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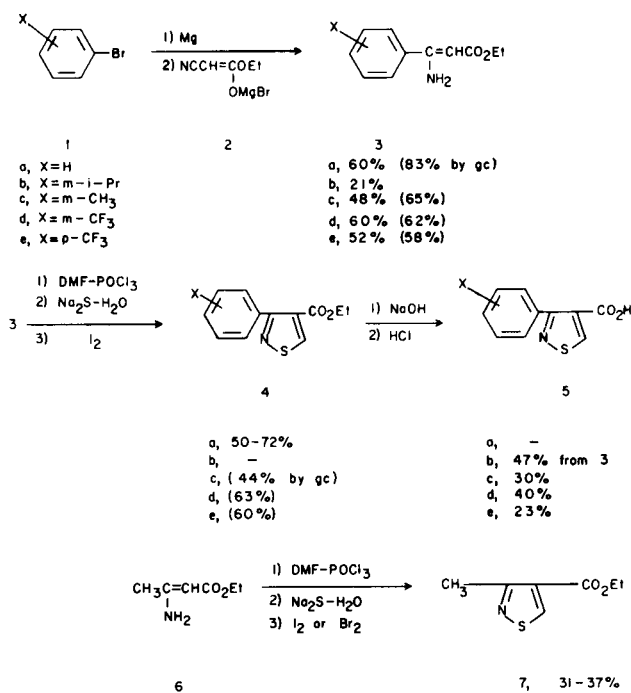
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A short, convenient route to 3-aryl-4-isothiazolecarboxylates is described in which aryl Grignard reagents are added to the magnesium enolate of ethyl cyanoacetate, and the resultant β -aminocinnamates are converted *via* a Vilsmeier-Haack reaction, thiation, and oxidation to the isothiazolecarboxylates.

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Several routes to 3-aryl-4-isothiazolecarboxylates and 5-substituted-3-aryl-4-isothiazolecarboxylates have been reported (1-10); these materials are of considerable interest as intermediates for penicillins (7,11-13). We report here a particularly convenient and short route to 3-aryl-4-isothiazolecarboxylic acids.

We prepared β -aminocinnamates **3a-e** in moderate yields by the addition of one equivalent of the appropriate aryl Grignard reagent to **2**, the enolate formed from phenylmagnesium bromide and ethyl cyanoacetate. Mavrodin (14) had found that reaction of equivalent amounts of phenylmagnesium bromide and ethyl cyanoacetate in ether produced **2**, which regenerated ethyl cyanoacetate upon hydrolysis. Mavrodin further reported that reaction of the enolate with additional phenylmagnesium bromide followed by hydrolysis gave ethyl benzoylacetate (14). Kovar, *et al.*, (15) employed this reaction with 45-100% excess Grignard reagent and with a milder hydrolysis step to prepare the intermediate ethyl β -aminocinnamate in 63-83% yields. We did not find the use of excess Grignard reagent to be advantageous. The reaction time had a significant effect; the yield of **3c** appeared to reach a maximum in four to nineteen hours and then decreased.



The β -aminocinnamates were converted to the ethyl 3-aryl-4-isothiazolecarboxylates **4a-e** by use of minor modifications of the procedure developed by Crenshaw and Partyka (4) for conversion of β -aminocinnamitrile to 3-phenyl-4-isothiazolecarbonitrile. Thiation of the intermediate from the Vilsmeier-Haack reaction proceeded equally well with sodium sulfide, sodium hydrosulfide, or ammonium sulfide. Oxidation of the resultant enethiol to **4** with either iodine or bromine gave the same yield. The crude **4a** prepared by this route was 97% pure. Compounds **4b-e** were converted without purification to the acids **5b-e** by hydrolysis. Pure samples of **4b-e** were prepared from the purified acids.

Ethyl β -aminocrotonate (**6**) was converted to ethyl 3-methyl-4-isothiazolecarboxylate (**7**) in 31-37% yields by the Vilsmeier-Haack reaction sequence. Isothiazole **7** has been prepared in 50-54% yield by treatment of **6** with thiophosgene and triethylamine (16,17). The thiophosgene method does not work with ethyl β -aminocinnamate (5).

EXPERIMENTAL

Melting points were determined in open capillaries with a Mel-Temp apparatus and are corrected. Boiling points are uncorrected. Gc analyses were performed on a 2 ft. x 0.25 in. column packed with 10% SE-30 on Chromosorb W. Gc yields were determined by gc analysis of solutions of weighed aliquots of crude products and chlorobenzene or *o*-dichlorobenzene as an internal standard. Analyses were calibrated by means of synthetic mixtures of pure products and internal standards.

General Procedure for Ethyl β -Aminocinnamates (3).

To a solution of 1.0 mole of phenylmagnesium bromide in *ca.* 600 ml. of ether was added dropwise 1.0 mole of ethyl cyanoacetate with stirring at -55 to -35° (exothermic reaction). A heavy precipitate formed that prevented stirring. The mixture was allowed to warm to 15°. Then, 1.0 mole of the appropriate arylmagnesium bromide in *ca.* 600 ml. of ether was added under dry nitrogen gas. The mixture was stirred at reflux. At various time intervals, aliquots were shaken with excess aqueous ammonium chloride and then were analyzed by gc. When the ethyl cyanoacetate was nearly all consumed and/or the product yield had reached a maximum, the reaction mixture was cooled to 10° and was poured slowly with stirring into 1.7 l. of ice-water mixture containing 2.0 moles of ammonium chloride. Then an ice-cold solution of 2.0 moles of hydrogen chloride in 500 ml. of water was added with stirring. The layers were shaken together and separated. The aqueous layer was extracted with two 400-ml. portions of ether. The ether layers were combined, dried (calcium

sulfate), and concentrated under aspirator vacuum to give crude product. After this material was analyzed by gc for yield data, it was purified by vacuum distillation.

Ethyl β -Aminocinnamate (**3a**).

For this particular derivative, 1.0 ml. of ethyl cyanoacetate was added to 2.0 moles of phenylmagnesium bromide. The reaction mixture was held at reflux for 19 hours. Workup gave crude product that was 93% **3a** (gc assay with internal standard); **3a** was obtained in 83% yield (corrected for purity). Two distillations of the crude product gave 99.9% pure ethyl β -aminocinnamate, b.p. 110-112° (0.2 torr) [lit. (15a) b.p. 110° (0.05 torr)] in 60% yield.

Ethyl β -Amino-*m*-isopropylcinnamate (**3b**).

The Grignard reagent from *m*-bromocumene (18) and enolate **2** were heated in ether at reflux for 19 hours and then allowed to stand at 23° for four days (19). After the usual workup, the crude product was distilled to give 80% pure **3b**, b.p. 139-142° (0.15 torr), in 21% yield (corrected for purity). Redistillation of a small sample gave a 97% pure sample of **3b**, b.p. 142-143° (0.15 torr) [ir analysis of the lower-boiling impurity indicated it to be bi(*m*-cumenyl)].

Anal. Calcd. for 97% C₁₄H₁₉NO₂-3% C₁₈H₂₂: C, 72.60; H, 8.24; N, 5.82. Found: C, 72.60; H, 8.46; N, 5.84.

Ethyl β -Amino-*m*-methylcinnamate (**3c**).

The reaction mixture was worked up after 4 hours at reflux. The crude product was 70% pure **3c** (65% yield, corrected for purity). Two distillations of the material gave 97% pure **3c**, b.p. 118° (0.05 torr), in 48% yield. A small sample was redistilled to give 100% pure **3c**, b.p. 118° (0.1 torr).

Anal. Calcd. for C₁₂H₁₅NO₂: C, 70.22; H, 7.37. Found: C, 70.31; H, 7.44.

Ethyl β -Amino-*m*-trifluoromethylcinnamate (**3d**).

Caution: A large scale preparation of *m*-trifluoromethylphenylmagnesium bromide resulted in an explosion (20).

Workup of the reaction mixture after 44 hours at reflux gave 75% pure **3d** in 62% yield (corrected for purity). Gc analysis of the crude product on a 10 ft. x 0.25 in. column packed with 5% SE-30 on chromosorb W revealed that the **3d** contained < 1% (none detected) of **3a**, which elutes later than **3d**. Distillation of the crude product gave 94% pure **3d**, b.p. 110-115° (0.05 torr), in 60% yield. Redistillation of a small sample gave 100% pure **3d**, b.p. 106-107° (0.06 torr).

Anal. Calcd. for C₁₂H₁₂F₃NO₂: C, 55.60; H, 4.67. Found: C, 55.42; H, 4.36.

Ethyl β -Amino-*p*-trifluoromethylcinnamate (**3e**).

Workup of the reaction mixture after 22 hours at reflux gave 75% pure **3e** in 58% yield (corrected for purity). Distillation of the crude product gave 93% pure **3e** (52% yield), b.p. 113-122° (0.08 torr). Redistillation of this material gave ca. 100% pure **3e**, b.p. 103° (0.08 torr), m.p. 45-50°.

Anal. Calcd. for C₁₂H₁₂F₃NO₂: C, 55.60; H, 4.67. Found: C, 55.76; H, 4.80.

General Procedure for Ethyl 3-Aryl-4-isothiazolecarboxylates (**4**).

To a solution of 0.10 mole of the appropriate ethyl β -aminocinnamate **3** in 90 ml. of reagent grade dimethylformamide was added 0.10 mole of phosphorus oxychloride with stirring at -60° under dry nitrogen gas. The mixture was allowed to warm (exothermic) to ca. 15-25° and then was stirred at 25° for 10 minutes. The solution was poured into an ice-cold solution of 0.11 mole of ium sulfide nonahydrate in 110 ml. of water with stirring at

0-25°. The resultant yellow mixture was stirred for 5 minutes and was extracted with 300 ml. of benzene and then with two 150-ml. portions of benzene. The benzene layers were combined and dried (calcium sulfate). To the benzene solution was added 25.4 g. (0.10 mole) of iodine in 200 ml. of benzene with stirring at 20-30° during a few minutes. The dark benzene solution was washed twice with aqueous potassium carbonate solution, twice with sodium thiosulfate solution, again with potassium carbonate solution, dried (calcium sulfate), and concentrated under vacuum to give the crude isothiazolecarboxylate.

Ethyl 3-Phenyl-4-isothiazolecarboxylate (**4a**).

In several experiments yields of **4a** ranged from 50-72%. The **4a** thus obtained was ca. 97% pure (gc assay) and was identical (ir, nmr, gc) with an authentic sample.

3-*m*-Cumenyl-4-isothiazolecarboxylic acid (**5b**).

The 6.1 g. of crude **4b** prepared from 5.8 g. of 80% pure **3b** was hydrolyzed with 4.0 g. (0.10 mole) of sodium hydroxide in 80 ml. of 50% aqueous ethanol at reflux for 1 hour. The solution was concentrated under vacuum. The residue was diluted with 200 ml. of water. The mixture was extracted three times with ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted three times with ether. These latter three ether extracts were combined and concentrated under vacuum. The residue was crystallized once from aqueous ethanol and from 1,2-dichloroethane-heptane (charcoal) to give 2.32 g. (47% from **3b**) of solid, m.p. 157-159°. A small sample was recrystallized to give a white solid, m.p. 158-160°.

Anal. Calcd. for C₁₃H₁₃NO₂S: C, 63.13; H, 5.30. Found: C, 62.94; H, 5.15.

Ethyl 3-*m*-Cumenyl-4-isothiazolecarboxylate (**4b**).

A mixture of 1.50 g. (0.00608 mole) of 3-(*m*-cumenyl)-4-isothiazolecarboxylic acid and 5 ml. (8.2 g., 0.069 mole) of thionyl chloride was heated at reflux on a steam bath for 30 minutes and was concentrated under vacuum. The residue was heated in 15 ml. of ethanol at reflux for 15 minutes; the solution was filtered and concentrated under vacuum to 90° (0.3 torr) to give 1.53 g. (92%) of oil; $n_D^{25} = 1.5684$; ir (film) 5.80 μ ; nmr (deuteriochloroform): δ 9.44 (s, 1, 5-H), 7.47 (m, 4, ArH), 4.34 (q, 2, CH₂), 3.03 (heptet, 1, CH), 1.33 (d, 6, CH₃), 1.25 (t, 3, CH₃).

Anal. Calcd. for C₁₅H₁₇NO₂S: C, 65.43; H, 6.22. Found: C, 65.46; H, 6.30.

3-*m*-Tolyl-4-isothiazolecarboxylic acid (**5c**).

Hydrolysis of the crude **4c** prepared (in 44% yield) from **3c** and several recrystallizations of the acid from 1,2-dichloroethane gave pure **5c** (30% from **3c**), m.p. 144.5-146°.

Anal. Calcd. for C₁₁H₉NO₂S: C, 60.26; H, 4.14. Found: C, 60.21; H, 4.04.

Ethyl 3-*m*-Tolyl-4-isothiazolecarboxylate (**4c**).

Treatment of **5c** with thionyl chloride and then ethanol gave **4c** as an oil in 98% yield; $n_D^{25} = 1.5823$; nmr (deuteriochloroform): δ 9.43 (s, 1, 5-H), 7.40 (m, 4, ArH), 4.32 (q, 2, CH₂), 2.43 (s, 3, CH₃), 1.27 (t, 3, CH₃).

Anal. Calcd. for C₁₃H₁₃NO₂S: C, 63.13; H, 5.30. Found: C, 63.27; H, 5.38.

3-(α,α,α -Trifluoro-*m*-tolyl)-4-isothiazolecarboxylic acid (**5d**).

The crude **4d** was hydrolyzed, and the resultant crude acid was crystallized once from benzene and several times from aqueous methanol (charcoal) to give pure **5d**, m.p. 122-124° and 136-138° (two crystal forms), in 40% yield from **3d**.

Anal. Calcd. for C₁₁H₆F₃NO₂S: C, 48.35; H, 2.21. Found:

C, 48.44; H, 2.22.

Ethyl 3-(α,α,α -Trifluoro-*m*-tolyl)-4-isothiazolecarboxylate (**4d**).

The ester **4d**, prepared in 97% yield, is an oil; ir (chloroform): 5.81 μ ; nmr (deuteriochloroform): δ 9.43 (s, 1, 5-H), 8.03-7.43 (m, 4, ArH), 4.30 (q, 2, CH₂), 1.23 (t, 3, CH₃).

Anal. Calcd. for C₁₃H₁₀F₃NO₂S: C, 51.82; H, 3.35. Found: C, 52.09; H, 3.50.

3-(α,α,α -Trifluoro-*p*-tolyl)-4-isothiazolecarboxylic acid (**5e**).

The reaction mixture from treatment of **3e** with DMF-phosphorus oxychloride was held at 45-50° for 15 minutes and then was processed in the usual way. The resultant **4e** (60% yield by gc analysis) was hydrolyzed to **5e**. The crude **5e** was crystallized three times from 1,2-dichloroethane to give pure **5e**, m.p. 195-196°, in 23% yield from **3e**.

Anal. Calcd. for C₁₁H₆F₃NO₂S: C, 48.35; H, 2.21. Found: C, 48.39; H, 2.24.

Ethyl 3-(α,α,α -Trifluoro-*p*-tolyl)-4-isothiazolecarboxylate (**4e**).

Acid **5e** was converted to the ester, which was crystallized from ethanol to give pure **4e**, m.p. 63-64°, in 51% yield; ir (mineral oil mull): 5.80 μ ; nmr (deuteriochloroform): δ 9.51 (s, 1, 5-H), 7.84 (s, 4, ArH), 4.33 (q, 2, CH₂), 1.27 (t, 3, CH₃).

Anal. Calcd. for C₁₃H₁₀F₃NO₂S: C, 51.82; H, 3.35. Found: C, 51.77; H, 3.35.

Ethyl 3-Methyl-4-isothiazolecarboxylate (**7**).

To a solution of 64.6 g. (0.50 mole) of ethyl β -aminocrotonate in 200 ml. of dry DMF was added, with stirring in a dry ice-acetone bath, 81.2 g. (48.5 ml., 0.53 mole) of phosphorus oxychloride during 5 minutes at -40 to +10° (exothermic reaction). The mixture was stirred for 10 minutes at 25° and then was poured into a cold solution of 144 g. (0.60 mole) of sodium sulfide nonahydrate in 1 l. of water. The yellow mixture was extracted with 300 ml. of benzene (the yellow solid dissolved) and then with three 200-ml. portions of benzene. The benzene layers were combined, dried (calcium sulfate), and split into halves, one for treatment with bromine and one for treatment with iodine.

The first half was treated with 12.85 ml. (40 g., 0.25 mole) of bromine in 50 ml. of benzene (exothermic reaction). The black reaction mixture was cooled to 23° and was extracted with 500 ml. of water. The water extract was back-extracted with 200 ml. of benzene. The benzene layers were combined, extracted four times with saturated sodium carbonate solution and once with aqueous sodium thiosulfate solution, dried (calcium sulfate), and distilled to give 19.44 g. of a mixture of solid and liquid. This material was added to 80 ml. of ether, and the mixture was extracted three times with water (the first water layer was acidic)

and once with potassium carbonate solution, dried, and distilled to give 15.7 g. (37%) of 100% pure **7**, b.p. 92-94° (3.5 torr) [lit. (17) b.p. 91.5-93° (3 torr)].

The second half of the benzene solution was treated with 63.5 g. (0.25 mole) of solid iodine. The mixture was stirred for 0.5 hour and was worked up as for the bromine oxidation. Distillation of the benzene solution gave 16.5 g. (39%) of 94% pure product, b.p. 83-98° (3 torr). Redistillation gave 13.4 g. (31%) of 98% pure product, b.p. 99-102° (7.5 torr).

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