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A CONVENIENT PREPARATION OF 1,2-DIACYLGLYCEROLS; o-IODOBENZOYL AS A PROTECTING GROUP

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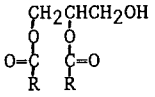
Summary. The o-iodobenzoyl moiety is a useful 3-hydroxyl protecting group in the synthesis of 1,2-diacylglycerols; it can be removed by chlorination followed by mild basic hydrolysis.

1,2-Diacylglycerols (1) are of considerable interest. Short chain derivatives ($2C_6$, $2C_8$, $2C_{10}$) are activators of protein kinase C,[2] whereas the longer chain diesters (e.g., $2C_{16}$) are precursors of typical phospholipid membrane components.[3] During syntheses of 1, a protecting group is required at the 3-hydroxyl (3-OH) while 1-OH and 2-OH are acylated. This prevents either direct acylation at 3-OH or acyl transfer from 2-OH.[4] Although a number of protecting groups are known,[4] there is always room for a group that is stable to moderate acid or base, but that can be easily removed under very mild conditions.[5]

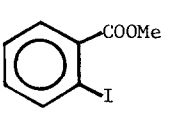
In the course of our studies of the o-iodosobenzoate catalysis of phosphate cleavage,[6] we observed that the standard[7] chlorination/aqueous bicarbonate oxidation of iodo to iodosyl, when applied to methyl o-iodobenzoate (2), afforded not methyl o-iodosobenzoate, but o-iodosobenzoic acid, isolated in 80% yield as 1-hydroxy-1,2-benziodoxolin-3-one, **3a**,[8] after acidification. A second product, presumably methanol, was not isolated, but it occurred to us that should this behavior prove general, o-iodobenzoyl might be a useful and unique protecting group in 1,2-diacylglycerol synthesis. Here, we demonstrate the successful application of this idea.

As an immediate test of the protection/deprotection sequence, benzyl alcohol was esterified with equimolar o-iodobenzoic acid (slight excess of dicyclohexyl-

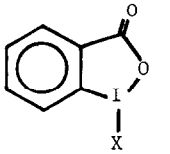


1

a, R=n-$C_{15}H_{31}$
b, R=n-C_7H_{15}

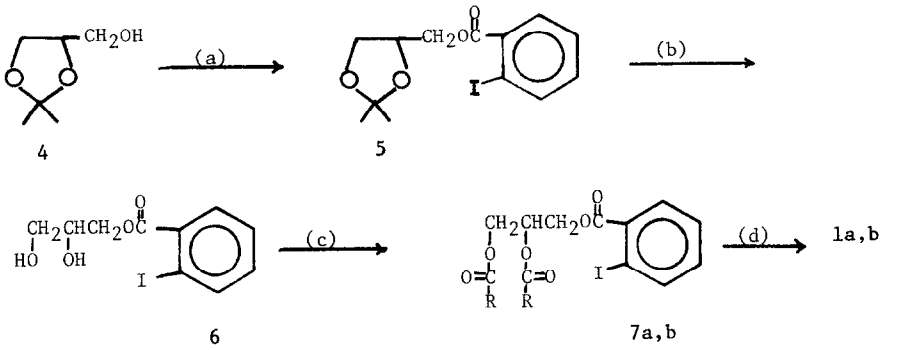


2



3 (**a**, X=OH; **b**, X=Cl)

SCHEME I



(a, R = n-$C_{15}H_{31}$; b, R = n-C_7H_{15})

(a) o-iodobenzoic acid, DCC, catalytic 4-dimethylaminopyridine (DMAP), CH_2Cl_2 25°C, 20 hrs. (b) 85% EtOH/H_2O, 0.3 ml 2N H_2SO_4, 25°C, 20 hrs; then 1 ml H_2O, reflux 1 hr. (c) RCOOH, DCC, catalytic DMAP, CH_2Cl_2, 25°C, 36 hrs. (d) Cl_2/CCl_4, 0-5°C, dark, 1-1.5 hrs, then satd. aq. methanolic Na_2CO_3 (or $NaHCO_3$), 0.5-1 hr.

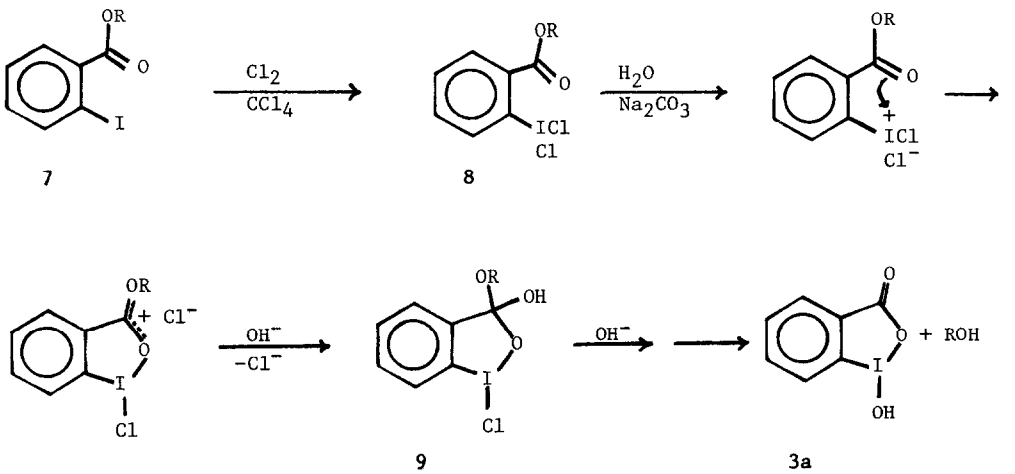
carbodiimide (DCC), catalytic 4-dimethylaminopyridine (DMAP),[9] CH_2Cl_2, 25°, 20 hrs) to yield 88% of benzyl o-iodobenzoate after chromatography on silica (10:1 hexane/EtOAc). The ester was then cleaved by chlorination[7] in CCl_4 (0°C, dark, slow stream of Cl_2, 3.5 hrs), followed by hydrolysis with saturated 3:1 aqueous methanolic $NaHCO_3$ solution (1 hr, vigorous stirring, pH 7-8). Continuous ethereal extraction (12 hrs) of the aqueous phase returned 89% of benzyl alcohol. Acidification of the aqueous phase to pH 2 with HCl gave 76% of 3b, mp 165-168°, identical (mp, tlc, nmr) to the material prepared by chlorination of o-iodobenzoic acid.[10]

Next, the o-iodobenzoate protecting group was utilized in syntheses of 1,2-dipalmitoylglycerol (**1a**) and 1,2-dioctanoylglycerol (1b), as outlined in Scheme I. Commercially available 1,2-isopropylidene-rac-glycerol (4, Aldrich) was esterified with o-iodobenzoic acid, affording 5[11] in 96% yield after chromatography on silica gel (5:1 hexane/EtOAc). Removal of the isopropylidene group was accomplished with acidic aqueous ethanol, affording 90% of the 3-glyceryl iodobenzoate ester, **6**,[12] after neutralization ($NaHCO_3$) and silica gel chromatography (2:3 Hexane/EtOAc).

Without further purification, **6** was esterified with either palmitic or octanoic acids yielding either **7a** or **7b**. Thus, 2-3 mmol of **6** was stirred with 2.1 equivalents of RCOOH, 2.14 equivalents of DCC and 10-15 mg of DMAP in CH_2Cl_2 at 25°C for 36 hrs. Filtration, removal of solvent, and chromatography over silica gel (10:1 hexane/EtOAc) afforded pure **7a**[13] (94%) or **7b**[14] (89%).

Deprotections of the diacylglyceryl esters, **7**, were carried out on 450-500 mg samples dissolved in 10-30 ml of dry CCl_4. A slow stream of chlorine was bubbled through the stirred, cooled (<5°C) solutions for 1-1.5 hrs. The deeply yellow product solutions were hydrolyzed by stirring for 0.5-1 hr at <5°C with saturated 2:1 H_2O/MeOH solutions of

SCHEME II



Na_2CO_3 at pH ≥ 7.5. The resulting CCl_4 phases, together with 3 x 10 ml CCl_4 extracts of the aqueous phases,[15] were dried (Na_2SO_4) and stripped, and the residues were chromatographed over silica gel (5:1 hexane/EtOAc) to give pure 1,2-diacylglycerols **1a** (85%) or **1b** (70%), identical by nmr and tlc with commercially available authentic samples (Sigma).

Thus, the readily available isopropylidene glycerol derivative **4** can be converted to 1,2-diacylglycerols **7a** or **7b** in overall yields of 69% or 54%, respectively, for the 4 step sequence of Scheme I. Central to this sequence is the novel 3-OH o-iodobenzoyl protecting group, that can be removed by chlorination/hydrolysis.

We offer the mechanism in Scheme II for the deprotection step. Chlorination of o-iodoester **7** in CCl_4 will give the yellow iododichloride **8**, which (under mildly basic hydrolytic conditions) should cyclize to **9**.[16] Hydrolysis of the hemiorthoester **9**, as well as I-Cl to I-OH conversion,[6] would be expected in aqueous base, and would yield iodosobenzoic acid **3a** and "ROH" (i.e., **1a** or **1b** from **7a** or **7b**).

Finally, we note that the sequence of Scheme I is currently best suited to the preparation of rac-1,2-diacylglycerols. When initiated with 85% optically pure (+)-**4** (Sigma), the sequence provided **7a** with only ~10% optical purity. We believe that the extensive racemization accompanies the **4** to **5** conversion, where (iodobenzoic) acid catalyzed 1,2 to 2,3 transketalization is possible.[17] The deketalization of **5** to **6** may also be subject to acid catalyzed racemization by sequential 3-2/2-1 transesterifications.[18]

In summary, the o-iodobenzoyl group is a novel protecting group for primary alcohols, and is easily removed under mild conditions.

Acknowledgement. We are grateful to the U.S. Army Research Office for financial support.

References and Notes

(1) Visiting Professor from Università di Padova; Fulbright Scholar, 1985-6.

(2) E.G. Lapetina, B. Reep, B.R. Ganong, and R.M. Bell, J. Biol. Chem., **260**, 1358 (1985).

(3) J.H. Fendler, "Membrane Mimetic Chemistry," Wiley, New York, 1982, pp. 121ff; H. Eibl, Angew. Chem. Int. Ed. Engl., **23**, 257 (1984), and references therein.

(4) R.G. Jensen and R.E. Pitas in "Advances in Lipid Research," Vol. 14, R. Paoletti and D. Kritchevsky, Ed., Academic Press, New York, 1976, pp.213-247. Other protective groups include tetrahydropyranyl, trityl and benzyl. Deprotection involves acidic cleavage or catalytic hydrogenation. See C.M. Lok, Chem. Phys. Lipids, **22**, 323 (1978); H. Eibl, J.O. McIntyre, E.A.M. Fleer, and S. Fleischer, Methods Enzym., **98**, 623 (1983).

(5) See, for example, J.B. Chattopadhyaya, C.B. Reese, and A.H. Todd, Chem. Commun., 987 (1979).

(6) R.A. Moss, P. Scrimin, and R.T. Rosen, Tetrahedron Lett., **28**, 251 (1987); see note 17.

(7) H.J. Lucas and E.R. Kennedy in "Organic Synthesis," Coll. Vol. 3, E.C. Horning, Ed., Wiley, New York, 1955, pp. 482-484. Peracetic acid oxidation of **2** also furnished **3**.

(8) See R.A. Moss, K.Y. Kim and S. Swarup, J. Am. Chem. Soc., **108**, 788 (1986), and references therein.

(9) For the use of dimethylaminopyridine in DCC-mediated condensations, see E.F.V. Scriven, Chem. Soc. Rev., **12**, 129 (1983).

(10) L.J. Andrews and R.M. Keefer, J. Am. Chem. Soc., **81**, 4218 (1959). Iodosobenzoic acid (**3a**) is converted to chloride **3b** under our reaction/workup conditions. Acidification with HCl is the transforming step; basic workup affords iodosobenzoic acid, **3a**.

(11) Nmr (δ, $CDCl_3$, 60 MHz): 1.33 and 1.42 (S, 6H, 2Me), 3.50-4.17 (m, 3H, CH_2CH), 4.37 (d, J~2Hz, 2H, CH_2OCO), 6.87-8.07 (m, 4H, aryl).

(12) Nmr (δ, $CDCl_3$, 60 MHz): 3.1-4.5 (m, 7H, aliphatic + 2OH), 6.83-8.00 (m, 4H, aryl).

(13) Nmr (δ, $CDCl_3$, 200 MHz): 0.85 (m, 6H, 2Me), 1.22 ("s", 48H, $2(CH_2)_{12}$), 1.60 (m, 4H, $2CH_2$ β to C-O), 2.30 (m, 4H, $2CH_2$ α to C-O), 4.1-4.6 (m, 4H, C_1 and C_3 CH_2), 5.40 (m, 1H, C_2-CH), 7.12 (t), 7.38 (t), 7.75(d), 7.95(d) (1 H each, aryl). Anal. C,H.

(14) The 200 MHz spectrum was nearly identical to that of **7a** except for an appropriately reduced intensity for the $2(CH_2)_4$ resonance at δ 1.22. Anal. C,H.

(15) Subsequent acidification of the aqueous phase with dilute HCl afforded chloro compound **3b**. For example, the yield of **3b** was 63% from the cleavage of **7b**.

(16) This mechanism is based on original suggestions of Andrews and Keefer.[10]

(17) H. Eibl, Chem. Phys. Lipids, **28**, 1 (1981). Indeed, control experiments revealed slow racemization of (+)-4 in CH_2Cl_2 solution with o-iodobenzoic acid. Other methods of esterification remain to be tested.

(18) F.R. Pfeiffer, C.K. Maio, and J.A. Weisbach, J. Org. Chem., **35**, 221 (1970).

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