USE OF MERCAPTOACETALDEHYDE DIMER IN A NOVEL THIENOANNELATION SEQUENCE. A SHORT SYNTHESIS OF TICLOPIDINE[1]

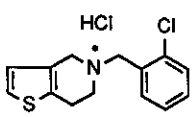
Owen W. Gooding* and Colin C. Beard

Institute of Organic Chemistry, Syntex Research, 3401 Hillview Avenue,
Palo Alto, CA 94304, USA

Abstract - A short synthesis of ticlopidine (**1**) was achieved by condensation of mercaptoacetaldehyde dimer (**2**) with piperidone (**3b**) in the presence of lithium diisopropylamide followed by dehydration.

The tetrahydroisoquinoline analog N-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (ticlopidine) (**1**) is a medicine widely prescribed for prevention of stroke and other cardiovascular/cerebrovascular conditions caused by platelet aggregation.[2] Ticlopidine and its analogs have been prepared[3] by methods generally applicable to isoquinolines,[4] employing various ring annelation methodologies to build the 6-membered, nitrogen-containing ring onto the aromatic thiophene ring. Of these the Pommeranz-Fritz[3c] and the Pictet-Spengler[5] methods are the most commonly used.

We envisioned a potentially shorter ticlopidine synthesis via thienoannelation of piperidone (**3b**) employing a mercaptoacetaldehyde synthon. Sequential aldol condensation/nucleophilic sulfur addition/dehydration would give ticlopidine directly. Mercaptoacetaldehyde is available only as its dimer, 2,5-dihydroxy-1,4-dithiane (**2**). Dimer (**2**) has been used for thiophene synthesis by reaction with: (1) activated nitriles affording 2-aminothiophenes (Gewald reaction),[6] (2) α,β-unsaturated aldehydes affording 2,5-dihydrothiophene-3-carboxaldehydes,[7a,b] or α,β-unsaturated ketones affording 3-acyl-2,5-dihydrothiophenes following dehydration,[7c] and (3) vinylphosphonates affording 3-carboxylated 2,5-dihydrothiophenes.[8] We report here the use of dimer (**2**) in a novel thienoannelation sequence resulting in a one-pot synthesis of ticlopidine.



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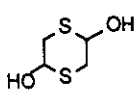

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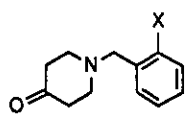
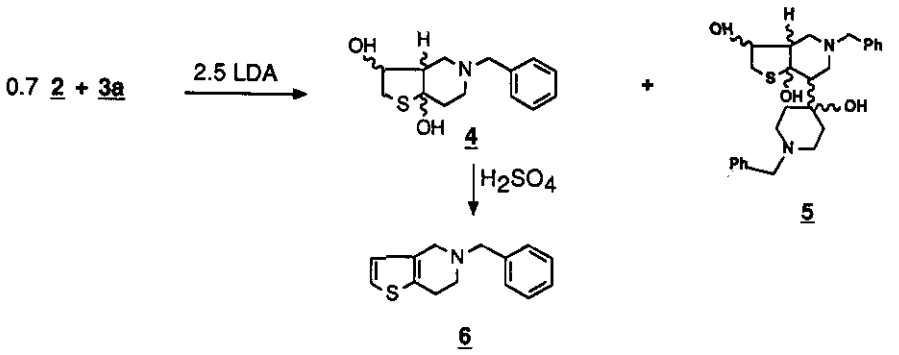


3a X = H

3b X = Cl

In initial experiments a mixture of commercially available piperidone (**3a**) (1 equiv.) and dimer (**2**) (0.7 equiv.) in THF at -20 °C was treated dropwise with lithium diisopropylamide mono(tetrahydrofuran) complex (LDA) (2.5 equiv.) (Scheme 1). After 5 h at this temperature an aqueous workup followed by silica gel chromatography afforded: recovered **3a** (13%), diol (**4**) as a diastereomeric mixture (59%), and side product (**5**) (20%).[9] Dehydration was

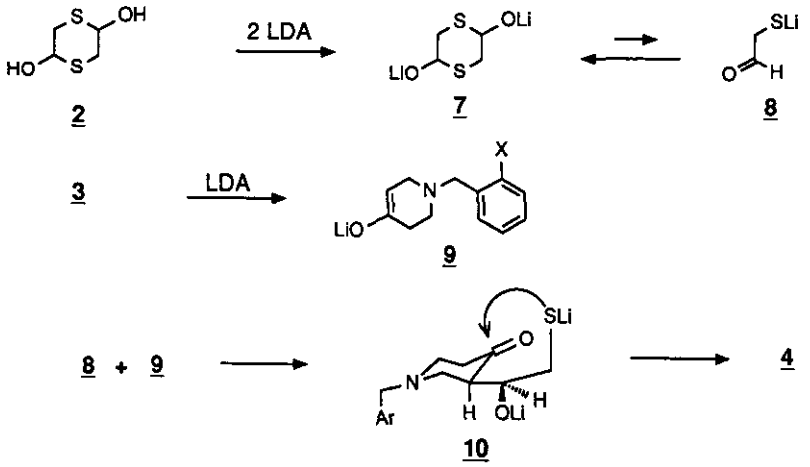
Scheme 1



accomplished in 85% yield by treatment of diol (**4**) with 10% w/w H_2SO_4 (60 °C, 4 h) affording deschloroticlopidine (**6**), isolated as the free base. Similar results were obtained when the procedures were repeated using piperidone (**3b**).[10]

A plausible mechanism involves an equilibrium between the dilithiated dimer (**7**) and monolithiated mercaptoacetaldehyde (**8**) (Scheme 2). The free aldehyde (**8**) present in the mixture could then condense with the piperidone enolate (**9**) to form the reactive intermediate (**10**) which would undergo rapid intramolecular nucleophilic addition affording **4** as the predominant product. The side product (**5**) could arise from aldol condensation of enolate (**9**) with ketone (**3**) prior to the desired condensation with the free aldehyde (**8**).[11,12]

Scheme 2



Efforts to optimize the reaction conditions were met with limited success. The bases $LiNH_2$, NaOEt, NaH, LiH, and potassium t-butoxide all gave slower reaction or caused dimer decomposition. Lithium hexamethyldisilazide gave results comparable to LDA and so offered no advantage. The use of other dipolar, aprotic solvents gave inferior results. All permutations on order of addition, including concomitant addition of reactants to LDA, caused reduced yields. Varying temperature from -78 °C to reflux showed that 0 °C was optimum, giving complete reaction in 1 hour. By omitting the isolation of diol (**4**) the two steps were successfully combined into a one-pot procedure without significant reduction in yield. The optimized experimental procedures for the synthesis of ticlopidine are given below.

EXPERIMENTAL

N-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**1**); One-pot procedure:

A mixture of N-(2-chlorobenzyl)-4-piperidone (10.0 g, 44.7 mmol), mercaptoacetaldehyde dimer (4.77 g, 31.3 mmol), and 450 ml of dry THF was cooled to 0 °C under nitrogen. To this stirred suspension was added lithium diisopropylamide mono (tetrahydrofuran) complex (74.7 ml, 112 mmol, 1.5 M in cyclohexane) dropwise over a 5 min period. Stirring was continued for 70 min at which time reaction was judged complete by tlc (silica gel, 75:25 ethyl acetate/hexane). The yellow solution was quenched with 50 ml of saturated aqueous ammonium chloride solution and the cooling bath was removed. After warming to 20 °C the solution was recooled to 0 °C and treated dropwise with concentrated sulfuric acid (15 ml). This mixture was then heated to reflux and the THF was removed by distillation. The residue was diluted with water (425 ml), cooled to 20 °C, and basified to pH = 9 with 50% sodium hydroxide solution. The free base was then extracted with ether (3 x 150 ml) and the extracts were dried (K_2CO_3) and concentrated in vacuo to 13.2 g of crude product. Chromatography over silica gel (150 g) using 12:88 ethyl acetate/hexane as eluent afforded 6.77 g of pure ticlopidine base as a clear oil (58%). The hydrochloride salt was obtained by treatment with anhydrous HCl in methanol. This material had physical and spectral properties identical to an authenic sample of ticlopidine obtained from Syntex Research and had spectral properties consistent with those reported.[3a]

REFERENCES

1. Contribution No. 831 from the Institute of Organic Chemistry, Syntex Research.
2. (a) J. J. Thebault, C. E. Blatrix, J. F. Blanehard, and E. A. Panak, J. Int. Med. Res., 1977, 5, 405, and those cited therein. (b) K. F. Mortel, J. L. Funk, J. S. Meyer, and L. Vanek, Drug Invest., 1991, 3, 61, and those cited therein.
3. (a) K. Satake, T. Imai, M. Kimura, and S. Morosawa, Heterocycles, 1981, 16, 1271. (b) J. P. Maffrand and R. Boigegrain, Heterocycles, 1979, 12, 1479. (c) J. P. Maffrand and F. Eloy, J. Heterocycl. Chem., 1976, 13, 1347.
4. For a review see: S. W. Schneller, Int. J. Sulfur Chem., 1972, B, 7, 309.
5. E. Braye, U.S. Patent 4,127,580, 1978 (Chem. Abstr., 1978, 90, 87431w).
6. S. Gronowitz, "Thiophene and Its Derivatives, Part 1", Wiley, New York, 1985, Chapter 1, pp. 42-59.
7. (a) W. Sucrow and H. W. Muller, Z. Naturforsch., 1982, 37b, 851. (b) European Patent 0234688A, 1987 (Chem. Abstr., 1987, 108, 150300k). (c) J. F. Honek, M. L. Mancini, and B. Belleau, Synth. Commun., 1984, 14, 483.
8. J. M. McIntosh and R. A. Sieler, J. Org. Chem., 1978, 43, 4431.
9. Physical data for compound 4: Ir (neat) 3375, 2934 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 7.33-7.23 (m, 5H), 4.28 (d, J = 4.5 Hz, 1H), 4.00-3.60 (br s, 2H exchanges with D_2O), 3.60-3.46 (q, AB, 2H), 3.25-3.20 (dd, J = 4.5, 12.1 Hz, 1H), 3.18-3.14 (d, J = 11.6 Hz, 1H), 2.83-2.79 (m, 1H), 2.75-2.68 (ddd, J = 1.9, 5.3, 6.0 Hz, 1H), 2.55-2.49 (dd, J = 5.3, 11.6 Hz, 1H), 2.36-2.27 (m, 1H), 2.10-2.04 (m, 2H), 1.63 (t, J = 11.6 Hz, 1H); ms (m/z) 266 (M^++1), 265 (M^+), 232, 218, 188, 174, 91; Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.42; H, 7.25; N, 5.28.
10. Obtained by alkylation of 4-piperidone, commercially available as the hydrate hydrochloride (Aldrich), with o-chlorobenzyl chloride in the presence of triethylamine in 1,2-dichloroethane (reflux, 24 h, 79%). Physical data for compound (**3b**): Ir (KBr pellet) 1715, 1330, 1135, 760 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ: 7.53-7.19 (m, 4H), 3.74 (s, 2H), 2.83 (t, J = 6.2 Hz, 4H), 2.47 (t, J = 6.2 Hz, 4H); ms (m/z) 223 (M^+), 125, 112, 98; Anal. Calcd for $C_{12}H_{14}NOCl$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.35; H, 6.53; N, 6.13.
11. J. March. "Advanced Organic Chemistry," 3 rd Ed., Wiley, New York, 1985, pp. 829-835.
12. Competition from the ketone condensing with itself appears to limit the scope of this reaction. Attempts to apply these reaction conditions to cyclohexanone invariably lead to complex mixtures of polymeric materials as judged by nmr spectroscopy. Therefore, this reaction seems to be limited to enolizable carbonyl compounds which are stable to the rather harsh reaction conditions (0 °C, 1 h).

Received, 10th June, 1991