$$R = [R_2NCO_2^-]/[R_2NH_2^+]$$

If we define

$$K_R = [R_2NCO_2^-][H^+]/[R_2NH][CO_2]$$

then $R = [H^+][HCO_3^-]K_R(DEA)/(K_a(CO_2)K_a(DEA))$. Taking the value of $K_a(CO_2)$ to be[13] 4.3×10^{-7} mol dm^{-3}, of K_a(DEA) to be[12] 3.0×10^{-9} mol dm^{-3}, and of K_R to be[14] 3.7×10^{-6}, and taking typical values of $[H^+]$ and $[HCO_3^-]$ to be 10^{-9} and 0.01 mol dm^{-3}, respectively, gives a value of R of 0.022. In our study[3] of DEA, most of the DEA would eventually form the alkylammonium hydrogen carbonate, even though the carbamate is the initial product. The further reaction from carbamate is very slow, as it proceeds via the free amine and carbon dioxide present at low concentrations in the reaction mixture.

Experimental Section

Materials. TEA and MEA were Analar grade, supplied by the Aldrich Chemical Co. Carbon dioxide was from cylinder (Distillers).

Kinetic Measurements. Aqueous solutions of amine and of carbon dioxide were mixed in a stopped-flow apparatus with conductimetric detection (Hi-Tech Scientific Ltd.) and product formation monitored as previously described.[2]

Registry No. MDEA, 105-59-9; TEA, 102-71-6; $MDEAH^+ \cdot HOCO_2^-$, 2604-14-0; $TEAH^+ \cdot HOCO_2^-$, 2471-07-0; CO_2, 124-38-9.

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General Procedure for the Synthesis of *o*-Aminophenylacetates by a Modification of the Gassman Reaction

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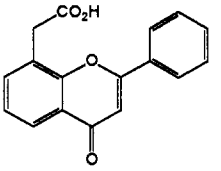
During the course of study directed toward the synthesis of a series of heteroaromatic analogues related to the novel NCI investigational antitumor agent FAA (**1**, flavone acetic acid),[1] we required *o*-aminophenylacetic acids of general formula **2**. These aniline derivatives seemed most easily obtained by using the synthesis of oxindoles as developed by Gassman[2] and adapted by Walsh.[3] This reaction is characterized by the ease of carrying out the procedures, the high yields considering that 5–6 steps are actually accomplished in a one-pot reaction, and the availability of starting materials.

The reaction as outlined in Scheme I for the synthesis of oxindoles can be used to prepare *o*-aminophenylacetic



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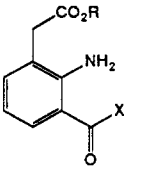

2a X=NH_2
2b X=OCH_2Ph

acid derivatives if the intramolecular addition of the amine to the carbonyl can be prohibited or at least discouraged from occurring. Gassman was able to isolate the relatively unstable amino ester **4a** in some cases,[2] but treatment with dilute acid, prolonged standing at room temperature, or heating gave the cyclized product, **5**. He was able to isolate the *o*-aminoacetic acid derivatives if the sulfide used in the reaction was (methylthio)acetamide (e.g., to give **4b**) or if the amine was acetylated by treating the reaction mixture with trimethylamine and acetyl chloride before purification or acid treatment. Walsh obtained *o*-aminophenylacetic acids by allowing the cyclization to the oxindole to take place and subsequently reopening the oxindole with boiling 3 N sodium hydroxide.[3] Ideally, we wanted to stop or at least hinder the cyclization to the oxindole **5**, thus avoiding the harsh conditions employed by Walsh to reopen the oxindole to the aniline acetic acid.

In our synthesis we were unable to use the acetamide sulfide or acetylation of the amine as a means of stopping the formation of the oxindole. In the case of the acetamide sulfide, conversion of the acetamide to an acid at some later stage of the synthesis was anticipated to be problematic because of the prolonged heating in acid or base that would be necessary to effect the hydrolysis. Similarly, trapping of the amine by acetylation would at some point require deprotection in the presence of the ester so that subsequent condensations on the amine could be carried out. Instead, we proposed to stop the intramolecular cyclization of the amine with the ester by changing the protecting group of the starting acetic acid sulfide to render the ester less susceptible to attack by the amine. The *tert*-butyl ester comes immediately to mind since it is easily removed under mild acidic conditions and bulky enough to provide steric hinderance to nucleophilic attack by the amine.

Compound **7**, the required *tert*-butyl ester of (methylthio)acetic acid, was synthesized by reacting the lithium salt of *tert*-butyl alcohol[4] with (methylthio)acetyl chloride[5] (**6**) in 51% yield. An alternative route[6] using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC) to couple (methylthio)acetic acid and *tert*-butyl alcohol at room temperature in methylene chloride gave only small amounts of the desired product.

The synthesis of the (*o*-aminophenyl)(methylthio)acetic acid esters **9** is illustrated in Scheme II. In a typical procedure, *tert*-butyl (methylthio)acetate (**7**) is treated with sulfuryl chloride[7] at −70 °C in methylene chloride followed by the addition of the appropriate aniline **8** and Proton Sponge (Aldrich) (as an HCl trap) to give the azasulfonium salt.[2b,7] This was treated directly with triethylamine and allowed to warm to room temperature to produce the desired Sommelett–Hauser rearrangement product in overall 85–90% yields. The *tert*-butyl esters **9** are quite stable to dilute acid and silica gel chromatog-

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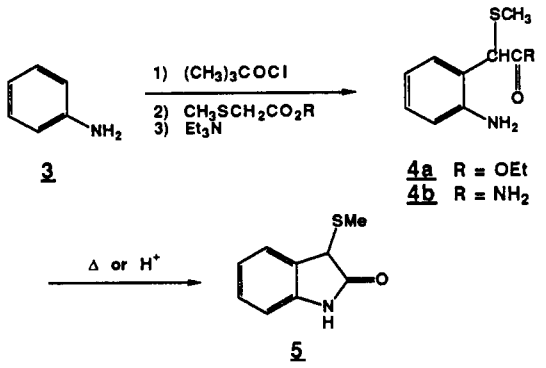
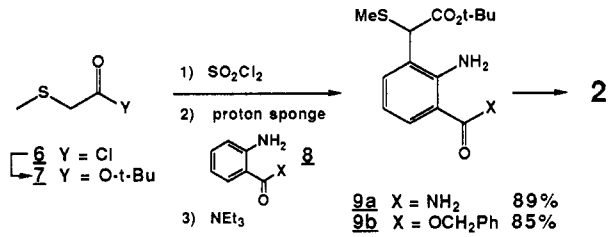
Scheme I



Scheme II



raphy in contrast to the methyl and ethyl esters which spontaneously form the oxindole. The resulting sulfides **9** can be treated with Raney nickel to remove the methylthio group and give the desired compounds **2** in 82–96% yield.

We propose that this modification of the Gassman reaction is a simple, efficient, and versatile route to *tert*-butyl *o*-aminophenylacetates and should expand the usefulness of this methodology.

Experimental Section

Boiling points and melting points are uncorrected. Nuclear magnetic resonance spectra were determined on a Varian Model EM-390 spectrometer operating at 90 MHz. Chemical shifts are reported in ppm (parts per million) relative to tetramethylsilane in chloroform-*d* solutions. Thin-layer chromatography (TLC) was performed on Analtech plates precoated with silica gel GF. Combustion analyses, mass spectra, and infrared spectra (either as neat samples or as Nujol mulls) were obtained by the Physical and Analytical Chemistry Unit of the Upjohn Co. Flash chromatography refers to the method as developed by Still[8] and utilized neutral silica gel (E. Merck, 40–63 mm). *tert*-Butyl alcohol was freshly distilled from calcium hydride under nitrogen. All other solvents were reagent grade distilled from glass (Burdick and Jackson). Reagents were used as purchased. All reactions were degassed and conducted under an inert atmosphere.

***tert*-Butyl (Methylthio)acetate (7).** *tert*-Butyl alcohol (110 mL) in 400 mL of anhydrous diethyl ether at 0 °C was treated dropwise with 1.6 M *n*-butyllithium in hexane (150 mL), stirred for 30 min at ambient temperature, and then treated dropwise with (methylthio)acetyl chloride[5] **6** (30 g, 240 mmol) in 100 mL of anhydrous diethyl ether. After 1 h at room temperature the suspension was washed with 2 × 100 mL of 1:1 brine/water, dried over anhydrous sodium sulfate, and distilled at 90–100 °C at house vacuum to give 20 g (51%) of *tert*-butyl (methylthio)acetate, **7** as a colorless oil: ^{1}H NMR δ 3.10 (s, 2 H), 2.20 (s, 3 H), 1.50 (s, 9 H); IR (neat) 2980, 1725, 1370, 1290, 1170, 1130, 950 cm^{-1}; HRMS calcd for $C_7H_{14}O_2S$ 162.0714, found 162.0700.

General Procedure for 9. *tert*-Butyl (methylthio)acetate (**7**, 12.0 g, 74 mmol) in methylene chloride (800 mL) at −70 °C was treated dropwise with sulfuryl chloride (5.9 mL, 73 mmol), stirred 30 min, then treated dropwise with a solution of Proton Sponge (16 g, 75 mmol) and anthranilamide (**8a**, 10.0 g, 73 mmol) in methylene chloride (1000 mL) over 1 h. The resulting pink slurry was then treated with triethylamine (12 mL, 86 mmol) and allowed to warm to room temperature. The mixture was washed with 3 × 250 mL water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. Flash chromatography on 200 g silica gel, eluting with 1:1 ethyl acetate–hexane, gave **9a** (19.5 g, 89%) as a pale yellow oil: ^{1}H NMR δ 7.5 (m, 2 H), 6.75 (m, 1 H), 6.4 (br s, 2 H), 6.0 (br s, 2 H), 4.5 (s, 1 H), 2.05 (s, 3 H), 1.5 (s, 9 H); IR (neat) 3350, 3345, 1725, 1660, 1560, 1370, 1260 cm^{-1}; HRMS calcd for $C_{14}H_{20}N_2O_3S$ 296.1194, found 296.1202; TLC R_f = 0.40 in 1:1 ethyl acetate–hexane. Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45. Found: C, 56.73; H, 6.84; N, 9.31.

The synthesis of **9b** was carried out in a similar manner beginning with **8b**[9] (6.5 g, 28 mmol). Flash chromatography with 10% ethyl acetate in hexane as eluent gave **9b** (9.38 g, 85%) as a pale yellow oil which solidified in the refrigerator: ^{1}H NMR δ 8.0 (m, 1 H), 7.2–7.6 (m, 5 H), 6.6 (m, 2 H), 6.5 (br s, 2 H), 5.3 (s, 2 H), 4.6 (s, 1 H), 2.1 (s, 3 H), 1.5 (s, 9 H); IR (Nujol mull) 3460, 1690, 1615, 1455, 1290, 1090, 755 cm^{-1}; HRMS calcd for $C_{21}H_{25}NO_4S$ 387.1504, found 387.1486; TLC R_f = 0.52 in 20% ethyl acetate in hexane. Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 65.05; H, 6.38; N, 3.74.

Raney Nickel Desulfurization. A solution of **9a** (14.5 g, 49 mmol) in absolute ethanol (400 mL) was stirred with Raney nickel (50 mL, washed to neutrality with water then with ethanol) at room temperature for 30 min, filtered through Celite, washing the filter cake with two 50-mL portions of tetrahydrofuran. The combined filtrates were concentrated in vacuo, and the resulting solid was triturated with 1:1 ethyl acetate–hexane to give **2a** (10.0 g, 82%): ^{1}H NMR δ 7.5 (m, 1 H), 7.15 (m, 1 H), 6.5 (m, 1 H), 6.1 (br s, 2 H), 5.8 (br s, 2 H), 3.5 (s, 2 H), 1.4 (s, 9 H); IR (Nujol mull) 3468, 3420, 1711, 1660, 1560, 1310, 1110 cm^{-1}; HRMS calcd for $C_{13}H_{18}N_2O_3$ 250.1317, found 250.1327; TLC R_f = 0.25 in 10% acetone in methylene chloride. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.09; H, 7.29; N, 10.95.

The synthesis of **2b** was carried out in a similar manner beginning with **9b** (8.4 g, 22 mmol) to give **2b** (7.2 g, 96%) as a yellow oil: ^{1}H NMR δ 7.9 (m, 1 H), 7.1–7.6 (m, 5 H), 6.6 (m, 2 H), 6.2 (br s, 2 H), 5.3 (s, 2 H), 3.3 (s, 2 H), 1.4 (s, 9 H); IR (neat) 3480, 3370, 1710, 1690, 1620, 1575, 1285, 1155, 1140 cm^{-1}; HRMS calcd for $C_{20}H_{23}NO_4$ 341.1627, found 341.1634; TLC R_f = 0.55 in 20% ethyl acetate in hexane. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.04; H, 6.92; N, 4.16.

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A Directed Metalation of *N*-*tert*-Butyl-*N*-methyl-2-methoxybenzamide. Short Syntheses of 2-Methoxy-6-methylbenzoic Acid and Lunularic Acid

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Introduction

Directed metalation of tertiary benzamides has been an area of considerable interest to synthetic chemists in recent years.[2] Tertiary benzamides and particularly *N*,*N*-diethylbenzamides, first reported by Beak[3] in 1977, are ex-

(1) Present Address: Cardiovascular Diseases Research Department, Searle Research and Development, c/o Monsanto Company, 700 Chesterfield Village Parkway, Chesterfield, MO 63198.

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