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APPLICATION OF THE CYANURATE-ISOCYANURATE REARRANGEMENT TO AMINE SYNTHESIS: PREPARATION OF 2-(2-THIENYL)ETHYLAMINE

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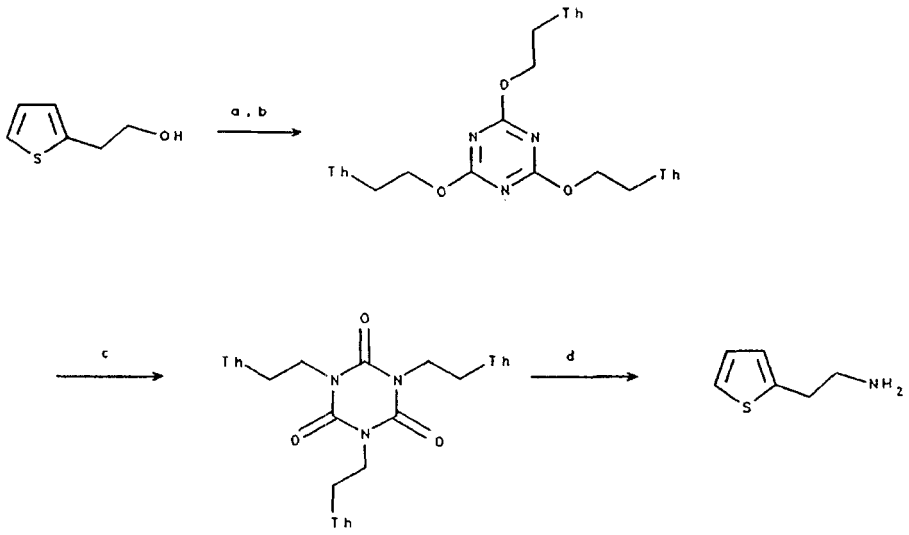
Abstract: This communication describes a new method for preparation of 2-(2-thienyl)ethylamine, an important pharmaceutical intermediate. The method is based on the O-to-N migration of an alkyl group via cyanurate-isocyanurate rearrangement.

2-(2-Thienyl)ethylamine is a key component of a myriad of biologically active materials. From relatively simple isothiocyanates and sulfonamides to highly elaborated 6,7-dihydro-4H-pyrimido[6,1-a]thieno[3,2-c]pyridin-4-ones, these derivatives possess analgesic,[1] antibacterial,[2] antifungal,[2] antiglaucoma,[3] antihypertensive,[1a,4] antiobesity,[5] and antiulcer activity;[6] they are also potent blood platelet aggregation inhibitors,[7] cardiac vasodilators,[8] 5-lipoxygenase inhibitors,[9] thromboxane A_2 receptor agonists,[10] and CNS agents.[11]

2-(2-Thienyl)ethylamine is available from thiophene via the alcohol,[12] nitrile,[13] 2-carbon amide,[14] 3-carbon amide,[15] and unsaturated nitro compound.[16] Of these, only the alcohol can be converted to 2-(2-thienyl)ethylamine without a functional group oxidation or reduction. However, the available amine syntheses from the alcohol are unattractive from a cost, safety, or environmental perspec-

tive. Thus, ammonia displacement of a suitable leaving group (Cl, Br, OMs, OTs) is problematic: overalkylation produces secondary and tertiary amines. Classical solutions to this overalkylation problem involve the use of "ammonia equivalents" such as sodium or potassium azide, potassium phthalimide (Gabriel Synthesis), or hexamethylenetetramine (Delepine Reaction). Synthesis by the Gabriel route necessitates disposal or costly recycle of by-product phthalic acid; synthesis by the Delepine route necessitates disposal of large volumes of by-products ammonia and formaldehyde. We now report a novel method for the alcohol-to-amine conversion based on an imidate-to-amide rearrangement.[17] Reaction of the alkoxide with commercially available and inexpensive cyanuric chloride affords a cyanurate. Rearrangement of the cyanurate affords an isocyanurate.[18] Finally, hydrolysis of the isocyanurate liberates 2-(2-thienyl)ethylamine.[19] Theoretically, the only byproducts of the overall conversion are chloride salts and carbon dioxide!



Th = 2-thienyl

a. −70°C, n-BuLi, THF-hexanes
b. 25°C to rfx, cyanuric chloride, THF-hexanes
c. 230°C, $n\text{-}Bu_4PBr$
d. rfx, NaOH, n-hexanol, 77.7% from 2-(2-thienyl)ethanol

Scheme 1. Synthesis of 2-(2-Thienyl)ethylamine

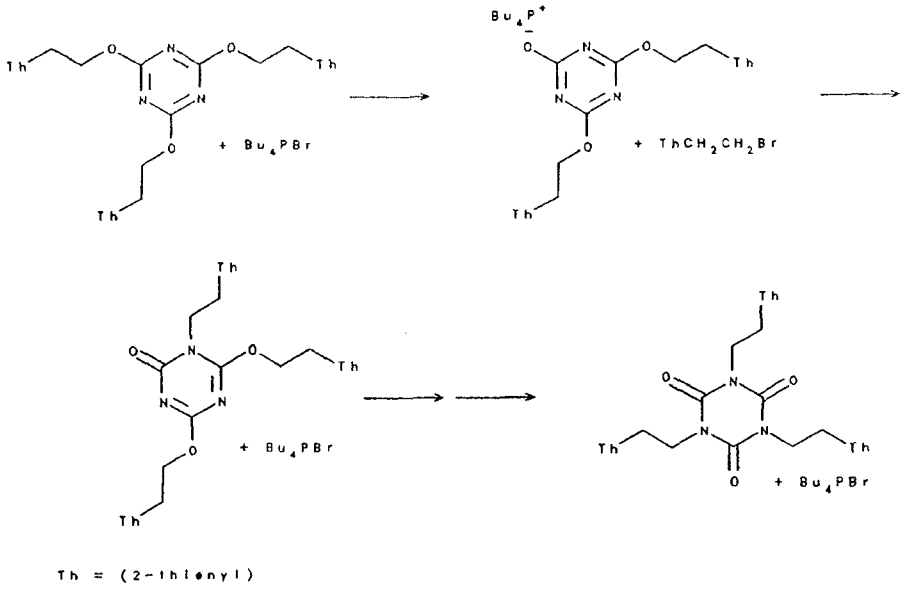
The cyanurate formation is efficient when the alkoxide-cyanuric chloride ratio is 3:1. We suggest that chloride displacement becomes more difficult as the ring becomes more electron rich [i.e., the reactivity order is $C_3N_3Cl_3$ > $C_3N_3Cl_2(OR)$ > $C_3N_3Cl(OR)_2$]. The last displacement is slow at 25°C but can be completed during the solvent recovery distillation. After a water wash to remove lithium chloride, the crude cyanurate can be recrystallized (90% yield based on *n*-butyllithium, alcohol, or cyanuric chloride) or used directly in the next step.

We were concerned about competitive formation 2-vinylthiophene at the high temperatures (250-270°C) typically required for cyanurate-isocyanurate rearrangement. Catalysis of the rearrangement by alkyl iodides is known. We now report that quaternary ammonium and phosphonium bromides are superior catalysts; rearrangement is observed at temperatures as low as 125°C. A mechanism for the tetrabutylphosphonium bromide catalyzed rearrangement is presented in **Scheme 2.**

Chloride catalyzed rearrangement is less efficient. No isocyanurate is observed when the crude cyanurate-lithium chloride mixture obtained after tetrahydrofuran-hexanes recovery is heated to 250°C. Lower yields of isocyanurate are obtained when lithium chloride is present during the tetrabutylphosphonium bromide catalyzed rearrangement.

Our initial efforts focused on recovery of the catalyst and isolation/purification of the isocyanurate. The crude isocyanurate-catalyst mixture can be slurried in ethyl ether. The insoluble catalyst is then filtered and the isocyanurate isolated from the mother liquors. While tetrabutylammonium bromide recoveries are consistently low, tetrabutylphosphonium bromide recoveries are >90%. 1,3,5-*tris*-(2-(2-Thienyl)ethylisocyanurate can be isolated from the mother liquors in 75-82% yield.

In more recent work, complete conversion of the cyanurate is observed after 2 h at 230°C using just 0.25 mol% tetrabutylphosphonium bromide. At this low catalyst loading, the crude isocyanurate-phosphonium bromide mixture can be directly hydrolyzed.



Scheme 2. A Mechanism for the Tetrabutylphosphonium Bromide Catalyzed Cyanurate-Isocyanurate Rearrangement

Isocyanurate hydrolysis proceeds via: 1) ring opening and decarboxylation to a biuret, 2) liberation of one amine and decarboxylation to a urea, and 3) hydrolysis of the urea. Thus, urea hydrolysis dictates the vigorous conditions required for efficient amine recovery (relux with granular sodium hydroxide in ethanol, *n*-butanol, or *n*-hexanol). In an optimal workup procedure, the suspension is cooled, the amine converted to the hydrochloride salt, and the alcohol recovered by distillation of the alcohol-water azeotrope. Basification, extraction, and distillation affords 2-(2-thienyl)ethylamine as a colorless liquid. Carrying through crude cyanurate and crude isocyanurate, we have converted 2-(2-thienyl)ethanol to 2-(2-thienyl)ethylamine (>99% GC) without an isolation in 77.7% overall yield.

Experimental:

Materials. 2-(2-Thienyl)ethanol (Fluka, >98%) was fractionally distilled at 0.4 mm Hg (b.p. 70-72°C). Cyanuric chloride (Fluka, >98%) was recrystallized from hexanes. All other materials were used as received. All reactions were conducted under an atmosphere of dry N_2.

2,4,6-*tris*-(2-(2-Thienyl)ethyl)cyanurate. *n*-Butyllithium (60 mL of 1.6 M in hexanes, 96.0 mmol) was added dropwise over 49 min at -70°C to a solution of 12.306 g (96.0 mmol) 2-(2-thienyl)ethanol in 50 mL dry THF. The alkoxide solution was stirred at -70°C for 15 min then warmed to -30°C. A solution of 5.901 g (32.0 mmol) cyanuric chloride in 50 mL dry THF was added dropwise at -20 to -30°C over 7 min. After the addition was complete, the mixture was allowed to warm to 25°C and stirred overnight.

The solvent was removed in vacuo. The residue was separated between 100 mL H_2O and 100 mL ethyl acetate. The aqueous layer was extracted with an additional 50 mL ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 14.437 g (98.2%) beige solid.

The solid was recrystallized from methanol (hot filter) to afford 13.241 g (90.0%) of short colorless needles, m.p. 85°C; NMR ($CDCl_3$) δ 3.30 (t,2H,CH_2C), 4.60 (t,2H,CH_2O), 6.89-6.95 (m,2H,=CH), 7.15 (dd,1H,=CHS).

1,3,5-*tris*-(2-(2-Thienyl)ethyl)isocyanurate. A mixture of 1.000 g (6.53 mmol) recrystallized cyanurate and 0.679 g (2.00 mmol) tetrabutylphosphonium bromide was heated in a sealed tube at 125°C for 44 h. After cooling to 25°C, the residual solid was slurried in 50 mL ethyl ether then suction filtered. The precipitate was washed with fresh ethyl ether then dried in vacuo to afford 0.611 g (90.0% recovery) of tan solid. The combined mother liquors were concentrated in vacuo to afford 0.947 g of orange syrup.

The syrup was purified by radial chromatography on silica gel. Ethyl acetate (40%) in hexanes eluted the isocyanurate. The eluent was concentrated in vacuo to afford 0.799 g (82.0%) of beige solid, m.p. 72-75°C; NMR ($CDCl_3$) δ 3.13

(dd,2H,CH_2C), 4.14 (dd,2H,CH_2N), 6.86 (m,1H,=CH), 6.94 (dd,1H,=CH), 7.17 (dd,1H,=CHS). This material can also be recrystallized from methanol.

2-(2-Thienyl)ethylamine. A mixture of 12.000 g (78.3 mmol) recrystallized isocyanurate, 7.833 g (0.196 mol) granular sodium hydroxide, and 30 mL *n*-butanol was refluxed for 72 h. The *n*-butanol was then recovered by distillation. The pot was cooled and 30 mL H_2O added. The layers were separated and the aqueous layer extracted with 10 mL toluene twice. The toluene was recovered from the combined organic layers by distillation. The residual oil was distilled at 3 mm Hg to afford 8.267 g (83.0%) of 2-(2-thienyl)ethylamine, b.p. 84.5-86°C; NMR ($CDCl_3$) δ 1.14-1.27 (br,2H,NH_2), 2.93-3.04 (m,4H,CH_2), 6.83 (dd,1H,=CH), 6.94 (dd,1H,=CH), 7.15 (dd,1H,=CHS).

2-(2-Thienyl)ethylamine (no isolations). *n*-Butyllithium (420 mL of 1.6 M in hexanes, 0.672 mol) was added dropwise at -70°C to a mixture of 86.144 g (0.672 mol) 2-(2-thienyl)ethanol in 200 mL dry THF. The resulting alkoxide solution was warmed to 25°C and a solution of 41.308 g (0.224 mol) cyanuric chloride in 200 mL dry THF was added dropwise at 25-30°C over 13 min.

The THF and hexanes were recovered by distillation. The residue was cooled and separated between 100 mL H_2O and 100 mL toluene. The aqueous layer was extracted with an additional 25 mL toluene. Toluene was recovered by distillation from the combined organic layers.

Tetrabutylphosphonium bromide (0.570 g, 0.250 mol%) was added to the residual clear, light brown oil and the mixture was heated at 230°C for 2.5 h.

The mixture was cooled then 300 mL *n*-hexanol and 59.14 g (1.48 mol) granular sodium hydroxide were added. The resulting suspension was refluxed for 2.5 h.

The mixture was cooled and 175 mL 12 N HCl was added dropwise at 25-30°C. *n*-Hexanol was recovered by distillation as the H_2O azeotrope (b.p. 90-94°C). The suspension was cooled and basified by addition of 50% NaOH at 25-30°C. Toluene (75 mL) was added and the layers separated. The aqueous layer was extracted with an additional 25 mL toluene. Toluene was recovered by

fractional distillation from the combined organic layers. The residual oil was distilled at 36 mm Hg to afford 66.43 g (77.7%) of colorless liquid, b.p. 113-117°C.

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