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REACTIONS OF 2-ACYLBENZOATES WITH DIMETHYLOXOSULPHONIUM METHYLIDE: A NOVEL ROUTE TO ISOCOUMARINS

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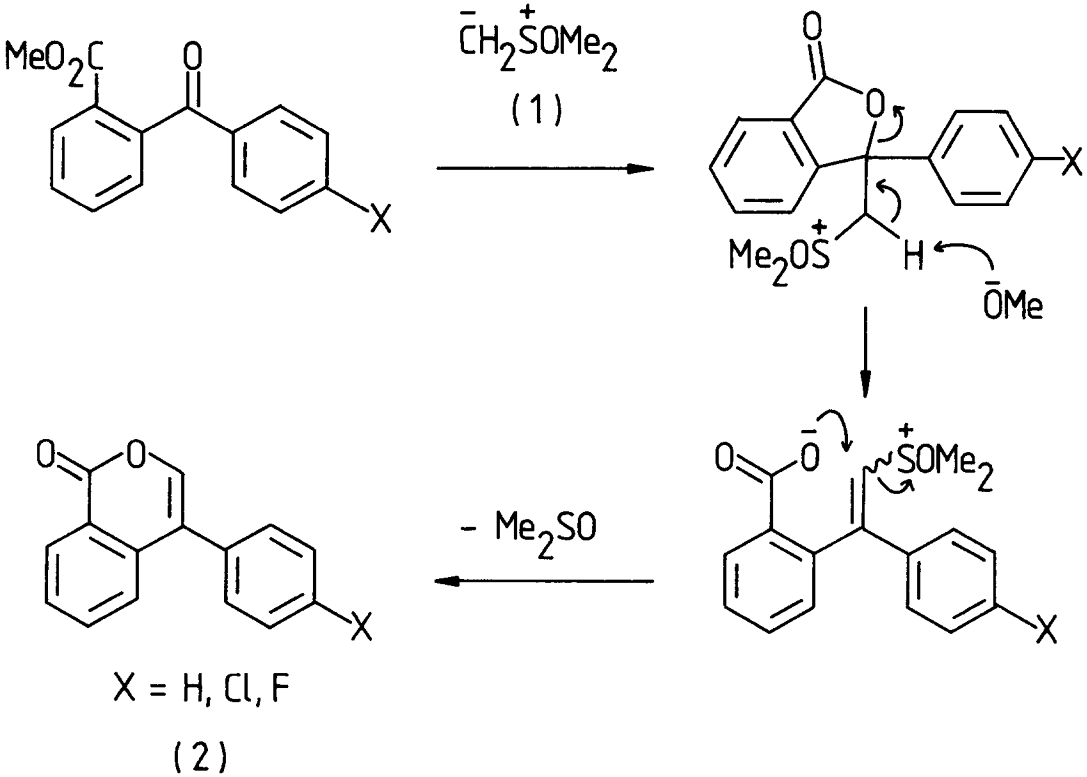
Abstract: Treatment of 2-benzoylbenzoates with dimethyloxosulphonium methylide (1) gives 4-phenylisocoumarins (2); methyl 2-acetylbenzoate gives 4-methylene-3,4-dihydroisocoumarin (3) under the same conditions.

Corey's method[1] for the conversion of ketones into epoxides using sulphonium or oxosulphonium ylides has found widespread use in organic synthesis. We have now discovered that treatment of 2-benzoylbenzoates with dimethyloxosulphonium methylide (1) does not lead to epoxides but, instead, directly to 4-phenylisocoumarins (2). We suggest that this takes place via the steps shown in Scheme 1.[2]

SCHEME 1

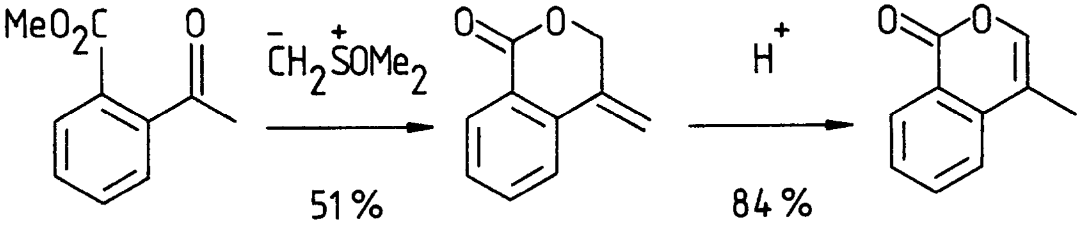


In a typical experiment, dry DMSO (30ml) was added to trimethylsulphoxonium iodide (2.44g, 11.1mmol) and sodium hydride (0.215g, 8.96mmol) and the mixture was stirred under nitrogen at room temperature until effervescence ceased (2 h.). The resulting ylide solution was added dropwise with stirring to methyl 2-(4-fluorobenzoyl)benzoate (2.20g, 8.53mmol) in dry DMF (40ml) cooled in an ice bath. The reaction mixture was heated at 50°C for 1.5 h., then diluted with water. Ether extracts were washed with water, dried and concentrated to give almost pure 4-(4-fluorophenyl)isocoumarin (1.062g, 51%) as an off-white solid.[3]

Under similar conditions, methyl 2-(4-chlorobenzoyl)benzoate gave 4-(4-chlorophenyl)isocoumarin (65%),[3] and methyl 2-benzoylbenzoate gave 4-phenylisocoumarin (52%).[3] Methyl 2-formylbenzoate gave only a very small yield of isocoumarin itself.

Interestingly, methyl 2-acetylbenzoate consistently gave only 4-methylene-3,4-dihydroisocoumarin (3)[4] under the same reaction conditions. On treatment with acid (6M hydrochloric acid, 100°C, 1 h.), this isomerised cleanly into the known compound, 4-methylisocoumarin (4)[5] (Scheme 2).

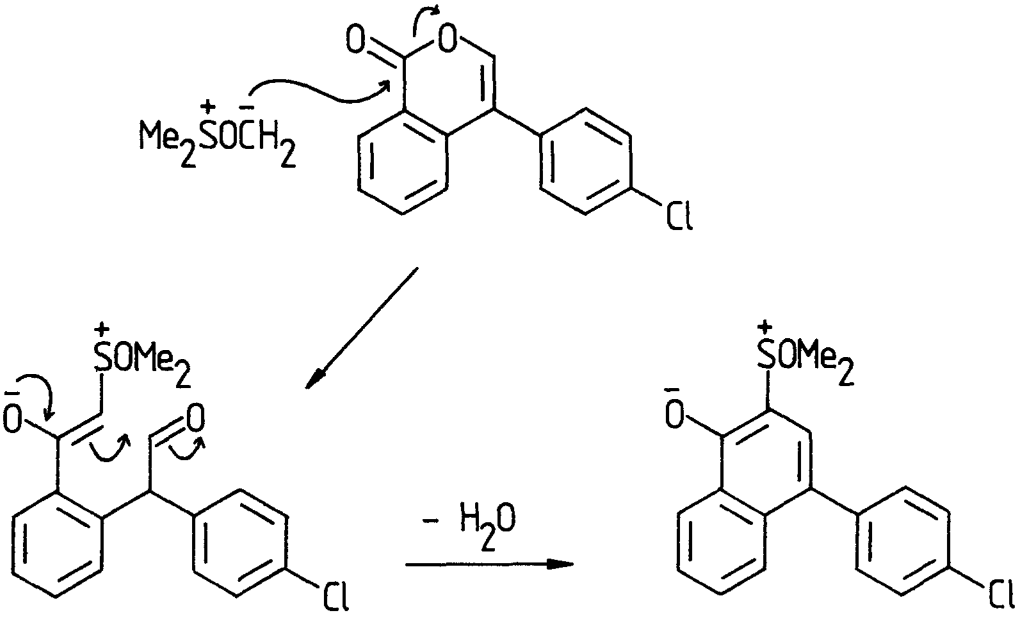
SCHEME 2



(3) (4)

We have found that it is important to use only one equivalent of the methylide (1) for the transformations described above. When methyl 2-(4-chlorobenzoyl)benzoate was treated with 2.2 equivalents of (1), extraction of the reaction mixture with dichloromethane gave none of the isocoumarin (2; X = Cl) but, instead, the stable ylide (5).[6,7] The intermediacy of the isocoumarin in this transformation was supported by a separate experiment in which treatment of 4-(4-chlorophenyl)isocoumarin with 1.1 equivalents of the methylide (1) gave the stable ylide (5) in a yield of 96%. A possible mechanism for this reaction is outlined in Scheme 3.

SCHEME 3



(5)

The method described in this Letter compares favourably with previously described syntheses[8] despite the moderate yields because it allows 4-substituted isocoumarins to be prepared with the minimum of purification directly from readily-available starting materials.

REFERENCES AND FOOTNOTES

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2. For related reactions see K. Nunami, M. Suzuki and N. Yoneda, J. Org. Chem., 1979, 44, 1887, and M. Chaykovsky, L. Benjamin, R. I. Fryer and W. Metlesics, J. Org. Chem., 1970, 35, 1178.

3. Analytical samples, recrystallised twice from methanol, were colourless crystalline solids with fully consistent spectroscopic data. 4-(4-Fluorophenyl)isocoumarin had m.p. 146-147°C; $\nu_{max.}$(nujol) : 1 766, 1 750s, 1 633, 1 609 cm^{-1}; $\lambda_{max.}$(MeOH): 224 (ϵ 29 400), 228 inf. (28 800), 266 (7 100), 275 inf. (6 200), 320 (4700) nm; ^1H n.m.r. (100MHz, $CDCl_3$): δ 7.05-7.76 (8H, m), 8.36 (1H, dd J 8 and 2Hz) p.p.m.; MS (EI): 240 (M^+, 88%), 212 (90%), 183 (100%) (Found: C, 74.9; H, 3.9%; $C_{15}H_9FO_2$ requires C, 75.00; H, 3.77%). 4-(4-Chlorophenyl)isocoumarin had m.p. 165-166°C (lit.[9] 172°C). 4-Phenylisocoumarin had m.p. 94-95°C (lit.[10] 96-97°C).

4. A colourless liquid, $\nu_{max.}$(film): 1 715s, 1 605 cm^{-1}; ^{1}H n.m.r. (90MHz, $CDCl_3$): δ 5.03 (2H, pseudotriplet J 1.2Hz), 5.44 (1H, t J 1.5Hz), 5.77 (1H, t J 0.9Hz), 7.32-7.71 and 8.12-8.24 (3H and 1H respectively, multiplets) p.p.m.; ^{13}C n.m.r. (22.5MHz, $CDCl_3$): δ 71.35, 113.61, 123.29, 123.69, 129.37, 130.48, 133.96, 135.23, 139.96, 164.47 p.p.m.; MS (EI): 160 (M^+, 33%), 131 (100%), 103 (50%).

5. M.p. 63-64°C (lit.[10] 65-66°C) with fully consistent spectroscopic data.

6. A colourless analytical sample, recrystallised from dichloromethane and ether, had m.p. 239-240°C (decomp.); $\nu_{max.}$(nujol): 1 198, 1 036 cm^{-1}; ^{1}H n.m.r. (400MHz, D_6-DMSO): δ 3.94 (6H, s), 7.09 (1H, s), ca. 7.4 (1H, m), 7.41 (2H, d J 8Hz), ca. 7.5 (1H, m), 7.50 (2H, d J 8Hz), 7.57 (1H, br d J 8Hz), 8.33 (1H, dd J 8 and 1Hz) p.p.m.; MS (EI): 332 and 330 (M^+, 39% and 100% respectively), 300 (37%), 269 (27%), 240 (55%), 205 (36%), 189 (72%) (Found: C, 65.4; H, 4.6%; M^+, 330.0487. $C_{18}H_{15}ClO_2S$ requires C, 65.35; H, 4.57%; M, 330.0481).

7. Heterocyclic relatives of the stable ylide (5) have been described. See, for example, T. Kappe, G. Korbuly and E. Pongratz, Monatsh. Chem., 1983, 114, 303.

8. The following review lists 10 approaches to isocoumarins: R. Livingstone in Rodd's Chemistry of Carbon Compounds, 2nd Edition, S. Coffey (Ed.), 1977, Vol.IV, Heterocyclic Compounds, Part E, 290-293.
Other more recent syntheses of isocoumarins have been reported by: E. V. Kuznetsov, D. V. Pruchkin, A. I. Pyshchev, and G. N. Dorofeenko, Khim. Geterotsikl. Soedin., 1978, 1320; B. K. Sarkhel, H. S. K. Mandilwar, and J. N. Srivastava, J. Indian Chem. Soc., 1979, 56, 913; J. N. Chatterjea, S. K. Mukherjee, C. Bhakta, H. C. Jha, and F. Zilliken, Chem. Ber., 1980, 113, 3927; R. H. Carter, M. J Garson, R. A. Hill, J. Staunton, and D. C. Sunter, J. Chem. Soc. Perkin I, 1981, 471; and R. P. Singh and J. N. Srivastava, Indian J. Chem., Sect. B, 1982, 21B, 104.

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