

EFFICIENT SYNTHESIS OF N-ALKYL TETRAHYDROISOQUINOLINES (THIQ) BY REDUCTIVE AMINATION FOLLOWED BY CATCH AND RELEASE PURIFICATION

Hephzibah J. Kumpaty¹ and Sukanta Bhattacharyya²

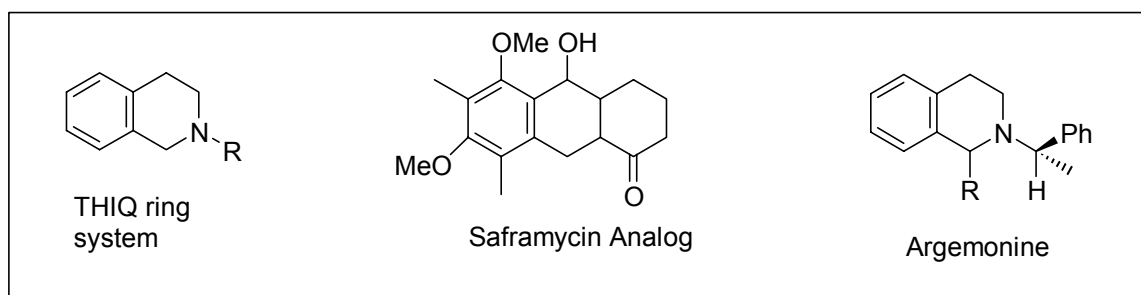
¹Department of Chemistry, University Of Wisconsin-Whitewater, WI, 53190

²Argonaut Technologies, 1101 Chess Drive, Foster City, CA 94404

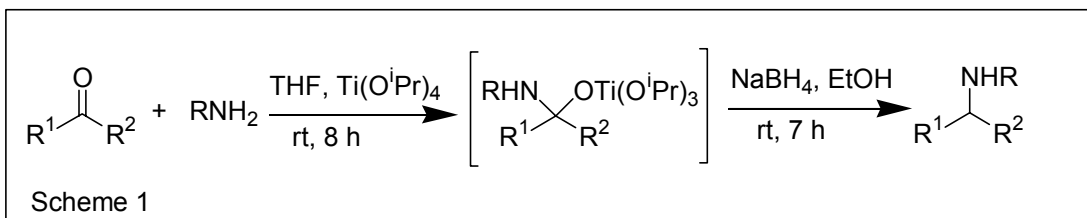
Abstract: An expedient access to N-alkylated tetrahydroisoquinolines (THIQ) is reported by reductive alkylation reactions in the presence of $\text{Ti}(\text{O}^i\text{Pr})_4$ and NaBH_4 . The N-alkylated THIQs were rapidly purified by “catch and release” purification using commercially available polymer-supported sulfonic acid (MP-TsOH) columns.

Introduction

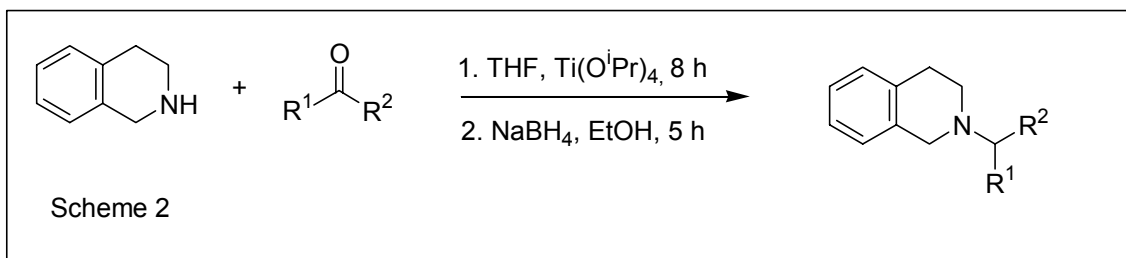
Development of novel methods for synthesis and purification of amines remains a topic of paramount importance in view of their versatile biological and medicinal properties. Amines and their carboxamide derivatives are the most prevalent structural moieties found in the comprehensive medicinal chemistry database. Tetrahydroisoquinolines (THIQs) are particularly important as a wide range of biological and pharmacological properties are prevalent in compounds containing THIQ ring systems such as β_3 adrenergic receptors, antimicrobial and antitumor activities.



Reductive amination of aldehydes and ketones is a powerful tool for the synthesis of amines. This approach is highly practiced for rapid access to diverse sets of amines due to the wide choice of starting amines and carbonyl compounds from the available chemical directory. Previously, we reported¹ a versatile reagent system for reductive amination using a combination of $\text{Ti}(\text{O}^i\text{Pr})_4$ and NaBH_4 (Scheme 1). The protocol works well with a variety of carbonyl compounds including enolizable aldehydes and ketones, and tolerates a variety of potentially acid-labile functional groups such as acetals, acetonides, N-Boc group, and silyl ethers.



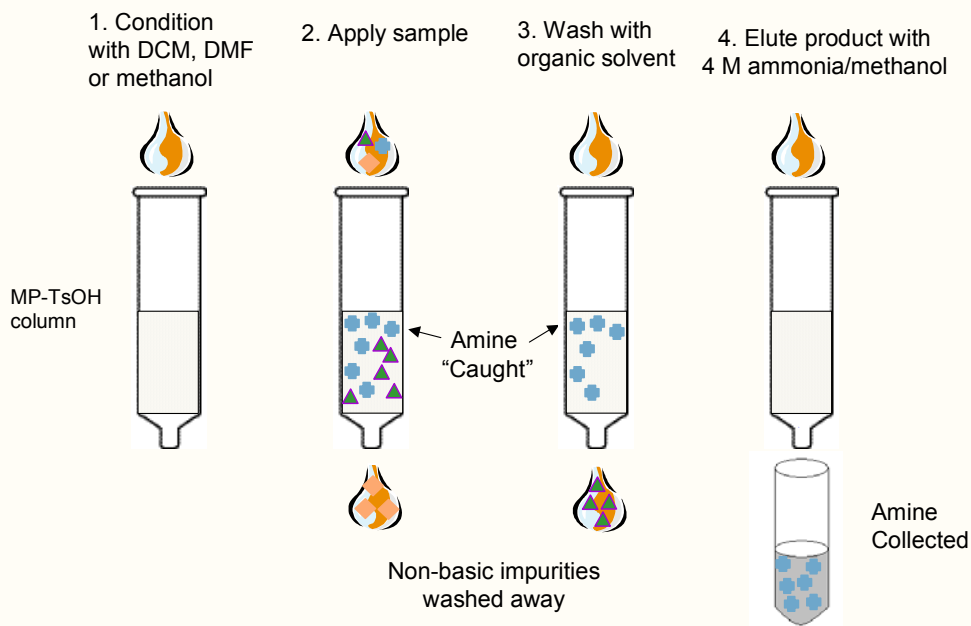
We report herein an efficient synthesis of *N*-alkylated THIQs using titanium isopropoxide and sodium borohydride (Scheme 2). Upon completion of the reaction, the *N*-alkylated THIQs were isolated by “catch and release” purification using polymer-supported sulfonic acid columns.



The MP-TsOH columns were highly effective at flow-through isolation and purification of the *N*-alkylated THIQs. When a solution containing the product THIQ was passed through a column of MP-TsOH, the amine was retained or

“caught” on the resin. After washing off the impurities, the product was “released” from the column by elution with a solution of ammonia in MeOH (Scheme 3).

Scheme 3: MP-TsOH Cartridges for Amine Purification



MP-TsOH is a sulfonated macroporous polystyrene resin that is a polymer-bound equivalent of p-toluenesulfonic acid (TsOH). The resin shows strong affinity for a wide variety of aliphatic, aromatic and heterocyclic amines that can be protonated to form a bound sulfonate salt. MP-TsOH columns are designed specifically for isolation and purification of amines. They can also be used to scavenge basic reagents, substrates, and reaction by-products. Amine salts of weak conjugate acids (e.g., acetate, trifluoroacetate) are exchanged onto the resin and are released as the free amine during the ammonia/methanol wash. The catch and release protocol allows an excellent way to extract amines from DMF or DMSO and subsequently concentrate amine from volatile ammonia/methanol solution.

Results and Discussion

The scope of the reaction was assessed using a structurally diverse set of aldehydes and ketones, and tetrahydroisoquinoline. The carbonyl compounds were allowed to react with tetrahydroisoquinoline and $\text{Ti}(\text{O}^i\text{Pr})_4$, followed by treatment with NaBH_4 under ambient conditions. The reactions were performed with 20% excess of the carbonyl substrates to drive the reactions for completion. Upon completion, the reaction mixtures were quenched with controlled amount of water (~10 equiv. with respect to titanium isopropoxide) and filtered. The filtrate was passed through a MP-TsOH column to retain the amine product, while the excess carbonyl compound and its reduced byproduct were washed off the column with DCM. The N-alkylated THIQ was released with ammonia/methanol to afford the product in >95% purity. In general, full retention of a range of N-alkyl THIQ was observed using a 1.5-fold molar excess of MP-TsOH relative to the amine. The results for a group of aromatic and aliphatic aldehydes and ketones are summarized in Table 1 and 2.

Conclusion

In summary, we have described an expedient access to N-alkylated tetrahydroisoquinolines (THIQ) by reductive alkylation reactions in the presence of $\text{Ti}(\text{O}^i\text{Pr})_4$ and NaBH_4 . The N-alkylated THIQs were conveniently isolated by “catch and release” purification using polymer-supported sulfonic acid (MP-TsOH) columns.

References

1. Bhattacharyya, S. *Tetrahedron Lett.* 1994, 35, 2401; Bhattacharyya, S. *J. Org. Chem.* 1995, 60, 4928; Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem Soc. Perkin Trans 1*, 1998, 2527;

Table 1: Synthesis N-Alkylated THIQs using Ketones

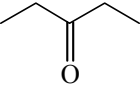
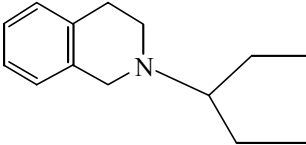
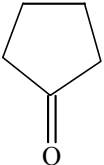
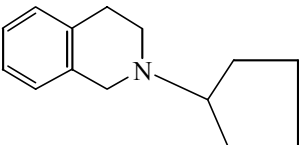
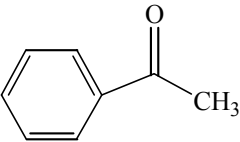
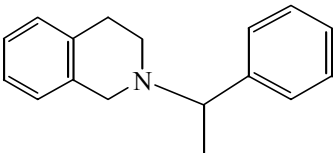
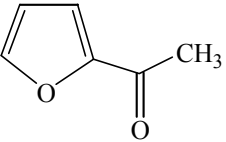
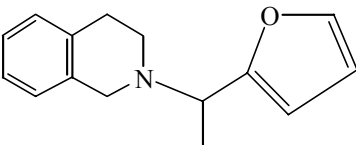
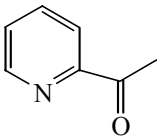
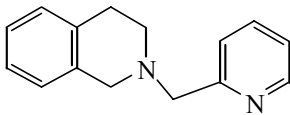
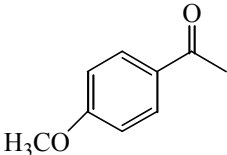
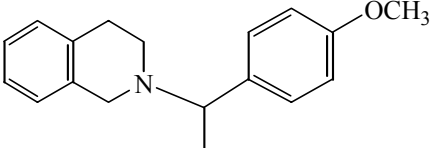
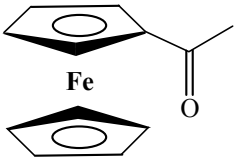
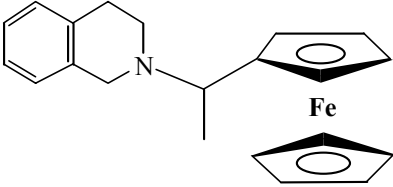
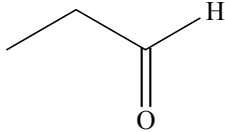
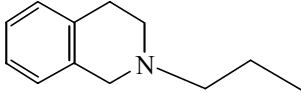
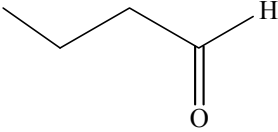
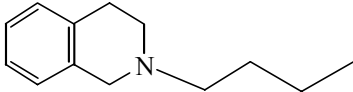
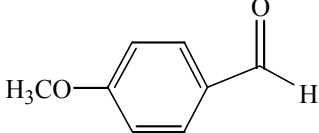
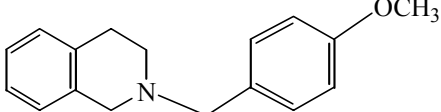
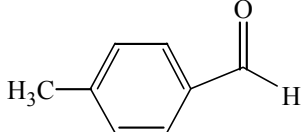
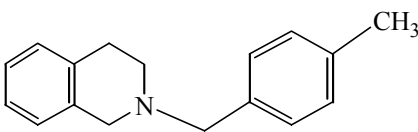
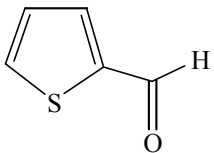
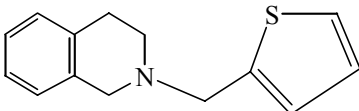
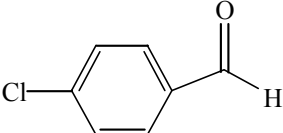
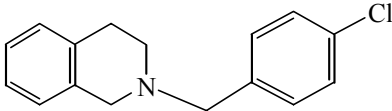
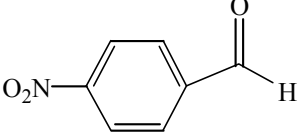
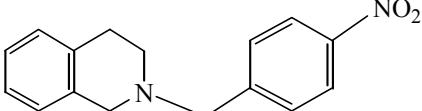
Ketonic Substrates	N-Alkylated THIQ	Yield
		85
		82
		86
		88
		72
		80
		75

Table2: Synthesis N-Alkylated THIQs using Aldehydes

Aldehyde Substrates	N-Alkylated THIQ	Yield
		78
		86
		88
		83
		78
		80
		71