Synthesis of 3,3-Diarylazetidines

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**ABSTRACT**

Diaryl heterocyclic amines are important building blocks in medicinal chemistry. While diarylpyrrolidines and diarylpyrrolidine structures are found in a variety of compounds used in drug discovery studies, the 4-membered ring diazepines are much less prominent in the medicinal chemistry literature. Presumably this is due to limited availability of diarylazetidine derivatives and few methods for the preparation of diarylazetidines. Herein, we describe a short and convenient method for the preparation of 3,3-diarylazetidines. Commercially available N-Boc-azetidin-3-one was readily converted into N-Boc-3-phenylazetidin-3-ol by the addition reaction of phenyllithium in THF at -78 °C. The N-Boc-3-phenylazetidin-3-ol was subsequently converted into N-Boc-3-phenylazetidin-3-ol by the addition reaction of phenyllithium in THF at -78 °C. The N-Boc-3-phenylazetidin-3-ol was afforded the desired 3,3-diarylazetidine ring system in good yields. The scope and limitations of this new synthetic route will be explored.

**INTRODUCTION**

Azetidine is a four-membered nitrogen-containing saturated heterocyclic ring that has recently become a molecular scaffold for the design and preparation of biologically active compounds. The azetidine ring has been recently identified as an important ring system for drug discovery. Azetidine derivatives have been widely used for as a scaffold for drug design encompassing several functional groups at different positions of the ring. Currently there are many drugs and clinical candidates that are azetidine derivatives. Diaryl heterocyclic compounds play an important role in pharmacology, and many of them are commercially used and studied for the treatment of a variety of diseases and disorders. The 3,3-diarylazetidine (1) that has been used as a laxative and exhibits antibacterial and anti-inflammatory activities. The 3-b lactam azetidine (2) is known to have sedative and hypnotic effects. The diaryl heterocyclic compounds play an important role in pharmacology, and many of them are commercially used and studied for the treatment of a variety of diseases and disorders. The 3,3-diarylazetidine (1) that has been used as a laxative and exhibits antibacterial and anti-inflammatory activities. The 3-b lactam azetidine (2) is known to have sedative and hypnotic effects.

**SYNTHESIS OF N-BOC-3-PHENYLAZETIDINE-3-OL:**

1. Boc-3-phenylazetidin-3-ol as a white solid (61%), m.p 95-96°C.

2. 1H NMR (300MHz, CDCl3): δ 7.58-7.6 (6H, m), 4.58 (s, 4H), 2.23 (s, 3H).

3. C NMR (75 MHz, CDCl3): 156.5, 143.4, 128.6, 127.7, 124.6, 80.0, 71.1, 64.4, 28.4.

**SYNTHESIS OF 3-(4-METHYLPHENYL)-3-PHENYL AZETIDINE OXALATE SALT:**

1. 1-Benzoyl-3-phenylazetidin-3-ol as a white solid (59%), m.p 172.8-176.1°C.

2. 1H NMR (300MHz, CDCl3): δ 7.4-7.5 (6H, m), 6.7-6.8 (1H, dd, J = 21Hz, 9Hz), 3.55 (s, 1H), 1.44 (s, 9H).

3. C NMR (75 MHz, DMSO): δ 162.7, 146.7, 148.9, 142.7, 136.5, 129.1, 126.1, 110.0, 48.6, 20.9.

**CONCLUSION**

The 3-(4-methylphenyl)-3-phenylazetidine was successfully synthesized from N-Boc-3-phenylazetidine via reaction with phenylthiophenylboronic acid in 61% yield. The subsequent Friedel-Crafts alkylation reaction in the presence of the Lewis acid catalyst aluminum chloride gave 3-(4-methylphenyl)-3-phenylazetidine in 89% yield. This two-step procedure provides the desired azetidine in good overall yield. The scope and limitations of this new synthetic route will be explored.

**REFERENCES**

2. Kaminska, AB. Synthesis of 1,3-diarylpyrrolidines from diaryl ketones. ARKIVOC 2003 (v), 9-18.

**ACKNOWLEDGMENTS**

We thank the National Institute on Drug Abuse (DA23916) and the University of New Orleans for the financial support of this research.