Synthesis of α-Azido and α-Amino Amides from N-[(Methylsulfonyl)oxy] Amides

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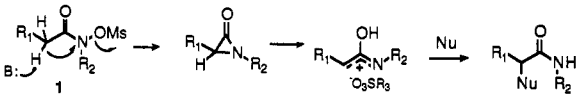
Effective new syntheses of 2-azido amides and 2-amino amides from *N*-(mesyloxy) amides 1 have been developed. 2-Azido amides are produced by treating 1 with sodium azide in the presence of 15-crown-5. 2-Amino amides result from the reaction of 1 with various amines. Regiochemical control in the preparation of 2-amino amides is possible by modulating the amine nucleophilicity by steric bulk.

Introduction

Recent reports from this laboratory have described the base-promoted conversion of *N*-(sulfonyloxy) amides 1 to 2-substituted amides.[1] Initial formation of an α-lactam by a Favorski-like, concerted 1,3-elimination is followed by ring opening to an ion pair.[2] Capture of the ion pair at the 2-position by nucleophiles gives the 2-substituted secondary amide products (eq 1). The reactivity of the



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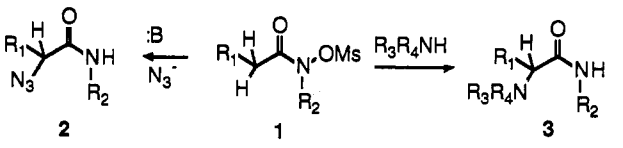
ion pair is such that even weak nucleophiles such as Cl^-, Br^-, and H_2O capture it effectively at the 2-position. Thus α-chloro, α-bromo, and α-hydroxy amides can be prepared in high yields by this reaction.[3] A conjugating substituent (aromatic or olefinic) at C-2 is required to acidify the α-proton but a variety of conjugating groups, *N*-alkyl groups, and sulfonyloxy leaving groups can be employed with good success.

An example of this type of reaction was reported by Kirby,[4] who suggested that an α-lactam was an intermediate. (α-Lactam intermediates are known to be produced in the reactions of both *N*-chloro amides[5] and 2-halo amides.[6]) A similar transformation has also been recently reported for *N*-(tosyloxy)-β-lactams which are converted to 3-substituted β-lactams.[7] It now appears that although the same overall transformation is observed, β-lactams probably react by a different mechanism that involves S_N2' displacement on an enol as the key step rather than α-lactam formation.[2,7a]

Scheme I



An important extension of this methodology would be to employ amines or amine equivalent nucleophiles in the reaction (Scheme I). For example, the use of azide as a nucleophile would give 2-azido amides **2**. This class of amide derivative is relatively unknown,[8] but α-azido amides have been shown to be excellent substrates for a Staudinger-based peptide coupling methodology.[9] The use of amine nucleophiles would lead to a simple synthesis of 2-amino amides **3**. Reduction of both **2** and **3** could give a general synthesis of 1,2-diamines with control of the substituents on the individual nitrogen atoms.

Vicinal diamines are important in medicinal chemistry,[10] as metal chelators,[11] and for the synthesis of heterocycles.[12] Despite their importance, however, methods for their preparation are often problematic[13] and new approaches are being reported continually.[14] The reduction of α-amino amides has been shown to be an effective route to 1,2-diamines,[15] but as Katritzky points out, α-amino amides are of limited accessibility.[13] If α-amino amides could be prepared by the reaction of *N*-(mesyloxy) amides with amine or amine equivalent nucleophiles, then a new and simple route to 1,2-diamines would result in which substituents attached to the amino nitrogens could be easily varied. We are pleased to report that both α-azido amides and α-amino amides can be prepared easily and in generally high yields by this strategy.

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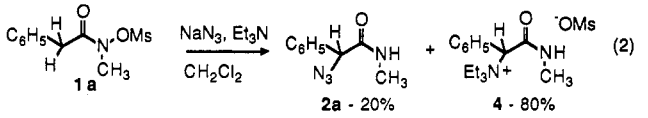
Results and Discussion

The reaction of *N*-(mesyloxy) amide **1a** with sodium azide and triethylamine in dichloromethane gave only low yields (≃20%) of α-azido amide product **2a**. Analysis of the crude product before aqueous workup and the material balance after aqueous workup suggested that the major product was the water-soluble triethylammonium salt **4** (eq 2). Under these reaction conditions the azide present



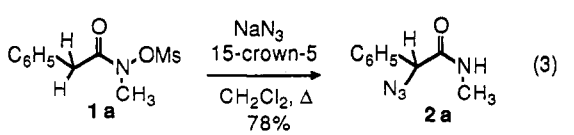
(2)

in solution does not compete effectively with triethylamine for capture of the ion pair intermediate. Changing the solvent to acetonitrile failed to improve the yield; using the more soluble tetramethylguanidinium azide gave only a slight increase in yield to 25%.[16] Miller reported that trimethylsilyl azide was useful in similar reactions in β-lactams;[7a] however, reaction of **1a** with triethylamine and trimethylsilyl azide failed to give any azide product **2a**.

It is clear that the nucleophilicity of azide is less than that of triethylamine in these reactions, even though their nucleophilic constants (*n* values) are comparable[17] and an excess of azide was employed. In contrast, the use of bromide as the nucleophile in these reactions resulted in capture of the ion pair by bromide to the exclusion of capture by triethylamine.[3] Thus when each is compared to triethylamine, it is clear that the effective nucleophilicity of bromide is much greater than that of azide under the conditions of these reactions, even though the *n* values are identical.[17] One factor which could explain these differences is the greater basicity of azide which results in stronger hydrogen bonding interactions with the ammonium ions in solution. The stronger H-bonding would reduce the nucleophilicity noticeably.

This analysis suggested that if azide could be used both as a base and as a nucleophile, then better yields would be possible because only a single nucleophilic species is present in solution to capture the ion pair. The addition of a crown ether also seemed advisable since it would give a more reactive base/nucleophile.

We were delighted to find that reaction of **1a** with 15-crown-5 (1 equiv) and sodium azide (10 equiv) in refluxing dichloromethane gave α-azido amide **2a** in 78% yield (eq 3). The reduced basicity of azide relative to triethylamine



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required that a higher temperature (42 °C rather than 25 °C) and longer reaction time (26 h rather than 5 h) was needed to drive the reaction to completion when triethylamine was omitted. The crude product, however, was quite pure indicating that competing reactions were negligible.

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Table I. Conversion of *N*-(Mesyloxy) Amides 1 to 2-Azido Amides 2 Using Sodium Azide and 15-Crown-5 in Refluxing Dichloromethane

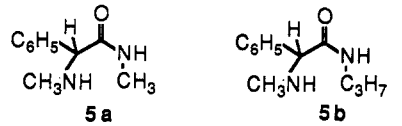
substrate	R_1	R_2	time (h)	yield (%)[a]
1a	C_6H_5	CH_3	26	78
1b	4-ClC_6H_4	CH_3	20	74
1c	4-$CH_3OC_6H_4$	CH_3	52	70
1d	1-$C_{10}H_7$	CH_3	45	80
1e	2-thienyl	CH_3	12	84[b]
1f	$C_6H_5CH{=}CH$	CH_3	6	75[c]
1g	C_6H_5	$CH_2C_6H_5$	50	72
1h	C_6H_5	c-C_6H_{11}	100	71
1i	C_6H_5	t-bu	90	85

[a] Isolated yield of purified product. [b] Must be purified immediately after the reaction as the product is unstable. [c] Must be purified immediately. Product is 71:29 mixture of the α- and γ-isomers due to rearrangement of the α-isomer.

Using this protocol, *N*-(mesyloxy) amides **1a–i** were converted to α-azido amides **2a–i** in similarly high yields (Table I). Notable is that a variety of conjugating groups at C-2 and a variety of *N*-alkyl groups can be used with good results. As the steric bulk of the *N*-alkyl substituent increases, however, the reaction time is increased markedly due to steric hindrance to closure to the α-lactam. Nevertheless, even for substrates with long reaction times, good yields are obtained and the crude products are relatively pure. This method is therefore an excellent way to prepare α-azido amides, whose utility as synthetic intermediates can now be fully developed.

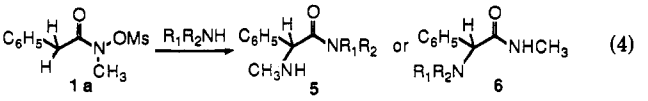
The facile formation of salt **4** from the reaction of **1a** with triethylamine[1] was good indication that amines would also react with **1a** and produce α-amino amides (Scheme I). Thus **1a** in dichloromethane was treated with methylamine (2.2 equiv) and stirred at room temperature until the starting material was consumed. Upon workup, α-amino amide **5a** was obtained in good yield. It was found that the point of attachment of the two *N*-methyl groups of **5a** could be easily assigned by their ^1H NMR signals. When the *N*-methyl group is an *N*-methyl amide group, it appears as a doublet at about 2.8 ($J \simeq 5$ Hz); when the *N*-methyl group is an *N*-methylamino substituent at C-2, it appears as a singlet at about δ 2.4.[2]

Reaction of **1a** with *n*-propylamine under the same conditions led to the formation of a single product (60%) whose structure was shown to be **5b** by spectral assignment



(*N*-methyl appears as a singlet at δ 2.41) and independent synthesis.[2] This product is formed by nucleophilic attack on the carbonyl carbon of the α-lactam intermediate which is initially formed from **1a**. The nucleophilicity of *n*-propylamine is sufficiently high to trap the α-lactam before it ring-opens to the ion pair.

A series of primary and secondary amines was reacted with **1a** and good yields of 2-(*N*-methylamino)phenylacetamides **5** were obtained (eq 4 and Table II, entries



(4)

1–6). Interestingly, *tert*-butylamine (entry 7) gave a mixture of *N*-*tert*-butyl amide **5g** (80%) and *N*-methyl amide **6g**

Table II. Conversion of 1a to α-N-(Methylamino) Amides 5 and 6 by Reaction with Amines in Dichloromethane at 25 °C

entry	product	R_1	R_2	time (h)	yield (%)[a]
1	**5a**	Me	H	19.0	84
2	**5b**	n-Pr	H	22.0	60
3	**5c**	$PhCH_2$	H	48.0	51
4	**5d**	c-C_6H_{11}	H	20.0	72
5	**5e**	Et	Et	5.0	68
6	**5f**	$-(CH_2)_5-$		4.0	60
7	**5g + 6g**	t-Bu	H	24.0	94[b]
8	**6h**	i-Pr	i-Pr	10.5	85
9	**6i**	c-C_6H_{11}	i-Pr	6.0	55
10	**6j**	c-C_6H_{11}	c-C_6H_{11}	60	42[c]

[a] Isolated yields of pure products. [b] An 80:20 mixture of **5g** and its regioisomer *N*-methyl-2-(*tert*-butylamino)phenylacetamide (**6g**) were produced. [c] *N*-methyl-2-(mesyloxy)phenylacetamide was isolated in 53% yield from this reaction.

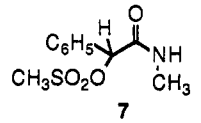
Table III. Comparison of Reaction Time and pK_a for the Reaction of Various Amines with N-(Mesyloxy) Amides in Dichloromethane at 25 °C

amine	pK_a[a]	reaction time (h)[b]
benzylamine	9.33	48
cyclohexylamine	10.66	20
n-propylamine	10.75	22
tert-butylamine	10.83	24
diethylamine	11.09	5
piperidine	11.12	4
diisopropylamine	11.13	10
triethylamine	11.01	5

[a] pK_a values taken from Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; IUPAC Analytical Division Butterworth: London, 1965. [b] Qualitative time required for starting material to react completely. Data taken from Table II.

(20%). The steric bulk of *tert*-butylamine is sufficient to reduce the rate of addition to the carbonyl carbon of the α-lactam to the point that ring opening to the ion pair becomes competitive. Nucleophilic trapping of the ion pair by *tert*-butylamine occurs at C-2 to give *N*-methylamide **6g**.

This finding demonstrated that the steric bulk of the amine nucleophile could be used to control the product regiochemistry. It was already known that triethylamine, a tertiary amine, gives only the 2-(triethylammonium) salt **4**.[1] When several α-branched secondary amines were reacted with **1a**, only the *N*-methyl amides **6h–j** were produced (Table II, entries 8–10). In fact, dicyclohexylamine gives only 42% of **6j** and the major product is *N*-methyl-2-(mesyloxy)phenylacetamide (**7**) (53%) which



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is formed by mesylate trapping of the ion pair.[1] In this instance the steric bulk of dicyclohexylamine reduces its nucleophilicity to the point that the mesylate ion, normally unreactive as a nucleophile in these systems, can compete as a nucleophile for the ion pair.

The results presented in Table II have several interesting aspects. In the first place the rate of reaction appears to be very sensitive to the basicity of the amine. A distinct correlation between the reaction times (qualitative measurements of the time required for the starting material to be absent by TLC analysis of the reaction mixture) and the pK_a of the amine is evident in Table III. Thus bulky secondary or tertiary amines are optimal in terms of reasonable reaction times. In addition their reduced nucleophilicity results in ring opening of the α-lactam to the ion pair and allows other nucleophiles to trap the ion pair and give 2-substituted amides.

Second, the transition states for α-lactam formation appear to be very crowded. While placement of a second substituent at C-2 is known to prevent α-lactam formation because of increased steric crowding at the transition state,[2] the data in Table II demonstrate that the steric bulk of the base also comes into play. Thus dicyclohexylamine has a similar pK_a value to other secondary amines, but it requires 60 h for complete reaction.

Finally control of the product regiochemistry is relatively straightforward by adjusting the nucleophilicity of the amine using steric effects. Normal primary and secondary amines trap the lactam effectively by attack on the carbonyl carbon. Branched chain secondary amines and tertiary amines fail to trap the lactam by carbonyl addition, but they do trap the more reactive ion pair produced by α-lactam ring opening.

In summary, effective new syntheses of 2-azido amides and 2-amino amides from *N*-(mesyloxy) amides have been developed. Regiochemical control in the latter is possible by modulating the amine nucleophilicity by steric bulk. The ease of preparation of these two classes of amide derivatives will now permit the utility of these compounds as synthetic intermediates to be fully developed.

Experimental Section

Melting points are uncorrected. Chemical shifts for both proton NMR spectra and ^{13}C NMR spectra are reported for chloroform-*d* solutions relative to Me_4Si. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Thin-layer chromatography was performed on silica gel 60 F254 plates from EM Reagents and visualized by UV irradiation or iodine vapor. Flash column chromatography was performed using silica gel 60 (230–400 mesh). *N*-(Mesyloxy)-*N*-alkylacetamides **1a–e,g,h** were prepared by literature methods[3] and were purified by either flash column chromatography or crystallization.

***N*-(Mesyloxy)-*N*-methyl-4-phenyl-3-butenamide (1f).** Styrylacetic acid was converted to *N*-hydroxy-*N*-methyl-4-phenyl-3-butenamide by the literature procedure[3] in 98% yield. It was obtained as a solid after a single crystallization (hexane/dichloromethane) and used without further purification: mp 65–66 °C; ^1H NMR δ 3.15–3.36 (two bs, 5 H, $COCH_2$, NCH_3), 6.19–6.53 (m, 2 H, CH = CHPh), 7.19–7.31 (m, 5 H, Ar*H*), 8.6–9.1 (bs, 1 H, O*H*); ^{13}C NMR δ 36.0, 36.1, 36.7, 120.8, 122.4, 126.2, 127.4, 127.9, 128.5, 133.3, 133.9, 137.0, 172.6; IR (neat) 3157 (NH, OH), 1617 (C=O) cm^{-1}. *N*-hydroxy-*N*-methyl-4-phenyl-3-butenamide was converted to **1f** by condensation with methanesulfonyl chloride according to the literature method[3] in 82% yield after column chromatography (hexane/ethyl acetate, 6:4): mp 72–74 °C; ^1H NMR δ 3.22 (s, 3 H, SCH_3), 3.43, 3.45 (two d, J = 7.67, 7.77 Hz, 2 H, CH_2Ph), 3.48 (s, 3 H, NCH_3), 6.52 (d, J = 15.94 Hz, 1 H, CH = C*H*Ph), 6.23–6.36 (dt, J = 14.24, 6.60, 6.73 Hz, 1 H, C*H*=CHPh), 7.23–7.41 (m, 5 H, Ar*H*); ^{13}C NMR δ 37.1, 37.7, 39.5, 120.6, 126.3, 127.7, 128.5, 134.2, 136.5, 174.0; IR ($CHCl_3$) 1699 (C=O); 1377, 1328, 1187, 1106 (O–SO_2) cm^{-1}.

General Procedure for the Preparation of *N*-Alkyl-2-azido-2-arylethanamides 2. To a solution of *N*-(mesyloxy) amide **1** in CH_2Cl_2 (80 mL per 2.0 mmol) is added 15-crown-5 ether (1 equiv) followed by sodium azide (10 equiv). The mixture was heated at reflux for 6–100 h (see Table I) until the starting material had been consumed as determined by TLC monitoring of the reaction mixture. The reaction mixture was concentrated, diluted with EtOAc (40 mL), washed with water (4 × 20 mL) and brine (20 mL), and dried over $MgSO_4$. After rotary evaporation, the relatively pure crude products were purified by flash column chromatography or by recrystallization.

***N*-Methyl-2-azido-2-phenylethanamide (2a)** was obtained from **1a** (500 mg, 2.05 mmol) as a crude semisolid (365 mg, 93%)

which on chromatography (hexane/ethyl acetate, 6:4) gave a white semisolid (304 mg, 1.6 mmol, 78%): ^{1}H NMR δ 2.87 (d, J = 4.90 Hz, 3 H, NCH_3), 5.06 (s, 1 H, N_3CH), 6.48 (bs, 1 H, NH), 7.36–7.44 (m, 5 H, ArH); ^{13}C NMR δ 26.4, 67.3, 127.8, 129.1, 135.1, 168.6; IR ($CHCl_3$) 3428 and 3335 (NH), 2108 (N_3), 1675 (C=O) cm^{-1}.

***N*-Methyl-2-azido-2-(4-chlorophenyl)ethanamide (2b)** was obtained from **1b** (1.12 g, 4.03 mmol) as a crude solid (900 mg, 99%) which on recrystallization (hexane/dichloromethane) gave a white solid (670 mg, 2.98 mmol, 74%): mp 67–68° C; ^{1}H NMR δ 2.85 (d, J = 4.83 Hz, 3 H, NCH_3), 5.03 (s, 1 H, N_3CH), 6.51 (bs, 1 H, NH), 7.34–7.37 (m, 4 H, ArH); ^{13}C NMR δ 26.4, 66.6, 129.0, 129.2, 133.6, 135.1, 168.1; IR ($CHCl_3$) 3425, 3312 (NH), 2109 (N_3), 1663 (C=O) cm^{-1}. Anal. Calcd for $C_9H_9ClN_4O$: C, 48.11; H, 4.03; N, 24.93. Found: C, 48.34; H, 4.19; N, 24.71.

***N*-Methyl-2-azido-2-(4-methoxyphenyl)ethanamide (2c)** was obtained from **1c** (1.1 g, 4.02 mmol) as a crude oil (880 mg, 99%) which on chromatography (hexane/ethyl acetate, 6:4) gave a light yellow solid (625 mg, 2.8 mmol, 70%): mp 43–44 °C; ^{1}H NMR δ 2.85 (d, J = 4.81 Hz, 3 H, NCH_3), 3.81 (s, 3 H, OCH_3), 5.00 (s, 1 H, N_3CH), 6.46 (bs, 1 H, NH), 6.92 (d, J = 8.70 Hz, 2 H, ArH), 7.29 (d, J = 8.88 Hz, 2 H, ArH); ^{13}C NMR δ 26.4, 55.3, 66.9, 114.5, 127.1, 129.1, 160.2, 168.9; IR ($CHCl_3$) 3312, 3076 (NH), 2111 (N_3), 1663 (C=O) cm^{-1}.

***N*-Methyl-2-azido-2-(1-napthyl)ethanamide (2d)** was obtained from **1d** (1.20 g, 4.09 mmol) as a crude oil (982 mg, 100%) which on chromatography (hexane/ethyl acetate, 6:4) gave a colorless oil (790 mg, 3.29 mmol, 80%): ^{1}H NMR δ 2.85 (d, J = 4.77 Hz, 3 H, NCH_3), 5.66 (s, 1 H, N_3CH), 6.33 (bs, 1 H, NH), 7.47–7.59 (m, 5 H, ArH), 7.89 (dd, J = 7.69, 2.01 Hz, 1 H, ArH), 8.05 (d, J = 8.24 Hz, 1 H, ArH); ^{13}C NMR δ 26.4, 65.1, 123.3, 125.2, 126.2, 127.0, 127.2, 129.0, 130.1, 130.6, 131.0, 134.1, 168.9; IR ($CHCl_3$) 3317 (NH), 2103 (N_3), 1659 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.31. Found: C, 64.69; H, 5.13; N, 23.49.

***N*-Methyl-2-azido-2-thienylethanamide (2e)** was obtained from **1e** (1.09 g, 4.01 mmol) as a crude solid (780 mg, 100%) which on chromatography (hexane/ethyl acetate, 6:4) gave a white solid (660 mg, 3.36 mmol, 84%): mp 84–85 °C; ^{1}H NMR δ 2.86 (d, J = 4.94 Hz, 3 H, NCH_3), 5.29 (s, 1 H, N_3CH), 6.50 (bs, 1 H, NH), 7.01–7.37 (m, 3 H, ArH); ^{13}C NMR δ 26.5, 62.6, 126.9, 127.1, 127.7, 142.8, 167.8; IR ($CHCl_3$) 3428, 3312 (NH), 2113 (N_3), 1674 (C=O) cm^{-1}. This product is unstable and must be isolated and characterized immediately after the reaction.

***N*-Methyl-2-azido-4-phenyl-3-butenamide (2f)** was obtained from **1f** (1.1 g, 4.08 mmol) as a crude solid (890 mg, 100%) which on chromatography (hexane/ethyl acetate, 6:4) gave an orange solid (662 mg, 3.06 mmol, 75%): mp 74–76 °C; ^{1}H NMR δ 2.86 (d, J = 4.98 Hz, 3 H, NCH_3), 4.68 (d, J = 7.86 Hz, 1 H, N_3CH), 6.42 (bs, 1 H, NH), 6.79 (d, J = 15.87 Hz, 1 H, CH=CHPh), 6.16–6.28 (ddd, J = 15.87, 8.01, 7.65 Hz, 1 H, CH=CHPh), 7.26–7.45 (m, 5 H, ArH); ^{13}C NMR δ 26.3, 26.4, 65.5, 65.9, 121.9, 126.9, 127.4, 128.6, 128.7, 128.8, 129.0, 135.3, 136.1, 139.6, 168.3; IR ($CHCl_3$) 3432, 3336 (NH), 2114 (N_3), 1676 (C=O) cm^{-1}. This product is unstable and undergoes 1,3-rearrangement to the γ-isomer. The spectral data given are for the α-isomer.

***N*-Benzyl-2-azido-2-phenylethanamide (2g)** was obtained from **1g** (700 mg, 2.19 mmol) as a crude solid (560 mg, 96%) which on recrystallization (hexane/dichloromethane) gave a white solid (425 mg, 1.6 mmol, 72%): mp 94–95 °C; ^{1}H NMR δ 4.48 (d, J = 5.72 Hz, 2 H, NCH_2), 5.12 (s, 1 H, N_3CH), 6.77 (bs, 1 H, NH), 7.23–7.48 (m, 10 H, ArH); ^{13}C NMR δ 43.6, 67.3, 127.7, 127.7, 128.7, 129.1, 129.2, 134.9, 137.6, 167.9; IR ($CHCl_3$) 3414, 3320 (NH), 2113 (N_3), 1674 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.29; N, 21.03. Found: C, 67.87; H, 5.34; N, 21.15.

***N*-Cyclohexyl-2-azido-2-phenylethanamide (2h)** was obtained from **1h** (1.25 g, 4.01 mmol) as a crude solid (1.03 g, 100%) which on recrystallization (hexane/dichloromethane) gave a white solid (738 mg, 2.86 mmol, 71%): mp 114–115 °C; ^{1}H NMR δ 1.10–1.97 (m, 10 H, c-C_6H_{11}), 3.75–3.81 (m, 1 H, NCH), 5.00 (s, 1 H, N_3CH), 6.31 (bs, 1 H, NH), 7.36–7.39 (m, 5 H, ArH); ^{13}C NMR δ 24.7, 25.4, 32.8, 32.9, 48.4, 67.3, 127.7, 129.0, 129.1, 135.2, 166.9; IR ($CHCl_3$) 3408 (NH), 2114 (N_3), 1671 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.68. Found: C, 64.90; H, 7.07; N, 21.82.

***N*-*tert*-Butyl-2-azido-2-phenylethanamide (2i)** was obtained from **1i** (1.14 g, 4.0 mmol) as a crude oil (925 mg, 99%) which on chromatography (hexane/ethyl acetate, 6:4) gave a colorless oil (792 mg, 3.4 mmol, 85%); ^{1}H NMR δ 1.36 (s, 9 H, t-Bu), 4.88 (s, 1 H, N_3CH), 6.55 (s, 1 H, NH), 7.32–7.44 (m, 5 H, ArH); ^{13}C NMR δ 28.5, 51.6, 67.3, 127.7, 129.0, 135.4, 167.0; IR ($CHCl_3$) 3399, 3321 (NH), 2105 (N_3), 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_4O$: C, 62.04; H, 6.94; N, 24.11. Found: C, 61.90; H, 6.89; N, 24.07.

General Procedure for the Synthesis of N-Alkyl-2-(alkylamino)-2-arylethanamides 5 and 6. To *N*-(mesyloxy) amide **1a** (2mmol) in CH_2Cl_2 (25 mL) at 0 °C was added an amine (4.4 mmol) in CH_2Cl_2 (15 mL) over a period of 30 min. The resulting solution was stirred at 0 °C for 1 h and at room temperature until the starting material was absent as determined by TLC analysis (hexane/ethyl acetate, 6:4). The solvent was removed and the residue was treated with 1 N NaOH, extracted with EtOAc (50mL), washed with water (2 × 10 mL), and dried over $MgSO_4$. After rotary evaporation, the product was purified by flash chromatography or crystallization.

***N*-Methyl-2-(methylamino)-2-phenylethanamide (5a)** was obtained from **1a** and methylamine (40% aqueous solution) as a white solid (300 mg, 1.67 mmol, 84%) after flash chromatography (hexane/ethyl acetate, 6:4), mp 80–81 °C, as previously described.[2]

***N*-Propyl-2-(methylamino)-2-phenylethanamide (5b)** was obtained from **1a** and *n*-propylamine as a solid (240 mg, 1.2 mmol, 60%) after flash chromatography (hexane/ethyl acetate, 6:4), mp 56–57 °C, as previously described.[2]

***N*-Benzyl-2-(methylamino)-2-phenylethanamide (5c)** was obtained from **1a** and benzylamine as an oil (240 mg, 1.02 mmol, 51%) after flash chromatography (hexane/ethyl acetate, 6:4); ^{1}H NMR δ 1.78 (s, 1 H, NH), 2.44 (s, 3 H, CH_3), 4.11 (s, 1 H, NCH), 4.46 (d, J = 6.03 Hz, 2 H, CH_2), 7.21–7.31 (m, 10 H, ArH), 7.46 (bs, 1 H, NH); ^{13}C NMR δ 35.4, 43.1, 69.7, 127.2, 127.3, 127.5, 128.0, 128.6, 128.7, 138.4, 139.3, 172.0; IR (neat): 3364 (NH), 1668 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.54; H, 7.02; N, 10.82.

***N*-Cyclohexyl-2-(methylamino)-2-phenylethanamide (5d)** was obtained from **1a** and cyclohexylamine as a crude solid (450 mg, 92%) which on recrystallization (hexane/dichloromethane) gave a white solid (350 mg, 1.44 mmol, 72%): mp 84–85 °C; ^{1}H NMR δ 1.19–1.99 (m, 10 H, c-C_6H_{11}), 2.44 (s, 3 H, CH_3), 3.79 (m, 1 H, NCH), 4.01 (s, 1 H, NCH), 7.09 (m, 1 H, NH), 7.33–7.35 (m, 5 H, ArH); ^{13}C NMR δ 24.8, 24.7, 25.5, 33.0, 33.1, 35.4, 47.5, 69.9, 127.2, 128.0, 128.7, 139.6, 170.8; IR($CHCl_3$) 3420 (NH), 1661 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.30; H, 8.88; N, 11.13.

***N*,*N*-Diethyl-2-(methylamino)-2-phenylethanamide (5e)** was obtained from **1a** and diethylamine as an oil (300 mg, 1.35 mmol, 68%): ^{1}H NMR δ 1.01 (t, J = 7.03 Hz, 3 H, CH_2CH_3), 1.11 (t, J = 7.03 Hz, 3 H, CH_2CH_3), 2.22 (s, 1 H, NH, exchangeable with D_2O), 2.35 (s, 3 H, NCH_3), 3.02–3.62 (m, 4 H, CH_2CH_3), 4.32 (s, 1 H, NCH), 7.31–7.33 (m, 5 H, ArH); ^{13}C NMR δ 12.9, 14.1, 34.5, 40.4, 41.3, 64.7, 127.7, 127.8, 128.8, 139.0, 170.9; IR(neat) 3345 (NH), 1646 (C=O) cm^{-1}.

***N*,*N*-Piperidinyl-2-(methylamino)-2-phenylethanamide (5f)** was obtained from **1a** and piperidine as a crude oil (300 mg, 77%) which on flash chromatography (hexane/ethyl acetate, 6:4) gave an oil (280 mg, 1.20 mmol, 60%); ^{1}H NMR δ 1.03 (br s, 1 H, NH), 1.52–1.55 (m, 6 H, CH_2), 2.35 (s, 3 H, CH_3), 3.29–3.32 (m, 4 H, CH_2), 4.43 (s, 1 H, NCH), 7.25–7.35 (m, 5 H, ArH); ^{13}C NMR δ 24.4, 25.5, 25.8, 34.5, 43.3, 46.2, 64.6, 127.6, 128.8, 138.8, 169.8; IR(neat): 3331 (NH); 1645 (C=O) cm^{-1}.

***N*-*tert*-Butyl-2-(methylamino)-2-phenylethanamide (5g)** was obtained from the reaction of **1a** and *tert*-butylamine as previously described.[2] It was produced as the major component of an 80:20 mixture with its regioisomer **6g**. These isomers were separated by preparative TLC ($CHCl_3$:CH_3OH = 95:5).

***N*-Methyl-2-(*tert*-butylamino)-2-phenylethanamide (6g)** was obtained from the reaction of **1a** and *tert*-butylamine as previously described.[2] It was separated from its regioisomer **5g** by preparative TLC ($CHCl_3$:CH_3OH = 95:5).

***N*-Methyl-2-(diisopropylamine)-2-phenylethanamide (6h)** was obtained from the reaction of **1a** and diisopropylamine as

a white solid (390 mg, 1.70 mmol, 85%) after flash chromatography (hexane/ethyl acetate, 6:4): mp 117–118 °C; ^{1}H NMR δ 0.83 (d, J = 6.66 Hz, 6 H, HC(CH_3)$_2$), 1.12 (d, J = 6.66 Hz, 6 H, HC(CH_3)$_2$), 2.91 (d, J = 5.07 Hz, 3 H, NCH_3), 3.25 (p, J = 7.60 Hz, 2 H, NC*H*), 4.64 (s, 1 H, NC*H*), 7.27–7.29 (m, 5 H, ArH), 7.64 (bs, 1 H, N*H*); ^{13}C NMR δ 21.1, 23.7, 26.1, 46.6, 64.0, 127.1, 128.0, 130.4, 138.7, 175.2; IR ($CHCl_3$) 3364 (N–H), 1662 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.66; H, 9.55; N, 11.20.

***N*-Methyl-2-(cyclohexylisopropylamino)-2-phenylethanamide (6i)** was obtained from the reaction of **1a** with isopropyl cyclohexylamine as a white solid (300 mg, 1.10 mmol, 55%) after flash chromatography (hexane/ethyl acetate, 6:4): mp 117–118 °C; ^{1}H NMR δ 0.81 (d, J = 6.56 Hz, 3 H, CH_3), 1.11 (d, J = 6.67 Hz, 3 H, CH_3), 0.9–1.9 (m, 10 H, ring CH_2), 2.6–2.8 (m, 1 H, NC*H*), 2.90 (d, J = 4.90 Hz, 3 H, NCH_3), 3.23 (p, J = 6.42 Hz, 1 H, NC*H*), 4.64 (s, 1 H, NC*H*), 7.26–7.30 (m, 5 H, Ar*H*), 7.69 (bs, 1 H, N*H*); ^{13}C NMR δ 21.3, 23.8, 25.8, 26.1, 26.3, 26.9, 32.6, 34.7, 47.3, 55.9, 64.3, 127.1, 128.0, 130.3, 138.9, 175.3; IR ($CHCl_3$) 3365 (N–H); 1662 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{28}N_2O$: C, 74.96; H, 9.78; N, 9.71. Found: C, 74.77; H, 9.51; N, 9.57.

***N*-Methyl-2-(dicyclohexylamino)-2-phenylethanamide (6j)** was obtained from the reaction of **1a** with dicyclohexylamine as a white solid (340 mg, 1.04 mmol, 52%) after flash chromatography (hexane/ethyl acetate, 6:4); ^{1}H NMR δ 0.90–1.82 (m, 20 H, c-C_6H_{11}), 2.62–2.78 (m, 2 H, NC*H*), 2.90 (d, J = 5.07 Hz, 3 H, NCH_3), 4.67 (s, 1 H, NC*H*), 7.27–7.29 (m, 5 H, ArH), 7.76 (bs, 1 H, N*H*); ^{13}C NMR δ 25.3, 25.8, 26.3, 26.8, 32.8, 34.7, 56.5, 64.6, 127.1, 127.9, 130.3, 139.1, 175.4; IR ($CHCl_3$) 3358 (N–H); 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{32}N_2O$: C, 76.78; H, 9.82; N, 8.53. Found: C, 76.69; H, 9.84; N, 8.44.

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Supplementary Material Available: Copies of ^{13}C NMR spectra (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.