ORGANIC LETTERS

2000
Vol. 2, No. 7
931−932

Synthesis of *trans*-2-(1-Aryl-1-methylethyl)cyclohexylamines

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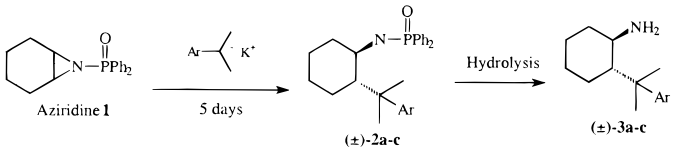
Received January 19, 2000

ABSTRACT

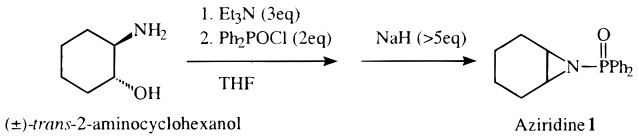


As a first example of opening a secondary aziridine with a tertiary carbanion, the title amines (3a–c, aryl = phenyl, 4-*tert*-butylphenyl, 2-naphthyl) were synthesized by opening *N*-(diphenylphosphinoyl)-7-azabicyclo[4.1.0]heptane, aziridine 1, with the corresponding α-potassium isopropylarenes, followed by hydrolysis of the resulting phosphinamides 2a–c.

Toward making chiral-stationary phases for high-performance liquid chromatography (HPLC)[1] based on highly enantioselective 8-phenylmenthyl derivatives,[2,3] we report a one-pot synthesis of *trans*-2-(1-aryl-1-methylethyl)cyclohexylamines (**3a**−**c**).[4] In analogy to the short synthesis of *trans*-2-(1-aryl-1-methylethyl)cyclohexanols from cyclohexene oxide,[5] the title compounds were made by opening strained *N*-(diphenylphosphinoyl)-7-azabicyclo[4.1.0]heptane, aziridine **1**, with α-potassium isopropylarenes and hydrolysis of the resulting phosphinamides (**2a**−**c**) as follows.

Aziridine **1** was synthesized[6] by diphosphinylation and base-promoted ring closing of *trans*-2-aminocyclohexanol[7] (Scheme 1). Recrystallization from hexanes and ethyl acetate

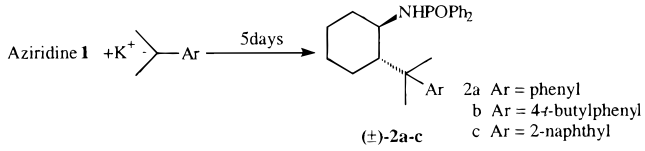
Scheme 1. Preparation of Aziridine **1**[6]



gave **1** as a white solid (mp 161−162 °C) in 75% yield. This one-pot synthesis of an activated aziridine also circumvented working with toxic 7-azabicyclo[4.1.0]-heptane.[8]

Three isopropylarenes were metalated with potassium *tert*-pentoxide and *n*-butyllithium[5] and reacted with aziridine **1** (Scheme 2).[4] Unlike the rapid opening of cyclohexene oxide

Scheme 2. Ring Opening of Aziridine **1**[4]



with 1 equiv of α-potassium isopropylarenes, opening aziridine **1** required up to 5 days and 5 equiv of nucleophile. Quenching the reactions with saturated ammonium chloride and purification, by radial chromatography or recrystallization, gave moderate yields of *trans*-2-(1-aryl-1-methylethyl)-*N*-(diphenylphosphinoyl)cyclohexylamines (phosphinamides **2a**−**c**) (Table 1). Increasing the reaction time to 9 days

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(2) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc*. **1975**, *97*, 6908.
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(5) Comins, D. L.; Salvador, J. M. *J. Org. Chem*. **1993**, *58*, 4656.
(6) Osborn, H. M. I.; Cantrill, A. A.; Sweeney, J. B.; Howson, W. *Tetrahedron Lett*. **1994**, *35*, 3159.
(7) Melting point (mp): 65−66 °C, 65 °C: Wilson, N. A. B.; Read, J. *J. Chem. Soc. Part VII*, **1935**, 1269.
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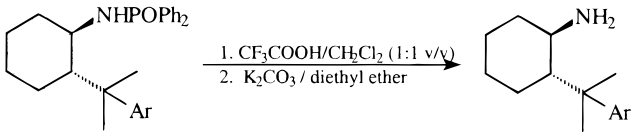
10.1021/ol005568r CCC: $19.00
Published on Web 03/08/2000

Table 1. Percent Yield and Melting Point of (±)-**2a**−**c**[4]

N-phosphinamide	yield (%)	mp (°C)
2a	70	171−172
2b	70	232−233
2c	35	98−100

decreased the yield of **2a** to 48%.[1] Attempted activation of **1** with $BF_3 \cdot Et_2O$[9] in the presence of an α-cumyl potassium suspension led only to the disappearance of the dark purple color[5] of the latter.[1] Nevertheless, to our knowledge, this is the first report of a secondary aziridine being opened by a tertiary carbanion.[10] Phosphinamides **2a**−**c** were subsequently hydrolyzed to the title amines **3a**−**c** in greater than 90% yield as shown in Scheme 3.[11]

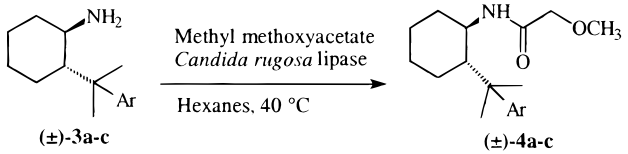
Scheme 3. Hydrolysis of Phosphinamides (±)-**2a**−**c**[11]



(±)-**2a-c** (±)-**3a-c**

We attempted to enantioselectively acylate amines (±)-**3a**−**c** in hexanes using the same commercially available lipase from *Candida rugosa* and lauroyl function that were previously used to kinetically resolve analogous cyclohexanols[5] and other chiral amines.[12,13] Methyl methoxyacetate[14] was selected as the acyl source since methyl laurate only produced ammonium laurate salts with (±)-**3a**.[4] Though methyl methoxyacetate reacted in less than 3 h with amines (±)-**3a**−**c** to make amides **4a**−**c**, Scheme 4, subsequent ^1H

Scheme 4. Attempted Resolution of Title Amines (±)-**3a**[4]



(±)-**3a-c** (±)-**4a-c**

NMR analysis[15] of diastereomer salts of remaining **3a** and (+)-mandelic acid showed little enantioselectivity. Further work on the synthesis of enantiomerically pure title amines is in progress.

Acknowledgment. We acknowledge the financial support of the Welch Foundation (Grant AH-1305), the NIH/MBRS (SO6GMO80120020) program, the UTEP University Research Institute (1992-1993), and the Department of Chemistry, UTEP.

Supporting Information Available: Experimental procedures and spectral data for compounds **1**, **2a** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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