Tetrahedron Letters,Vol.24,No.42,pp 4507-4510,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

2. BORON TRIFLUORIDE ACTIVATED 3-THIAZOLINES. A VERSATILE SYNTHESIS OF THIOPHENES

Clifford N. Meltz and Robert A. Volkmann*

Central Research, Pfizer Inc.

Groton, Connecticut 06340

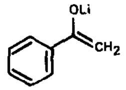
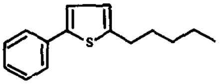
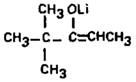
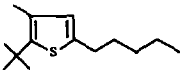
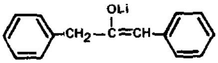
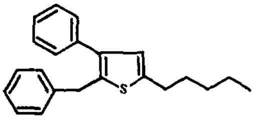
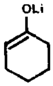
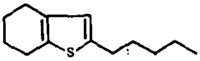
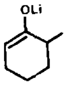
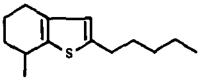
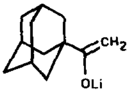
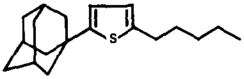
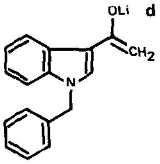
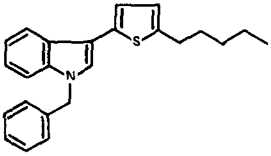
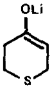
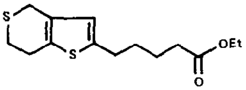
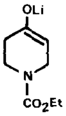
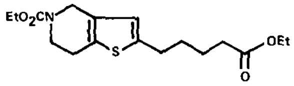
Summary: Thiazolidines generated by the addition of ketone enolates to boron trifluoride activated 2,2,5-trialkyl-3-thiazolines undergo a facile acid catalyzed conversion to di- and trisubstituted thiophenes.

Considerable effort has been devoted to the synthesis of thiophenes.[1] Most monosubstituted thiophenes can be easily obtained by direct thiophene substitution (i.e., via metallation[2] or electrophilic substitution[3] reactions). The synthesis of polysubstituted thiophenes, however, is more difficult and often involves both ring closure and aromatic substitution reactions.[4] In connection with our investigation into the reactions of Lewis acid activated imines, we have developed a novel synthesis which appears well suited for the construction of di- and trisubstituted thiophenes.

In the previous communication,[5] we examined the addition of a variety of nucleophiles to boron trifluoride activated 2,2,5-trisubstituted-3-thiazolines I.[6] The condensation of ketone enolates 2 was of particular interest since the thiazolidine products 3 contain an electrophilic carbonyl functionality in addition to the masked electron rich nitrogen and sulfur atoms. Acid treatment (10:1 TFA:H_2O) of crude 3, in fact, furnished cleanly thiophenes 4,[7,8] the formation of which formally involves thiazolidine ring hydrolysis, attack of the ketone by the liberated thiol and the concomitant elimination of ammonia and water.

With this methodology, two carbon atoms from the 3-thiazolines and two from the ketone enolates are incorporated into the thiophene ring. The availability of structurally diverse ketones provides significant flexibility in establishing two of the substituents (R_1 and R_2) on the thiophene ring. The third substituent (R) is established by the 5-substituent of the 3-thiazoline. While symmetrical ketones (entries 3, 4, 8 and 9) or ketones capable of enolizing in one direction (entries 1, 2, 6, 7) are well suited for this technique, other

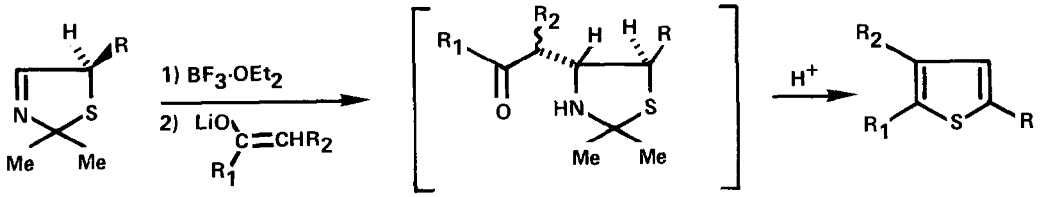
THIOPHENE SYNTHESIS

Entry	Lithium Enolate[a]	3-Thiazoline 1[b]	Thiophene	Yield[c]
1		R = $(CH_2)_4CH_3$		80%
2	 $CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\overset{OLi}{C}=CHCH_3$	R = $(CH_2)_4CH_3$		89%
3		R = $(CH_2)_4CH_3$		71%
4		R = $(CH_2)_4CH_3$		87%
5		R = $(CH_2)_4CH_3$		60%
6		R = $(CH_2)_4CH_3$		70%
7		R = $(CH_2)_4CH_3$		65%
8		R = $(CH_2)_4CO_2Et$		50%
9		R = $(CH_2)_4CO_2Et$		30%

[a] Formed by the treatment of the corresponding ketones with LDA (THF, -78°) [b] reference 6

[c] Yields are reported for chromatographically pure products and have not been optimized [d] reference 9

ketones (entry 5) can also be employed providing that one of the enolates is preferentially generated.



1 2 3 4

References and Notes

1. For the most recent review see: O. Meth-Cohn in "Comprehensive Organic Chemistry", Vol. 4, ed. P. G. Sammes. Pergamon Press, Oxford, 1979, p. 789.
2. B. J. Wakefield, "The Chemistry of Organolithium Compounds"; Pergamon Press, Oxford, 1974.
3. G. Marino, *Adv. Heterocyclic Chem.*, *13*, 235 (1971).
4. S. Gronowitz, *ibid*, *1* 1 (1963).
5. C. N. Meltz and R. A. Volkmann, *Tetrahedron Lett.*, 000 (1983).
6. R. A. Volkmann, J. T. Davis and C. N. Meltz, *J. Am. Chem. Soc.*, *105*, 000 (1983); M. Thiel, F. Asinger, K. Schmiedel, *Liebigs Ann. Chem.* *611*, 121 (1958); F. Asinger, H. Offermanns, *Angew. Chem. Int. Ed.* *Eng.* *6*, 907 (1967).
7. A typical procedure is illustrated in the formation of 2-pentyl-5-phenylthiophene (entry 1). To a THF solution (25 mL) at 0° containing 2,2-dimethyl-5-pentyl-3-thiazoline (1.40 g, 7.57 mmol) under a nitrogen atmosphere was added over a 1 min period boron trifluoride etherate (931 µl, 7.57 mmol). The solution was stirred for 1 hr at 0° and then cooled to -78°. In a separate flask, LDA was generated by the addition of BuLi (7.57 mmol) to a THF solution (20 mL) cooled to -78° containing diisopropylamine (1.058 ml, 7.57 mmol). This LDA solution was allowed to warm to ca. -25° and was recooled to -78° and stirred for 1 hr. A THF solution (5 mL) containing acetophenone (909 mg, 7.57 mmol) was added dropwise to the LDA solution and was stirred at -78° for 0.3 hr. The lithium enolate solution was then added quickly (ca. 10 sec) in one portion (*via* cannulation) to the BF_3 imine solution (-78°). The resultant solution was stirred at -78° for 2 hr, was quenched with AcOH (433

µl,7.57 mmol) and was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and extracted with aqueous $NaHCO_3$ and brine. The organic extract was dried ($MgSO_4$) and concentrated to afford crude adduct 3 which was dissolved in TFA (30 mL). Water (3 mL) was added and the solution was stirred for 2 hr (25°) and concentrated. The residue was dissolved in CH_2Cl_2 and extracted with aqueous $NaHCO_3$ and brine. The organic extract was dried ($MgSO_4$) and concentrated *in vacuo* to afford crude product which was passed through silica gel (1:1 hexane:CH_2Cl_2) to afford 1.39 g (80%) of product, mp 45-46°.

8. NMR and IR spectra were entirely consistent with the assigned structures and satisfactory combustion analyses were obtained.
9. We thank Dr. J. P. Dirlam for a generous supply of 1-benzyl-3-acetylindole (Brit. 869,775).

(Received in USA 20 June 1983)