ORGANIC LETTERS

2007
Vol. 9, No. 10
1987−1990

The Kulinkovich Reaction in the Synthesis of Constrained *N,N*-Dialkyl Neurotransmitter Analogues

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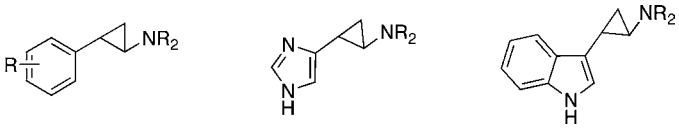
Received March 9, 2007

ABSTRACT

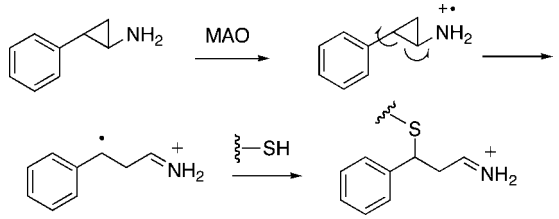


An intermolecular Ti(IV)-mediated cyclopropanation reaction has been used to synthesize substituted 2-phenylcyclopropylamines and constrained analogues of the neurotransmitters histamine and tryptamine. Many hydroxy- and methoxy-substituted phenylcyclopropylamines are known to inhibit monoamine oxidase and have been shown to mimic hallucinogens. These compounds were made in 1 to 5 steps from readily available starting materials.

The conformational constraint of biologically significant molecules has long been used as a technique to understand and improve the activity of these compounds. Use of a cyclopropane to rigidify a molecule is ideal because it introduces minimal steric bulk and negligible influence on electronics. There are examples of cyclopropyl analogues of neurotransmitters that have shown interesting biological properties beyond those held by their linear counterparts.

Burger and Yost[1] first reported the synthesis and monoamine oxidase (MAO) inhibitory activity of *trans*-2-phenylcyclopropylamine, a compound that is used to treat depression. Silverman elucidated the mechanism of inactivation shown in Scheme 1, which illustrates that the cyclopropane is necessary for inactivation.[2] Similar cyclopropylamines have also shown stimulatory activity in neurotransmitter receptors.[3]

Scheme 1. Inactivation of Monoamine Oxidase



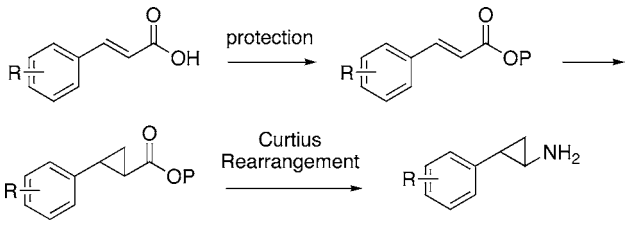
Typically, the synthetic approaches to these structures involve the cyclopropanation of cinnamate derivatives by a Simmons−Smith reaction,[4] dimethylsulfoxonium methylide,[5] or diazomethane.[6] A Curtius rearrangement then produces the amine.[7] Scheme 2 outlines this basic route.

In addition, *N*,*N*-dialkylated aminocyclopropylamines have shown activity in 5-hydroxytryptamine (5-HT) and dopamine (DA) receptors. Particularly potent 5-HT-receptor agonists were 2- and 3-hydroxyphenyl-*N*,*N*-dipropylcyclopropylamines.[8]

(1) Burger, A.; Yost, W. L. *J. Am. Chem. Soc.* **1948**, *70*, 2198−2201.
(2) (a) Silverman, R. *Acc. Chem. Res.* **1995**, *28*, 335−342. (b) Silverman, R. B. *J. Biol. Chem.* **1983**, *258*, 14766−14769.
(3) (a) Aldous, F. A. B.; Barrass, B. C.; Brewster, K.; Buxton, D. A.; Green, D. M.; Pinder, R. M.; Rich, P.; Skeels, M.; Tutt, K. J. *J. Med. Chem.* **1974**, *17*, 1100−1111. (b) Nichols, D. E.; Woodard, R.; Hathaway, B. A.; Lowy, M. T.; Yom, K. W. *J. Med. Chem.* **1979**, *22*, 458−460.
(4) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1−131.
(5) Kaiser, C.; Trost, B. M.; Beeson, J.; Weinstock, J. *J. Org. Chem.* **1965**, *30*, 3972−3975.
(6) Arvidsson, L. E.; Johansson, A. M.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Magnusson, T.; Carlsson, A.; Lindberg, P.; Andersson, B.; Sanchez, D.; Wikstrom, H.; Sundell, S. *J. Med. Chem.* **1988**, *31*, 92−99.
(7) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511−3511.

10.1021/ol0705907 CCC: $37.00
Published on Web 04/21/2007

Scheme 2. General Synthesis of Cyclopropylamines from Cinnamic Acids



Naturally occurring heterocyclic ethylamines, such as tryptamine and histamine, are essential for normal biological functions. Many tryptamine derivatives have been isolated from nature and have shown interesting biological activity. 5-HT is a common neurotransmitter and several similar compounds have found pharmacological use as serotonin reuptake inhibitors, while others are known for their psychoactive properties.

The syntheses of *trans*-2-(3-indoyl)cyclopropylamines were reported by Nichols (Figure 1a).[9] Some of these

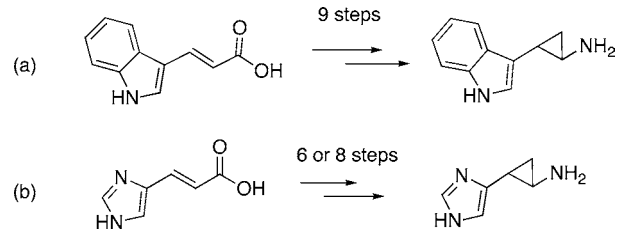


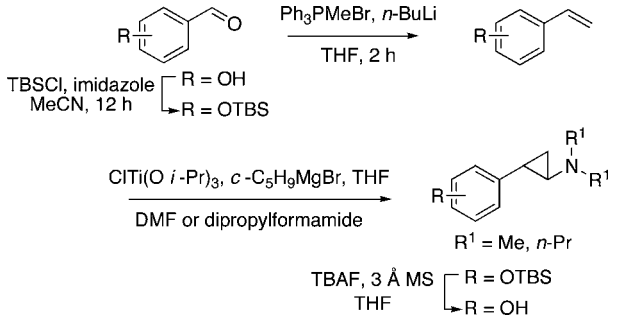
Figure 1. 2-(4-Imidazolylcyclopropylamine) and 2-(3-indoyl)-cyclopropylamine.

analogues were found to be antagonists of the 5-HT_{2C} receptor. Much like the phenylamine analogues, the indolylcyclopropane was made by reaction with diazomethane and a subsequent Curtius rearrangement to afford the amine. A slightly different approach was undertaken by Eftink to obtain both *cis*- and *trans*-cyclopropanes.[10]

Various homeostatic processes are controlled by the neurotransmitter histamine. The H_3 receptor regulates the synthesis and release of histamine, and exerts some influence on other neurotransmitters.[11] Conformationally restricted analogues have been designed to bind to the H_3 receptor selectively. These compounds can have potential therapeutic effects in a number of neurological disorders. The first synthesis of 2-(4-imidazolylcyclopropylamine) was achieved by Burger et al.[12] An imidazole-substituted cyclopropane was made from urocanic acid, using an approach similar to the synthetic route employed to make phenylcyclopropylamines (Figure 1b). An analogous route was subsequently used by de Esch,[13] and diastereoselective syntheses have also been reported by Shuto[14] and Phillips.[15] The 2-(4-imidazolyl)-cyclopropylamine was reported to be a potent MAO inhibitor in vitro.

The interesting biological properties of these compounds prompted us to report an alternate synthesis requiring fewer steps than those described above. The amino variant of the Kulinkovich reaction[16] was applied to various styrenes to obtain methyl- and propylcyclopropylamines. To access the hydroxy-substituted phenylcyclopropylamines, commercially available hydroxybenzaldehydes were protected before they were converted to the corresponding styrene by a Wittig reaction. The coupling of these olefins with dimethylformamide or dipropylformamide provided the cyclopropylamines in good yields (Scheme 3).

Scheme 3. Synthesis of Phenyl-Substituted Cyclopropylamines



A variety of styrenes, easily obtainable from affordable aldehydes, were cyclized to the products shown in Table 1.[7,17,18]

The primary amines of entries 1−7 are known, and many display significant MAO inhibitory activity[19] or, in the case

(8) Vallgaarda, J.; Appelberg, U.; Arvidsson, L.-E.; Hjorth, S.; Svensson, B. E.; Hacksell, U. *J. Med. Chem.* **1996**, *39*, 1485−1493.
(9) (a) Vangveravong, S.; Kanthasamy, A.; Lucaites, V.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1998**, *41*, 4995−5001. (b) Vangveravong, S.; Nichols, D. E. *J. Org. Chem.* **1995**, *60*, 3409−3413.
(10) Raj, T. T.; Eftink, M. R. *Synth. Commun.* **1998**, *28*, 3787−3794.
(11) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. *Nature* **1983**, *302*, 832−837.
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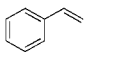
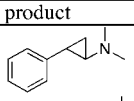
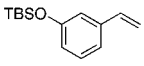
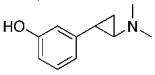
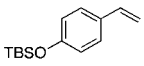
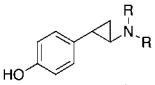
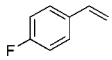
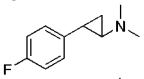
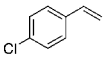
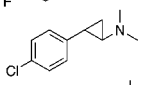
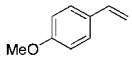
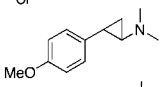
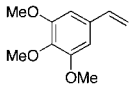
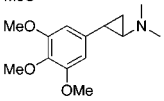
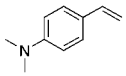
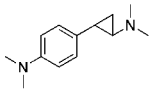
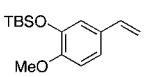
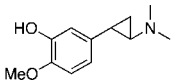
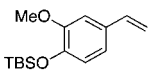
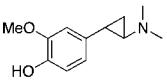
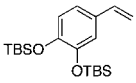
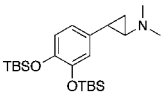
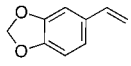
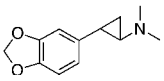
(14) (a) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.-i.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2003**, *46*, 1980−1988. (b) Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669−1677.
(15) Khan, M. A.; Yates, S. L.; Tedford, C. E.; Kirschbaum, K.; Phillips, J. G. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3017−3022.
(16) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234−234. (b) Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584−1585. (c) Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111−114.
(17) To avoid polymerization, the styrenes were used immediately after their preparation.
(18) Wiedemann, S.; Rauch, K.; Savchenko, A.; Marek, I.; de Meijere, A. *Eur. J. Org. Chem.* **2004**, 631−635.
(19) (a) Sherry, R. L.; Coutts, R. T.; Baker, G. B. *Drug Dev. Res.* **1999**, *48*, 61−69. (b) Sherry, R. L.; Baker, G. B.; Coutts, R. T. *Biol. Psychol.* **1990**, *28*, 539−543. (c) Coutts, R. T.; Rao, T. S.; Baker, G. B.; Micetich, R. G.; Hall, T. W. E. *Cell. Mol. Neurobiol.* **1987**, *7*, 271−290. (d) Fuller, R. W.; Kaiser, C. *Biochem. Pharmacol.* **1980**, *29*, 3328−3330. (e) Rao, T. S.; Coutts, R. T.; Baker, G. B.; Hall, T. W.; Micetich, R. G. *Proc. West. Pharmacol. Soc.* **1986**, *29*, 279−281. (f) Sherry-McKenna, R. L.; Baker, G. B.; Mousseau, D. D.; Coutts, R. T.; Dewhurst, W. G. *Biol. Psychol.* **1992**, *31*, 881−888.

Table 1. Substituted 2-Phenyldimethylcyclopropylamines

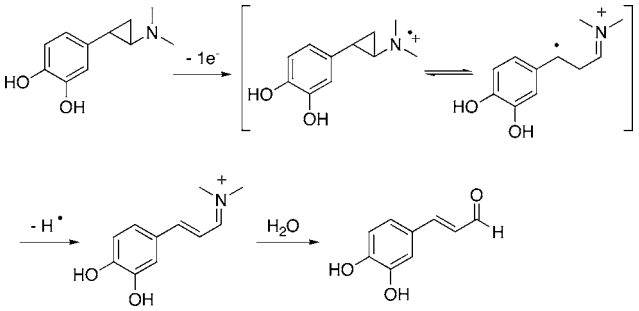
entry	substrate	product	yield (%)[a]
1[18]			78
2[7]			58[b]
3[7]			R = Me: 74[b] R = Pr: 31[b]
4			58
5			49
6			52
7			42
8			59
9			68[b]
10			65[b]
11			55
12			45

[a] Isolated yields. [b] Yield over 2 steps: cyclopropanation and deprotection.

of (trimethoxyphenyl)cyclopropylamine (entry 7), psychotomimetic properties.[20] Because Arvidsson et al.[7] showed that phenolic *N*,*N*-dipropylcyclopropylamines were more potent than primary cyclopropylamines, we believe the dimethylamines in Table 1 will also exhibit activity. Entries 8−10 represent novel cyclopropylamines expected to possess interesting biological properties because of the high activity of the corresponding phenethylamines. For example, 3-hydroxy-4-methoxyphenethylamine is a plant alkaloid that can be found, along with mescaline, in certain plants growing in the southwestern United States.[21] It has been hypothesized that methylated catacholamines could play a role in Parkinson's disease.[22] Also, 4-dimethylaminophenethylamine is a nonselective and reversible MAO inhibitor.[23] Entry 12 bears resemblance to the psychoactive drug methylenedioxymethamphetamine (MDMA, Ecstasy). Although this compound has been reported in a patent, which describes its synthesis in 8 steps,[24] exact biological data and full characterization are lacking. It is very likely that such a compound could have stimulatory activity of neurotransmitter receptors similar to MDMA.

Deprotection of the 3,4-disiloxyphenylcyclopropylamine (entry 11) did not result in the desired dihydroxyphenylcyclopropylamine. While cyclopropane appeared to be present in the crude product mixture, caffeic aldehyde was isolated in 90% yield upon purification (Scheme 4). We

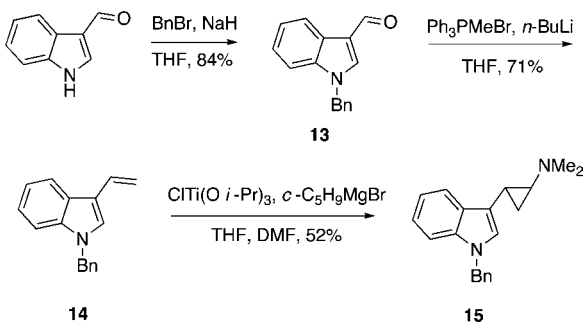
Scheme 4. Fragmentation of Dihydroxyphenylcyclopropylamine



believe this transformation occurred through an oxidative mechanism, which has been well-investigated by Cha[25] and Iwata.[26] Facile fragmentation was likely due to the electron-rich phenyl and the presence of ambient oxygen and water during purification.

Our synthesis of tryptamine analogues is shown in Scheme 5. Although we have used the Kulinkovich reaction in the

Scheme 5. Indolylcyclopropylamine



presence of unprotected indoles,[27] indole carboxaldehyde required protection before undergoing a Wittig reaction. The resulting vinyl indole was cyclized with a formamide to give **15**.

(20) (a) Cooper, P. D.; Walters, G. C. *Nature* **1972**, *238*, 96−98. (b) Walters, G. C.; Cooper, P. D. *Nature* **1968**, *218*, 298−300.

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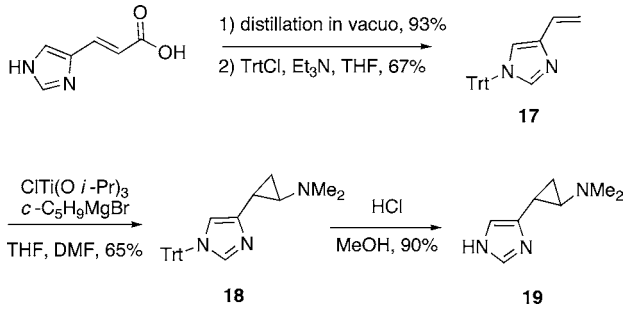
(23) (a) Reyes-Parada, M.; Scorza, M. C.; Silveira, R.; Dajas, F.; Costa, G.; Tipton, K. F.; Cassels, B. K. *Biochem. Pharmacol.* **1994**, *47*, 1365−1371. (b) Bennington, F.; Morin, R. D.; Clark, L. C., Jr. *J. Org. Chem.* **1956**, *21*, 1470−1472.

To use the Kulinkovich reaction in the synthesis of imidazolyl cyclopropylamines, a slightly different approach was used. As seen in Scheme 6, urocanic acid was decar-

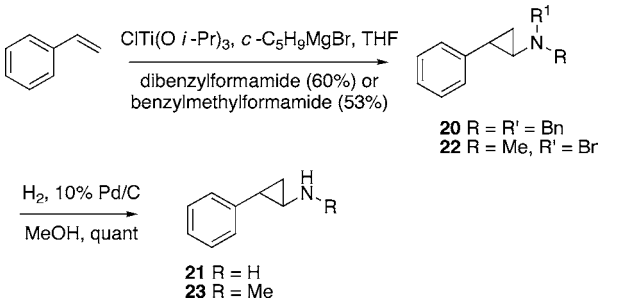
Scheme 6. Imidazolylcyclopropylamine



boxylated to vinyl imidazole by distillation under reduced pressure. Trityl protection of the imidazole preceded intermolecular cyclization with dimethylformamide.[28] Deprotection of compound **18** gave cyclopropylamine **19**.

N,*N*-Dimethylcyclopropylamines were synthesized largely due to the simplicity of obtaining dimethylformamide. It may, however, be desirable to synthesize primary and secondary amines, as many of these compounds are known to be biologically active. By coupling the olefins with benzylformamides, benzylated cyclopropylamines are obtained. These compounds can be deprotected easily by hydrogenation (Scheme 7), as previously established by de Meijere.[29]

Scheme 7. Synthesis of Primary and Secondary Aminocyclopropanes



In conclusion, we have demonstrated a facile synthesis of biologically important cyclopropylamines. The application of the Kulinkovich reaction gives cyclopropane-constrained *N*,*N*-dimethyl analogues of histamine, tryptamine, and substituted phenethylamines in fewer steps than previously reported. Biological evaluation of the novel compounds is underway.

Acknowledgment. We thank the NSF (CHEM-1030958), Wyeth, and the University of Pennsylvania for financial support. Additionally, a fellowship provided by the NSF (DGE-0231923 005) aided this work. We are also grateful to Dr. George Furst and Dr. Rakesh Kohli (University of Pennsylvania) for technical assistance.

Supporting Information Available: Experimental procedures and characterization data of all compounds and ^{1}H and ^{13}C NMR spectra of the final products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0705907

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