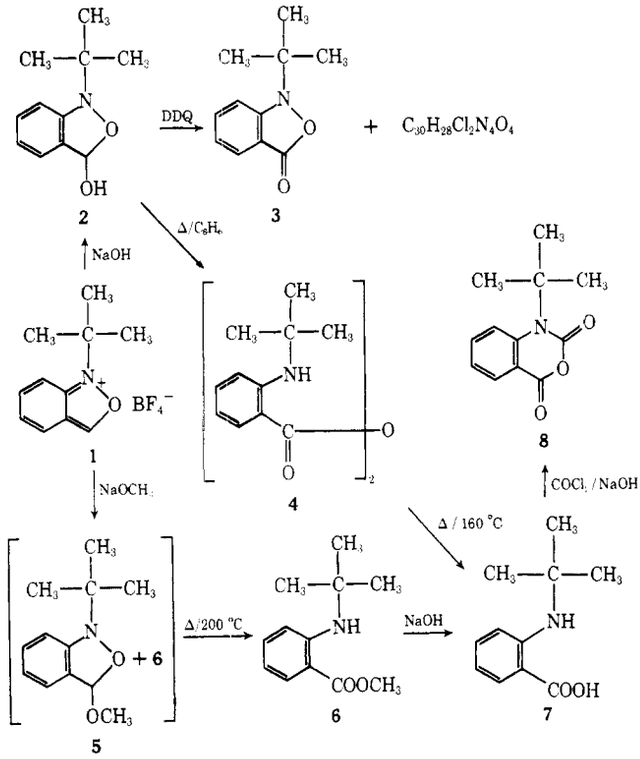
Synthetic Utility of 1-*tert*-Butyl-2,1-benzisoxazolium Tetrafluoroborate

Robert V. Coombs

Department of Medicinal Chemistry, Pharmaceutical Division, Sandoz, Inc., East Hanover, New Jersey 07936

Received November 15, 1976

Previous work by us[1] demonstrated that although *o*-aminobenzaldehydes and -benzophenones bearing a *tert*-butyl group on the nitrogen atom could not be obtained by standard alkylation procedures, one efficient route was via the corresponding 1-*tert*-butyl-2,1-benzisoxazolium salts. While the chemistry of such salts has been extended in a study of their reactions with carbon and nitrogen nucleophiles,[2] we now wish to report that using oxygen nucleophiles the salt **1** yields intermediates which can be converted to the previously unknown *N*-*tert*-butylanthranilic acid **7** and its derivatives.



Addition of **1** to a slight excess of aqueous sodium hydroxide and extraction with benzene gave, in high yield, **2**, characterized in particular by the absence of a carbonyl absorption band in its infrared spectrum. Oxidation of **2** at room temperature in benzene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) yielded two products which could be separated by chromatography on silica gel. The less polar was a crystalline material of unknown structure, but with a probable molecular weight of 578 (mass spectrum) suggesting condensation of two molecules of *tert*-butylanthranilic acid with one molecule of the hydroquinone and elimination of water. The more polar proved to be the 2,1-benzisoxazolin-3-one, **3**. Characteristically its carbonyl absorption occurred at 1765 cm^{-1} and while it could not be crystallized, on combined gas chromatography–mass spectrometry it gave a single peak and a molecular ion at *m/e* 191, as required by its structure.

In an attempt to thermally isomerize the derivative **2**, it was heated, as in previous examples,[1] to a temperature of 160 °C. Extensive decomposition occurred, although a low yield of the expected *N*-*tert*-butylanthranilic acid, **7**, could be isolated. However, heating **2** under reflux in benzene led to a new crystalline product in high yield which was shown to be the anhydride **4**. Again, the infrared spectrum of **4** proved diagnostic, *two* carbonyl bands at 1680 and 1735 cm^{-1} being present. Further, a correct molecular ion was found in the mass spectrum and the pattern of the aromatic protons in the NMR spectrum was superimposable on that from the anthranilic acid **7**, demonstrating the symmetry of the structure. This example is believed to be the first *N*-alkylanthranilic acid anhydride, although *N*-aryl substituted derivatives have been reported.[3] Heating **4** above its melting point also gave the acid **7** in low yield. Subsequently, a more practical synthesis of the acid **7** was developed.

Treatment of a suspension of the salt **1** in benzene with a solution of sodium methoxide in methanol gave in quantitative yield a mixture of the two products **5** and **6** in a ratio of ca. 5:1. This mixture could be readily analyzed by NMR since clearly separated *tert*-butyl and methyl signals could be seen along with a singlet at δ 6.18 due to the C-3 hydrogen atom in the isomer **5**. Integration of this singlet identified **5** as the major product. The ratio of **5**:**6** produced from **1** was essentially unchanged under all experimental variations attempted, and it was not possible to obtain **5** uncontaminated with **6**. Heating the crude product under nitrogen at 200 °C for 6 h cleanly converted it to the pure ester **6**. Hydrolysis of **6** in methanolic sodium hydroxide solution then gave the acid **7** in good yield. Although numerous N-substituted anthranilic acids have been prepared because of their synthetic versatility, nevertheless, the simple *N*-*tert*-butyl derivative **7** has not been previously described.

Finally, reaction of an aqueous solution of the sodium salt of **7** with a solution of phosgene in benzene[4] gave *N*-*tert*-butyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (**8**), i.e. *N*-*tert*-butylisatoic anhydride. Isatoic anhydrides have been found to be even more useful than the corresponding anthranilic acids,[5] and further work to exploit these new *N*-*tert*-butyl derivatives is underway.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Infrared spectra were measured on a Model 457 Perkin-Elmer spectrophotometer in methylene chloride; NMR spectra in deuteriochloroform solution with tetramethylsilane as an internal standard, on a Varian T-60 instrument. Microanalyses were carried out in our analytical unit.

1-*tert*-Butyl-2,1-benzisoxazolium Tetrafluoroborate (1). To a solution of 11.9 g (0.1 mol) of anthranil in 50 mL of nitromethane were added 8.9 g (0.12 mol) of *tert*-butyl alcohol and 20 mL of a 50% aqueous solution of fluoroboric acid. The resulting solution was left at room temperature for 24 h and then diluted with 500 mL of anhydrous ether. The crystalline precipitate so obtained was filtered off, dissolved in 50 mL of acetone, and reprecipitated by the addition of 250 mL of ether. There resulted 10.1 g of **1** (38%): mp 132–134 °C; NMR (D_2O) δ 1.95 (s, 9), 7.4–8.3 (m, 4), 10.8 (s, 1).

Anal. Calcd for $C_{11}H_{14}BF_4NO$: C, 50.2; H, 5.4; N, 5.3. Found: C, 50.2; H, 5.5; N, 5.5.

1-*tert*-Butyl-2,1-benzisoxazolin-3-ol (2). To a suspension of 13.1 g (0.05 mol) of **1** in 100 mL of benzene were added 25 mL of a 2 N solution (0.05 mol) of sodium hydroxide with vigorous stirring. After stirring at room temperature for 30 min, the two layers were separated and the aqueous phase was extracted twice with 25 mL of benzene. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure at a temperature below 40 °C. The residue was crystallized from pentane to yield 7.2 g of **2** (74%): mp 101–103 °C; NMR (Me_2SO) δ 1.24 (s, 9), 6.4–7.5 (m, 6).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.2. Found: C, 68.3; H, 7.6; N, 7.1.

1-*tert*-Butyl-2,1-benzisoxazolin-3-one (3). A solution of 0.25 g (0.0013 mol) of **2** and 0.30 g (0.0013 mol) of DDQ in 10 mL of benzene was stirred at room temperature for 48 h. The precipitate which formed was filtered off and the filtrate was washed with 10 mL of a 5% solution of sodium dithionite, 10 mL of a 10% solution of potassium carbonate, and 10 mL of water. The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in a small volume of methylene chloride and applied to a column of silica gel. Elution with more methylene chloride gave a first fraction, 68 mg, which crystallized from ether/hexane: mp 194–196 °C; *m/e* 578 ($C_{30}H_{28}Cl_2N_4O_4$); IR 3410, 2270, and 1715 cm^{-1}. Further elution with

methylene chloride gave **3**, 0.14 g, as an oil: *m/e* 191; IR 1765 cm^{-1}; NMR δ 1.40 (s, 9), 7.0–8.0 (m, 4).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.8; N, 7.3. Found: C, 68.9; H, 6.8; N, 7.4.

***N-tert*-Butylanthranilic Acid Anhydride (4).** A solution of 5.2 g (0.027 mol) of **2** in 100 mL of benzene was refluxed for 18 h using a Dean-Stark water trap. The solution was then evaporated to dryness and the residue crystallized from ether/pentane to give 3.7 g of **4** (75%): mp 92–94 °C; IR 3390, 1735, and 1680 cm^{-1}; NMR δ 1.48 (s, 18), 6.4–8.1 (m, 8), 8.20 (broad s, 2); *m/e* 368.

Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.7; H, 7.7; N, 7.6. Found: C, 71.5; H, 7.9; N, 7.8.

Methyl *N-tert*-Butylanthranilate (6). To a suspension of 26.3 g (0.10 mol) of **1** in 250 mL of benzene was added a solution of 6 g (0.11 mol) of sodium methoxide in 25 mL of methanol. After stirring the mixture at room temperature for 30 min, 50 mL of water was added and the benzene layer was separated. It was washed once with 50 mL of water and then dried (Na_2SO_4) and evaporated. The residue, 21 g (100%), was a yellow oil which was shown by NMR analysis to contain 1-*tert*-butyl-3-methoxy-2,1-benzisoxazoline (**5**) and **6** in a ratio of 5:1.

For **5**: NMR δ 1.32 (s, 9), 3.48 (s, 3), 6.18 (s, 1) 6.90–7.4 (m, 4).

This crude mixture was maintained under nitrogen at 200 °C for 6 h and then distilled under high vacuum to give 17.6 g of **6** (84%): bp 75–78 °C (0.1 mm); mp 32–34 °C; NMR δ 1.46 (s, 9), 3.82 (s, 3), 6.4–8.0 (m, 5).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8. Found: C, 69.6; H, 8.3; N, 6.9.

***N-tert*-Butylanthranilic Acid (7).** To a solution of 15.5 g (0.075 mol) of **6** in 100 mL of methanol was added a solution of 4 g (0.1 mol) of sodium hydroxide in 10 mL of water. After refluxing for 4 h the solution was evaporated under reduced pressure and the residue was dissolved in 100 mL of water. The aqueous solution was washed with 50 mL of ether and then made neutral with 2 N hydrochloric acid. It was extracted with three 50-mL volumes of ether and the combined ether extracts were dried (Na_2SO_4) and concentrated. The residue crystallized to yield 12.2 g (84%) of **7**: mp 151–153 °C; NMR (Me_2SO) δ 1.38 (s, 9), 6.4–8.0 (m, 4).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.3. Found: C, 68.4; H, 8.1; N, 6.9.

***N-tert*-Butyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (8).** To a solution of 8 g (0.04 mol) of **7** in 100 mL of water containing 3.2 g (0.08 mol) of sodium hydroxide and some solid carbon dioxide was added, with vigorous stirring, 50 mL of a 12.5% solution (0.06 mol) of phosgene in benzene. The stirring was continued for 4 h when the benzene was removed under reduced pressure and the precipitate was filtered off. The solid was dissolved in methylene chloride and the solution dried (Na_2SO_4). Concentration of the solution and addition of ether gave 4.3 g (52%) of **8**: mp 110–112 °C; IR 1790 and 1750 cm^{-1}; NMR δ 1.76 (s, 9), 7.0–8.2 (m, 4).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.7; H, 6.0; N, 6.4. Found: C, 66.0; H, 6.2; N, 6.3.

Registry No.—**1**, 24766-87-8; **2**, 61752-02-1; **3**, 61752-03-2; **4**, 61752-04-3; **5**, 61752-05-4; **6**, 61752-06-5; **7**, 61752-07-6; **8**, 61752-08-7; anthranil, 271-58-9; *tert*-butyl alcohol, 75-65-0.

References and Notes

(1) R. V. Coombs and G. E. Hardtmann, *J. Org. Chem.*, **35**, 2440 (1970).
(2) Y. Nakagawa, O. Aki, and K. Sirakawa, *Chem. Pharm. Bull.*, **20**, 2209 (1972).
(3) M. Goodman, N. Arbiter, and G. Powell, *J. Am. Chem. Soc.*, **55**, 4292 (1933).
(4) G. E. Hardtmann, G. Koletar, and O. R. Pfister, *J. Heterocycl. Chem.*, **12**, 565 (1975).
(5) G. M. Coppola, G. E. Hardtmann, and O. R. Pfister, *J. Org. Chem.*, **41**, 825 (1976).

Nitrile Sulfides. Synthesis of 5-Aryl-1,2,4-thiadiazole-3-carboxylates

Robert K. Howe,* Terry A. Gruner, and John E. Franz

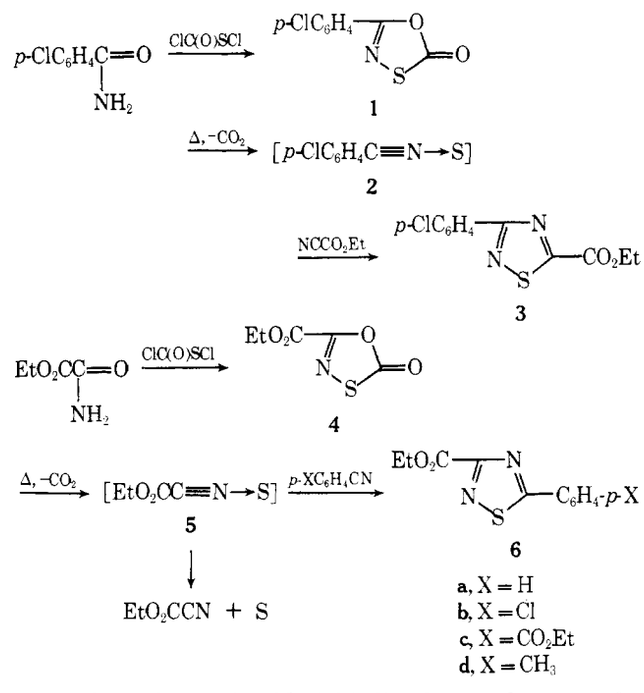
Research Department, Monsanto Agricultural Products Company, St. Louis, Missouri 63166

Received November 23, 1976

We reported recently[1] preparation of 3-aryl-1,2,4-thiadiazole-5-carboxylates in excellent yields by 1,3-dipolar cycloaddition reactions of aryl nitrile sulfides with ethyl cyanoformate, as exemplified by the synthesis of **3**, a new compound. Synthesis of the heretofore unknown, isomeric 5-aryl-1,2,4-thiadiazole-3-carboxylates now has been accomplished by cycloaddition of ethoxycarbonylnitrile sulfide (**5**) to aryl nitriles. Nitrile sulfide **5** was generated and trapped in situ by thermolysis of oxathiazolone **4** in excess aryl nitrile.

Table I. Thiadiazole-3-carboxylates 6 from Thermolysis of 4 in Aromatic Nitriles at 190 °C

Mol ratio, *p*-XC_6H_4-CN/4	Registry no.	Product	Registry no.	% yield of 6 GC	% yield of 6 Isolated
10	100-40-0	**6a**	61689-35-8	26	
35		**6a**		62	33
10	623-03-0	**6b**	61689-36-9	69	61
10	7153-22-2	**6c**	61689-37-0	53	23.5
10	104-85-8	**6d**	61689-38-1	16	7



The dependence of yield of thiadiazole **6** on the para substituent (Table I) is in general agreement with qualitative predictions based on the generalized perturbation theory,[2] with the assumption that the reaction is dipole–HOMO controlled. Electropositive substituents will raise the dipolarophile LUMO level, decreasing the rate of the cycloaddition reaction, and electronegative substituents will lower the dipolarophile LUMO level, increasing the rate of the cycloaddition reaction.[2,3] Coulombic effects will reinforce these frontier orbital effects.[2,3] The yield of thiadiazole depends on the relative rates of cycloaddition of **5** and decomposition of **5** to ethyl cyanoformate and sulfur. Thermolysis of neat oxathiazolone **4** at 235–290 °C (bath temperature) gave ethyl cyanoformate (48% distilled yield), carbon dioxide (94%), and sulfur (96%). Ethyl cyanoformate is both relatively volatile (bp 115–116 °C) and thermally unstable[4] and was found to disappear completely within 86 h from benzonitrile solution heated at reflux. Thus, the measured yields (GC analysis) of ethyl cyanoformate in the cycloaddition reactions did not account fully for the balance of oxathiazolone that was thermolyzed but not converted to thiadiazole.

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp apparatus and are corrected. Infrared spectra were obtained