Application of the Smiles Rearrangement to the Synthesis of 5,7-Disubstituted Xanthone-2-carboxylic Acids (1)

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The depside-like esters **3a** and **3b** underwent a Smiles rearrangement on treatment with base. The resulting diphenyl ethers **4a** and **4b** were converted into the xanthonecarboxylic acids **6a** and **6b** which are not readily accessible by other routes.

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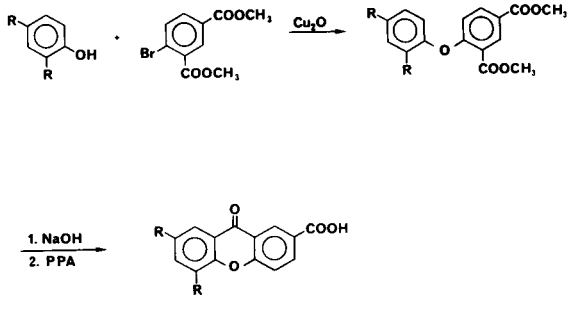
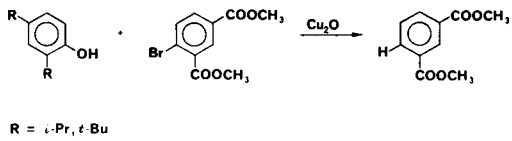
5,7-Disubstituted xanthone-2-carboxylic acids are known to possess potent antiallergy activity (2,3). They are usually prepared by a modified Ullmann reaction (4) of dimethyl 4-bromoisophthalate with a 2,4-disubstituted phenol, followed by saponification and cyclization (5) (Scheme I).

SCHEME I



However, when the phenol carries a bulky group in the ortho position, the Ullman reaction takes an entirely different course. The major (R = *i*-Pr) or even exclusive (R = *t*-Bu) product turns out to be dimethyl isophthalate, formed by reductive debromination with the phenol presumably acting as a hydrogen donor (Scheme II).

SCHEME II

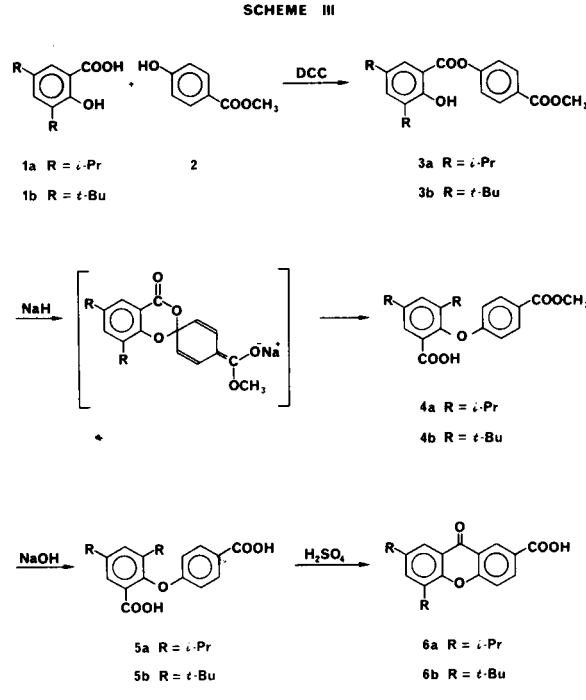


R = *i*-Pr, *t*-Bu

In order to circumvent this problem, the following strategy was adopted. Reaction of the commercially available 3,5-diisopropyl- (**1a**) or 3,5-di-*t*-butylsalicylic acid (**1b**) with methyl 4-hydroxybenzoate (**2**) in the presence of dicyclohexylcarbodiimide (6) gave the depside (7) type esters **3a** and **3b** in good yield. It was postulated that on treatment with a base, these esters would undergo a Smiles rearrangement (8) producing the diphenyl ether derivatives **4a** and **4b**, provided that ester hydrolysis (9) could be prevented by using a non-nucleophilic base in an aprotic, polar solvent. Indeed, reaction of **3a** or **3b** with slightly more than one equivalent of sodium hydride in dimethyl formamide at room temperature led to a rapid, smooth rearrangement in the desired sense.

The remaining ester group was then conventionally hydrolysed, and the resulting dicarboxylic acids **5a** and **5b** cyclized with sulfuric acid to afford the desired xanthonecarboxylic acids **6a** and **6b** in good yields (Scheme III).

SCHEME III



The above scheme should be easily applicable to other 3,5-disubstituted salicylic acids, provided that the substituents are not electron-withdrawing (8).

EXPERIMENTAL

Melting points (uncorrected) were obtained on a Mel-Temp apparatus, infrared spectra with a Perkin-Elmer 237 grating instrument, nmr spectra using a Varian A-60 or HA-100 spectrometer, and mass spectra with either an Atlaswerke CH-4 or CH-7 instrument. Combustion analyses were performed by Syntex Analytical Research and Atlantic Microlab, Atlanta.

4-Carbomethoxyphenyl 3,5-diisopropylsalicylate (**3a**).

A solution of 2.22 g (10 mmoles) 3,5-diisopropylsalicylic acid, 1.67 g (11 mmoles) of methyl 4-hydroxybenzoate, and 2.47 g (12 mmoles) of dicyclohexylcarbodiimide in 60 ml of dry tetrahydrofuran was stirred for 18 hours under an atmosphere of dry nitrogen. The dicyclohexylurea was filtered off and the filter cake washed with ether. Evaporation of the filtrate *in vacuo* gave an oil which was chromatographed on silica gel (hexane-ethyl acetate 9:1) to provide 2.64 g (74%) of a colorless solid. Crystallization from methanol gave colorless leaflets, mp 58-59°; ms: m/e (% relative intensity) 356 (5), 205 (100).

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.50; H, 6.99.

4-Carbomethoxyphenyl 3,5-Di-*t*-butylsalicylate (**3b**).

This compound was obtained in an analogous manner to that described for **3a** above (10 mmole scale) and furnished **3b** as a solid (72%) which crystallized from methanol as colorless needles, mp 119-120°; ms: m/e (% relative intensity) 384 (4), 233 (100).

Anal. Calcd. for $C_{23}H_{20}O_5$: C, 71.85; H, 7.34. Found: C, 71.89; H, 7.29.

2-(4-Carbomethoxyphenoxy)-3,5-diisopropylbenzoic Acid (**4a**).

Sodium hydride (50% oil emulsion, 210 mg, 4.38 mmoles) was added to a solution of **3a** (1.2 g, 3.37 mmoles) in 35 ml of dry dimethylformamide. After stirring at room temperature under nitrogen for 20 minutes, the reaction mixture was quenched with dilute hydrochloric acid. The resulting precipitate was filtered off, washed with water and dried. Crystallization from acetone-hexane gave 1.08 g (90%) of **4a**, mp 179-180°; ms: m/e (% relative intensity) 356 (77), 341 (87), 323 (100), 205 (55), 189 (43), 175 (84).

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.84; H, 6.65.

2-(4-Carbomethoxyphenoxy)-3,5-di-*t*-butylbenzoic Acid (**4b**).

The rearrangement of **3b** was performed similarly to that described for **3a** (3.96 mmole scale), except that the reaction time was only 10 minutes. The product (91%) crystallized from methanol, mp 230-231°; ms: m/e (% relative intensity) 384 (46), 369 (100), 351 (16), 233 (36), 169 (16).

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.96; H, 7.06.

2-(4-Carboxyphenoxy)-3,5-diisopropylbenzoic Acid (**5a**).

A solution of **4a** (900 mg, 2.53 mmoles) and sodium hydroxide (680 mg, 15 mmoles) in ethanol (20 ml) containing water (4 ml) was refluxed for 30 minutes. The hot solution was acidified with dilute hydrochloric acid and cooled. The crystalline product was filtered off, washed with water and dried to give 720 mg (83%) of **5a**, mp 287-289°; ms: m/e (% relative intensity) 342 (67), 327 (95), 309 (100), 205 (48).

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.38; H, 6.56.

2-(4-Carboxyphenoxy)-3,5-di-*t*-butylbenzoic Acid (**5b**).

Saponification of **4b** (1.1 g, 2.86 mmoles) in a fashion analogous to that of **4a** provided **5b** (930 mg, 88%), mp 342-344°; ms: m/e (relative intensity) 370 (39), 355 (100), 337 (45), 233 (20).

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.22; H, 7.24.

5,7-Diisopropylxanthone-2-carboxylic Acid (**6a**).

The dicarboxylic acid **5a** (700 mg, 1.97 mmoles) was dissolved in 10 ml of 96% sulfuric acid. After standing at room temperature for 18 hours, the yellow solution was poured into ice. The white precipitate was filtered off, washed with water and dried to afford 625 mg (93.5%) of the desired xanthonecarboxylic acid **6a**, mp 248-249.5° (tetrahydrofuran-ethanol); ir (potassium bromide): ν max 1690, 1650 cm^{-1}; uv (ethanol): λ max 251 (log ϵ 4.68), 345 nm (3.75); ms: m/e (% relative intensity) 324 (44), 309 (100), 267 (23).

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.88; H, 6.12.

5,7-Di-*t*-butylxanthone-2-carboxylic Acid (**6b**).

Cyclization of **5b** (850 mg, 2.3 mmoles) in 96% sulfuric acid (10 ml) was conducted in a fashion analogous to that of **5a** except that in this case, the reaction was complete after 2 hours at room temperature. The product **6b** (760 mg, 94%) had mp 256-258° (ethanol-water); ir (potassium bromide): ν max 1690, 1650 cm^{-1}; uv (ethanol): λ max 250 (log ϵ 4.71), 344 nm (3.77); ms: m/e (% relative intensity) 352 (21), 337 (100), 281 (10).

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.90; H, 6.94.

REFERENCES AND NOTES

(1) Contribution No. 626 from the Institute of Organic Chemistry, Syntex Research.

(2) J. R. Pfister, R. W. Ferraresi, I. T. Harrison, W. H. Rooks, and J. H. Fried, *J. Med. Chem.*, **21**, 669 (1978).

(3) A. C. Barnes, P. W. Hairsine, S. S. Matharu, P. J. Ramm, and J. B. Taylor, *ibid.*, **22**, 418 (1979).

(4) R. J. R. Bacon and O. J. Stewart, *J. Chem. Soc.*, 4953 (1965).

(5) J. R. Pfister, R. W. Ferraresi, I. T. Harrison, W. H. Rooks, A. P. Roszkowski, A. Van Horn, and J. H. Fried, *J. Med. Chem.*, **15**, 1032 (1972).

(6) S. Neelakantan, R. Padmasani, and T. R. Seshadri, *Tetrahedron*, **21**, 3531 (1965).

(7) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963, p 566.

(8) W. E. Truce, E. M. Kreider, and W. W. Brand, *Org. React.*, **18**, 99 (1970).

(9) The base-induced cleavage (potassium hydroxide-methanol) of depsides is well known: Y. Asahina and H. Akagi, *Chem. Ber.*, **68**, 1130 (1935).