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Preparation of Tertiary Alkyl Carbinamines, Propargylamines, and α-Heteroarylamines by Ketone-Based Aminoalkylation

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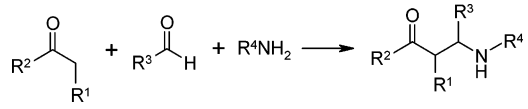
Ketones **6a**−**i** were converted into their benzotriazolylamine adducts **8a**−**i** either directly from the corresponding ketone **6a** or via enamines **7b**−**i**. Adducts **8a**−**i** on treatment with Grignard reagents, lithium phenylacetylide, or heteroaryllithiums gave tertiary alkyl carbinamines **9a**−**h** (47−61%), propargylamines **10a**−**i** (30−98%), and α-heteroarylamines **11a**−**k** (44−85%), respectively.

Introduction

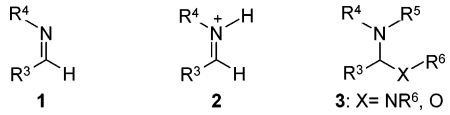
Aminoalkylation is the introduction of a CRR′NR″R‴ group into an organic compound. The most important and widely used aminoalkylation of CH-acidic compounds is the Mannich reaction.[1] In a classical Mannich reaction, an enolizable aldehyde or ketone, which serves as the CH-acidic substrate, is α-aminomethylated by formaldehyde and a secondary amine to generate a β-amino carbonyl compound (Mannich base) (Scheme 1). The classical Mannich reaction, although it soon became a key for the synthesis of pharmaceuticals and natural products,[2] was restricted to the use of formaldehyde as the central component. Moreover, classical Mannich procedures involved drastic conditions and long reaction times, which in many cases resulted in the formation of unwanted byproducts.

The great versatility of Mannich reaction has led to the development of advantageous variants[1] such as preformed aldimines **1**,[3a−c] iminium ions **2**,[3c] aminals **3**,[3d] or hemiaminals[3e−g] as Mannich electrophiles. These preformed reagents ensure a high concentration of electrophile and thus require lower temperatures and shorter reaction times. In addition, these procedures extend somewhat the utility of Mannich reaction to aldehydes other than formaldehyde (e.g., to arylaldehydes) and also to primary amines (Scheme 2). Most of these preformed intermediates still require a Lewis acid activator for the subsequent reaction with nucleophiles and are limited to the use of nonenolizable aldehydes as starting materials.

SCHEME 1. Classic Mannich Reaction



SCHEME 2. Mannich Variants



Benzotriazole-mediated aminoalkylations have greatly broadened the utility of Mannich-type reactions to nonenolizable and enolizable aliphatic, aromatic, and heteroaromatic aldehydes and primary, secondary, aromatic, aliphatic, and heteroaromatic amines.[4] Alkyl glyoxylates[5a] and *N*-alkylglycine ethyl esters[5b] have also been em-

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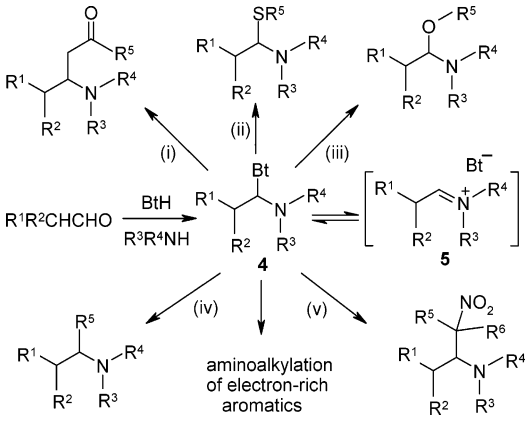
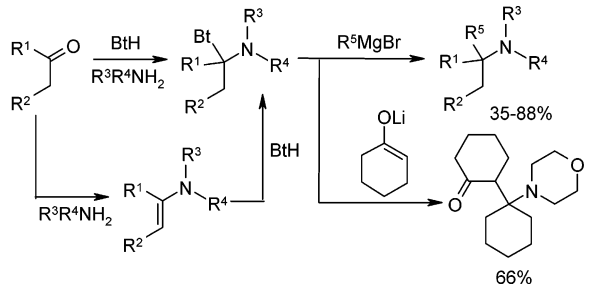
SCHEME 3. Benzotriazole-based Aminoalkylating Reagents from Aldehydes



ployed in condensations to prepare *tert*-α-amino esters. Key intermediates *N*-aminoalkylbenzotriazoles **4** are in dynamic equilibrium with iminium cations **5**,[4c] which can be trapped effectively by a large variety of nucleophiles. Accordingly, benzotriazole methodology has been extensively utilized for the *N*-alkylation of aromatic amines,[6a,b] heteroaromatic amines,[6b] aliphatic amines,[6c,d] ammonia,[6e,f] and hydroxylamines[6g] and for aminoalkylation of ketones,[7] nitro compounds,[8] alcohols,[9] thiols,[9] amides,[10] and electron-rich aromatics[11] (Scheme 3). Benzotriazole methodology has proven to be a versatile approach toward the synthesis of a variety of nonchiral[12a−c] and chiral heterocycles.[12d,e] The diastereoselectivities achieved are often comparable to yet another complementary approach, nucleophilic substitution of the cyano substituent from α-aminonitriles.[13]

However, attempts to prepare α-aminonitriles[14] or benzotriazole-based amionoalkylating reagents[15a] derived from ketones and a secondary amine encountered more difficulty. Previously published successful examples were mostly limited to unhindered aliphatic cyclic and acyclic ketones (Scheme 4).[15] Benzotriazolyl adducts from unsubstituted 5-, 6-, and 7-membered cyclic ketones and secondary aliphatic cyclic amines have been prepared successfully and utilized for the preparation of pharmaceutically active, highly branched tertiary alkyl carbinamines via nucleophilic replacement of the benzotriazole moiety by Grignard reagents and $NaBH_4$.[15a] One example of the preparation of a Mannich base has been documented[15b] as the *N*-(aminoalkyl)benzotriazole adduct prepared from pentan-3-one via the enamine derivative 1-(1-ethylprop-1-enyl)pyrrolidine.[15c]

SCHEME 4. Benzotriazole-based Aminoalkylating Reagents from Ketones



R^1R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-; R^1 = Et, R^2 = Me; NR^3R^4 = NHBn; pyrrolidinyl, piperidinyl, morpholinyl; R^5 = H, Bu, Bn, Ph, 4-MePh, 4-ClPh

We now report the preparation of *N*-(aminoalkyl)-benzotriazoles from unhindered and hindered aliphatic cyclic and acyclic ketones and secondary amines and their use as aminoalkylating reagents for the preparation of tertiary alkyl carbinamines, propargylamines and α-heteroarylamines.

Results and Discussion

Preparation of Benzotriazolyl Adducts 8a−i from Ketones 6a−i. Addition of enamines **7b−i** of ketones **6b−i** to benzotriazole gave adducts **8b−i** after 30 min. The ^{1}H NMR spectra of the reaction mixture indicated the complete formation of the adducts **8b−i** in deuterated chloroform within 0.5 h as evidenced by the complete disappearance of the signal for the enamine proton at 4.3−4.8 ppm. Moreover, the ^{1}H and ^{13}C NMR spectra of the adduct **8b** were identical to the one prepared earlier via a three-component condensation of cyclohexanone, pyrrolidine and benzotriazole.[15a] In the present study, adduct **8a** was prepared using an analogous three component condensation in 85% yield.[15a] Adducts **8a−e** were previously fully characterized by NMR spectroscopy and elemental analysis.[15a] Enamines made either from aromatic amines or aromatic ketones failed to add BtH as monitored by the ^{1}H NMR spectra.

Unlike adducts **8a−e** prepared from cyclic ketones or their enamine derivatives **7a−e**, the corresponding adducts prepared from enamines **7f−i** derived from acyclic aliphatic ketones decomposed readily in moist air to the starting ketone, amine, and benzotriazole.[15c] Enamines **7g−n** were prepared using the literature procedures.[24]

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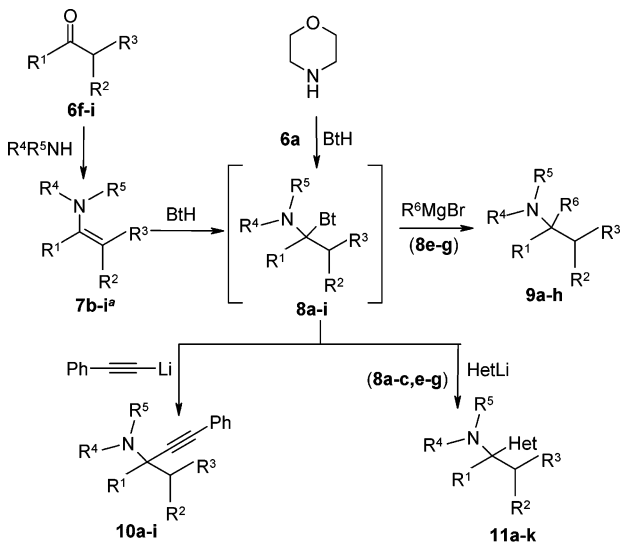
For this study, the benzotriazolyl adducts **8b**−**i** prepared by the addition of benzotriazole to the corresponding enamines **7b**−**i** were treated directly with various nucleophiles, without isolation or purification, to give tertiary alkyl carbinamines **9**, propargylamines **10**, and α-heteroarylamines **11** (Scheme 5).

Preparation of Tertiary Alkyl Carbinamines 9a−**h.** Previously, the most common approach for the synthesis of tertiary alkyl carbinamines has been the Bryulants reaction of α-aminonitriles (Scheme 6).[16] Starting α-aminonitriles are generated by Strecker reaction of an aldehyde, amine, and a cyanide source[17a] and quaternary centers α to the cyano substituent are often created by lithiation−substitution.[17b] Although, the direct preparation of such substrates from unhindered cyclic ketones and a secondary amine[18a,b] proceeds smoothly at 20 °C, reactions using aliphatic acyclic ketones require prolonged heating periods.[15d] Recently, the use of high pressures for the preparation of α-aminonitriles from relatively hindered aliphatic ketones and aromatic secondary amines has been reported.[14] Most examples of Bryulants substitution of a nitrile group by a Grignard reagent utilize α-aminonitriles derived from aldehydes or cyclic ketones.[18] This methodology has been used for the preparation of several compound classes of great pharmaceutical interest including analgesics,[18c,f,19a] anesthetics,[19b] CNS agents[19c,d] and tools for the study of dopamine re-uptake complex.[19e] 1-(1-Phenylcyclohexyl)-piperidine (PCP) and its analogues constitute a special class of compounds prepared by this methodology.[19f]

SCHEME 5



6,7,8	R1	R2	R3	R4	R5
a	-(CH2)4-		H	-(CH2)2O(CH2)2-	
b	-(CH2)4-		H	-(CH2)4-	
c	-(CH2)4-		H	-(CH2)5-	
d	-(CH2)3-		H	-(CH2)2O(CH2)2-	
e	-(CH2)5-		H	-(CH2)2O(CH2)2-	
f	Et	Me	H	-(CH2)2O(CH2)2-	
g	Pr	Et	H	-(CH2)2O(CH2)2-	
h	Et	Me	H	Et	Et
i	Me	Me	Me	-(CH2)2O(CH2)2-	

While complementary to Bryulants reaction of α-aminonitriles, benzotriazole methodology is of wider scope and avoids side reactions due to nucleophilic attack on the nitrile substituent. Stirring benzotriazole and a ketone-derived enamine at rt for 30 min in Et_2O/THF forms benzotriazolyl adducts which can be used for further aminoalkylation of appropriate nucleophiles. The results shown in Table 1 demonstrate that a wide range of Grignard reagents can be employed for which the replacement of the benzotriazolyl group by an alkyl group proceeded smoothly. Treatment of the adduct **8e** prepared in situ with benzylmagnesium bromide gave the corresponding product **9a** in 47% yield (Scheme 5, Table 1). Similarly, reaction of the adduct **8f** with phenyl- or benzylmagnesium bromide gave **9b** and **9c** in 50% and 60% yields, respectively. Nucleophilic replacement of the benzotriazolyl moiety from adduct **8g** using phenyl-, benzyl-, and *n*-butylmagnesium bromide gave novel compounds **9d**−**f** in 61%, 47%, and 48% yields, respectively. Importantly, reaction of the adduct **8g** with vinyl- or allylmagnesium bromide provided an easy access to allylic and homoallylic amines **9g** and **9h**, respectively, in 51% and 56% yields. The structures of all of the novel tertiary alkyl carbinamines **9a**−**h** were fully characterized by their ^1H and ^{13}C NMR spectra and elemental analysis.

Alkynylation of Benzotriazolyl Adducts 8a−**i with Lithium Phenylacetylide: Preparation of Propargylamines 10a**−**i.** Propargylamines are biologically active[20a−d] and are important synthetic intermediates.[20e] The most common preparative methods for propargylamines include copper-catalyzed alkynylation of enam-

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SCHEME 6

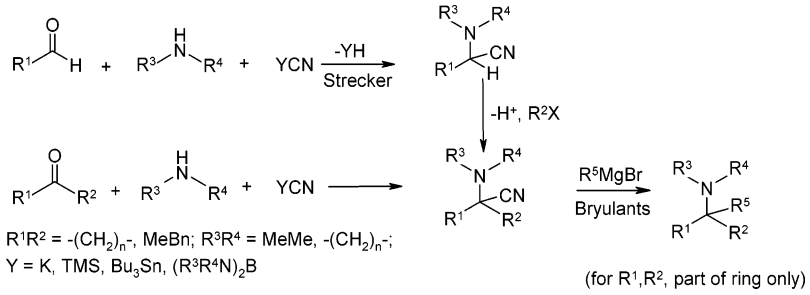


TABLE 1. Reaction of Bt-Adducts 8e–g with Grignard Reagents R^6MgBr: Preparation of Tertiary Alkyl Carbinamines 9a–h (Scheme 5)

Bt-Adduct	R^1	R^2	R^3	R^4	R^5	R^6	9,Y(%)
8e	$-(CH_2)_5-$		H	$-(CH_2)_2O(CH_2)_2-$		Bn	**9a** (47)
8f	Et	Me	H	$-(CH_2)_2O(CH_2)_2-$		Ph	**9b** (50)
8f	Et	Me	H	$-(CH_2)_2O(CH_2)_2-$		Bn	**9c** (60)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		Ph	**9d** (61)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		Bn	**9e** (47)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		Bu	**9f** (48)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		vinyl	**9g** (51)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		allyl	**9h** (56)

TABLE 2. Reaction of Bt-Adducts 8A–i with Lithio Phenylacetylene: Preparation of Propargylamines 10A–i (Scheme 5)

Bt-Adduct	R^1	R^2	R^3	R^4	R^5	Product, Y(%)
8a	$-(CH_2)_4-$		H	$-(CH_2)_2O(CH_2)_2-$		**10a** (98)
8b	$-(CH_2)_4-$		H	$-(CH_2)_4-$		**10b** (67)
8c	$-(CH_2)_4-$		H	$-(CH_2)_5-$		**10c** (43)
8d	$-(CH_2)_3-$		H	$-(CH_2)_2O(CH_2)_2-$		**10d** (47)
8e	$-(CH_2)_5-$		H	$-(CH_2)_2O(CH_2)_2-$		**10e** (52)
8f	Et	Me	H	$-(CH_2)_2O(CH_2)_2-$		**10f** (92)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		**10g** (80)
8h	Et	Me	H	Et	Et	**10h** (30)
8i	Me	Me	Me	$-(CH_2)_2O(CH_2)_2-$		**10i** (31)

TABLE 3. Reaction of Bt-Adducts 8A–c,e–g with Heteroaryl Lithiums: Preparation of α-Heteroarylamines 11A–k (Scheme 5)

Bt-Adduct	R^1	R^2	R^3	R^4	R^5	Het	Product, Y(%)
8a	$-(CH_2)_4-$		H	$-(CH_2)_2O(CH_2)_2-$		2-thiophenyl	**11a** (85)
8b	$-(CH_2)_4-$		H	$-(CH_2)_4-$		2-thiophenyl	**11b** (47)
8c	$-(CH_2)_4-$		H	$-(CH_2)_5-$		2-thiophenyl	**11c** (71)
8e	$-(CH_2)_5-$		H	$-(CH_2)_2O(CH_2)_2-$		2-thiophenyl	**11d** (55)
8f	Et	Me	H	$-(CH_2)_2O(CH_2)_2-$		2-thiophenyl	**11e** (73)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		2-thiophenyl	**11f** (66)
8a	$-(CH_2)_4-$		H	$-(CH_2)_2O(CH_2)_2-$		2-thiazolyl	**11g** (51)
8b	$-(CH_2)_4-$		H	$-(CH_2)_4-$		2-thiazolyl	**11h** (54)
8e	$-(CH_2)_5-$		H	$-(CH_2)_2O(CH_2)_2-$		2-thiazolyl	**11i** (44)
8f	Et	Me	H	$-(CH_2)_2O(CH_2)_2-$		2-thiazolyl	**11j** (72)
8g	Pr	Et	H	$-(CH_2)_2O(CH_2)_2-$		2-thiazolyl	**11k** (80)

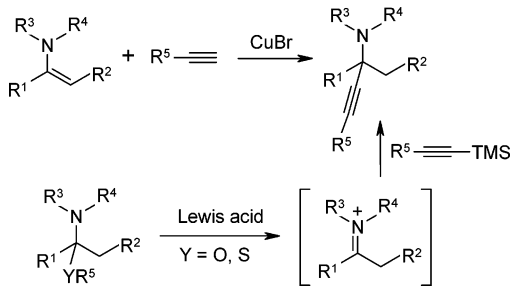
ines,[21] addition of acetylides to ketimines,[20b] and Lewis acid-catalyzed addition of lithio- or silylalkynes to hemiaminals via iminium ion intermediates[22a,b] (Scheme 7).

Treatment of benzotriazolyl adducts **8a–i** with lithium phenylacetylide gave the desired propargylamines **10a–i** in 30–98% yield (Scheme 5, Table 2). Alkynylation of relatively hindered benzotriazolyl adduct **8i** prepared from 4-(1,2-dimethylprop-1-enyl)morpholine (**7i**) gave the corresponding product **10i** in a low yield (31%). Compounds **10a–i** displayed signals for the alkynyl carbons from 85 to 92 ppm. Propargylamines **10a–i** were characterized by ^1H and ^{13}C NMR spectroscopy and elemental analysis.

Preparation of α-Heteroarylamines. α-Heteroarylamines have frequently been prepared by the Bryulants method but only for the α-aminonitriles that are prepared from aldehydes.[19a,b,23a] α-Thiazolylamines demonstrate analgesic[19b] and anaesthetic[19b] activities. α-Thiophenylamines are analgesics,[19a] antimycotics,[23b] anticonvulsants,[23c] neuroprotectants,[23d] and regulators of gastrointestinal tract motility[23e] and serve as important tools for the study of drug-binding sites.[23a]

Nucleophilic replacement of benzotriazolyl group from adducts **8a–c**, **e–g** was effected by using lithiated aromatic heterocycles such as thiophenyllithium and thiazolyllithium (Scheme 2, Table 3) to obtain α-thiophenylamines **11a–f** and thiazolylamines **11g–k** in 44–85% yields. Signals for the thiophene ring were observed at 7.17 (d), 6.95 (dd), and 6.81 (d) ppm in the ^1H NMR

SCHEME 7



spectra and at 149, 126, 124, and 123 ppm in the ^{13}C NMR spectra. The thiazole ring was evidenced by the presence of two doublets for the aromatic protons in the region 7.78−7.25 ppm in the ^{1}H NMR spectra and by the signals at 179, 141, and 119 ppm in the ^{13}C NMR spectra. The novel compounds **11c**−**k** were also characterized by elemental analysis. No major byproducts were formed in the case of low-yielding reactions, and the crude products contained the desired compound and unreacted starting material according to GC−MS examination.

Conclusions

Benzotriazole-assisted one-pot addition of nucleophiles to ketone-derived enamines described herein represents a general and versatile approach to the *N-tert*-alkylation of secondary amines. The present method provided a complementary approach to the methods described earlier, specifically for the Bruylants approach which is limited to the aldehyde and cyclic ketones substrates. We have now prepared various highly hindered novel *N*-tertiary alkylated tertiary amines in good to excellent yields. The particularly mild reaction conditions, simple procedure, easily available starting materials, and reasonable yields offer significant advantages.

Experimental Section

All of the reactions were carried out under N_2. THF and Et_2O were distilled from sodium/benzophenone prior to use. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). Column chromatography was performed on silica gel 200−425 mesh using hexanes/EtOAc (10:1). Enamines **7b**−**e** were purchased from commercial sources and used without purification.

2-(1-Morpholinocyclohexyl)-1*H*-1,2,3-benzotriazole (8a): white needles (from hexanes−ethyl acetate); yield 85%; mp 129−131 °C (lit.[15a] mp 132−134 °C); ^{1}H NMR δ 7.90−7.88 (m, 2H), 7.39−7.36 (m, 2H), 3.75−3.64 (m, 4H), 2.92 (apparent t, J = 4.7 Hz, 2H), 2.77−2.38 (m, 8H), 2.34 (apparent t, J = 4.7 Hz, 2H), 1.50−1.88 (m, 6H); ^{13}C NMR δ 142.8, 125.9, 118.1, 85.0, 67.4, 45.4, 33.6, 25.2, 22.2. Anal. Calcd for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56. Found: C, 67.39; H 7.93; N, 19.91.

4-(1-Benzylcycloheptyl)morpholine (9a): colorless oil; yield 47% (0.39 g); ^{1}H NMR δ 7.27−7.16 (m, 5H), 3.72 (apparent t, J = 4.5 Hz, 4H), 2.68−2.66 (m, 6H), 1.78 (dd, J = 14.7, 7.5 Hz, 2H), 1.60−1.50 (m, 4H), 1.42−1.26 (m, 6H); ^{13}C NMR δ 139.2, 130.6, 127.4, 125.5, 67.9, 61.3, 45.9, 41.1, 35.8, 28.8, 22.3. Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.27; H, 10.21; N, 5.39.

4-[1-(2-Phenylethynyl)cyclohexyl]morpholine (10a): yellow solid (from hexanes−ethyl acetate); yield 98% (0.79 g); mp 93−94 °C (lit.[25] mp 100−102 °C); ^{1}H NMR δ 7.40−7.34 (m, 2H), 7.23−7.19 (m, 3H), 3.72−3.69 (m, 4H), 2.67−2.65 (m, 4H), 2.00−1.90 (m, 2H), 1.68−1.58 (m, 2H), 1.58−1.48 (m, 2H), 1.48−1.36 (m, 2H), 1.30−1.10 (m, 2H); ^{13}C NMR δ 131.7, 128.2, 127.8, 123.4, 89.8, 86.4, 67.5, 58.8, 46.6, 35.4, 25.7, 22.7. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 79.90; H, 8.56; N, 5.11.

4-[1-(2-Thienyl)cyclohexyl]morpholine (11a): colorless microcrystals (from hexanes−ethyl acetate); yield 85% (0.64 g); mp 60−61 °C (lit.[26] mp 56−57 °C); ^{1}H NMR δ 7.20 (dd, J = 5.1, 0.8 Hz, 1H), 7.00 (dd, J = 3.6, 5.1 Hz, 1H), 6.83 (dd, J = 3.6, 0.8 Hz, 1H), 3.67 (apparent t, J = 4.5 Hz, 4H), 2.40 (apparent t, J = 4.5 Hz, 4H), 2.01−1.93 (m, 4H), 1.76−1.68 (m, 2H), 1.48−1.39 (m, 4H); ^{13}C NMR δ 145.8, 126.1, 124.2, 123.2, 67.8, 59.7, 45.7, 35.4, 26.0, 22.1.

4-[1-(1,3-Thiazol-2-yl)cyclohexyl]morpholine (11g): pink microcrystals (from hexanes−ethyl acetate); yield, 51% (0.39 g); mp 95−96 °C; ^{1}H NMR δ 7.78 (d, J = 3.3 Hz, 1H), 7.28 (d, J = 3.3 Hz, 1H), 3.67 (apparent t, J = 4.5 Hz, 4H), 2.48 (apparent t, J = 4.5 Hz, 4H), 2.17−2.02 (m, 4H), 1.76−1.70 (m, 2H), 1.51−1.36 (m, 4H); ^{13}C NMR δ 172.7, 141.5, 117.9, 67.6, 61.9, 45.8, 34.3, 25.7, 21.8. Anal. Calcd for $C_{13}H_{20}N_2OS$: C, 61.87; H, 7.99; N, 11.10. Found: C, 61.59; H, 8.02; N, 10.93.

2-[1-(1-Pyrrolidinyl)cyclohexyl]-1,3-thiazole (11h): red oil; yield 54% (0.38 g); ^{1}H NMR δ 7.80 (d, J = 3.3 Hz, 1H), 7.27 (d, J = 3.3 Hz, 1H), 2.64 (apparent t, J = 6.3 Hz, 4H), 2.27−2.20 (m, 2H), 2.05−1.98 (m, 2H), 1.72−1.57 (m, 5H), 1.48−1.37 (m, 5H); ^{13}C NMR δ 172.1, 141.6, 117.6, 61.3, 44.9, 36.5, 25.7, 23.5, 22.3. Anal. Calcd for $C_{13}H_{20}N_2S$: C, 66.06; H, 8.53; N, 11.85. Found: C, 65.76; H, 8.63; N, 12.20.

Supporting Information Available: Procedures for the preparation of compounds **8a**−**i** and **9**−**11** and characterization data for compounds **9b**−**h**, **10b**−**i**, and **11b**−**f**,**i**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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