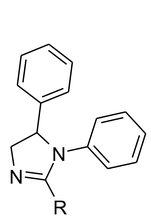
Synthesis of novel trisubstituted imidazolines.

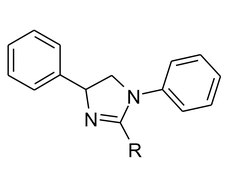
Frederick J. Lakner, Matthew A. Parker, Boris Rogovoy, Alexander Khvat, Alexander Ivachtchenko
Department of Chemistry, ChemDiv Inc., San Diego, California 92121

Why imidazoline derivatives?

2-Substituted imidazolines are well represented in medicinal chemistry, particularly the class of adrenergic drugs related to clonidine and tetrahydrozoline. It is rare, however, for such drugs to take advantage of the sp^3 character of the ethylene bridge. Because substitution at this position provides chirality and non-planarity—and thus a unique potential for fine-tuning target selectivity—we have undertaken a study of such structures. In particular, we are interested in 2-substituted 1,4- and 1,5-diarylimidazolines as illustrated by the model phenyl substitution below. A general and versatile synthetic approach to each system is presented herein.



A



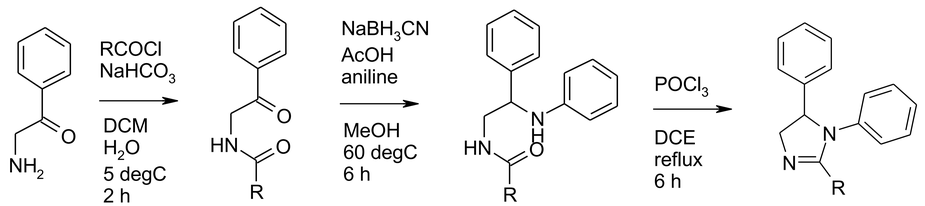
B

R = Me, *i*-Pr, Ph

Goals of this study:

- ➢Simplicity.
- ➢Efficiency.
- ➢Properties of products (eg. pKa, stability, etc.)
- ➢Product distribution (in reduction of **5**) as a function of R.

A) Synthetic approach—1,5-diarylimidazolines

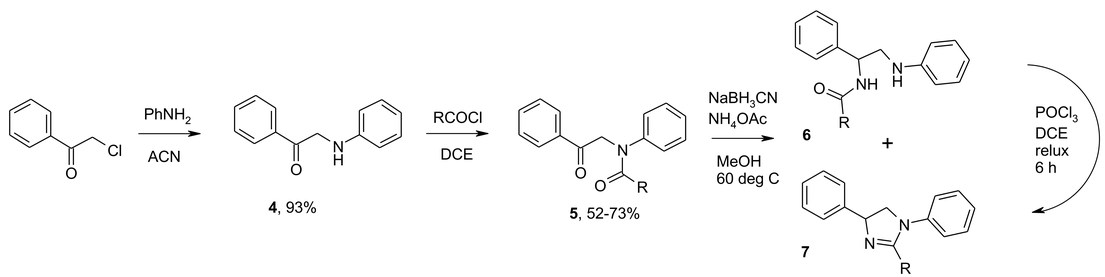


1, 99% **2**, 40-50 % **3**, 95 %

➢Reduction of **1** was not terribly efficient, even using 5-fold excess of aniline. The main side-product was ketone reduction to the corresponding alcohol. This side reaction was even more prevalent with H_2/Pd-C and also with anilinium formate/Pd-C.

➢Cyclization/dehydration of **2** was quite effective using phosphorus oxychloride.

B) Synthetic approach—1,4-diarylimidazolines *(An acyl migration occurred!)*



4, 93% **5**, 52-73% **6** + **7**

➢Obtaining ketoamide **5** is a simple 2-step process.

➢Reduction of **5** resulted in spontaneous partial cyclization and acyl migration. The mixture was fully cyclized without purification so that **7** was isolated with high yield.

➢Ratio of **6**/**7** in crude reaction mixture = 73:27 (R = Me), 18:82 (R = i-Pr), 85:15 (R = Ph).

Results and conclusions:

➢For the purposes of library production, the diversity elements are 2-amino(or Cl)ketones, acid chlorides, and anilines. Since many of each of these are commercially available, thousands of members of each sub-library A & B are potentially accessible.

➢During reductive ammoniation of **5**, the degree of spontaneous cyclization was quite dependent upon the steric and electronic influences of R.

➢These imidazolines were stable to 0.5 M HCl and 0.3 M KOH/MeOH at r.t. for days.

Related Literature

A Novel Approach for Solid-Phase Synthesis of Substituted Imidazolines and Bis-Imidazolines Achyuta N. Acharya, John M. Ostresh, and Richard A. Houghten**J. Org. Chem.* **2001,** *66,* 8673-8676.

Further studies

➢Product distribution (reduction of **5**) as a function of reaction conditions and reductant.

➢Scope and limitations.

➢Enantioselective synthesis.

For further information

…please contact *FLakner@chemdiv.com*