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Resolution of 1-arylalkylamines with 6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)hydrogen phthalate

Hari Babu Mereyala,* Liyakat Fatima and Pallavi Pola

Speciality, Gas Based Chemicals and Processes Division, Indian Institute of Chemical Technology, Hyderabad 500-007, India

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Abstract—The resolving ability of a new acidic resolving agent, the hydrogen phthalate of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **1**, against various 1-arylalkylamines **2a**–**k** is described. Treatment of **1** with amines **2a**–**f** to obtain diastereomeric salts **1**·(*S*)**2a**–**f** in 2-propanol allowing the corresponding (*S*)-amines **2a**–**f** to be recovered in good yield and 61–89% ee. Recrystallization in dichloromethane/hexane, and regeneration gave the amines in enhanced enantiomeric purity (>98% ee). **1** resolved 1-phenylpropylamine **2f** in high enantiomeric purity (99% ee) than 1-phenylethylamine **2g** (11% ee) and *o*- and *m*-methoxy **2h**–**i**, *o*-chloro-**2j** and *p*-fluoro-**2k** substituted 1-arylamines (11–19% ee). A possible chiral recognition mechanism based on the ability of **1** to exist in two conformations is described.

Resolution through diastereomeric salt formation is the most widely used method for separating enantiomers of a given racemic acid or base.[1] This classical technique still constitutes the most important methodology for the industrial manufacture of pure enantiomers.[2] Systematic investigation studies on the resolution of 1-arylalkylamines have identified the following criteria for rational design of acidic resolving agents[3] (i) similarity in molecular length between a target racemate and a resolving reagent,[3d] (ii) presence of hydrogen-bonding and van der Waals interactions,[3c,e,j,k] (iii) hydrophobic water insoluble carboxylic acids to facilitate isolation of uncontaminated liberated base.[3a] The acidic resolving agents tried for this purpose contained the carboxylic group attached to the stereogenic carbon.

Highly efficient chiral discrimination exhibited by enantiomerically pure isopropylidene glycerol hydrogen phthalate[4] bearing a stereogenic carbon remote from the carboxylic acid has been attributed to conformational restriction of the dioxolane in line with proven empirical guidelines. The success of the resolutions presented indicated the versatility of isopropylidene glycerol hydrogen phthalate in the resolution of monosubstituted 1-phenylethylamines irrespective of the position of the substituent.[4d] Despite the design of resolving agents there is a need to develop newer ones to understand the criterion for chiral descrimination.

Here, we describe our studies concerning the resolution of 1-arylalkylamines by the use of carbohydrate derived acidic resolving agent.[5] We have chosen the hydrogen phthalate of D-galactopyranose bearing two α,α-dimethyldioxolane rings because of its ability to exist in at least two conformations due to flipping of the pyranose ring. In each one of the conformers the phthalate group is perhaps aligned over one of the dioxolane rings. The recognition mechanism if operated would lead to preferential crystallization of (*R*)- and (*S*)-isomers by the two conformers.

Reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **3**[6] [100 g, 0.38 mol] and phthalic anhydride [56.0 g, 0.38 mol] in dry pyridine [62 mL] according to the usual procedure and work up gave 6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)hydrogen phthalate **1** in quantitative yield as a syrup; $[\alpha]_D^{25} = +8.4$ [*c* 2.0, $CHCl_3$] [98.9% de by HPLC] (Scheme 1). Compound **1** was characterized from ^1H NMR spectrum by the appearance of H-1′ at δ 5.65 (d, 1H, $J_{1,2} = 5.8$ Hz) and aromatic protons at δ 7.50–7.75 (m, 4H); FAB-MS, *m*/*z* 409 (M^++H).

We first sought to understand the effect of substitutents at the *para* position of 1-arylethylamines. Thus treatment of *p*-alkyl-(methyl, ethyl), *p*-halo-(Cl, Br)

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* Corresponding author. Tel.: +91-40-27193137; fax: +91-40-27160387/27160757; e-mail: mereyalahb@rediffmail.com

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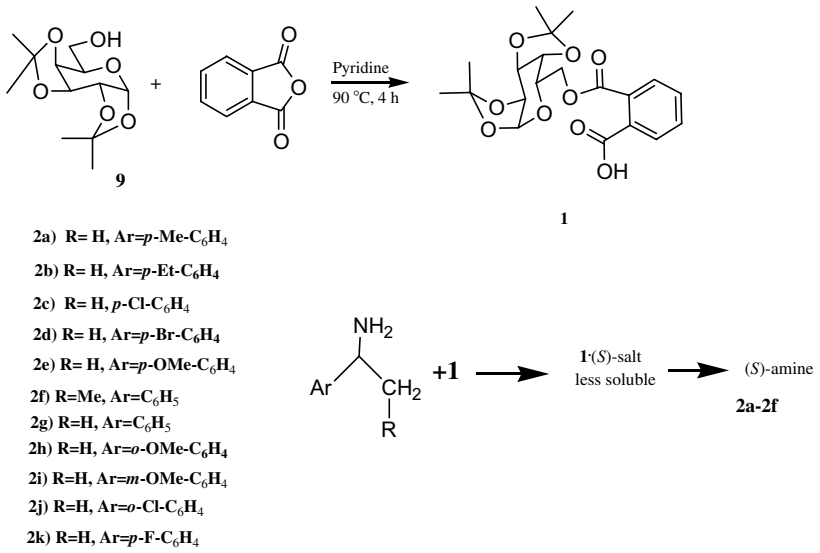

Scheme 1.

p-methoxy substituted 1-arylethylamines **2a**–**e** and 1-phenylpropylamine **2f**, respectively, with stoichiometric amount of **1** in boiling 2-propanol and cooling to −15 °C yielded white crystalline precipitates **1**·(*S*)**2a**–**f**, which after usual extractive procedures afforded the corresponding amines (*S*)**2a**–**f** in moderate enantiomeric purity (61–88% ee) and in good yield (Table 1, entries i–vi). However, a similar treatment of 1-phenylethylamine and amines bearing *o*-, *m*-substituents **2g**–**k** with **1** in 2-propanol did not result in the formation of any salts, the solvent was removed to obtain a thick syrup, which was partitioned into two phases by addition of dichloromethane/hexane (2:3) to isolate insoluble and soluble fractions containing **1**·(*S*)**2g**–**k** and **1**·(*R*)**2g**–**k** salts, respectively, which on decomposition gave the corresponding amines (*S*)**2g**–**k** and (*R*)**2g**–**k**, respectively, in low enantiomeric purity (11–25% ee) (Table 1, entries vii–xi). Recrystallization of salts **1**·(*S*)**2a**–**f** from CH_2Cl_2/*n*-hexane at rt (1:1, 4 mL/g) or 2-propanol (6 mL/g) followed by decomposition resulted in the recovery of their corresponding amines (*S*)**2a**–**f** with increased enantiomeric purity (>98% ee).

A possible chiral discrimination mechanism might involve the following steps. The resolving agent **1** recognizes the (*R*)- and (*S*)-amines by approaching them by columbic attraction. The process requires a favourable conformation of the galactopyranose ring possessing two dioxolane rings and a phthalate group. The conformers could be present in chair/boat forms with alignment of phthalate over one of the dioxalane rings thereby facilitating recognition phenomena. These

Table 1. Resolution of 1-arylalkylamines **2a**–**k** by 6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)hydrogen phthalate (**1**)[a]

Entry	(*RS*)-Amine	**1**·(*S*)-salt (% yield)[b], $[\alpha]_D$[d]		(*S*)-Amine[e], Ee[c] (% yield)[b], $[\alpha]_D$[d]		Reference
	2	Resolution	Recrystallization	Resolution	Recrystallization	
i	**a**	(99.0), −40.9	(78.7), −43.4	84.3, (88.1), −27.5[f]	98.7, (65.7), −32.4[f]	4b
ii	**b**	(91.4), −42.6	(73.4), −45.1	88.3, (81.2), −15.6[g]	99.4, (74.4), −18.9[g]	—
iii	**c**	(94.5), −38.2	(62.5), −42.3	61.0, (93.0), −14.6[f]	98.9, (64.1), −23.4[f]	4b
iv	**d**	(96.2), −36.2	(77.9), −38.5	64.1, (94.0), −16.0[g]	99.2, (78.3), −24.8[g]	4a
v	**e**	(95.4), −42.2	(76.2), −45.3	60.3, (86.0), −17.1[f]	98.1, (64.1), −28.8[f]	4a
vi	**f**	(94.5), −35.3	(79.1), −39.1	84.7, (89.0), −16.0[f]	99.1, (77.8), −18.8[f]	4b
vii	**g**	(91.6), −26.7	—	11.7, (90.2), − 3.5[f]	—	4a
viii	**h**	(87.8), −31.6	—	13.6, (85.7), −8.0[g]	—	4b
ix	**i**	(82.3), −29.8	—	15.2, (80.8), −3.4[g]	—	4d
x	**j**	(83.6), −28.7	—	18.6, (82.3), −10.3[h]	—	4d
xi	**k**	(41.8), −31.9	—	25.3, (89.6), −4.8[f]	—	—

[a] All crystallizations were carried out using equivalent amounts of racemic amines and **1**.
[b] Yield of the crystallized diastereomeric salt based on half amount of the racemic amine.
[c] % Enantiomeric excess of the amines determined by reverse-phase chiral HPLC analysis on Crownpak CR(+) column from Daicel (elutant aq $HClO_4$ at pH 1.5).[7]
[d] At 25 °C.
[e] Specific rotation was determined and the value at concentrations and temperatures comparable to those in the literature.
[f] *c* 2.0, MeOH.
[g] *c* 1.0, MeOH.
[h] *c* 1.5, MeOH.

observations are similar to those observed for hydrogen phthalate of isopropylidene glycerol[4c,8] except the dioxolane rings present on **1** are not flexible.

In summary, we have investigated the applicability of carbohydrate derived, new acidic resolving agent **1** for the resolution of ten 1-arylalkylamines **2a**–**k**. A common chiral discrimination mechanism seems to work allowing to obtain the (*S*)-isomer.[3] 1-Arylethylamines bearing alkyl (methyl, ethyl), halo-(Cl, Br) and methoxy substitutents at *para* position of the phenyl group were resolved to obtain the corresponding (*S*)-amines in good enantiomeric purity. The amines bearing electron donating substituents in the *ortho* and *meta* positions were resolved less efficiently. Rational design of carbohydrate derived resolving agents by modification of the pyranose and dioxolane rings to understand the conformer based chiral recognition phenomena is in progress.

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