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A highly efficient resolution protocol for 2′-halo-α-methylbenzylamines

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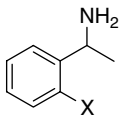
Abstract—A highly efficient resolution protocol for 2′-halo-α-methylbenzylamines is reported. Commercially available and inexpensive mandelic acid can be used for the resolution of the Br, Cl, and F derivatives to >99% de in a single crystallization. In addition, the reduction of acetophenone oximes using borane-dimethylsulfide is presented as a method for the preparation of racemic amine precursors.

1. Introduction

The process of resolving enantiomers through diastereomeric salt formation is a widely used method for obtaining optically enriched acids or bases.[1] As part of an ongoing development program, we required large quantities of 2′-halo-substituted α-methylbenzylamines (Fig. 1, **1a**–**c**) in high optical purity.

There are numerous asymmetric synthetic strategies that afford enantiomerically enriched α-methylbenzylamines.[2] However, from our standpoint, a resolution-based process was more practical for two reasons: (1) the degree of enantiomeric enrichment required for our purposes (>99% ee) might exceed the capacity of available asymmetric methods. In this case, a secondary salt-based chiral upgrade would still be required, and (2) if a relatively inexpensive resolving agent could be found, the ease and cost of resolving the racemic amine might outweigh the benefits of an asymmetric synthesis.[1b]

The literature contains many reports of the resolution of various α-methylbenzylamines, including the use of chiral acids such as 6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)hydrogen phthalate,[3] isopropylidene glycerol hydrogen phthalate,[4] 3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid,[5] mandelic acid,[6] substituted mandelic acids,[6a,7] tartaric acid,[8,9] *N*-Ac-L-leucine derivatives,[10] and malic acid.[9b] Surprisingly, there are few examples of the resolution of 2′-halo-α-methylbenzylamines,[3–5,6e,10] and those examples produced only modest enantioselectivity, or required multiple crystallizations to achieve high levels of enantioenrichment. Our goal was to develop a general and efficient resolution protocol, employing a single resolving agent that could be applied to the series depicted in Figure 1.



X = Br, Cl, F

1a-c

Figure 1. 2′-Halo-α-methylbenzylamines (**1a**–**c**).

2. Results and discussion

At the outset, a general and mild approach was needed to obtain large quantities of racemic 2′-halo-substituted α-methylbenzylamines, as racemate was not commercially available. There is a large body of literature regarding the preparation of racemic versions of these compounds. Starting from the ketone, reductive amination, including the Leuckart reaction,[11] can be used. Oximes and oxime ethers can be converted to the corresponding amine utilizing both catalytic and non-catalytic transfer hydrogenation agents,[12] lithium

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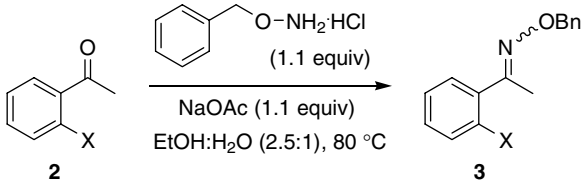
aluminum hydride,[13] and various methods which use combinations of metals and hydride reducing agents.[14] Borane-based reduction methods have been reported less frequently in the literature,[15] despite the fact that they are mild in comparison to other reduction protocols. We chose this as the starting point for our studies since we expected minimal reduction of the carbon–halogen bond with these relatively mild reagents.

Table 1 shows the results of oxime formation using an optimized procedure for the condensation of the corresponding ketone (**2a**–**c**) with *O*-benzylhydroxylamine, which was found to be the optimal oxime substrate for reduction to the amine. Both cis and trans regioisomers were obtained as products, and notably were used without further purification following an aqueous workup.

With the oximes in hand, investigations into the reduction focused on utilizing mild boron reagents to produce the racemic amine. It was found that 2 equiv of borane-dimethylsulfide effected the reduction efficiently and preserved the aryl–halogen bond, producing the desired amine in good yields (Table 2). An acid/base extractive workup yielded the desired amine without need for further purification. This reduction process was demonstrated on scale with 287 g of 2-fluoroacetophenone oxime (**3c**) (Table 2, entry 3), and found to produce amine with equivalent yield and quality to smaller scale experiments.

With an efficient process for racemic amine in hand, a preliminary screen of several commercially available chiral resolving agents was performed with 2′-fluoro-α-methylbenzylamine (Table 3). Ethyl acetate was chosen as the initial screening solvent to evaluate any solubility difference between the diastereomeric salts while maximizing crystallization. In some cases, methanol was employed as a co-solvent to facilitate dissolution of the acid

Table 1. Synthesis of 2-halo-*O*-benzylacetophenone oximes **3a**–**c**

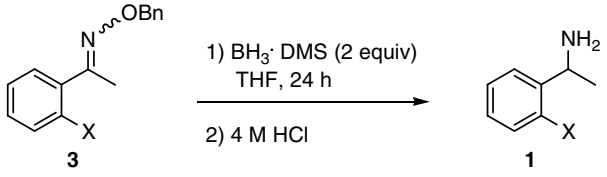


2 **3**

Entry	Ketone	X	Oxime	Yield[a] (%)
1	**2a**	Br	**3a**	96
1	**2b**	Cl	**3b**	96
3[b]	**2c**	F	**3c**	96

[a] Isolated yields.
[b] 170 g reaction.

Table 2. Synthesis of α-methylbenzylamines **1a**–**c**

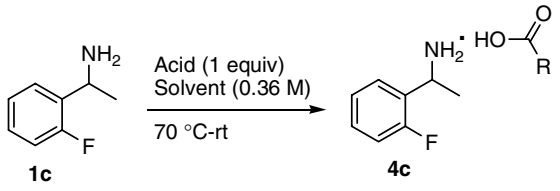


3 **1**

Entry	Oxime	X	Temperature (°C)	Amine	Yield[a] (%)
1	**3a**	Br	rt	**1a**	72
2	**3b**	Cl	rt	**1b**	68
3[b]	**3c**	F	40	**1c**	66

[a] Isolated yields, average of two reactions.
[b] 287 g reaction.

Table 3. Results of initial resolving agent screen



1c **4c**

Entry	Acid	Solvent	Yield (%)	de[a] (%)
1	(*S*)-(+)-Mandelic acid	EtOAc	NA	5.7
2	L-Malic acid	EtOAc	NA	0.4
3	(*S*)-(+)-2-Phenylglycine	EtOAc/MeOH (5:3), 0.22 M	NA	NA[b]
4	(*S*)-(−)-2-Pyrrolidine-5-carboxylic acid	EtOAc	NA	6.7
5	*N*-Acetyl-L-phenylalanine	EtOAc/MeOH (10:3), 0.27 M	NA	0.7
6	*N*-Acetyl-L-leucine	EtOAc/MeOH (10:3), 0.27 M	NA	0.7
7	(*S*)-(−)-2-Pyrrolidine-5-carboxylic acid	EtOH	NA	NA[b]
8	(*S*)-(−)-2-Pyrrolidine-5-carboxylic acid	MeOH	NA	NA[b]
9	(*S*)-(+)-Mandelic acid	MeOH	NA	NA[b]
10	(*S*)-(+)-Mandelic acid	EtOH	22	93
11	(*S*)-(+)-Mandelic acid	IPA	41	89
12	(*S*)-(+)-Mandelic acid	EtOH/IPA (3:2), 0.72 M	39	98
13	(*S*)-(+)-Mandelic acid	EtOH/IPA (1:1), 0.72 M	34	99

[a] Determined by chiral GC.
[b] No crystallization observed.