Synthesis of 3,3-Diarylazetidines

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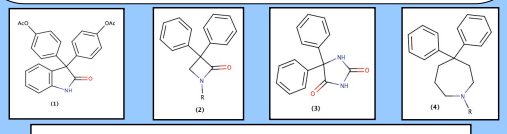
ABSTRACT

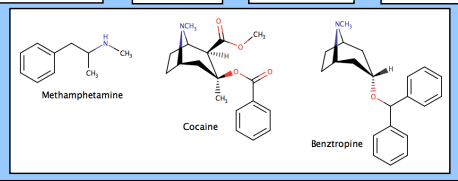
Diaryl heterocyclic amines are important building blocks in medicinal chemistry. While diarylpyrrolidine and diarylpiperidine structures are found in a variety of compounds used in drug discovery studies[1], the 4-membered ring diarylazetidines are much less prominent in the medicinal chemistry literature. 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 obtained in a high yield and high purity. Subsequent arylation of N-Boc-3-phenylazetidine-3-ol using a Friedel-Crafts reaction conditions (toluene/$AlCl_3$) afforded the desired 3,3-diarylazetidine ring system in good yields. The scope and limitations of this new synthetic sequence for the preparation of 3,3-diarylazetidines will be presented.

INTRODUCTION

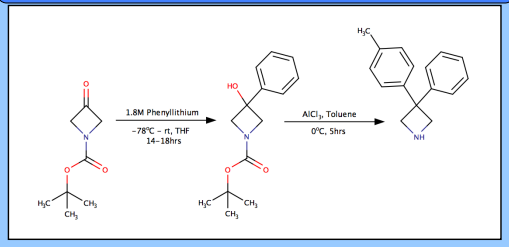
Azetidine is a four-membered nitrogen-containing saturated heterocyclic ring that has recently become a molecular scaffold for the design and preparation of biologically active compounds[1]. The azetidine ring has been recently identified as an important ring system for drug discovery. Azetidine derivatives have been widely used for as a scaffold for drug design encompassing several functional groups at different positions of the ring[1]. Currently there are many drugs and clinical candidates that are azetidine derivatives.

Diaryl heterocycle compounds play an important role in pharmaceuticals, and many of them are commercially used and studied for the treatment of a variety of diseases and disorders. The 3,3-diaryloxindoles **(1)** that has been used as a laxative and exhibits antibacterial and anti-inflammatory activities. The β-lactam azetidine **(2)** is known to have sedative and hypnotic effects[2]. The diaryl imidizolidine Dilantin® **(3)** is used currently used as an anticonvulsant. The azepane **(4)** analogs have serotonin effects[1]. This synthesis of these diaryl heterocyclic compounds are time-consuming multistep procedures. Herein, the synthesis of an unsymmetric diaryl azetidine will be described in two steps from the respective N-Boc-azetidinone in moderate to good yield.

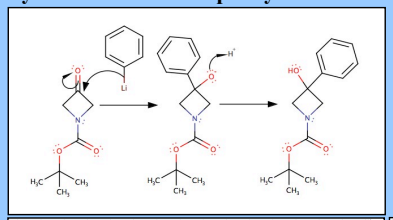


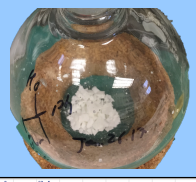


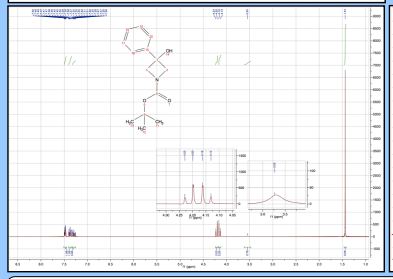
Proposed Synthetic Scheme for Synthesis of 3,3-Diaryl Azetidine

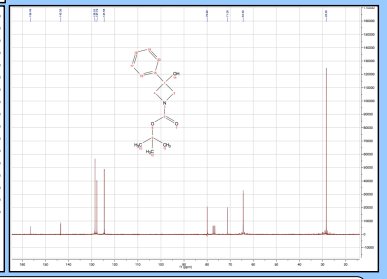


Synthesis of N-Boc-3-phenylazetidine-3-ol:



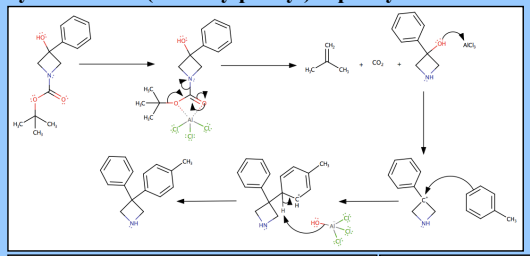


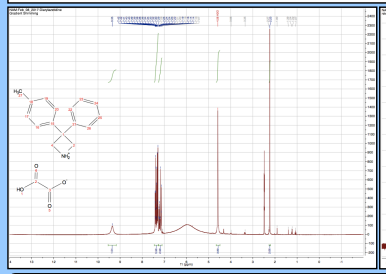


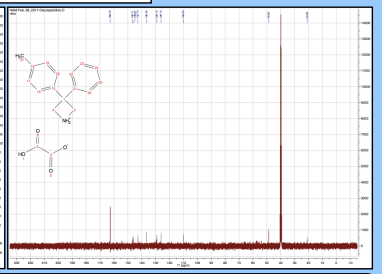


1-Boc-3-phenylazetidine-3-ol as a white solid (61%), mp 93.6-95.6°C.
^{1}H NMR (300MHz, $CDCl_3$): δ 7.50-7.26 (m, 5H), 4.18 (dd, J = 21Hz, 9Hz), 3.55 (s, 1H), 1.44 (s, 9H).
^{13}C NMR (75MHz, $CDCl_3$): δ 156.5, 143.4, 128.6, 127.7, 124.6, 80.0, 71.1, 64.4, 28.4.

Synthesis of 3-(4-methylphenyl)-3-phenylazetidine Oxalate salt:



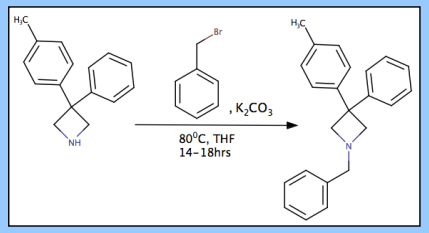




3-(4-Methylphenyl)-3-phenylazetidine Oxalate salt as a white solid (59%), mp 172.8-176.1°C.
^{1}H NMR (300MHz, DMSO): δ 9.35 (s, 2H), 7.42-7.29 (m, 5H), 7.25-7.14 (m, 4H), 4.58 (s, 4H), 2.23 (s, 3H).
^{13}C NMR (75 MHz, DMSO): δ 162.7, 146.7, 145.9, 142.7, 136.5, 129.1, 126.1, 110.0, 48.6, 20.9.

Future construction of novel 1-Substituted-3,3-Diarylazetidine

In the future, the synthesis of novel 1-alkyl-3,3-diarylazetidine and 1-aryl-3,3-diarylazetidine will be investigated. Conversion of 3,3-diarylazetidine into N-substituted azetidine derivatives via an alkylation reaction of the amine will be attempted. The biological evaluation of these novel 1-alkyl-3,3-diarylazetidines and 1-aryl-3,3-diarylazetidines will be explored as potential psychotherapeutic agents and antidepressants.



CONCLUSION

The 3-(4-methylphenyl)-3-phenylazetidine was successfully synthesized from N-Boc-3-azetidinone via reaction with phenyllithium to furnish N-Boc-3-phenylazetidin-3-ol 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 59% yield. This two-step procedure provide the desired azetidines in good overall yield. The scope and limitations of this new synthetic route will be explored.

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ACKNOWLEDGMENTS

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