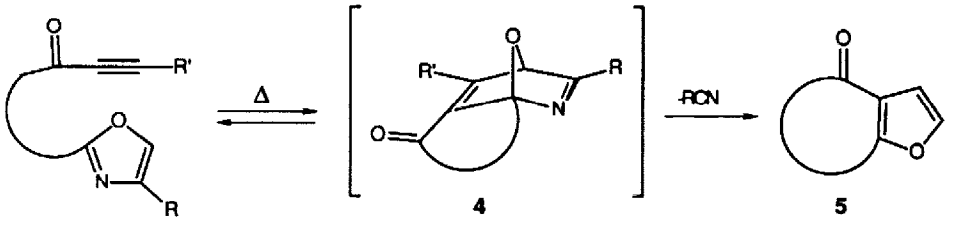


1



2 X=S
3 X=O

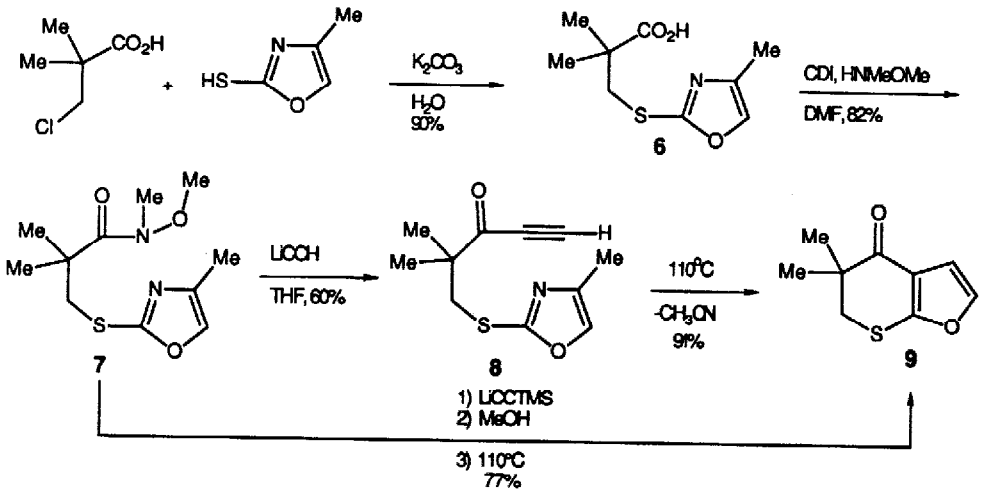
An appealing alternative to the Friedel-Crafts chemistry is the intramolecular version of the Diels-Alder reaction of an oxazole and an acetylene. (Scheme I). The initial bicyclic intermediate **4** is not isolated but instead undergoes a reverse Diels-Alder reaction with loss of R-CN to generate the fused furan derivative **5**. This process has been developed and utilized extensively by Jacobi and co-workers.[4] Theoretically, the tether can be of any length and incorporate atoms other than carbon.



4 **5**

Scheme I

For our purposes a sulfur atom was required in the connecting chain. A typical example is described below. Alkylation of 2-mercapto-4-methyl oxazole[5] wtih chloropivalic acid in water at room temperature gave a 90% yield of compound **6** (Scheme 2). Conversion of **6** to a Weinreb[6] type intermediate **7** proceeded smoothly (82%) in DMF with N,O-dimethylhydroxylamine and carbonyldiimidazole. The reaction of **7** with lithium acetylide ethylenediamine complex in THF gave, after aqueous work up, a 60% yield of acetylenic ketone **8**. In general the use of lithium trimethylsilyl acetylene followed by methanol workup to remove the trimethylsilyl group gave cleaner reactions and higher yields of acetylenic ketones. Ketone **8** was converted cleanly (91%) to furan **9** when heated in toluene at reflux for five hours.



Scheme 2

It was subsequently found that the three step conversion of amide **7** into furan **9** could be accomplished in one pot without isolation of the intermediate ketone(s).[7] The annulation has been extended to the 5 and 7 membered ring versions as well (Table 1).[8] In conclusion we have demonstrated the viability of this approach in the synthesis of various sulfur containing fused furan derivatives. The elaboration of these systems into suitable medicinal agents and their pharmacological properties will be reported elsewhere.

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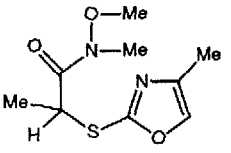
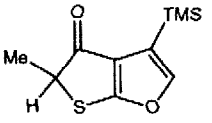
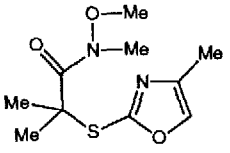
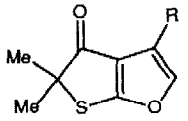
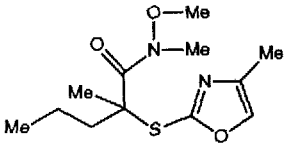
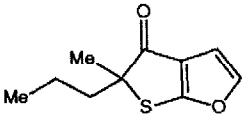
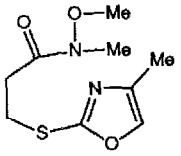
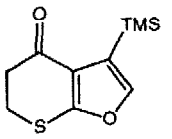
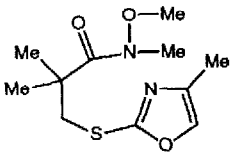
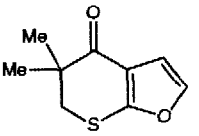
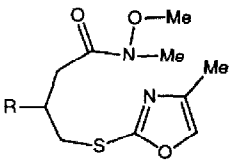
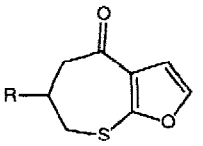
REFERENCES AND NOTES

(1) (a) M. F. Sugrue, P. Gautheron, J. Grove, P. Mallorga, H. Schwam, M. P. Vlader, J. J. Baldwin, G. S. Ponticello, ARVO, Sarasota, Florida, May 1-6, 1988. (b) E. A. Lippa, H. A. Von Deufer, H. M. Hofman, F. Brunner-Ferber Arch. Ophthalmol., in press. (c) R. Hennekes, et al Invest. Ophthalmol. Vis. Sci. 29(Suppl.), 82, (1988). (d) M. F. Sugrue, J. J. Baldwin, J. P. Springer, P. S. Anderson, M. E. Christy, P. Gautheron, J. Grove, P. Mallorga, G. S. Ponticello J. Med. Chem., submitted for publication.

Table I

Entry	Amide	Method [a]	Product [b]	Yield [c]
1		A		81%
2		A		R = TMS 85%
3		B		R = H 63%
4		B		74%
5		A		20% [9]
6		B		88%
7		B		R = H 58%
8		C		R = Me 50%

a) Method A : i. TMSCCLi, THF ii. Toluene reflux. Method B : i. TMSCCLi, THF ii. Methanol workup iii. Toluene reflux. Method C : i. HCCLi · EDA Complex , THF ii. Ethyl benzene, reflux. b) All new compounds were characterized by the appropriate spectral and analytical means. c) Yields refer to isolated and purified materials.

(2) (a) I. Degani, R. Fochi, G. Spunta Ann. Chim. (Rome) 58, 263 (1968). (b) P. Cagniant, D. Cagniant, Bull. Soc. Chim. Fr., 2172 (1966). (c) G. S. Ponticello, M. B. Freedman, C. N. Habecker, P. A. Lyle, S. L. Varga, M. E. Christy, W. C. Randall, J. J. Baldwin J. Med. Chem. 30, 591 (1987). (d) G. S. Ponticello, M. B. Freedman, C. N. Habecker, M. K. Holloway, J. S. Amato, R. S. Conn, J. J. Baldwin J. Org. Chem. 53, 9 (1988).

(3) P. Cagniant, G. Kirsch, D. Cagniant C. R. Hebd. Seances Acad. Sci. Ser. C, 284(8), 339 (1977).

(4) (a) P. A. Jacobi, T. Craig J. Am. Chem. Soc., 100, 7748 (1978). (b) P. A. Jacobi, D. G. Walker, I. M. A. Odeh J. Org. Chem., 46, 2065 (1981). (c) P. A. Jacobi, H. G. Selnick J. Am. Chem. Soc., 106, 3041 (1984). (d) P. A. Jacobi, C. S. R. Kaczmarek, U. E. Udodong Tetrahedron Lett., 25, 4859 (1984). (e) P. A. Jacobi, R. F. Frechette Tetrahedron Lett., 28, 2937 (1987). (f) P. A. Jacobi, M. Egbertson, R. F. Frechette, C. K. Miao, K. T. Weis Tetrahedron 44, 3327 (1988).

(5) C. K. Bradsher, W. J. Jones J. Org. Chem., 32, 2079 (1967).

(6) S. M. Weinreb, S. Nahm Tetrahedron Lett., 22, 3815 (1981).

(7) A typical procedure is described for entry 6. A solution of 10.08 g (102 mmol) of trimethylsilyl acetylene in 350 mL THF at 0° C was treated with 102 mL of a 1 **M** solution of LiHMDS. The solution was allowed to stir at 0° C for 5 minutes. A solution of 20.4 g (78 mmol) of amide **7** in 100 mL THF was then added and the reaction allowed to warm to room temperature for 0.5 hr. The reaction mixture was then poured into 1 L of water and extracted several times with ether. The ether layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude material was dissolved in 200 mL methanol and concentrated to effect desilylation. The crude ketone **8** was then taken up in 700 mL toluene and heated at reflux for 5 hr under an inert atomosphere. The reaction was cooled to ambient temperature, concentrated and chromatographed directly on silica gel using 9:1 hexane/ethyl acetate as eluent to give 12.7 g (88%) of furan **9** as a viscous oil. ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 2.1 Hz, 1H) 6.78 (d, J = 2.1 Hz, 1H) 3.17 (s, 2H) 1.30 (s, 6H; IR, $CHCl_3$ 2885, 1675, 1550, 1505 cm^{-1}; High resolution mass spec. calcd. for $C_9H_{10}O_2S$: 182.0241 Found: 182.0399.

(8) Physical and Spectral data for representative compounds: Amide **7** MP = 45° C; ^{1}H NMR $CDCl_3$ δ 7.33 (q, J = 1.2 Hz, 1H), 3.68 (s, 3H), 3.50 (s, 2H), 3.19 (S, 3H), 2.13 (d, J = 1.2 Hz, 1H), 1.38 (s, 6H); IR $CHCl_3$ 3000, 1645, 1500, 1460 cm^{-1}; High resolution mass spec. calcd. for $C_{11}H_{18}N_2O_3S$: 258.1038 Found: 258.1032. Entry 3 Amide: ^{1}H NMR $CDCl_3$ δ 7.45 (br s, 1H), 3.8 (s, 3H), 3.26 (s, 3H), 2.16 (br s, 3H), 1.63 (s, 6H); IR $CHCl_3$ 3150, 3000, 2960, 1605, 1480 cm^{-1}; High resolution mass spec calcd. for $C_{10}H_{16}N_2O_3S$: 244.1881 Found: 244.0872. Entry 3 Furan: ^{1}H NMR $CDCl_3$ δ 7.53 (d, J = 2.1 Hz, 1H), 6.64 (d, J = 2.1 Hz, 1H), 1.68 (s, 6H); IR $CHCl_3$ 3040, 3010, 2960, 1690, 1550, 1510 cm^{-1}; High resolution mass spec. calcd. for $C_8H_8O_2S$: 168.0221 Found: 168.0229.

(9) The low yield is apparently due to the instability of the intermediate acetylenic ketone which undergoes a competitive β-elimination of the mercapto oxazole moiety.

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