Efficient Synthesis of *N*-Alkyl Tetrahydroisoquinolines by Reductive Amination

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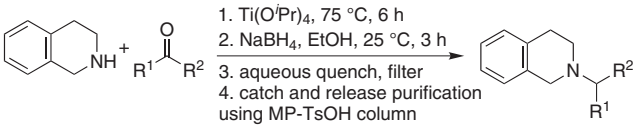
Abstract: An expedient access to diverse *N*-alkyl 1,2,3,4-tetrahydroisoquinolines is reported by reductive amination of aldehydes and ketones with tetrahydroisoquinoline (THIQ) in the presence of Ti(O*i*-Pr)$_4$ and $NaBH_4$. The *N*-alkyl THIQ products were rapidly purified by flow-through catch and release technique using commercially available polymer-supported sulfonic acid, MP-TsOH columns.

Key Words: reductive amination, tetrahydroisoquinoline, Ti(O*i*-Pr)$_4$, $NaBH_4$, polymer-supported sulfonic acid column

Synthesis of amines is a topic of paramount interest as amines and their derivatives are the most prevalent structural moieties found in the comprehensive medicinal chemistry database.[1] In particular, synthesis of tetrahydroisoquinoline (THIQ) derivatives is an objective of high priority as numerous natural products and synthetically derived molecules containing the THIQ ring system exhibit versatile biological and pharmacological properties.[2] A few significant examples include antitumor and antimicrobial activities,[3] 5-HT_{1A} receptor antagonism[4] and stimulation of β_3 adrenergic receptors.[5] Another noteworthy example includes the design and synthesis of sterically constrained analogs of medicinally important peptides by incorporating THIQ moieties in their amino acid framework.[6] Very recently, the synthesis and screening of a series of *N*-alkyl THIQ derivatives as selective dopamine D_3 receptor ligands have been reported in the literature.[7]

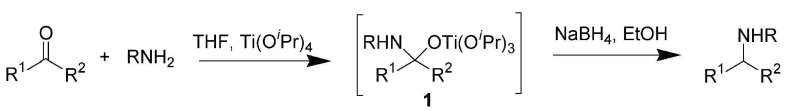
Reductive amination[8] of carbonyl compounds is a very powerful tool for chemists to target the synthesis of structurally diverse primary, secondary and tertiary amines. The sequence proceeds through the formation of an imine or iminium intermediate upon reaction of a carbonyl compound with ammonia, primary amine or secondary amine followed by in situ reduction to an amine of higher order. In the context of our continued investigations on amine synthesis[9] by reductive amination, we reported previously a versatile reagent system for reductive amination using a combination of Ti(O*i*-Pr)$_4$ and $NaBH_4$.[10] The reaction may proceed (Scheme 1) through an intermediate titanium(IV) complex **1**,[11] which is either reduced directly or via equilibration of **1** with a transient iminium species in the presence of $NaBH_4$.

We describe[12] here an efficient method for the synthesis of *N*-alkyl THIQ derivatives. Reductive amination of aldehydes and ketones with THIQ was performed in the presence of Ti(O*i*-Pr)$_4$ and $NaBH_4$ (Scheme 2). Upon completion of the reaction, the *N*-alkyl THIQ compounds were rapidly isolated in their pure forms by catch and release purification using commercially available polymer-supported sulfonic acid, MP-TsOH columns[13] in analogy to silica-based SCX columns reported in the literature.[14]



Scheme 2

The scope of the present synthesis was evaluated using a structurally diverse set of aldehydes and ketones, and 1,2,3,4-tetrahydroisoquinoline (THIQ). The carbonyl compounds were allowed to react with THIQ and neat Ti(O*i*-Pr)$_4$ at 75 °C followed by the addition of EtOH and $NaBH_4$ under ambient conditions. A 20% molar excess of carbonyl compounds and 2-fold molar excess of Ti(O*i*-Pr)$_4$ were employed to drive the reactions for completion. The results obtained from a group of ketones and aldehydes are summarized in Tables 1 and 2, respectively.



Scheme 1

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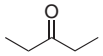
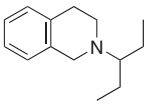
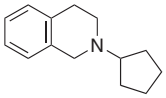
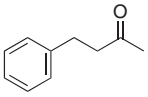
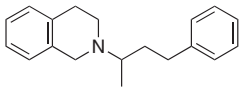
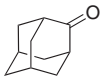
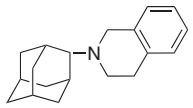
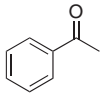
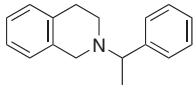
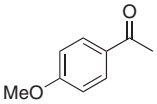
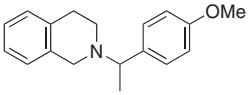
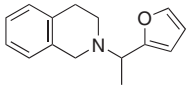
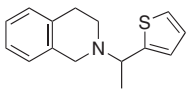
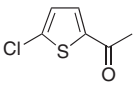
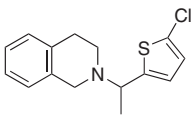
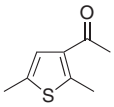
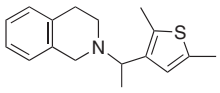
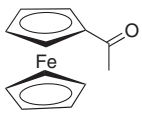
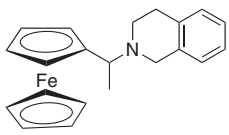
Typically, the intermediate titanium(IV) complex similar to **1** was allowed to form first by stirring a mixture of the carbonyl compound, THIQ and Ti(O*i*-Pr)$_4$ at 75 °C for six hours. Absolute EtOH was then added followed by $NaBH_4$, and the resulting mixture stirred for another three hours at room temperature. The initial workup process involved aqueous quenching of the reaction mixture followed by filtration of the resulting inorganic precipitate and extraction with CH_2Cl_2.

The product *N*-alkyl THIQ derivatives were rapidly isolated in their pure forms by catch and release purification using MP-TsOH columns[13] similar to silica-supported SCX columns.[14] The combined organic extracts were added onto an MP-TsOH column, preconditioned with CH_2Cl_2. The solution was allowed to flow through the column, followed by washing with CH_2Cl_2 to remove the non-basic impurities such as the excess carbonyl compound and its reduced byproduct. Finally, the product *N*-alkyl THIQ was released from the MP-TsOH column by the addition of a solution of NH_3 in MeOH. The NH_3 exchanged with the *N*-alkyl THIQ on the column, releasing it into the solution. Evaporation of the solvent typically afforded analytically pure *N*-alkyl THIQ samples. 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 macroporous polystyrene-supported sulfonic acid, MP-TsOH has a typical loading of 3.0 mmol/g, which is 3–4 times higher than that of SCX, silica-based sulfonic acid. Other advantages of MP-TsOH include the stability of polystyrene support under a broad range of pH as opposed to silica-based SCX, and the absence of contamination of amine products with particulates that sometimes happen with SCX by media decomposition.[15]

As demonstrated in Table 1, the protocol worked well using a broad set of ketones with varied reactivity profiles. This includes both aliphatic and less reactive aromatic ketones, sterically hindered ketones, heterocyclic ketones, ferrocenyl ketones as well as enolizable ketones. Thus, the enolizable aliphatic ketones (entries 1–3) underwent reductive amination with THIQ affording the corresponding *N*-alkyl THIQ derivatives in high yields. The reaction using the sterically hindered ketone, 2-adamantanone (entry 4) afforded *N*-adamantyl THIQ in good yield. Likewise, *N*-alkyl THIQ derivatives were obtained in good to high yields from the reactions using acetophenones (entries 5 and 6), and heterocyclic ketones containing furan (entry 7) and thiophene (entries 8–10) moieties. Ferrocenyl methyl ketone (entry 11) also provided the corresponding THIQ derivative in good yield. Table 2 summarizes the reactions using a set of aldehyde substrates. A number of aliphatic, heterocyclic and aromatic aldehydes were reacted with THIQ to produce the corresponding tertiary amines in high yields.

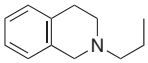
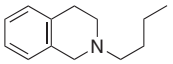
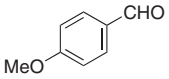
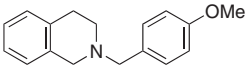
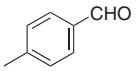
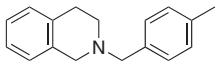
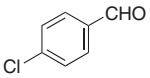
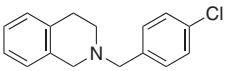
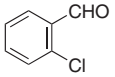
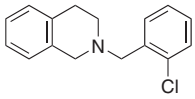
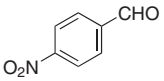
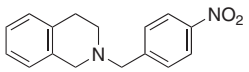
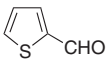
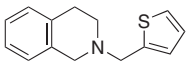
In summary, we have described a highly effective synthesis of *N*-alkyl THIQ derivatives by reductive amination of aldehydes and ketones with THIQ in the presence of Ti(O*i*-Pr)$_4$ and $NaBH_4$. The *N*-alkyl THIQs were rapidly purified by flow-through catch and release technique using commercially available polymer-supported sulfonic acid, MP-TsOH columns. We believe this rapid synthesis and purification protocol will find significant applications in organic synthesis.

Table 1 Reductive N-Alkylation of THIQ with Ketones

Entry	Ketone	Product Amine	Yield (%)
1			85
2			84
3			80
4			78
5			85
6			87
7			88
8			86
9			78
10			85
11			77

[1]H NMR spectra were obtained using a 300 MHz Bruker AM spectrometer, using $CDCl_3$ as the solvent with TMS as the internal reference. ^{13}C NMR spectra were obtained at 75.5 MHz in $CDCl_3$. Elemental analyses were performed at Atlantic Microlab Inc., Georgia, USA. Mass spectra were recorded on an EI-500 spectrometer at the University of Wisconsin-Milwaukee. Analytical TLC was performed on pre-coated Alumina plates with fluorescent indicator us-

Table 2 Reductive N-Alkylation of THIQ with Aldehydes

Entry	Aldehyde	Product Amine	Yield (%)
1	CH_3CH_2CHO		85
2	$CH_3CH_2CH_2CHO$		86
3			88
4			85
5			82
6			82
7			78
8			84

ing anhyd solvents, followed by UV visualization as necessary. The products were characterized by their ^1H and ^{13}C NMR spectral data, and elemental or mass spectral analyses.

Reductive Amination Using 1,2,3,4-Tetrahydroisoquinoline (THIQ) and Carbonyl Compounds; General Procedure

A mixture of THIQ (1.0 mmol), Ti(O*i*-Pr)$_4$ (0.6 mL, 2 mmol) and the respective carbonyl compound (1.2 mmol) was allowed to stir at 75 °C under an atmosphere of N_2 for 6 h. The reaction mixture was next cooled to r.t. under N_2, and absolute EtOH (2.0 mL) and $NaBH_4$ (0.12 g, 3 mmol) were added in sequence. The reaction mixture was further allowed to stir for 3 h at ambient temperature and quenched with water (2.0 mL). The resulting white inorganic precipitate was separated by filtration and washed with CH_2Cl_2 (10 mL). The organic layer was separated and the product *N*-alkyl THIQ was rapidly isolated in its pure form by catch and release purification using polymer-supported sulfonic acid, MP-TsOH columns.[13]

For catch and release purification, the organic solution was added onto a MP-TsOH column (0.5 g/6 mL, 1.5 mmol) preconditioned with CH_2Cl_2 (4 mL). The solution was allowed to flow through the MP-TsOH column, followed by washing with CH_2Cl_2 (3 × 2 mL) to remove the non-basic impurities such as the excess carbonyl compound and its reduced byproduct. Finally, the product *N*-alkyl THIQ was released from the column by the addition of a solution of NH_3 in MeOH (4 M, 4 mL). Concentration of the resulting solution typically afforded the *N*-alkyl THIQ in high yield and purity (Tables 1 and 2). In most of the cases, the catch and release purification protocol afforded analytically pure samples. In certain cases, however, preparative TLC or flash chromatography (Et_2O–MeOH, 9:1) was performed to obtain analytical samples.

Table 1, Entry 1

^1H NMR: δ = 1.04 (t, *J* = 6 Hz, 6 H), 1.51 (quintet, *J* = 5.8 Hz, 2 H), 1.66 (quintet, *J* = 5.8 Hz, 2 H), 2.42 (quintet, *J* = 6 Hz, 1 H), 2.83 (m, 4 H), 3.50 (s, 2 H), 6.99–7.32 (m, 4 H).

EIMS: *m*/*z* calcd for $C_{14}H_{21}N$: 203.3; found: 203.0.

Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.96; H, 10.14; N, 6.88.

Table 1, Entry 2

^1H NMR: δ = 1.59–1.62 (m, 8 H), 2.81 (quintet, *J* = 6 Hz, 1 H), 2.82 (t, *J* = 5.8 Hz, 2 H), 2.92 (t, *J* = 5.8 Hz, 2 H), 3.70 (s, 2 H), 6.82–7.28 (m, 4 H).

^{13}C NMR: δ = 24.1, 29.0, 30.6, 49.6, 55.3, 66.8, 125.5, 125.9, 126.6, 128.4, 134.2, 134.8.

EIMS: *m*/*z* calcd for $C_{14}H_{19}N$: 201.3; found: 201.0.

Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.26; H, 9.54; N, 6.98.

Table 1, Entry 3

^1H NMR: δ = 1.18 (d, *J* = 6.6 Hz, 3 H), 1.77 (m, 1 H), 2.05 (m, 1 H), 2.75–3.00 (m, 5 H), 3.86 (q, *J* = 6.7 Hz, 2 H), 3.94 (d, *J* = 14.7 Hz, 2 H), 7.00–7.37 (m, 9 H).

EIMS: *m*/*z* calcd for $C_{19}H_{23}N$: 265.18; found: 265.0.

Anal. Calcd for $C_{19}H_{23}N$: C, 85.99; H, 8.74; N, 5.28. Found: C, 85.63; H, 8.53; N, 5.57.

Table 1, Entry 4

^1H NMR: δ = 1.18–1.56 (m, 14 H), 2.72–2.90 (m, 5 H), 3.70 (d, *J* = 10.8 Hz, 2 H), 7.15 (m, 4 H).

EIMS: *m*/*z* calcd for $C_{19}H_{25}N$: 267.0; found: 267.0.

Anal. Calcd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.24. Found: C, 84.96; H, 9.28; N, 5.20.

Table 1, Entry 5

^1H NMR: δ = 1.61 (d, *J* = 6.6 Hz, 3 H), 2.92 (m, 2 H), 3.67 (m, 2 H), 3.69 (q, *J* = 6.7 Hz, 1 H), 3.94 (d, *J* = 14.8 Hz, 2 H), 7.23 (m, 4 H), 7.73 (m, 5 H).

^{13}C NMR: δ = 20.0, 29.2, 47.9, 53.5, 64.3, 125.4, 125.9, 126.7, 126.8, 127.5, 128.2, 128.5, 130.8, 134.5, 135.1, 144.2.

EIMS: *m*/*z* calcd for $C_{17}H_{19}N$: 237.3; found: 237.0.

Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 85.71; H, 8.03; N, 5.56.

Table 1, Entry 6

^1H NMR: δ = 1.53 (d, *J* = 6.7 Hz, 3 H), 2.81–2.90 (m, 3 H), 3.50–4.00 (m, 7 H), 6.86–7.37 (m, 8 H).

EIMS: *m*/*z* calcd for $C_{18}H_{21}NO$: 267.3; found: 267.0.

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.90; H, 7.89; N, 5.44.

Table 1, Entry 7

^1H NMR: δ = 1.54 (d, *J* = 7 Hz, 3 H), 2.66–2.93 (m, 4 H), 3.73 (d, *J* = 14.4 Hz, 2 H), 3.97 (q, *J* = 7 Hz, 1 H), 6.24 (d, *J* = 32 Hz, 1 H), 6.35 (d, *J* = 33 Hz, 1 H), 6.9–7.15 (m, 4 H), 7.40 (s, 1 H).

^{13}C NMR: δ = 15.8, 29.6, 47.0, 51.9, 56.7, 106.9, 106.6, 109.6, 125.4, 125.8, 126.5, 128.5, 134.3, 135.0, 141.4, 155.5.

EIMS: *m*/*z* calcd for $C_{15}H_{17}NO$: 227.3; found: 227.0.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.22; H, 7.51; N, 5.93.

Table 1, Entry 8
^{1}H NMR: δ = 1.60 (d, *J* = 6.5 Hz, 3 H), 2.60–2.93 (m, 4 H), 3.82 (q, *J* = 14.7 Hz, 2 H), 4.15 (q, *J* = 6.7 Hz, 1 H), 6.87–6.97 (m, 4 H), 7.09–7.19 (d, *J* = 3.5 Hz, 2 H), 7.25 (dd, *J* = 8.7, 3.5 Hz, 1 H).

EIMS: *m*/*z* calcd for $C_{15}H_{17}NS$: 243.3; found: 243.0.

Anal. Calcd for $C_{15}H_{17}NS$: C, 74.03; H, 7.04; N, 5.76. Found: C, 74.02; H, 7.07; N, 5.61.

Table 1, Entry 9
^{1}H NMR: δ = 1.51 (d, *J* = 6.4 Hz, 3 H), 2.75–3.1 (m, 4 H), 3.90 (m, 2 H), 6.70–7.31 (m, 7 H).

EIMS: *m*/*z* calcd for $C_{15}H_{16}ClNS$: 277.07; found: 277.0.

Anal. Calcd for $C_{15}H_{16}NClS$: C, 64.85; H, 5.80; N, 5.04. Found: C, 65.25; H, 5.65; N, 5.02.

Table 1, Entry 10
^{1}H NMR: δ = 1.44 (d, *J* = 6.6 Hz, 3 H), 2.37 (s, 3 H), 2.42 (s, 3 H), 2.64 (m, 1 H), 2.83 (m, 3 H), 3.60 (m, 2 H), 3.83 (d, *J* = 14.8 Hz, 1 H), 6.60 (s, 1 H), 7.04–7.15 (m, 4 H).

^{13}C NMR: δ = 13.9, 15.1, 19.0, 29.1, 47.7, 53.6, 57.2, 125.0, 125.4, 125.8, 126.7, 128.6, 130.5, 134.5, 135.0, 139.3.

EIMS: *m*/*z* calcd for $C_{17}H_{21}NS$: 271.04; found: 271.0.

Anal. Calcd for $C_{17}H_{21}NS$: C, 75.23; H, 7.80; N, 5.16; S, 11.81. Found: C, 75.05; H, 7.81; N, 4.96; S, 11.92.

Table 1, Entry 11
^{1}H NMR: δ = 2.06 (d, *J* = 6.9 Hz, 3 H), 2.71–2.50 (m, 1 H), 2.72–2.86 (m, 3 H), 3.51 (d, *J* = 14.6 Hz, 1 H), 3.71 (d, *J* = 14.7 Hz, 1 H), 3.89 (q, *J* = 6.8 Hz, 1 H), 4.16–4.25 (m, 9 H), 6.99–7.17 (m, 4 H).

^{13}C NMR: δ = 16.7, 29.7, 46.1, 51.1, 58.5, 66.9, 67.2, 67.6, 68.5, 69.3, 69.8, 72.3, 87.0.

EIMS: *m*/*z* calcd for $C_{21}H_{23}FeN$: 345.2; found: 345.0.

Anal. Calcd for $C_{21}H_{23}FeN$: C, 73.05; H, 6.71; N, 4.06. Found: C, 72.77; H, 6.49; N, 3.82.

Table 2, Entry 1
^{1}H NMR: δ = 1.06 (t, *J* = 7.2 Hz, 3 H), 1.69 (quintet, *J* = 7.4 Hz, 2 H), 2.51 (t, *J* = 5.3 Hz, 1 H), 2.7–3.1 (m, 5 H), 3.63 (s, 1 H), 4.04 (s, 1 H), 7.23 (m, 4 H).

EIMS: *m*/*z* calcd for $C_{12}H_{17}N$: 175.2; found: 175.0.

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.66; H, 9.38; N, 8.25.

Table 2, Entry 2
^{1}H NMR: δ = 0.91 (t, *J* = 6.4 Hz, 3 H), 1.41 (sextet, *J* = 6.5 Hz, 2 H), 2.51 (t, *J* = 6 Hz, 2 H), 2.66–2.71 (m, 4 H), 2.96 (t, *J* = 6 Hz, 2 H), 3.63 (s, 2 H), 7.02–7.36 (m, 4 H).

EIMS: *m*/*z* calcd for $C_{13}H_{19}N$: 189.3; found: 189.0.

Table 2, Entry 3
^{1}H NMR: δ = 2.76 (t, *J* = 6 Hz, 2 H), 2.94 (t, *J* = 6 Hz, 2 H), 3.42 (s, 1 H), 3.71–3.77 (m, 2 H), 3.84 (s, 3 H), 4.05 (s, 1 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 7.02–7.17 (m, 4 H), 7.34 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR: δ = 29.0, 50.4, 55.1, 55.9, 62.0, 113.5, 114.2, 125.4, 125.9, 126.5, 128.5, 130.1, 130.3, 131.9, 134.3, 134.8, 158.6.

EIMS: *m*/*z* calcd for $C_{17}H_{19}NO$: 253.1; found: 253.0.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.66; H, 8.01; N, 5.75.

Table 2, Entry 4
^{1}H NMR: δ = 2.37 (s, 3 H), 2.73 (t, *J* = 5.9 Hz, 2 H), 2.91 (t, *J* = 5.9 Hz, 2 H), 3.60 (s, 2 H), 3.64 (s, 2 H), 7.10 (m, 4 H), 7.18–7.31 (dd, *J* = 11.7, 2.8 Hz, 4 H).

EIMS: *m*/*z* calcd for $C_{17}H_{19}N$: 237.3; found: 237.0.

Table 2, Entry 5
^{1}H NMR: δ = 2.85 (t, *J* = 5.8 Hz, 2 H), 2.95 (t, *J* = 5.5 Hz, 2 H), 3.74 (s, 2 H), 3.87 (s, 2 H), 7.03–7.38 (m, 8 H).

EIMS: *m*/*z* calcd for $C_{16}H_{16}ClN$: 257.0; found: 257.0.

Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; N, 5.43. Found: C, 74.52; H, 6.06; N, 5.33.

Table 2, Entry 6
^{1}H NMR: δ = 2.85 (t, *J* = 5.8 Hz, 2 H), 2.95 (t, *J* = 5.5 Hz, 2 H), 3.74 (s, 2 H), 3.87 (s, 2 H), 7.03–7.38 (m, 8 H).

EIMS: *m*/*z* [M + H] calcd for $C_{16}H_{16}ClN$: 257.0; found: 257.0.

Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; N, 5.43. Found: C, 74.98; H, 6.06; N, 5.33.

Table 2, Entry 7
^{1}H NMR: δ = 2.75 (t, *J* = 5.8 Hz, 2 H), 2.93 (t, *J* = 5.5 Hz, 2 H), 3.75 (s, 2 H), 3.79 (s, 2 H), 6.98–7.68 (m, 8 H).

EIMS: *m*/*z* calcd for $C_{16}H_{16}N_2O_2$: 268.3; found: 268.0.

Table 2, Entry 8
^{1}H NMR: δ = 2.90 (t, *J* = 5.7 Hz, 2 H), 3.02 (t, *J* = 5.7 Hz, 2 H), 3.81 (s, 2 H), 4.01 (s, 2 H), 6.9–7.2 (m, 7 H).

EIMS: *m*/*z* calcd for $C_{14}H_{15}NS$: 229.3; found: 229.0.

Anal. Calcd for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11. Found: C, 73.28; H, 6.48; N, 6.00.

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References

(1) (a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55. (b) Henkel, T.; Brunne, R. M.; Mueller, H.; Reichel, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 643.

(2) See for example: (a) Nielsen, T. E.; Diness, F.; Meldal, M. *Curr. Opin. Drug Discov. Dev.* **2003**, *6*, 801. (b) Griffith, M. C.; Dooley, C. T.; Houghten, R. A.; Kiely, J. S. In *Molecular Diversity and Combinatorial Chemistry Libraries and Drug Discovery*; Chaiken, I. M.; Janda, K. D., Eds.; American Chemical Society: Washington DC, **1996**, 50. (c) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903; and references therein. (d) Gray, N. M.; Cheng, B. K.; Mick, S. J.; Lair, C. M.; Contreras, P. C. *J. Med. Chem.* **1989**, *32*, 1242. (e) Herbert, R. B. In *Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D.; Roberts, M. F.; Zenk, M. H., Eds.; Springer-Verlag: Berlin, **1985**, 213.

(3) (a) Scott, J. D.; Williams, R. D. *Chem. Rev.* **2002**, *102*, 1669. (b) Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545.

(4) Mokrosz, M. J.; Bojarsky, A. J.; Duszynska, B.; Tatarczynska, E.; Klodzinska, A.; Deren-Wesolek, A.;

Charakchieva-Minol, S.; Chojnacka-Wojcik, E. *Bioorg. Med. Chem.* **1999**, *7*, 287.
(5) Parmee, E. R.; Brockunier, L. L.; Singh, S. B.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Liu, Y.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2283.
(6) (a) Gibson, A. C.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585. (b) Thomas, J. B.; Atkinson, R. N.; Vinson, N. A.; Catanzaro, J. L.; Perretta, C. L.; Fix, S. E.; Mascarella, S. W.; Rothman, R. B.; Xu, H.; Dersch, C. M.; Cantrel, B. E. *J. Med. Chem.* **2003**, *46*, 3127; and references therein.
(7) Mach, U. R.; Hackling, A. E.; Perachon, S.; Ferry, S.; Wermuth, C. G.; Schwartz, J.-E.; Sokoloff, P.; Stark, H. *ChemBioChem* **2004**, *5*, 508.
(8) Reductive amination reactions are extensively reviewed, see for example: Baxter, E. W.; Reitz, A. B. *Org. React. (N.Y.)* **2002**, *59*, 1; and references 1-17 therein.
(9) For example, see: (a) Bhattacharyya, S.; Rana, S.; Gooding, O. W.; Labadie, J. *Tetrahedron Lett.* **2003**, *44*, 4957. (b) Bhattacharyya, S.; Gooding, O. W.; Labadie, J. *Tetrahedron Lett.* **2003**, *44*, 6099. (c) Bhattacharyya, S.; Tamanaha, L.; Vo, L.; Labadie, J. *Comb. Chem. High Throughput Screening* **2000**, *3*, 117.
(10) For example, see: (a) Kumpaty, H. J.; Bhattacharyya, S.; Rehr, E. W.; Gonzalez, A. M. *Synthesis* **2003**, 2206. (b) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463; and references cited therein.
(11) (a) Imwinkelried, R.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1496. (b) Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Synthesis* **1988**, 238.
(12) The work was presented in part by: Kumpaty H. J., Bhattacharyya S.; 228th ACS National Meeting, Philadelphia; American Chemical Society: Washington, DC, August 2004; paper ORGN-701
(13) The macroporous polystyrene-supported sulfonic acid, MP-TsOH columns (part number: 800477-0050-C) were obtained from Argonaut Technologies.
(14) (a) Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997**, *38*, 3357. (b) Shuker, A. J.; Siegel, M. G.; Matthews, D. P.; Weigel, L. O. *Tetrahedron Lett.* **1997**, *38*, 6149. (c) Lawrence, M. R.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553.
(15) (a) Thurman, E. M.; Mills, M. S. In *Solid-Phase Extraction: Principles and Practice*; Wiley: New York, **1998**, 55. (b) Thurman, E. M.; Mills, M. S. In *Solid-Phase Extraction: Principles and Practice*; Wiley: New York, **1998**, 131.