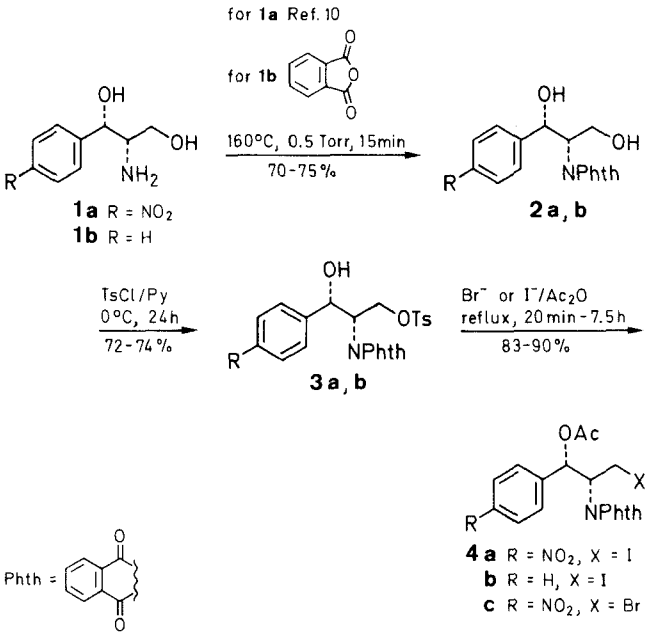
An Efficient Synthesis of (1*S*,2*S*)-1-Acetoxyl-1-aryl-3-halo-2-phthalimidopropanes

Armin Boerner,* Gudrun Voß

Central Institute of Organic Chemistry, Department of Complex Catalysis, Academy of Sciences of the GDR, Buchbinderstr. 5/6, DDR-2500 Rostock, German Democratic Republic

Dedicated to Professor Helmut Kristen on the occasion of his 60th birthday

A convenient synthesis of 3-halo derivatives of chiral 2-amino-1-aryl-1,3-propanediols in good overall yield has been developed using a regioselective esterification with *p*-toluenesulfonyl chloride and successive replacement of the *p*-toluenesulfonate group by iodide or bromide in acetic anhydride.



During the synthesis of optically pure L-norpseudoephedrine from (1*S*,2*S*)-2-amino-1-aryl-1,3-propanediols **1a,b**[1] we became interested in a synthetic route leading to the corresponding 3-halo derivatives.

The direct regioselective replacement of the primary hydroxy group by chloride or bromide using 2-acetoxybenzoyl chloride or *N*-bromosuccinimide failed, yielding mixtures of 1- and 3-halo substituted **1b**.[2] The reaction with thionyl chloride gave only the 1-chloro derivative.[3] These results display the high reactivity of the secondary hydroxy group, which shows a remarkable difference to related polyhydroxy compounds. Therefore earlier investigations[4,5] started with the selective protection of the benzylic hydroxy group, but this approach can be associated with attack at C-1,[6] and hence not suitable for our purpose. The same holds for other methods.[7]

The regioselective esterification of the primary hydroxy group using convenient *N*-protected derivative of the amino alcohols **1a,b** with *p*-toluenesulfonyl chloride, followed by replacement of the *p*-toluenesulfonate by halogen, seemed a more promising route.

Other authors[8] used a multistep procedure to obtain the corresponding 3-mesyloxy derivative. Attempts to substitute the mesyloxy group by iodide or chloride, failed; protecting groups such as benzoyl or acetyl resulted in the formation of oxazolines,[8,9] or acyl group migration.[8]

Theoretically the *N*–Cbo derivatives should be correctly protected for the tosylation of the primary hydroxy group. However, the 3-tosyloxy compounds were obtained as the sole product, which rapidly decomposed during purification using column chromatography.

We now report, that under appropriate conditions the phthaloyl protected amino alcohols are convenient starting materials for the regioselective introduction of halogen.

Starting with the phthalimido derivatives **2a**[10] and **2b** respectively, the tosyloxy compounds **3a,b** were obtained in good yield (Table 1) and were more stable than the corresponding *N*–Cbo derivatives. Esterification of the diols **2** in pyridine with *p*-toluenesulfonyl chloride (1.1 mol per mol of diol) at 0 °C gave regioselectively the 3-tosyloxy compounds. Raising the temperature to 80 °C and enhancing the molar ratio of *p*-toluenesulfonyl chloride to 3 gave the 1,3-bis(tosyloxy) compounds as the main products. Surprisingly, substitution of the tosyloxy group by iodide or bromide in hexamethylphosphoric triamide, dimethyl sulfoxide or acetone, solvents normally used for this substitution, gave the desired compounds in poor yield. However, acetic anhydride, which is seldom employed for this reaction, gave the halo derivatives **4a,b** and **4c** respectively in good to excellent yield and is compatible with several iodides and bromides (Table 2). Acetylation of the secondary hydroxy group takes place concomitantly.

Our results indicate that the selection of the amino protective group is important for the regioselective introduction of halogen into such amino diols. It should be mentioned that the reactions occur without racemisation as shown by transforming the halogenated products to optically pure (*S*,*S*)-norpseudoephedrine.[1,12]

Analytical TLC analyses were performed using glass plates precoated with silica gel G type 60 supplied by Merck: visualization was accomplished by spraying with H_2SO_4, followed by heating at 200 °C.

All solvents and reagents were commercially available (reagent grade) and used without further purification. (1*S*,2*S*)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol (**1a**) was obtained from VEB Berlin-Chemie. (1*S*,2*S*)-2-Amino-1-phenyl-1,3-propanediol (**1b**) was purchased from Merck. In the workup procedures the solvents were evaporated with a rotatory evaporator supplied by VEB Jenaer Glaswerke. *N*-Phthaloyl derivative **2a** was prepared as described in Ref. 10.

(1*S*,2*S*)-1-Phenyl-2-phthalimido-1,3-propanediol (2b):
Amino alcohol **1b** (6.68 g, 0.04 mol) and phthalic anhydride (7.2 g, 0.49 mol) are mixed and heated without solvent for 15 min at 160 °C under vacuum (0.5 Torr) to remove the water produced in the reaction. The melting cake thus obtained is crushed and purified by recrystallization.

Table 1. Selected Data of Compounds Prepared

Product	Yield[a] (%)	mp (°C)[b] (solvent)	$[\alpha]_D^{20}$[c] (c = 1, acetone)	Molecular Formula[d] or Lit. mp (°C)	^{1}H-NMR (solvent/TMS)[e] δ, J(Hz)
2a	75	226–229 (MeOH)	+69.7	223–224[10]	DMSO-d_6: 2.90–3.98 (m, 2H), 4.00–4.45 (m, 1H), 4.75 (t, 1H, J = 5.4, exchange with D_2O), 4.95–5.24 (m, 1H), 5.88 (d, 1H, J = 4.4, exchange with D_2O), 7.30–8.15 (m, 8H)
2b	70	164–168 (MeOH)	+41.4	$C_{17}H_{15}NO_4$ (297.3)	DMSO-d_6: 2.80–4.05 (m, 2H), 4.05–4.44 (m, 1H), 4.67 (t, 1H, J = 5.3, exchange with D_2O), 5.52 (d, 1H, J = 4.2, exchange with D_2O), 7.35 (s, 5H), 7.84 (s, 4H)
3a	74	187–190 (benzene)	+19.8	$C_{24}H_{20}N_2O_8S$ (496.5)	$CDCl_3$: 2.33 (s, 3H), 4.58 (AB of ABX, J_{AB} = 11.1, J_{AX} = 5.0), 4.82–5.20 (m, 3H), 7.00–8.16 (m, 12H)
3b	72	170–174 (MeOH)	+ 2.0	$C_{24}H_{21}NO_6S$ (451.5)	$CDCl_3$: 2.29 (s, 3H), 4.10–4.30 (m, 2H), 4.22–4.98 (m, 2H), 5.05–5.20 (m, 1H), 6.95–7.90 (m, 13H)
4a	90	192–193 (BuOH)	+56.7	$C_{19}H_{15}IN_2O_6$ (494.2)	$CDCl_3$: 1.93 (s, 3H), 3.45 (AB of ABX, J_{AB} = 10.2, J_{AX} = 4.4, J_{BX} = 12.0), 4.55–4.95 (m, 1H), 6.29 (d, 1H, J = 8.3), 7.50–8.34 (m, 8H)
4b	90	179–183 (MeOH)	+37.7	$C_{19}H_{16}INO_4$ (449.2)	$CDCl_3$: 1.84 (s, 3H), 3.41 (AB of ABX, J_{AB} = 10.2, J_{AX} = 4.1, J_{BX} = 12.2), 4.55–4.95 (m, 1H), 6.22 (d, 1H, J = 9.5), 7.25–7.93 (m, 9H)
4c	83	185–188 (MeOH)	+65.5	$C_{19}H_{15}BrN_2O_6$ (447.2)	$CDCl_3$: 1.95 (s, 3H), 3.62 (AB of ABX, J_{AB} = 10.7, J_{AX} = 4.4), 4.65–5.00 (m, 1H), 6.33 (d, 1H, J = 8.3), 7.50–8.30 (m, 8H)

[a] Yield of isolated pure products.
[b] Corrected, measured with a micro heating table Boetius.
[c] Determined on a Jena-Zeiss Polamat A polarimeter at 5.46 and 578 nm in a 1 dm cell and expressed in the sodium D-line.
[d] Satisfactory microanalysis obtained: C, H, N, X ±0.3%.
[e] Recorded on a 80 MHz Tesla BS 487 C spectrometer using TMS as internal standard.

Table 2. 3-Halo Derivatives **4a**, **4c** Prepared from **3a** in Acetic Anhydride

Product	Halogenide	Reaction Time[a]	Yield (%)[b]
4a	LiI[c]	20 min	90
4a	NaI[c]	45 min	90
4a	KI[c]	60 min	90
4a	NEt_3HI[c]	100 min	90
4a	NMe_4I[c]	100 min	90
4c	LiBr[d]	7.5 h	83
4c	NaBr[d]	7.5 h	83

[a] Time after quantitative conversion determined by TLC.
[b] Yield of isolated product.
[c] 1.5 mol per mol of **3a**.
[d] 3 mol per mol of **3a**.

(1*S*,2*S*)-1-Aryl-2-phthalimido-3-tosyloxy-1-propanol 3; General Procedure:

To a stirred solution of the protected amino alcohol **2** (0.01 mol) in dry pyridine (20 mL) *p*-toluenesulfonyl chloride (2.1 g, 0.011 mol) is added. The mixture is stirred at 0 °C for 4 h and kept overnight at r.t. Then the solution is slowly poured into H_2O (100 mL). The mixture is extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts are washed with 5% aq H_2SO_4 (50 mL), 5% aq $NaHCO_3$ (50 mL), H_2O (50 mL), dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure gives the crude product which is purified as indicated in Table 1.

(1*S*,2*S*)-1-Acetoxy-1-aryl-3-halo-2-phthalimidopropanes 4a–c; General Procedure:

To **3a**, **3b** (0.01 mol), dissolved in acetic anhydride (30 mL), the halogenide as specified in Table 2 is added. The mixture is heated under reflux and is monitored by TLC. After the complete reaction of the starting material the mixture is poured into H_2O (300 mL). The crude 3-halo derivative is filtered off, washed with H_2O, and recrystallized.

Received: 2 August 1989; revised: 11 December 1989

(1) Boerner, A.; Krause, H.-W. *Tetrahedron Lett.* **1989**, *30*, 929.
(2) Ramaiah, P.; Rao, A.S. *Org. Prep. Proced. Int.* **1987**, *19*, 173.
(3) Matsumoto, T.; Hata, K. *J. Am. Chem. Soc.* **1957**, *79*, 5506.
(4) Miyamoto, M. *J. Pharm. Soc. Japan* **1952**, *72*, 669.
(5) Ikuma, S. *J. Pharm. Soc. Japan* **1959**, *79*, 939.
(6) Welsh, L.H. *J. Org. Chem.* **1967**, *32*, 119.
(7) Acher, F.; Juge, S.; Wakselman, M. *Tetrahedron* **1987**, *43*, 3721.
(8) Fodor, G.; Kiss, J.; Sallay, I. *J. Chem. Soc.* **1951**, 1858.
(9) Giordano, C.; Cavicchioli, S.; Levi, S.; Villa, M. *Tetrahedron Lett.* **1988**, *29*, 5561.
(10) Terada, A.; Ito, H.; Nagawa, M. Sankyo Kenkyusho Nempo **1963**, *15*, 42; *C.A.* **1964**, *60*, 11924.
(11) Roedig, A., in: *Houben-Weyl*, 4th ed., Vol. V/4, Georg Thieme Verlag, Stuttgart, 1960, p. 620.
(12) Boerner, A.; Krause, H.-W. *J. Prakt. Chem.* **1990**, *332*, in press.