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An Efficient Synthesis of 2-Ethyl-7-chloro-4-methylthieno[4,3,2-e,f][3]benzazepine (SK&F 106686) via Bromomethylation of 2-Ethyl-5-chlorobenzo[b]thiophene

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AN EFFICIENT SYNTHESIS OF 2-ETHYL-7-CHLORO-4-METHYLTHIENO[4,3,2-e,f][3]BENZAZEPINE (SK&F 106686) *VIA* BROMOMETHYLATION OF 2-ETHYL-5-CHLOROBENZO[b]THIOPHENE

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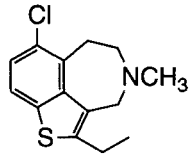
Abstract: *The synthesis of 2-ethyl-3-bromoethyl-5-chlorobenzo[b]thiophene (**6**) is described using a unique phase transfer catalyzed bromoethylation of 2-ethyl-5-chlorobenzo[b]thiophene (**5**). Compound **6** was converted in six steps and in 55% overall yield to the angiotension II antagonist, SK&F 106686 (**1**).*

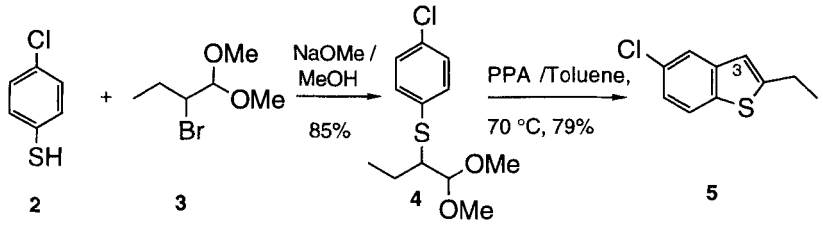
Antagonists of postjunctional vascular α_1/α_3 adrenoceptors (angiotension II receptors) on smooth muscle tissue have been indicated for treating prostatic hypertrophy, peripheral vascular disease, congestive heart failure, and hypertension.[1] In that regard, an intense effort was mounted to develop an efficient synthesis of 2-ethyl-7-chloro-4-methylthieno[4,3,2-ef][3]benzazepine SK&F 106686 (**1**), which has demonstrated pharmacological activity as an angiotension II antagonist.



(1) (SK&F 106686)

The original Medicinal Chemistry synthesis of **1** required 11 steps, starting from 4-chlorothiophenol, furnishing **1** in 12% overall yield. A much more efficient and direct approach envisioned developing a new synthesis starting with the readily available 2-ethyl-benzo[b]thiophene (**5**) which we have been able to synthesize in two steps from 4-chlorothiophenol (**2**) and 2-bromobutyraldehyde dimethyl acetal[2] (**3**) (Scheme I). Incorporation of a halomethyl functionality at the 3-position of **5** would provide a facile access to **1**.

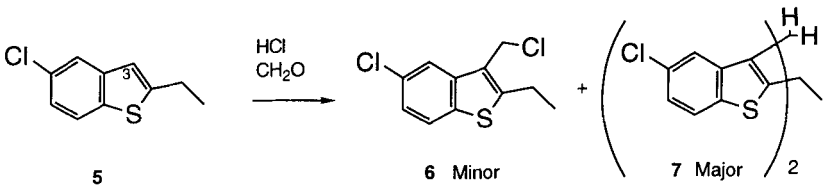
Scheme I

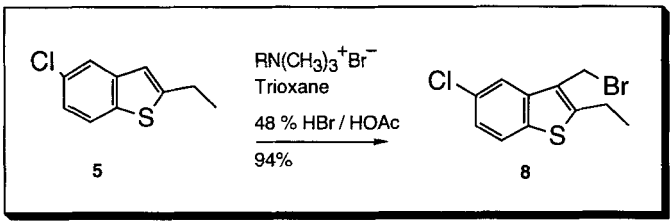


There is ample literature precedent for synthesis of 3-halomethyl-2-unsubstituted-benzo[b]thiophenes which are normally accessible by α-halogenation of the parent 3-methyl compound[3a,b] or alternatively by chloromethylation of the parent benzo[b]thiophene.[3c] We felt that any attempt to selective halogenate the 3-methyl group of 2-ethyl-3-methyl-5-chlorobenzo[b]thiophene would have a low probability of success because of the anticipated similarity in reactivities of the two alkyl substituents. Since C–3 of the benzo[b]thiophene parent ring system is relatively electron rich,[4] electrophilic halomethylation at that site would be a more appropriate alternative. However, when chloromethylation was attempted on 2-ethyl-3-chlorobenzo[b]thiophene (**5**), only the di-substituted methane **7** could be obtained under a variety of chloromethylating conditions (Scheme II). Evidently,

the benzylic cation derived from **6** competes more effectively for **5** than does the chloromethylating agent.

Scheme II

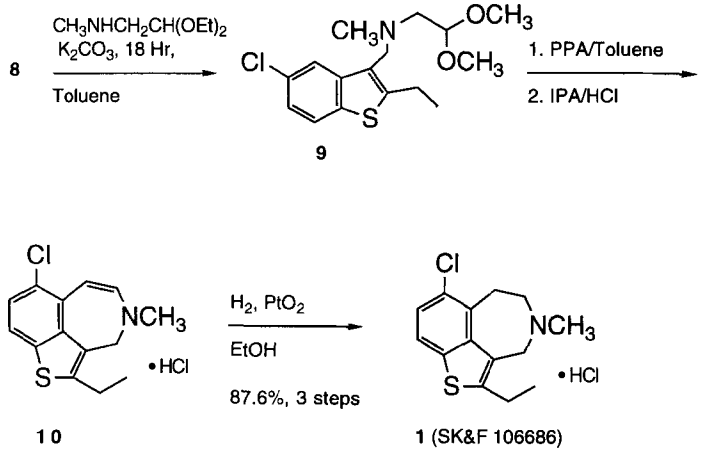




With the failure of chloromethylation to provide useful quantities of **6**, we were intrigued by the work of Mitchell[5] who reported excellent results for the bromomethylation of certain aromatic compounds using phase transfer catalysis. To our delight, when bromomethylation of **5** was conducted using trioxane in 48% HBr / HOAc employing myristyl or cetyl trimethylammonium bromide as phase transfer catalysts, nearly quantitative yields of **8** were consistently provided in various laboratory and reactor sizes up to 200 L scale.[6,7] The reaction did not proceed without catalyst being present and was less effective with other phase transfer catalysts. With 2-ethyl-3-bromomethylbenzo[b]thiophene (**8**) now in hand, we turned our attention toward the synthesis of **1** as outlined in Scheme III.

The 2-ethyl-3-bromomethylbenzo[b]thiophene (**8**) was aminated in 82% yield with methylaminoacetaldehyde dimethyl acetal in toluene to form methyl-

Scheme III



aminobenzo[b]thiophene **9**. Acetal **9** was cyclized to benzazepine **10** with PPA in toluene and isolated as a stable alcoholated hydrochloride salt. The resulting benzazepine **10** was hydrogenated over platinum in ethanol to yield 2-ethyl-7-chloro-4-methylthieno[4,3,2-e,f][3]benzazepine (**1**) (SK&F 106686), as the hydrochloride salt in 87.6% over 3 steps.

In conclusion, we have demonstrated a concise (5 steps) and convenient synthesis of SK&F 106686 in 55% overall yield from 4-chlorothiophenol. This methodology employs a novel phase transfer catalyzed bromomethylation of 2-ethyl-3-chlorobenzo[b]thiophene (**5**) and offers a viable pathway for the synthesis of many other previously not readily accessible benzo[b]thiophenes.

Experimental section

2-(4-Chlorophenylthio)butyraldehyde Dimethyl acetal (4). A degassed solution of sodium methoxide in methanol (25% solution, 413 g, 1.91

mol) was added to a degassed cooled (–10 °C) of 96.5% pure 4-chlorothiophenol (**2**) (250 g, 1.68 mol) in toluene (1.50 L) and DMF (125 mL) at such a rate that the reaction temperature did not exceed 0–5 °C. A degassed solution of 2-bromobutyraldehyde dimethylacetal (**3**)[2] (420.8 g, 2.0 mol) in toluene (500 mL) was then added at such a rate that the reaction temperature did not exceed 10 °C. Sodium iodide (26.0 g, 0.17 mol) was now added in one portion. All volatiles were then distilled under nitrogen at atmospheric pressure until the pot temperature reached 110 °C. The residual solution was refluxed 3 h and cooled to 0–5 °C. Deionized water (1.0 L) was added at such a rate that the temperature did not exceed 15 °C. The aqueous layer and brown interface material were discarded and the organic phase extracted with deionized water (2 x 1.25 L) and brine solution (1.25 L). The organic phase was concentrated by distillation *in vacuo* (~ 20 mm) until a pot temperature of 174 °C was reached. The pot residue, containing desired product, was 931.2 g of pale-yellow oil, 90.6% purity (*w/w* GC assay), 84.9% yield and was normally used as obtained: colorless oil [b.p. 112 °C (0.05 torr)]; ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 2H), 7.25 (m, 2H), 4.31 (m, 1H), 3.40–3.38 (*J*=12.3 Hz, 6H), 3.10–3.05 (m, 1H), 1.86–1.80 (m, 1H), 1.59–1.48 (m, 1H), 1.09–1.05 (t, *J*=7.4 Hz, 3H). MS (CI)/NH_3 *m/e* 260 $(M)^+$, 229 $(M + H - CH_3OH)^+$, 214 $[Cl\text{-}Ph\text{-}SC(CH_2CH_3)=C\text{-}NH_3]^+$, 75$[CH(OCH_3)=OCH_3]^+$; Anal. Calcd. for $C_{12}H_{17}ClO_2S$: C, 55.27; H, 6.57; Cl, 13.59, S, 12.30. Found C, 55.17; H, 6.44; Cl, 13.50; S, 12.14.

2-Ethyl-5-chlorobenzol[b]thiophene (5). A mixture of polyphosphoric acid (2.5 kg) and toluene (2.55 L) was heated to 70 °C under a nitrogen atmosphere and a solution of 2-(4-chlorophenylthio)butyraldehyde dimethyl acetal (**4**) (929.2 g, 92.6% purity by *w/w* GC assay, 3.3 mol) was added in one portion.

The two phase reaction mixture was heated to 105–110 °C for ~6 h. The reaction mixture was cooled to 55 °C and deionized water (40.0 L) added over 16 minutes at such a rate that the temperature did not exceed 75 °C. The mixture was cooled to 15 °C and neutralized by the addition of concentrated NH_4OH (3.8 L) The organic phase was separated and washed with 1 : 1 saturated brine, deionized water (2 x 4.6 L), and filtered. The organic phase, which gave a 82.9% solution assay, was concentrated *in vacuo* and the residue distilled under vacuum using a steam heated condenser. The fraction boiling at 120–143 °C (1.0–1.5 mm Hg) was collected to afford 2-ethyl-5-chorobenzo[b]thiophene (**5**) (565.9 g, 90.5% purity *w/w* GC assay, 2.88 mol, 79% yield) as a yellow oil that solidified on cooling and was used as obtained for the next step. If desired, the product **5** may be further purified by recrystallization from 2-propanol: white solid, m.p. 51–52 °C and b.p. 95–105 °C (0.5 torr); ^{1}H NMR ($CDCl_3$) δ 7.66–7.63 (m, 2 H), 7.21 (dd, *J*=2.0, 8.5 Hz, 1H), 6.94 (s, 1H), 2.93 (q, *J*=7.5 Hz, 2H), 1.37 (t, *J*=7.5 Hz, 3H); IR (KBr) 3422, 3000–3100, 2800–3000, 1580, 1560, 1435, 1416, 1077, 883, 803, cm^{-1}; MS (CH_4) *m/e* 197 $(M+H)^+$, 225 $(M+C_2H_5)^+$ 181, 145; Anal. Calcd. for $C_{10}H_9ClS$: C, 61.06; H, 4.61; Cl, 18.02, S, 16.30. Found C, 61.00; H, 4.54; Cl, 18.04; S, 16.06.

2-Ethyl-5-chloro-3-bromomethylbenzo[b]thiophene (6). In a 12 L, round-bottomed, 3-necked flask equipped with a mechanical stirrer under nitrogen flow, was added 2.25 L of 48% hydrobromic acid and 0.26 L of acetic acid. The 5-chlorobenzo[b]thiophene (**5**) (563 g, 2.6 mol) was dissolved in 0.26 L of acetic acid and was added to the 12 L reaction flask bulkwise. To this suspension was added in one portion 1,3,5-trioxane (432 g, 4.66 mol) and the cetyl or myristyltrimethylammonium bromide (18.9 g, 0.05 mol). The suspension was

allowed to stir 36 h after which time TLC (100% hexanes) showed predominantly the desired product with very little starting material remaining. Water (2 L) was added and the suspension was filtered, washed with water, and dried under vacuum to yield 780 g of 91% pure solid product (2.44 mol, 94% yield); m.p. 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 7.71–7.66 (m, 2H), 7.29–7.25 (m, 1H), 4.65 (s, 2H), 2.96 (q, *J*=7.6 Hz, 2H), 1.38 (t, *J*=7.6 Hz, 3H); IR (KBr) 2971, 2931, 1583, 1559, 1453, 1419, 1202, 1142, 1079, 869, 839, 799, 594, 557 cm^{-1}; MS (CI) *m/e* 289 $(M+H)^+$; Anal. Calcd. for $C_{11}H_{10}BrClS$: C, 45.62; H, 3.48; S, 11.07. Found C, 45.62; H, 3.47; S, 11.13.

2-Ethyl-5-chloro-N-methyl-N-(2,2-dimethoxy)ethyl-3-benzo[b] thiophenylmethylamine (9). In a 100 mL reaction flask containing 5.0 g (36 mmol, 2.1 eq) of potassium carbonate and 43 mL of toluene was dissolved 2-ethyl-3-bromomethyl-5-chlorobenzo[b]thiophene (**6**) (5.0 g, 17 mmol) and methylaminoacetaldehyde dimethyl acetal (2.26 g, 19 mmol). The suspension was stirred at room temperature 18 h after which time TLC (20% ethyl acetate / hexanes) showed the absence of starting material. The reaction mixture was quenched by the addition of 30 mL of distilled water. The phases were allowed to separate and the organic phase was washed with brine then dried over $MgSO_4$. The solvent was removed under vacuum to yield the desired product; 4.62 g (0.014 mol, 82% yield). This material may be used as obtained in the cyclization step or converted to its oxalate salt. The oxalate salt was obtained in a 1 : 0.75 ratio (basic amine : oxalic acid) from hot ethyl acetate; m.p. 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J*=2.0 Hz, 1H), 7.62 (d, *J*=8.5 Hz, 1H), 7.20 (dd, *J*=2.0, 8.4 Hz, 1H), 4.56 (t, *J*=5.4 Hz, 1H), 3.6 (s, 2H), 3.36 (s, 6H), 2.95 (q, *J*=7.6 Hz, 2H), 2.6 (d, *J*=5.5 Hz, 2H), 2.22 (s, 3H), 1.32 (t, *J*=7.6 Hz, 3H); IR (KBr) 3400, 3000–3200,

2800–3000, 1718, 1662, 1635, 1589, 1468, 1441, 1205, 1128, 1074, 1055, 910, 868, 806, cm^{-1}; MS (CI) *m/e* 328 $(M+H)^+$, 296 $(M+H-CH_3OH)^+$; Anal. Calcd. for $C_{32}H_{44}Cl_2N_2O_8S_2$ (dimer): C, 51.98; H, 5.86; N,3.46. Found (1.5 $C_2O_4H_2$ oxalate•HCl•1/4H_2O): C, 51.80; H, 5.85; N, 3.35.

2-Ethyl-7-chloro-3,4-dihydro-4-methylthieno[4,3,2-ef][3] benzazepine (10). To a 3-necked flask containing an air driven stirrer, a condenser and nitrogen inlet/outlet tubes was added 185.2 g of PPA and 145 mL of toluene. Without stirring under a nitrogen atmosphere, the contents were warmed to 55 °C at which time stirring was initiated and heating was discontinued. At this point, 204 mL of a 40% toluene solution of acetal **9** was added *via* an addition funnel at such a rate that the temperature did not exceed 80 °C. The desired temperature range to effect cyclization is 72–78 °C. As the solution of **9** was added, the reaction solution changed color from clear, orange to blue, black. At the end of the addition, heating was resumed and applied so as to maintain the desired temperature of 78–82 °C until TLC indicated the disappearance of starting material. The reaction mixture was cooled down to the 50–55 °C range. Care should be exercised to avoid cooling below 50 °C since the lower PPA phase will become too viscous to stir. The reaction was quenched by cautiously adding 400 mL of water over 15 minutes with stirring to ensure complete mixing. Toluene (300 mL) was added in one portion followed by 275 mL of NH_4OH. The pH of the reaction mixture was adjusted so that it remained within the 8.5–9 range. The reaction was stirred an additional 30 minutes and cooled to 5–10 °C. The organic phase was separated and washed with brine. The solvent may be removed, but normally the solution is concentrated and used as obtained as a toluene concentrate (30% toluene, *w/w* GC assay). The benzazepine **9** was converted to its hydrochloride salt in isopropanol. This salt was isolated as a stable hydrate which contained ~20%

isopropanol and was used as obtained: ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J*=8.4 Hz, 1H), 7.20 (d, *J*=8.5 Hz, 1H), 6.33 (d, *J*=9.9 Hz, 1H), 5.82 (d, *J*=10.0 Hz, 1H), 4.13 (s, 2H), 3.0 (s, 3H), 2.85 (q, *J*=7.4 Hz, 2H), 1.32 (t, *J*=7.4 Hz, 3H); IR (Neat) 2967, 2930, 2869, 2801, 1625(s), 1418, 1167, 1155, 1055, 1032, 861, 772 cm^{-1}; MS (CI) *m/e* 264 $(M+H)^+$, 263 $(M)^+$; 228 $(M+H-HCl)^+$.

2-Ethyl-7-chloro-4-methylthieno[4,3,2-ef][3]benzazepine (SK&F 106686)(1). The benzazepine (**10**), as its hydrochloride salt, was dissolved in 95% ethanol (8 mL/g). To this solution was added platinum oxide (1.5 *w/w* %) and the ethanolic suspension was kept under hydrogen pressure (50–55 psi) at room temperature for 2–4 h. At the end of this time TLC (MeOH / ethyl acetate / hexanes, 2/4/6 *v/v* ratio) showed the absence of (**10**). The catalyst was removed by filtration and the solvent was removed under vacuum. The crude organic solution was dried then concentrated to yield the desired product as a hydrochloride salt. The crude product was recrystallized from ethyl acetate in 87.6% yield: m.p. 233–235 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (d, *J*=8.4 Hz, 1H), 7.15 (d, *J*=8.5 Hz, 1H), 3.91 (s, 2H), 3.32 (t, *J*=6.0 Hz, 2H), 3.08 (t, *J*=6.0 Hz, 2H), 2.85 (q, *J*=7.4 Hz, 2H), 2.45 (s, 3H), 1.31 (t, *J*=7.4 Hz, 3H); IR (KBr) 3465, 3406, 3000–3100, 2800–3000, 1636, 1570, 1420–1480, 1070, 1015, 826, cm^{-1}; MS (CI) *m/e* 266 $(M+H)^+$, 251 $(M+H-CH_3)^+$; 230 $(M+HCl)^+$; Anal. Calcd. for $C_{14}H_{17}Cl_2NS$: C, 55.63; H, 5.67; N,4.63; S, 10.61; Cl, 23.46. Found: C, 55.56; H, 5.66; N, 4.70; S, 10.34; Cl, 23.33.

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