An Efficient Large Scale Synthesis of 4-Isopropyl- and 4-Isopropyl-6-methoxybenzisothiazolones

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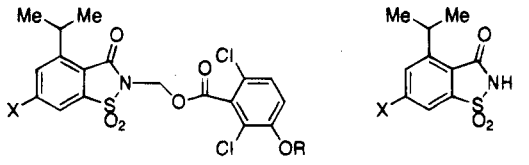
Human leukocyte elastase (HLE) is a serine proteinase that is stored as the mature inactive enzyme in neutrophils. The enzyme is released when neutrophils degranulate at sites of inflammation. The extracellular activity of HLE is tightly regulated by endogenous inhibitors such as α-1 proteinase inhibitor (α_1-PI) and secretory leukocyte protease inhibitor (SLPI). Free HLE has been implicated as a mediator in the etiology of a number of pulmonary disorders, for example, emphysema,[1] cystic fibrosis,[2] and chronic bronchitis.[3]

In conjunction with our program to discover inhibitors of HLE for potential use in such disorders, we have discovered a novel class of potent mechanism-based inhibitors represented by WIN 63294 and 63759. Kilogram quantities of benzisothiazolone (BIT) intermediates **1a** and **1b** were needed for analog synthesis in structure–activity relationship (SAR) studies and for further in vivo studies with WIN 63759.

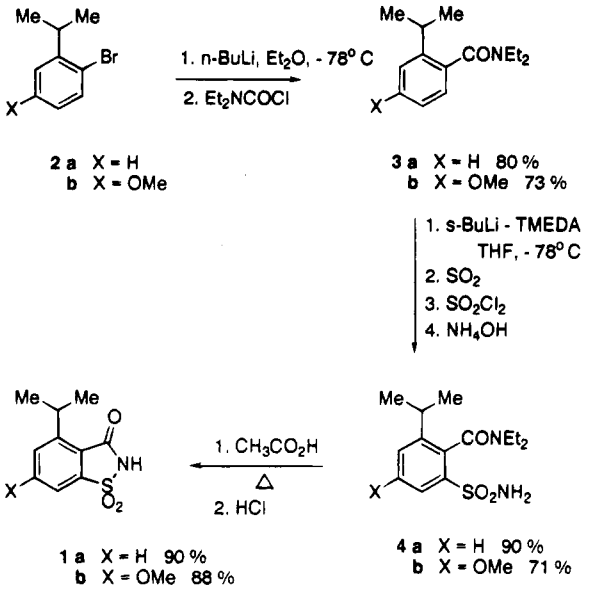


WIN 63294 X = H $K_i^* = 0.008$ nM

WIN 63759 X = OMe $K_i^* = 0.014$ nM

A practical process that could be conducted on a large scale to convert readily available starting materials to the desired targets was sought. Numerous syntheses of benzisothiazolones have been recorded in the literature since the first reported synthesis in 1879;[4] however, the reported syntheses were not suitable for our needs. Two general and complimentary approaches for the synthesis of substituted benzisothiazolones have been reported from these laboratories.[5,6] Though satisfactory for the small scale preparation of **1a** and **1b**, these methods were not amenable to the large scale synthesis of these BIT intermediates due to the following: the first method necessitated the use of large excess of corrosive and hygroscopic hydroxylamine *O*-sulfonic acid,[5] and the other required the use of organocopper reagents and benzyl mercaptan.[6] In this paper we report a convenient and practical large scale synthesis of 4-isopropyl and 4-isopropyl-6-methoxy benzisothiazolones as illustrated in Scheme 1.

Scheme 1



Commercially available 2-bromo-1-isopropylbenzene[7] was subjected to the metal–halogen exchange reaction with n-butyllithium in ether at 0 °C and quenching the resulting anion at −60 °C with *N,N*-diethylcarbamoyl chloride furnished the corresponding *N,N*-diethyl-2-isopropylbenzamide (**3a**) in 80% yield. The benzamide **3a** was previously prepared by Beak and co-workers[8,9] in two steps in 39% overall yield from commercially available *N,N*-diethylbenzamide.

The ortho-lithiation[10] of **3a** with *sec*-butyllithium in ether containing TMEDA at −78 °C afforded the ortho-lithio species, which was treated with excess liquid sulfur dioxide to provide the lithium sulfinate derivative,[11] which without isolation was reacted with sulfuryl chloride to give the sulfonyl chloride derivative.[12] Treatment of the crude sulfonyl chloride with 28% ammonium hydroxide gave the sulfonamide **4a**[13] in 90% yield. Cyclization of this intermediate sulfonamide in refluxing glacial acetic acid provided the desired benzisothiazolone **1a** as its diethylamine salt. Acidification of the resulting salt with concentrated hydrochloric acid furnished **1a** in 90% yield.

In the similar manner, 4-isopropyl-6-methoxy BIT **1b** was synthesized in 46% overall yield from 4-bromo-3-isopropyl-1-methoxybenzene (**2b**).[14]

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(13) Alternatively, the sulfonamide **4a** could be prepared in 85% yield on a 5 mmol scale by treating the lithium sulfinate salt with an aqueous solution of hydroxylamine *O*-sulfonic acid.[5]

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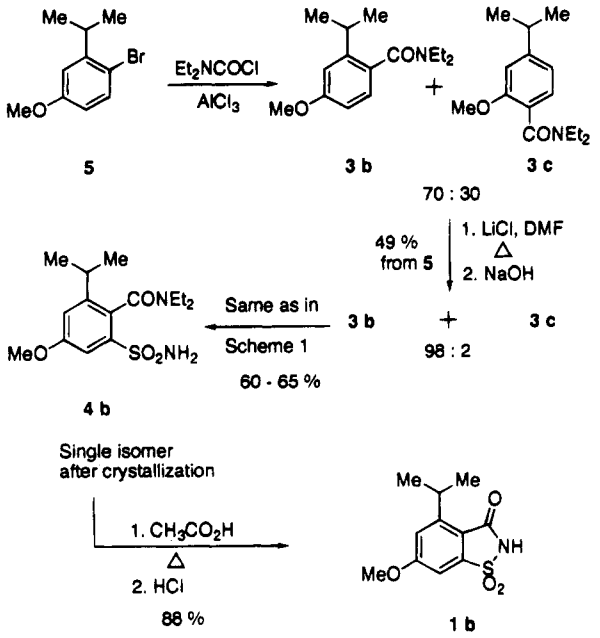
Scheme 2



In a different approach (Scheme 2) for the synthesis of **1b**, we explored the direct introduction of diethylcarbamoyl group on compound **5**.[15] Thus, 3-isopropyl-1-methoxybenzene was acylated with diethylcarbamoyl chloride in the presence of aluminum chloride to furnish a mixture of **3b** and **3c** in a 70:30 ratio. Our efforts to improve this ratio under a variety of reaction conditions were unsuccessful. Since the separation of the two isomers **3b** and **3c** was difficult and impractical on a large scale (>50 g), we decided to investigate the selective demethylation of **3c** with the expectation that the resulting phenol could be easily removed by washing with aqueous alkali. Treatment of a mixture of **3b** and **3c** with lithium chloride[16] in refluxing DMF resulted in selective demethylation of **3c**. Extractive workup followed by fractional distillation provided **3b** in 49% yield from **5**. HPLC analysis of this compound indicated it to be essentially the desired isomer **3b** contaminated with 2% of the undesired isomer **3c**.[17] This mixture without further purification was subjected to directed metalation and subsequent reactions as shown in Scheme 2 to afford **4b** as a single isomer after crystallization. Treatment of **4b** with acetic acid under reflux gave **1b** in 88% yield.

In conclusion, we have successfully developed a simple and practical large scale synthesis of 4-isopropyl- and 4-isopropyl-6-methoxybenzisothiazolones. This novel process uses readily available, inexpensive starting materials and avoids use of hydroxylamine *O*-sulfonic acid as an aminating reagent. Considering the importance of benzisothiazolone derivatives in the pharmaceutical, polymer, and flavor industries,[4] we believe this process should find applications for the synthesis of a variety of substituted benzisothiazolones.

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(17) The outcome of this regioselective demethylation may be rationalized in terms of release of steric crowding between the methoxy and amide substituents in **3c**.

Experimental Section

Reactions involving organometallic reagents were run under a N_2 atmosphere. Solvents and reagents from commercial sources were used without further purification. Melting points (Pyrex capillary) are uncorrected. ^1H NMR coupling constants are reported in Hz and spectra were run on either a 200-, 270-, or 300-MHz instrument. RP-HPLC column: Inertsil ODS-2, 5 μm, 250 × 4.6 mm.

***N,N*-Diethyl-2-isopropylbenzamide (3a).** To a solution of 2-bromo-1-isopropylbenzene (50 g, 0.25 mol) in 500 mL of anhyd Et_2O at 0–5 °C was added a solution of n-butyllithium (2.5 M, 100 mL) over a period of 10 min. After the addition was complete, the cooling bath was removed and the solution was stirred at ambient temperature for 6 h. To this mixture was then added at −60 °C a solution of *N,N*-diethylcarbamoyl chloride (34 g, 0.25 mol) in 50 mL of anhyd Et_2O at such a rate that the reaction solution temperature did not rise above −50 °C (about 20 min). When the addition was complete, the stirring reaction solution was allowed to warm to room temperature for over 1 h and diluted with 100 mL of water. The organic layer was washed once with saturated NaCl, dried ($MgSO_4$), and concentrated to give the crude product as a pale yellow oil. Kugelrohr distillation at 80–90 °C/0.1 mm gave 44 g (80%) of **3a** as a colorless oil (lit.[13] bp 100–115 °C/0.6 mm).

***N,N*-Diethyl-2-isopropyl-6-sulfamoylbenzamide (4a).** A solution of **3a** (44 g, 0.2 mol) in 30 mL of anhyd Et_2O was added dropwise to a stirring solution of 1:1 *sec*-butyllithium–TMEDA complex (0.22 mol) in anhyd ether (600 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 30 min and then allowed to warm to −50 °C over 30 min. After maintaining the temperature at −50 °C for 10 min the reaction mixture was cooled to −78 °C (during this time, some of the lithiated species precipitated from solution).

To this mixture was then added a precooled (−60 °C) solution of sulfur dioxide (50 g) in 50 mL of anhyd Et_2O via cannula over a period of 10 min. A white powdery precipitate of aryllithium sulfinate separated out almost immediately. After the addition, the reaction mixture was allowed to warm to 0 °C over 1 h. Sulfuryl chloride (54 g, 0.4 mol) was added dropwise over 15 min to this stirring suspension at 0 °C. After stirring for an additional 30 min, the reaction solution was warmed to rt and the white precipitate was filtered and washed with 200 mL of Et_2O. The combined filtrate was concentrated to afford crude sulfonyl chloride (63.8 g, 100% yield) as a faint yellow oil, which was homogenous by silica gel TLC (15/85 EtOAc/hexane). For the purpose of obtaining analytical data, a small amount of this material was purified by flash chromatography on a silica gel column: IR (Nujol) cm^{-1} 1630, 1589, 1460, 1380; ^1H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.2), 1.23–1.41 (m, 9H), 2.99–3.18 (m, 3H), 3.52 (sex., 1H), 3.71 (sex., 1H), 7.55 (t, 1H, J = 8), 7.70 (d, 1H, J = 7.5), 7.97 (d, 1H, J = 8). Anal. Calcd for $C_{14}H_{20}NO_3SCl$: C, 52.91; H, 6.34; N, 4.41. Found: C, 52.92, H, 6.41; N, 4.34.

The crude sulfonyl chloride (63.8 g, 0.2 mol) was dissolved in 150 mL of THF and the solution was cooled to 0 °C. Concentrated 28% ammonium hydroxide (60 mL) was added in portions at such a rate that the reaction temperature was maintained below 10 °C. After the addition, the reaction mixture was warmed to room temperature and stirring continued for 15 min. Removal of the solvent under reduced pressure left a residue which was acidified with 2 N HCl to pH 1. The precipitate was filtered and washed with 200 mL portions of water and hexane and dried under vacuum at 60 °C to furnish **4a** (54 g, 90%): mp 161–162 °C; IR (Nujol) cm^{-1} 3310, 1600, 1340; ^1H NMR ($CDCl_3$) δ 1.03–1.33 (m, 12H), 2.94–3.67 (m, 5H), 5.3 (sbr, 2H), 7.46 (t, 1H, J = 7.7), 7.55 (d, 1H, J = 7.5), 7.87 (d, 1H, J = 7.4). Anal. Calcd for $C_{14}H_{22}N_2O_3S$: C, 56.35; H, 7.43, N, 9.39. Found: C, 56.05; H, 7.46; N, 9.55.

4-Isopropylbenzisothiazolone (1a). A solution of **4a** (60 g, 0.2 mol) in 400 mL of glacial acetic acid was kept at reflux for 24 h, cooled, and concentrated on a rotary evaporator to give an oily residue. This material was dissolved in 500 mL of H_2O and adjusted to pH 1 with 2 N HCl. The crude product was collected by filtration, washed with water, and dried under vacuum at 60 °C. Recrystallization from Et_2O/hexane gave 40 g (90%) of pure **1a**: mp 177–178 °C; IR (Nujol) cm^{-1} 1718, 1569, 1325; ^1H NMR ($CDCl_3$) δ 1.30 (d, 6H, J = 6.8), 4.26 (quin, 1H,

J = 6.86), 7.71–7.82 (m, 3H). Anal. Calcd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.26; H, 4.87; N, 6.20.

***N,N*-Diethyl-2-isopropyl-6-methoxybenzamide (3b).** Compound **3b** was prepared analogous to **3a** from 150 g of **2b**, yielding 120 g (73%) of benzamide **3b** as a colorless oil after kugelrohr distillation (bp 100–120 °C/0.1 mm): IR (neat) cm^{-1} 1690, 1608, 1424; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7.0), 1.16–1.28 (m, 9H), 2.97 (quin, 1H, J = 6.8), 3.12–3.78 (m, 4H), 6.73 (dd, 1H, J = 8.2), 6.68 (d, 1H, J = 2.3), 7.06 (d, 1H, J = 8.3). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.06; H, 9.34; N, 5.52.

***N,N*-Diethyl-2-isopropyl-4-methoxy-6-sulfamoylbenzamide (4b).** Compound **4b** was made analogously to **4a** from 88 g of **3b** in 71% yield: mp 136–137 °C (EtOAc/hexane); IR (Nujol) cm^{-1} 3133, 1719, 1610; ^1H NMR ($CDCl_3$) δ 1.08–1.31 (m, 12H), 2.85–3.65 (m, 5H), 3.87 (s, 3H), 7.03 (d, 1H, J = 2.5), 7.41 (d, 1H, J = 2.5). Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.53. Found: C, 54.60; H, 7.35; N, 8.42.

4-Isopropyl-6-methoxybenzisothiazolone (1b) was made in the same manner as **1a** from 82 g of **4b** in 88% yield after recrystallization from EtOAc/hexane: mp 186–187 °C; IR (Nujol) cm^{-1} 1719, 1610, 1328; ^1H NMR ($CDCl_3$) δ 1.27 (d, 6H, J = 6.9), 3.94 (s, 3H), 4.14 (quin, 1H, J = 6.9), 7.17 (m, 2H). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.80; H, 5.04; N, 5.34.

***N,N*-Diethyl-2-isopropyl-6-methoxybenzamide (3b).** To a suspension of aluminum chloride (266 g, 2.0 mol) in 1100 mL of dichloroethane at 0–5 °C was added a solution of diethylcarbamoyl chloride (270 g, 2.0 mol) in 100 mL of dichloroethane over a period of 45 min. After the addition was over, the cooling bath was removed and the solution was stirred at ambient temperature for 15 min. To this mixture was then added 300 g (2.0 mol) of 3-methoxy-1-isopropylbenzene in one portion and the resulting mixture was kept at reflux on a steam bath for a period of 2 h. After cooling to room temperature, the reaction mixture was poured into a cold 2 N HCl solution (2000 mL). The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2 (400 mL). The combined extracts washed once with saturated NaCl solution, dried (Na_2SO_4), and concentrated to give the crude products as an oil. This oil was subjected to distillation under reduced pressure and the fraction boiling at 145–150 °C/1 mm was collected to give a mixture of **3b** and **3c** (460 g, 92%). HPLC analysis of this sample indicated it to be a mixture in a ratio of 70:30. (RP-HPLC t_R = 8.48 and 10 min respectively). For the purpose of obtaining analytical data, a small amount of **3c** was isolated pure by flash chromatography (SiO_2, 6:4 Et_2O–hexane): IR (Film) cm^{-1} 1632, 1460, 1254; ^1H NMR ($CDCl_3$) δ 1.03 (t, 3H, J = 7.1), 1.2–1.25 (m, 9H), 2.88 (quin, 1H, J = 6.95), 3.15 (q, 2H, J = 7.1), 3.56 (m, 2H), 3.81 (s, 3H), 6.73 (s, 1H), 6.82 (d, 1H, J = 7.36), 7.09 (d, 1H, J = 8). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.09; H, 9.47; N, 5.51.

To the solution of this mixture (169 g, 0.68 mol) in DMF (350 mL) was added anhyd lithium chloride (85 g, 2.02 mol) and the resulting mixture was heated to reflux for 24 h, cooled, poured into water, and extracted with EtOAc (3 × 300 mL). The organic extracts were washed with 2 N aqueous NaOH, water, and dried (Na_2SO_4). After filtration and concentration, the residue obtained (95 g) was subjected to kugelrohr distillation at 130 °C/0.2 mm to give essentially **3b** (90 g) contaminated with a trace amount (2%) of **3c**. This product was used as such for the next step.