Reaction of Malononitrile with Carbon Disulfide in an Aqueous Alkaline Medium

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A characteristic compound, 4,6-diamino-3,5-dicyano-2H-1-thiopyran-2-thione (**1**), was easily obtained in good yield from malononitrile and carbon disulfide in aqueous alkali. Compound **1** also was obtained by the reaction of the dimer (**2**) of malononitrile with carbon disulfide in an aqueous alkaline medium. The structure of **1** was proposed on the basis of ir and nmr spectra together with the course of the reaction. The ir spectrum showed two separate absorptions at 2200 cm^{-1} (conjugated CN stretching) and 2210 cm^{-1} (nonconjugated CN stretching). The nmr spectrum showed only one peak, which had a characteristic broad shape of an amino group (δ 8.50, NH_2). Thus the formation of **1** was believed to proceed through intermediate **3**, that is, to involve attack of carbon disulfide on the active methylene of **2**.

Along with **1**, a small amount of the trimer of malononitrile and di(ammoniomercapto)methylenecyanothioacetamide (**4**) were isolated from the reaction product. The structures of the latter two compounds were assigned on the basis of ir and nmr spectra and the courses of syntheses. The trimer was believed to be 4,6-diamino-3,5-dicyano-2-cyanomethylpyridine (**5**), which is different from the one obtained by Pleuger and Pape.[2]

The reaction of malononitrile and carbon disulfide in liquid ammonia gave di(ammoniomercapto)methylenemalononitrile (**6**). This type of compound is generally prepared by the action of alkoxide.[3] Compound **1** could not be synthesized by the reaction of **6** and malononitrile.

When ethyl cyanoacetate was treated with carbon disulfide in the presence of aqueous ammonia, it gave di(ammoniomercapto)methylenecyanoacetamide (**7**). In addition, a small amount of a compound ($C_9H_{17}N_5O_3S_2$), which is possibly a molecular compound of cyanoacetamide and ethyl di(ammoniomercapto)methylenecyanoacetate, was isolated. This compound, on oxidation with hydrogen peroxide, gave colorless needles, mp 223–224°. The uv spectrum resembled that of 3,5-di(methylacetylmethylene)-1,2,4-trithiole,[4] and thus the structure was tentatively designated 3,5-di(cyanocarbethoxymethylene)-1,2,4-trithiole (**8**).

Further, **7** was treated with acetic acid to give 5-amino-4-carbamoyl-1,2-dithiole-3-thione (**9**).[5] Compound **6**, unlike **7**, did not afford the corresponding dithiole on the same treatment, but **4**, which was prepared from **6** by addition of hydrogen sulfide, gave 5-amino-4-cyano-1,2-dithiole-3-thione (**10**).[5] Compound **6** on treatment with acetic acid was converted into a trimer of dimercaptomethylenemalononitrile.

Compounds **4**, **6**, and **7** were converted to the respective dimethyl derivatives for the purpose of confirmation of structure.[3]

The structures of **9** and **10** are mainly based on the characteristic uv spectra. These two compounds have been synthesized by Söderbäck from the corresponding dimercaptoethylene and sulfur[6] (Scheme I).

Experimental Section

Preparation of 4,6-Diamino-3,5-dicyano-2H-1-thiopyran-2-thione (**1**). **Method A.**—A mixture of malononitrile (bp 104–106° (7 mm), 50 g, 0.76 mol), carbon disulfide (114 g, 1.5 mol), and 280 ml of aqueous ammonia (28%) was stirred at room temperature for 6 hr. The yellow solid product was collected, washed with water and ether, recrystallized from pyridine, and dried at 130° for 6 hr to give yellow needles (**1**): yield 51 g (62%). This compound turned brownish near 300°. *Anal.* Calcd for $C_7H_4N_4S_2$: C, 40.39; H, 1.94; N, 26.92; S, 30.75; mol wt, 208.13. Found: C, 40.41; H, 2.05; N, 27.08; S, 30.32; mol wt (mass spectroscopy), 208. Uv max (99% EtOH) 253 mμ (br, log ϵ 4.10), 276 (4.09), 331 (3.93), 391 (4.16); ir (KBr) 3400 (w), 3310 (s), 3280 (sh), 3220 (s), 3140 (s, ν_{NH_2}), 2210, 2200 (s, ν_{CN}), 1650, 1630 (vs, δ_{NH_2}), 1545 cm^{-1} (*vs.* $\nu_{conj\ C=C}$); nmr (DMSO-d_6) δ 8.50 (br, 4, NH_2).

When the crude product of the above anhydrous sample was recrystallized from pyridine–water, **1** had 1 mol of water of crystallization. This compound turned brownish near 300°. *Anal.* Calcd for $C_7H_6N_4OS_2$: C, 37.17; H, 2.67; N, 24.78; S, 28.80; mol wt, 226.0. Found: C, 37.28; H, 2.93; N, 25.04; S, 28.35; mol wt, 225.4 (vapor-pressure osmometer, in acetone).

Method B.—A mixture of malononitrile (25 g, 0.38 mol), carbon disulfide (57 g, 0.75 mol), and 10 g of sodium hydroxide in 100 ml of water was shaken for 24 hr, yield 5 g (12.5%). The ir spectrum was identical with that of **1** prepared by method A.

Method C.—Malononitrile dimer (**2**) was prepared according to Carboni's tetrahydrofuran method.[7] Compound **1** was prepared, in the same way as in method A, from malononitrile dimer (20 g, 0.15 mol), carbon disulfide (15 g, 0.2 mol), and 150 ml of aqueous ammonia (28%), yield 29 g (93%). The structure determination was based on the ir spectrum.

Isolation of Malononitrile Trimer and Di(ammoniomercapto)-methylenecyanothioacetamide (**4**).—The reaction mixture in the case of method A, freed from **1**, was kept overnight in an icebox. About 10 g of a yellow material precipitated. Recrystallization from pyridine–water yielded 0.5 g of a light yellow powder. *Anal.* Calcd for $C_9H_6N_6$: C, 54.24; H, 2.82; N, 41.98; mol wt, 198.2. Found: C, 54.24; H, 2.64; N, 41.77; mol wt (mass spectroscopy), 198. Ir (KBr) 3430, 3340 (s), 3240 (m, ν_{NH_2}), 2960 (m, ν_{CH_2}), 2218 (m, ν_{CN}), 2200 cm^{-1} (vs, $\nu_{conj\ CN}$). nmr (DMSO-d_6) δ 7.45 (s, 4, NH_2), 3.95 (s, 2, CH_2). From the above analytical results, the compound was believed to be 4,6-diamino-3,5-dicyano-2-cyanomethylpyridine (**5**).

The filtrate from which **1** and the above trimer (**5**) were removed was concentrated to about one-half volume under reduced pressure at 40–45° and kept overnight in an icebox. The yellow precipitates obtained were recrystallized from water, washed with ethanol, and dried: yellow plates (**4**), yield 6.1 g (3.9%), mp 136–137° dec (slow heating), 153–156° dec (rapid heating). *Anal.* Calcd for $C_4H_{10}N_4S_3$: C, 22.86; H, 4.86; N, 26.66; S, 45.68; mol wt, 210.15. Found: C, 23.23; H, 4.83; N, 26.56; S, 45.36; mol wt, 214.7 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 288 mμ (sh, log ϵ 2.88), 310 (2.97), 370 (3.07); ir (KBr) 3310 (s, ν_{NH}), 3080, 2960 (s, br, $\nu_{NH_4^+}$), 2180 (s, ν_{CN}), 1590 (s, $\nu_{C=N}$), 1505 (m, $\nu_{conj\ C=C}$), 1415 cm^{-1} (s, br, $\delta_{NH_4^+}$). The compound produced a violet coloration on sodium nitroprusside test.

Methylation of 4.—To a solution of **4** (1.8 g) and sodium hydroxide (0.8 g) in 100 ml of water was added dropwise 5 g of di-

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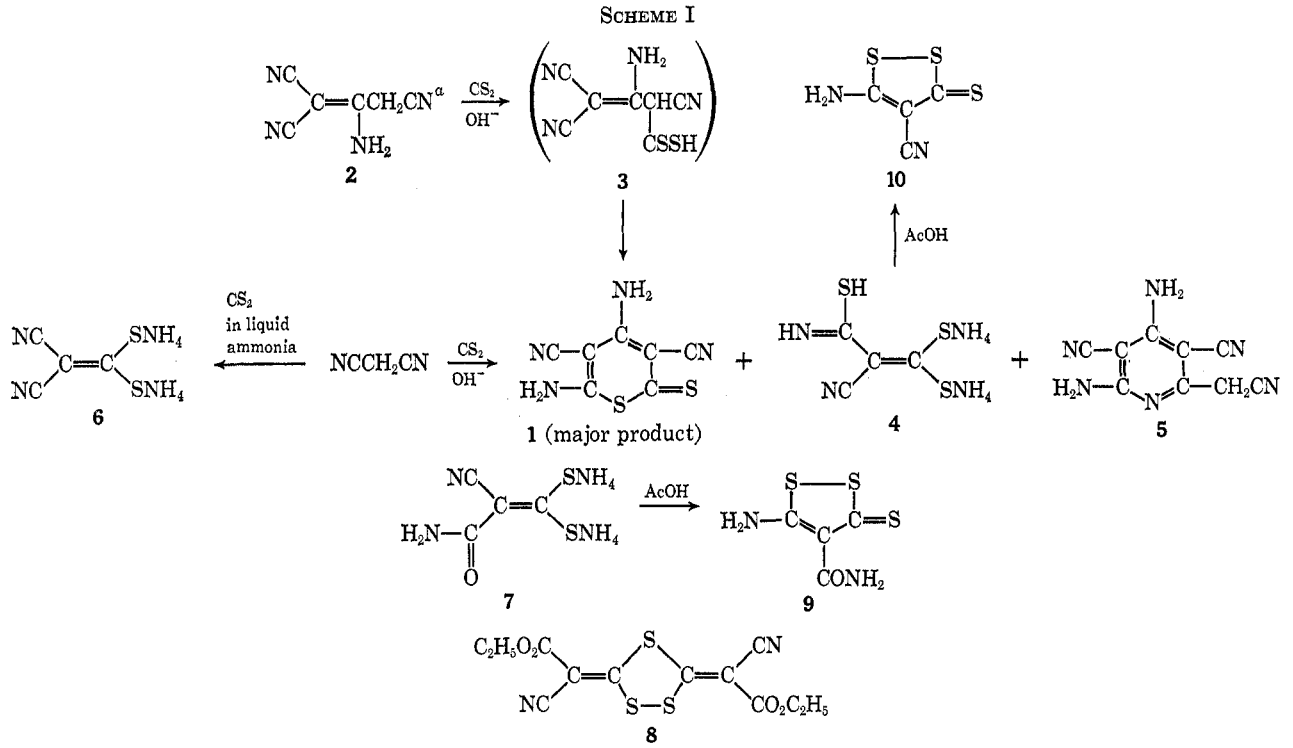
SCHEME I



[a] The structure of the dimer of malononitrile was considered to assume enamine form on the basis of the ir spectrum which showed two separate absorptions (2210 and 2200 cm^{-1}) of the two cyano groups and the nmr spectrum of NH_2 (δ 8.50 in DMSO-d_6).

methyl sulfate under stirring. The yellow material was collected and recrystallized from pyridine–water: yellow needles, yield 1.5 g (86%), mp 219–220°. *Anal.* Calcd for $C_6H_8N_2S_3$: C, 35.30; H, 3.95; N, 13.72; S, 47.03; mol wt, 204.14. Found: C, 35.52; H, 4.14; N, 14.00; S, 46.97; mol wt, 213.5 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 245.5 mμ (log ϵ 4.05), 315 (3.94), 367.5 (4.27); ir (KBr) 3320 (s, ν_{NH}), 2990 2910 (w, ν_{CH_3}), 2192 (s, ν_{CN}), 1605 (vs, $\nu_{C=N}$), 1480 (m, $\nu_{C=C}$), 1380 cm^{-1} (vs, δ_{CH_3}); nmr (DMSO-d_6) δ 2.60 (s, 3, CH_3), 2.50 (s, 3, CH_3). The compound was di(methylthio)-methylenecyanothioacetamide. It produced a violet coloraton on sodium nitroprusside test.

Treatment of 4 with Acetic Acid.—To 4 (2 g) in 100 ml of water was added acetic acid (4.5 ml). The reaction mixture was allowed to stand for 1 hr at room temperature. The crude product was collected and recrystallized from pyridine–water to give yellow prisms, yield 1.2 g (72%). *Anal.* Calcd for $C_4H_2N_2S_3$: C, 27.60; H, 1.15; N, 16.10; S, 55.50; mol wt, 174. Found: C, 27.97; H, 0.85; N, 16.35; S, 55.25; mol wt, 180.0 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 233.5 mμ (log ϵ 4.06), 283 (sh, 3.87), 311 (4.09), 369 (3.68); ir (KBr) 3350, 3250, 3160 (s, ν_{NH_2}), 2200 (s, $\nu_{conj\ CN}$), 1620 (vs, δ_{NH_2}), 1510 cm^{-1} (vs, ν_{ring}); nmr (DMSO-d_6) δ 9.58 (s, br, 2, NH_2). The compound was 5-amino-4-cyano-1,2-dithiol-3-thione (10). The uv spectrum agreed with that reported by Mayer, *et al.*[5] The ir spectrum also agreed with that measured by Söderbäck's method.[6]

Preparation of Di(ammoniomercapto)methylenemalononitrile (6).—A mixture of malononitrile (25 g, 0.38 mol), carbon disulfide (57 g, 0.75 mol), and *ca.* 200 ml of liquid ammonia was stirred for 30 min under cooling by Dry Ice–methanol. The reaction mixture then was allowed to stand at room temperature. A yellow solid material was recrystallized from methanol–chloroform to give light yellow plates: yield 65.5 g (98%); mp 141–142° dec (slow heating), 156–158° dec (rapid heating). *Anal.* Calcd for $C_4H_8N_4S_2$: C, 27.12; H, 4.59; N, 30.90; S, 36.41; mol wt, 176.14. Found: C, 27.00; H, 4.81; N, 30.83; S, 36.30; mol wt, 160.0 (vapor-pressure osmometer, in acetone).

The compound was methylated with dimethyl sulfate by the same method as above (see methylation of 4). Recrystallization from methanol yielded 1.5 g of colorless needles [$(CH_3S)_2$-$C_2(CN)_2$]: yield 86%, mp 83–84° (lit.[3] mp 80–81°), undepressed by the addition of an authentic specimen.[3]

Treatment of 6 with Acetic Acid.—Compound 4 (3.3 g, 0.02 mol) and acetic acid (2.2 ml, 0.04 mol) in 100 ml of water was kept overnight at room temperature. A yellow solid material was collected and recrystallized from DMSO to give a yellow powder, yield 2 g (74%). The compound had formula $(C_4H_2N_2S_2)_3$. *Anal.* Calcd for $C_{12}H_6N_6S_6$: C, 33.81; H, 1.41; N, 19.70; S, 45.10; mol wt, 426.6. Found: C, 33.90; H, 1.41; N, 19.82; S, 45.05; mol wt, 420 (vapor-pressure osmometer, in acetone).

Conversion of 6 into 4.—Compound 6 (8 g) was dissolved in 100 ml of ethanol, and hydrogen sulfide was passed through for 30 min. The reaction mixture was shaken for an additional 3 hr; 0.5 g of 4 was obtained. The compound was identified as 4 by a mixture melting point test. Compound 4 was converted into 10 on treatment with acetic acid as mentioned above.

Preparation of Di(ammoniomercapto)methylenecyanoacetamide (7).—A mixture of ethyl cyanoacetate (120 g, 1.1 mol), carbon disulfide (161 g, 2.1 mol), and 360 ml of aqueous ammonia (28%) was stirred at room temperature for 8 hr. The crude product was collected and recrystallized from water–acetone to give light yellow prisms: yield 83 g (40%), mp 147–148° dec (slow heating), *ca.* 170° dec (rapid heating). *Anal.* Calcd for $C_4H_{10}OS_2$: C, 24.74, H, 5.19; N, 28.86; S, 32.99; mol wt, 194.15. Found: C, 25.05; H, 5.11; N, 28.65; S, 32.83; mol wt, 181.9 (vapor-pressure osmometer, in H_2O). Uv max (H_2O) 312 mμ (sh, log ϵ 3.75), 340 (3.76); ir (KBr) 3280, 3225, 3110 (m, ν_{NH_2}), 3000 (m, br, $\nu_{NH_4^+}$), 2185 (s, ν_{CN}), 1663 (m, ν_{CO}), 1625 (s, δ_{NH_2}), 1500 (s, $\nu_{conj\ C=C}$), 1415 cm^{-1} (s, br, $\delta_{NH_4^+}$); nmr (D_2O) δ 4.85 (s, 8, NH_4^+).

Compound 7 also was prepared from cyanoacetamide. A mixture of cyanoacetamide (17 g, 0.2 mol), carbon disulfide (30 g, 0.4 mol), and 140 ml of aqueous ammonia (28%) was refluxed at 70–80° for 8 hr. Compound 7 which was obtained weighed 18 g (yield 45%).

Compound 7 was methylated using dimethyl sulfate as mentioned above. The methylated compound was recrystallized from methanol to give colorless needles, yield 77%, mp 84°. *Anal.* Calcd for $C_6H_8N_2OS_2$: C, 38.30; H, 4.29; N, 14.89; S, 34.05; mol wt, 188.14. Found: C, 38.25; H, 4.29; N, 14.70; S, 33.85; mol wt, 186.5 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 324 mμ (log ϵ 4.13); ir (KBr) 3400, 3290, 3220, 3185 (s, ν_{NH_2}), 2930 (w, ν_{CH_3}), 2200 (s, ν_{CN}), 1650 (vs, ν_{CO}), 1610 (s, δ_{NH_2}), 1490 (s, $\nu_{conj\ C=C}$), 1385 cm^{-1} (s, δ_{CH_3}); nmr (DMSO-d_6) δ 7.05 (br, 2, NH_2), 2.70 (s, 3, CH_3), 2.55 (s, 3, CH_3).

Isolation of $C_9H_{17}N_5O_3S_2$.—The filtrate from which 7 was removed was kept overnight in an icebox. The yellow material

obtained was recrystallized from water: yellow prisms, mp 129–130° dec, yield 6 g (9%).

Anal. Calcd for $C_9H_{17}N_5O_3S_2$: C, 35.19; H, 5.54; N, 22.80; S, 20.85; mol wt, 307. Found: C, 35.13; H, 5.62; N, 22.51; S, 21.28; mol wt, 285 (vapor-pressure osmometer, in H_2O). Uv max (H_2O) 281.5 mμ (br, log ε 3.59), 343 (4.26); nmr (D_2O) δ 4.85 (s, 8, NH_4^+), 4.13 (q, 2, CH_2, J = 7 cps), 1.28 (t, 3, CH_3, J = 7 cps).

The compound was methylated with dimethyl sulfate. Colorless needles of ethyl di(methylthio)methylenecyanoacetate were obtained. Recrystallization from methanol yielded 1.3 g (92%), mp 55–56°, undepressed by the addition of an authentic specimen.[3]

When the compound was treated with hydrogen peroxide (1%), colorless needles (**8**) of mp 223–224° were obtained. The product was recrystallized from pyridine–water.

Anal. Calcd for $C_{12}H_{10}N_2O_4S_3$: C, 42.15; H, 2.93; N, 8.19; S, 28.05; mol wt, 342. Found: C, 42.22; H, 3.00; N, 8.29; S, 27.99; mol wt, 326.7 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 230 mμ (log ε 4.37), 335 (4.35); ir (KBr) 2992, 2977 (m, ν_{CH}), 2220 (s, ν_{CN}), 1689 (sh, ν_{CO}), 1669, 1658 cm^{-1} (vs, $\nu_{C=C}$); ir ($CHCl_3$) 2985 (m, ν_{CH}), 2200 (s, ν_{CN}), 1690 (sh, ν_{CO}), 1683 cm^{-1} (s, $\nu_{C=C}$); nmr (DMSO-d_6) δ 4.30 (q, 4, CH_2, J = 7 cps), 1.27 (t, 6, CH_3, J = 7 cps). The structure was tentatively designated 3,5-di(cyanocarbethoxymethylene)-1,2,4-trithiole (**8**). This trithiole was also obtained by treating ethyl di(sodiomercapto)methylenecyanoacetate with hydrogen peroxide (5%).

Preparation of 5-Amino-4-carbamoyl-1,2-dithiole-3-thione (9).—Compound **7** (18 g, 0.09 mol) was dissolved in 100 ml of water. To this solution was added acetic acid (10 ml) and the solution was stirred at room temperature for 1 hr. The crude product was recrystallized from pyridine–water: yellow prisms, mp 247–248° dec (slow heating), *ca.* 258° dec (rapid heating), yield 8 g (45%). *Anal.* Calcd for $C_4H_4N_2OS_3$: C, 25.01; H, 2.10; N, 14.58; S, 49.95; mol wt, 192.09. Found: C, 25.31; H, 2.16; N, 14.47; S, 49.95; mol wt, 173.1 (vapor-pressure osmometer, in acetone). Uv max (99% EtOH) 240.5 mμ (log ε 3.96), 286 (sh, 3.90), 314.5 (4.54), 364.5 (3.93); ir (KBr) 3220 (s), 3140 (w), 3020 (w, ν_{NH_2}), 1650 (sh, ν_{CO}), 1640 (vs, δ_{NH_2}), 1550 cm^{-1} (vs, $\nu_{conj\ C=C}$); nmr (DMSO-d_6) δ 10.35 (br, 2, $CONH_2$), 8.70 (br, 2, NH_2). The uv spectrum of **9** agreed with that reported by Mayer, *et al.*[5]

When **9** was treated with dimethyl sulfate, methyl carbamoylcyanodithioacetate (light yellow prisms, mp 233–234°)[3] and a small amount of sulfur were obtained.

Registry No.—Malononitrile, 109-77-3; carbon disulfide, 75-15-0; **1**, 24571-55-9; **4**, 24571-56-0; **4** (methylated), 24571-57-1; **6**, 24571-58-2; **7**, 24571-59-3; **7** (methylated), 17823-69-7; **8**, 2631-93-8; **9**, 5147-79-5; **10**, 5147-74-0; **5**, 24571-64-0.

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Synthesis of 2-*t*-Butylaminobenzophenones and Benzaldehydes

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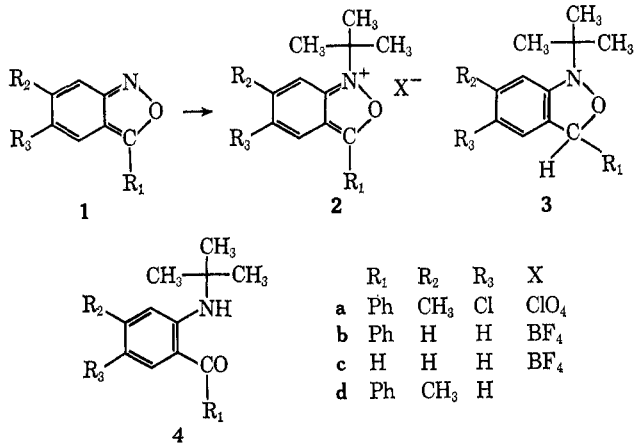
During work on a program aimed at the synthesis of various 2(1H)-quinazolinones,[1] the need arose for monoalkylated 2-aminobenzophenones as intermediates. Although many monoalkyl derivatives can be prepared by standard procedures, attempts to extend these to the introduction of the *t*-butyl group led to very limited or no success. We now wish to report a novel route to these compounds which has been realized in excellent overall yield.

Whereas 3-phenyl-2,1-benzisoxazoles (**1**) are reduced completely by lithium aluminum hydride to 2-aminobenzhydrols,[2] less powerful reagents such as metal–acid combinations[3,4] or catalytic hydrogenation[5,6] give 2-aminobenzophenones. No intermediates retaining the heterocyclic ring were detected in these cases. Possibly then, formation of the quaternary salt from the benzisoxazole and subsequent reduction might yield alkylated aminobenzophenones, but the required salts had not previously been isolated.[7] The SN1 alkylation of substituted isoxazoles had been described,[8] however, and not only was the reaction particularly efficient with *t*-butyl alcohol but the perchlorate salts were readily isolable.

Application of this procedure to several 2,1-benzisoxazoles (**1**) gave the desired salts (**2**) in good yield. Addition of sodium borohydride to a suspension of the salt (*e.g.*, **2a**) in ethanol led to rapid solution, and work-up yielded a colorless crystalline product identified from its spectral properties as the intermediate 1-*t*-butylbenzisoxazoline (**3a**). This compound proved to be surprisingly stable but it was noticed while determining the melting point that on continued heating the melt became an intense yellow which did not disappear on subsequent cooling. Spectral analysis of a sample of the yellow product isolated by chromatography showed that a thermal isomerization had occurred, the desired 2-*t*-butylaminobenzophenone (**4a**) having been cleanly formed. It was then found that this isomerization occurred in the three cases examined, heating the neat material at 160° for 4 hr being sufficient to effect better than 90% conversion.



	R_1	R_2	R_3	X
a	Ph	CH_3	Cl	ClO_4
b	Ph	H	H	BF_4
c	H	H	H	BF_4
d	Ph	CH_3	H	

The use of this sequence to prepare 2-*t*-butylaminobenzaldehyde (**4c**) in good yield is particularly interesting since 2-aminobenzaldehydes in general polymerize on contact with acid,[9] the presence of which is

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