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Resolution of 1-arylethylamines with 5-(1,2-*O*-isopropylidene-3,6-anhydro-α-D-glucofuranosyl) hydrogen phthalate

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Abstract—The potential of the hydrogen phthalate of 1,2-*O*-isopropylidene-3,6-anhydro-α-D-glucofuranose **1** obtainable by the reaction of phthalic anhydride with 1,2-*O*-isopropylidene-3,6-anhydro-α-D-glucofuranose **8** as a new resolving agent is shown. The salts between **1** and (*RS*)-1-arylethylamines **2-6** and (*RS*)-1-arylpropylamine **7** selectively crystallize **1**·(*R*)-salts allowing the recovery of the corresponding (*R*)-amines **2–7**. The more soluble **1**·(*S*)-salts were analogously processed to obtain (*S*)-amines, respectively. In all of the cases (*R*)- and (*S*)-amines **2–7** were obtained in high chemical yield and enantiomeric excess >98%. Resolving agent **1** has been recovered in a quantitative yield and high purity.

Approximately 80% of drugs currently in development are chiral. Although some may be prepared by chiral synthesis, many will be produced through the resolution of racemate.[1] In spite of revolutionary advances in catalytic asymmetric synthesis and enzymatic kinetic resolution methods, the diastereomeric salt crystallization method still constitutes[2] the most practical way to separate a racemic mixture. The resolution of 1-arylethylamines by a diastereomeric salt formation method has been studied via the use of acidic resolving agents such as mandelic acid and its related derivatives,[3] naphthylglycolic acid[4] and the hydrogen phthalate of isopropylidene glycerol.[5] Notwithstanding these advances, there is still a need for designing an acidic resolving agent that is (i) efficient against a wide range of primary and secondary racemic amines, (ii) abundantly available, (iii) water insoluble for recovery in common organic solvents and (iv) has good chemical and configurational stability. We focused our attention on overcoming these short falls while targeting the development of a new chiral acidic resolving agent making use of abundantly available carbohydrate templates.

Herein we report the development of a new acidic resolving agent, the hydrogen phthalate of 1,2-*O*-isopropylidene-3,6-anhydro-α-D-glucofuranose **1** which has proved to be efficient in resolving a range of (*RS*)-1-arylethylamines **2–6** and (*RS*)-1-phenylpropylamine **7**.

The salts between **1** and the isomers of 1-phenyl-**2**, 1-(4-bromophenyl)-**3**, 1-(4-chlorophenyl)-**4**, 1-(4-methylphenyl)-**5**, 1-(2-naphthyl)-ethylamine **6** and 1-phenylpropylamine **7** selectively crystallized the **1**·(*R*)-diastereomeric salt from methanol allowing the recovery of (*R*)-1-arylethylamines from the corresponding racemate in high chemical yields and enantiomeric excesses (Scheme 1, Table 1). The corresponding (*S*)-1-arylethylamines were also isolated from the more soluble **1**·(*S*)-salts present in the mother liquors in high yield and enantiomeric excess.

Reaction of 1,2-*O*-isopropylidene-3,6-anhydro-α-D-glucofuranose **8**[6] (40 g, 0.16 mol) and phthalic anhydride (23.35 g, 0.16 mol) in dry pyridine (24 ml) according to the usual procedure and work up gave **1** in a quantitative yield as a syrup; $[\alpha]_D^{25} = +15.0$ (*c* 2.0, $CHCl_3$) [(99.4%, by HPLC). Compound **1** was characterized by a ^1H NMR spectrum with the appearance of H-1′ at δ 5.88 (d, 1H, $J_{1,2} = 4.3$ Hz), H-5 at δ 5.20–5.40 (m, 1H) and aromatic protons at δ 7.45–7.95 (m, 4H); FAB-MS, *m*/*z* 351 (M^++H). The crude oily hydrogen phthalate **1** (21 g, 60 mmol) was diluted in methanol (80 ml),

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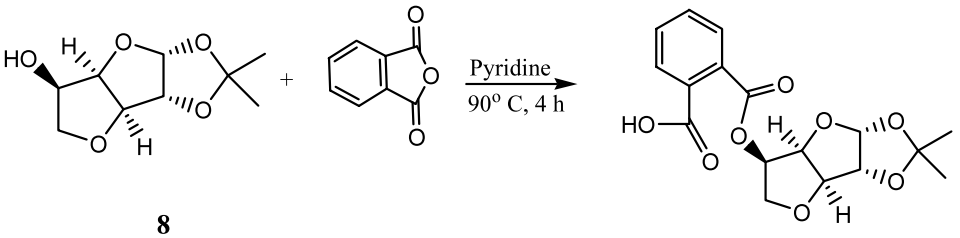
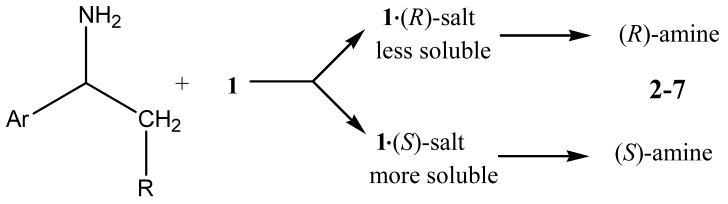


8 **1**

2) R= H, Ar=C_6H_5
3) R= H, Ar=p-Br-C_6H_4
4) R= H, Ar=p-Cl-C_6H_4
5) R= H, Ar=p-Me-C_6H_4
6) R= H, Ar=2-Naphthyl
7) R= Me, Ar=C_6H_5



Scheme 1.

treated with (*RS*)-**2** (7.2 g, 60 mmol) briefly boiled for 3 min and allowed to slowly cool (3 h) to 15°C. The precipitate formed was filtered and washed with cold methanol (20 ml) to obtain 13.1 g the corresponding **1**·(*R*)-**2** diastereomeric salt (Table 1). The salt was treated with 10% aq. HCl (100 ml) after which dichloromethane (100 ml) was added to recover the hydrogen phthalate **1** quantitatively. The acidic aqueous phase was neutralized with 10% aq. $NaHCO_3$ (80 ml) and extracted into dichloromethane (50 ml) to isolate 3.30 g of (*R*)-**2** (Table 1, entry i in high e.e (98.8%) on the basis of HPLC on a chiral Crownpak (CR^+) column. The mother liquors were concentrated to a residue and recrystallized in chloroform/hexane to afford 12.95 g (27 mmol) of the diastereomeric salt **1**·(*S*)-**2**, (entry i). After analogous treatment it gave 3.28 g of (*S*)-**2** in good yield and e.e (99.0%) (entry i). All the other (*RS*)-1-aryl ethylamines **3**–**6** (60 mmol) and (*RS*)-1-phenylpropylamine **7** (60 mmol) were resolved efficiently by this procedure to obtain (*R*)- and (*S*)-amines **3**–**7** respectively in good yield and e.e (Table 1, entries ii–vii). 13.0 g of the diastereomeric **1**·(*R*)-**4** salt obtained by the first crystallization (entry iii) was recrystallized in dichloromethane/hexane to obtain 11.7 g (90%) of salt, that on decomposition gave (*R*)-**4** (97% yield) in enhanced purity (99.3% e.e). In all cases, the resolving agent **1** was recovered quantitatively and in good purity. Further investigations about **1**'s reuse and additional application may reveal its full potential.

In summary the development and application of a new acidic resolving agent hydrogen phthalate of 1,2-*O*-isopropylidene-3,6-anhydro-α-D-glucofuranose **1** that can be used to obtain enantiomerically pure (>98%) (*R*)- and (*S*)-1-arylethylamines from the corresponding racemates has been achieved. Among several other carbohydrate templates studied for the purpose, **1** was found to be superior. Its stability, quantitative recovery and

Table 1. Preparation of (*R*) and (*S*)-1-arylethylamines from the corresponding racemates by selective crystallization of the respective salts with **1**[a]

Entry	(*RS*)-Amine	**1**·(*R*)-Salt (%yield[b]), mp[c], $[\alpha]_D$[e]	**1**·(*S*)-salt (%yield[b]), mp[c], $[\alpha]_D$[e]	(*R*)-Amine[f] (%yield[b]), $[\alpha]_D$, ee[d]	(*S*)-Amine[f] (%yield[b]), $[\alpha]_D$, ee[d]
i	**2**	(92.8), 142, +22	(90.3), 134, +25	(97.4), +29.4, 98.8	(97.7), −29.5, 99.0
ii	**3**	(91.0), 150, +19	(89.3), 125, +12	(97.6), +24.3, 98.7	(98.8), −24.2, 98.5
iii	**4**	(91.8), 148, +28	(89.5), 127, +26	(96.7), +23.2, 98.5	(97.1), −23.1, 98.6
iv	**5**	(92.2), 134, +12	(87.0), 126, +11	(98.5), +32.1, 99.0	(97.0), −31.9, 98.7
v	**6**	(91.6), 135, −23	(86.1), 130, −19	(96.8), +20.4, 98.9	(96.5), −20.6, 99.0
vi	**7**	(89.5), 140, +22	(90.5), 130, +26	(97.8), +19.8, 98.9	(98.1), −19.7, 98.6

[a] All crystallizations were carried out using equivalent amounts of racemic amines and **1**.
[b] Relative to the theoretical amount.
[c] In °C.
[d] % Enantiomeric excess of the amines determined by reverse-phase chiral HPLC[7] analysis on a Crownpak$(CR)^+$ column from Daicel (elutant aq. $HClO_4$ at pH 1.5).
[e] At 25°C.
[f] Specific rotation was determined and the value compared at the concentration and temperature referred to in their corresponding references.[5]

ability to resolve both the enantiomers indicate the potential of the resolving agent. Application of the resolving agent for other amines will be reported in due course.

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