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# Novel Syntheses of α-Morpholinoamides from α,α-Dichloroacetamides

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**Abstract:** Dichloroacetamides, on heating with benzotriazole, morpholine, and triethylamine, produce, in a one-pot reaction, α-benzotriazolyl-α-morpholinoacetamides **4a**,**b**. Intermediates **4a** and **4b** react with nucleophiles such as allylsilanes, silyl ethers, and organozinc reagents to afford diverse α-morpholinoamides.

α-Aminoamides are biologically active and have been claimed as antiinflammatory,[1] antibacterial,[2] anticonvulsant,[3] and cerebro-protective[4] agents.

α,α-(Disubstituted-morpholino)amides have previously been prepared by two main routes. In the first, a secondary amine such as morpholine reacts with an α-chloroamide to form the α-morpholinoamide.[1−5] This method is restricted by the availability of the α-chloroamide and is used mainly to prepare simple α-morpholinoamides. A second preparation of α-morpholinoamides is by reaction of γ-carboxy-α,β-unsaturated amides with morpholine[6] and is naturally restricted to the preparation of α-amino-γ-carboxyamides.

*N*-(α-Aminoalkyl)benzotriazoles have been recognized as versatile intermediates for the preparation of a wide variety of amines by nucleophilic displacement of the benzotriazolyl group.[7] Condensations of benzotriazole with an aldehyde or ketone and a primary or secondary amine readily give *N*-(α-aminoalkyl)benzotriazoles, usually in high yields and purity.[7a] A similar approach to α-aminoamides would require the preparation of *N*-(α-aminocarbamoylmethyl)benzotriazoles that are not easily available by the aforementioned simple condensations.

We now report the development of a novel method for the preparation of *N*-(α-aminocarbamoylmethyl)benzotriazoles **4a**,**b** and an easy access from **4a**,**b** to a variety of α-morpholinoamides, utilizing the leaving group ability of benzotriazole in nucleophilic substitutions.

**Preparation of Benzotriazolyl Intermediates 4a,b.** Acid-catalyzed replacement of the methoxy group by the benzotriazolyl group has been used to prepare benzotriazolyl intermediates from easily available ketals.[7a,8] Accordingly, we prepared the dimethoxyacetamido derivative **3a** in 93% yield by the reaction of dichloroacetamide **2a** with sodium methoxide. Dichloroacetamide **2a** was readily obtained in 87% yield from dichloroacetyl chloride and benzylamine following the Schotten−Baumann procedure.[9] However, attempts to replace, successively or simultaneously, both methoxy groups in **3a** by one benzotriazolyl and one morpholine moiety failed. Finally, treatment of dichloroamide **2a** simultaneously with 1 equiv of benzotriazole and 1 equiv of morpholine in the presence of triethylamine provided the desired 2-(1*H*-1,2,3-benzotriazol-1-yl)-*N*-benzyl-2-morpholinoacetamide (**4a**) in 60% yield. No competing displacement of the newly attached benzotriazolyl group in **4a** by another morpholine moiety occurred. Similarly, starting from *dl*-α-methylbenzylamine (**1b**), the *N*-(α-aminocarbamoylmethyl)benzotriazole intermediate **4b** was obtained in 35% yield as a mixture of diastereomers in a 1:1 ratio, as determined by the $^1$H NMR spectrum (Scheme 1).

**Reactions of Synthons 4a,b with Allylsilanes and Silyl Ethers.** Lewis acid promoted reaction of allylsilanes with benzotriazolyl intermediates has been well studied.[7c] Using a similar approach, we examined the direct preparation of α-(allylamino)amides from synthons **4a**,**b**. Nucleophilic replacement of the benzotriazolyl group in **4a** with 1 equiv of allyltrimethylsilane (**5a**) and (2-methylpropenyl)trimethylsilane (**5b**) in the presence of $BF_3$·$Et_2O$ gave the allylic α-aminoamides **6a** and **6b** in 67 and 72% yields, respectively. The structures of the α-(allylamino)amides **6a** and **6b** are supported by their $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum of **6a** showed no signals for any benzotriazolyl moiety in the aromatic region at 8.08 and 7.35−7.45 ppm but did demonstrate the appearance of vinylic protons signals at 5.20−5.31 ppm. The H(2) signal in **6a** was shifted upfield from that in **4a** and now appeared as a well-defined triplet at 3.19 ppm. The $^1$H NMR spectrum of **6b** also showed similar changes in addition to the appearance of a new signal at 1.81 ppm due to the three protons of C(4)-methyl group. Similar treatment of **4b** with allyltrimethylsilane (**5a**) gave **6c** in 73% yield. $^1$H and $^{13}$C NMR spectra revealed **6c** as a mixture of two diastereomers in a 3:1 ratio. α-(Allylamino)amides are potentially useful as building blocks, as γ,δ-double bonds can easily be transformed into other functionalities.[10] Although reac-

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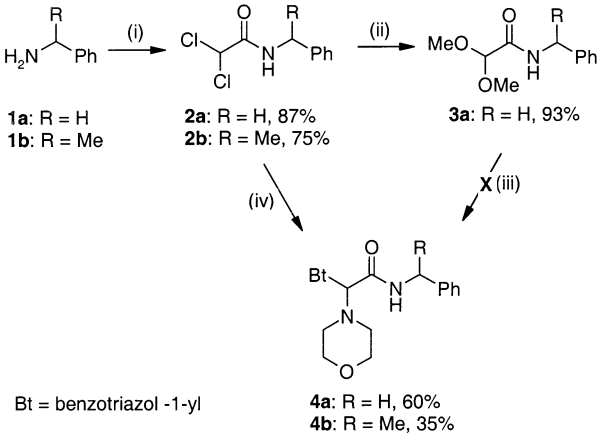
**SCHEME 1**[a]



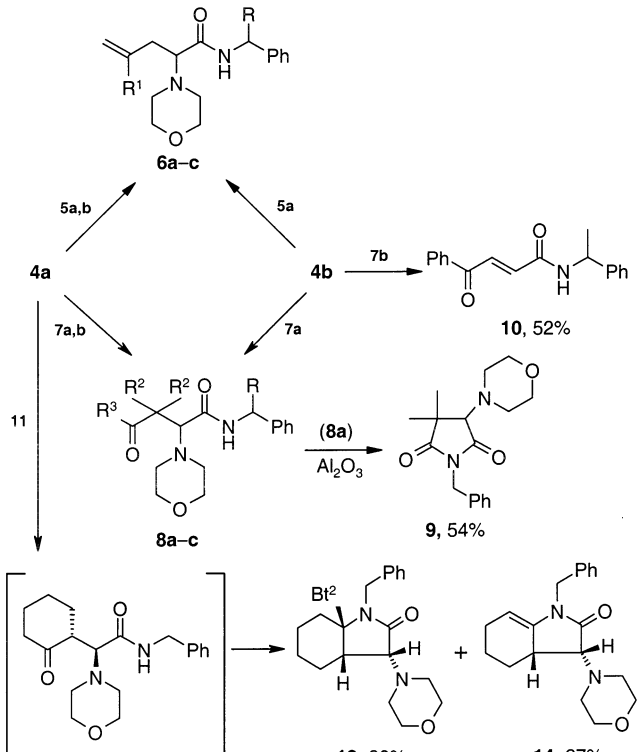

[a] Key: (i) $Cl_2CHCOCl$, $Et_3N$, $CH_2Cl_2$; (ii) NaOMe, THF; (iii) BtH, morpholine, *p*-TSA, PhMe; (iv) BtH, morpholine, $Et_3N$, 100 °C.

tions of α-imino esters with allylic organometallic compounds have been reported extensively to prepare allylic α-amino esters,[11] there is no report on similar preparation of α-aminoamides from α-iminoamides probably owing to the low reactivity of α-iminoamides. Thus, benzotriazolyl intermediates **4** offer an easy and efficient route for the direct preparation of α-(allylamino)amides.

Use of silyl enol ethers as nucleophiles produced the expected γ-oxo-α-aminoamides. Thus, reaction of synthon **4a** with 1-methoxy-2-methyl-1-propenyl trimethylsilyl ether (**7a**) and 1-phenylvinyl trimethylsilyl ether (**7b**) gave **8a** and **8b** in 72 and 63% yields, respectively. The $^1$H NMR spectrum of **8a** showed a singlet for the methoxy protons at 3.69 ppm; the two methyls at C(2) resonated as separate singlets at 1.32 and 1.29 ppm. The $^{13}$C NMR spectrum showed the appearance of a new carbonyl signal at 177.9 ppm due to the 4-oxo moiety in **8a**. Similarly, $^1$H NMR spectrum of **8b** showed signals in the aromatic region due to the benzoyl group and two protons at C(3) resonated separately (as a doublet of doublets) at 4.50 and 4.42 ppm, respectively.

Although **8a** could be purified by recrystallization from dichloromethane, attempted column chromatography on $Al_2O_3$ resulted in its conversion into the cyclized diketoamide **9**. Compounds **8a** and **9** were characterized by their $^1$H and $^{13}$C NMR spectra and by microanalysis. After cyclization, the singlet for methoxy protons at 3.69 ppm in **8a** disappeared and the two methyls at C(2) (as separate singlets at 1.32 and 1.29 ppm) shifted upfield to 1.25 and 1.23 ppm, respectively. The disappearance of the C(4) oxo-carbonyl signal at 177.9 ppm in the $^{13}$C NMR spectrum and the presence of a downfield signal at 182.0 ppm due to the new imido-carbonyl further confirmed the cyclization of **8a** to **9**. However, similar reaction of **4b** with silyl ether **7a**, followed by chromatographic purification on $Al_2O_3$, furnished **8c** in 62% yield, without any further reaction. Compound **8c** was obtained as a mixture of diastereomers in a 1:1 ratio as determined by its $^1$H NMR spectrum. Reaction of **4b** with silyl ether

**SCHEME 2**




| | R | $R^1$ | Y(%) |
|---|---|---|---|
| **6a** | H | H | 67 |
| **6b** | H | Me | 72 |
| **6c** | Me | H | 73 |

| | R | $R^2$ | $R^3$ | Y(%) |
|---|---|---|---|---|
| **8a** | H | Me | OMe | 72 |
| **8b** | H | H | Ph | 63 |
| **8c** | Me | Me | OMe | 62 |

**7b** resulted in the formation of α,β-unsaturated amide **10** in 52% yield, apparently via loss of morpholine moiety from the initially formed product in the reaction mixture. The $^1$H NMR spectrum of **10** showed the olefinic protons each as a doublet at 8.03 and 7.18 ppm with a coupling constant of 15.0 Hz, which further supports the formation of **10** as a single *E*- isomer (Scheme 2).[12]

Interestingly, Lewis acid mediated reaction of **4a** with 1-(trimethylsiloxy)cyclohex-1-ene (**11**) gave products **13** and **14**. Formation of **13** and **14** appears to be a result of intramolecular cyclization of the secondary amide functionality onto the keto group of the initially formed product **12** in the reaction mixture.[13] Compounds **13** and **14** were characterized by their $^1$H and $^{13}$C NMR spectra and by elemental analyses or high-resolution MS data. *J*(3-H,3a-H) values of 9.9 and 9.3 Hz in **13** and **14**, respectively, correspond to those of cis isomers in similar structures.[14a] Also, similar ring formations have been

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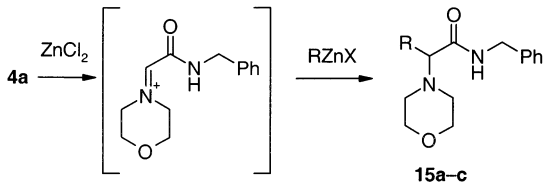
**SCHEME 3**




| 15 | R | Y(%) |
|---|---|---|
| **a** | *n*-$C_5H_{11}$ | 52 |
| **b** | $C_6H_5$ | 52 |
| **c** | *p*-$CH_3C_6H_4$ | 32 |

reported to be more favorable with substituents at the ring junction in cis orientation as compared to that in trans,[14b−d] so we believe that Bt[2] and 3a-H in **13** are in cis-orientation (Scheme 2).

**Nucleophilic Substitution of 4a with Organozinc Reagents.** Nucleophilic substitution of the benzotriazolyl group in **4a** by alkyl and aryl groups was achieved by treatment of **4a** with alkyl- or arylzinc reagents prepared in situ by reaction of zinc chloride with the corresponding Grignard reagents. Excess zinc chloride functions as a Lewis acid to facilitate the loss of benzotriazolyl anion and forms an iminium cation, which can be easily attacked by organozinc reagents.[15] α-Aminoamides **15a−c** were obtained in 32−52% yields and the structures were confirmed by their $^1$H and $^{13}$C NMR spectra and by elemental analyses or high-resolution MS data. $^1$H and $^{13}$C NMR spectra of **15a−c** showed the disappearance of signals for benzotriazolyl moiety and appearance of the expected signals corresponding to the alkyl or aryl functionality. These results illustrate the general applicability of this method for the preparation of a variety of α-morpholinoamides (Scheme 3).

In summary, we have introduced a convenient method for the preparation of a variety of α-morpholino amides via readily available benzotriazole intermediates **4a** and **4b**.

## Experimental Section

*N*-Benzyl-2,2-dichloroacetamide (**2a**) and *N*-(1-phenylethyl)-2,2-dichloroacetamide (**2b**) were prepared by literature methods.[9]

***N*-Benzyl-2,2-dimethoxyacetamide (3a).**[16] *N*-Benzyl-2,2-dichloroacetamide (**2a**) (1.0 g, 4.54 mmol) was dissolved in THF (25 mL), and NaOMe (0.54 g, 10 mmol) was added. The mixture was stirred at 20 °C overnight. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was dried on $MgSO_4$ and evaporated in vacuo to give product **3a** as a colorless oil: yield 93%; $^1$H NMR $\delta$ 7.33−7.26 (m, 5H), 6.96 (brs, 1H), 4.73 (s, 1H), 4.46 (d, $J$ = 5.9 Hz, 2H), 3.38 (s, 6H); $^{13}$C NMR $\delta$ 167.0, 137.6, 128.5, 127.6, 127.4, 99.7, 53.6, 42.9.

**Procedure for the Preparation of 2-(1*H*-1,2,3-Benzotriazol-1-yl)-*N*-benzyl-2-morpholinoacetamide (4a) and 2-(1*H*-1,2,3-Benzotriazol-1-yl)-2-morpholino-*N*-(1-phenylethyl)acetamide (4b).** A mixture of benzotriazole (2.38 g, 20 mmol), dichloroacetamide **2a** or **2b** (20 mmol), morpholine (1.74 mL, 20 mmol), and $Et_3N$ (5.56 mL, 40 mmol) was heated with stirring at 100 °C for 5 h. After being cooled to 20 °C, the reaction mixture was dissolved in ethyl acetate and then washed with 5% $NaHCO_3$ and water. The organic layer was dried over anhydrous $Na_2SO_4$. Removal of the solvent gave **4a** or **4b** as a semisolid residue, which was dried under vacuum and used directly for the subsequent reactions.

**2-(1*H*-1,2,3-Benzotriazol-1-yl)-*N*-benzyl-2-morpholinoacetamide (4a):** yield 60%; $^1$H NMR $\delta$ 8.08 (d, $J$ = 8.1 Hz, 1H), 7.66 (brs, 1H), 7.35−7.45 (m, 8H), 6.17 (s, 1H), 4.59−4.61 (m, 2H), 3.66−3.71, (m, 4H), 2.66−2.74 (m, 2H), 2.55 (brs, 2H).

**2-(1*H*-1,2,3-Benzotriazol-1-yl)-2-morpholino-*N*-(1-phenylethyl)acetamide (4b):** yield 35%; $^1$H NMR $\delta$ 8.10−7.10 (m, 10H), 6.18 (s, 0.5H, one isomer), 6.11 (s, 0.5H, another isomer), 5.40−5.10 (m, 1H), 3.90−3.50 (m, 4H), 3.00−2.40 (m, 4H), 1.60−1.40 (m, 3H).

**General Procedure for the Reaction of 4a or 4b with Allylsilanes and Silyl Ethers.** To a solution of **4a** or **4b** (1 mmol) and allylsilanes **5a**,**b** or silyl ethers **7a**,**b** or **11** (2 mmol) in dry $CH_2Cl_2$ (10 mL) was added $BF_3$·$Et_2O$ (0.24 mL, 2 mmol) at 0 °C, and the mixture was stirred for 3 h. Then the reaction mixture was allowed to warm to 20 °C and stirred for another 10 h. The mixture was washed with 5% $NaHCO_3$ and $H_2O$, and the combined aqueous phase was extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and evaporated in vacuo to give a residue, which was purified by column chromatography on $Al_2O_3$ using hexanes/EtOAc (2:1) as eluent to give the products **6a−c**, **8b−c**, **9**, **10**, **13**, or **14**. Compound **8a** was purified by recrystallization of the residue obtained after workup.

***N*-Benzyl-2-morpholino-4-pentenamide (6a):** white prisms (from ethyl acetate/hexanes); mp 73−74 °C; yield 67%; $^1$H NMR $\delta$ 7.60−7.40 (m, 6H), 6.15−5.90 (m, 1H), 5.31−5.20 (m, 2H), 4.70−4.54 (m, 2H), 3.90−3.70 (m, 4H), 3.19 (t, $J$ = 6.0 Hz, 1H), 2.86−2.58 (m, 6H); $^{13}$C NMR $\delta$ 172.0, 138.5, 135.1, 128.8, 127.8, 127.5, 117.5, 69.4, 67.2, 50.9, 43.3, 32.6. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.72; H, 8.40; N, 10.48.

***N*-Benzyl-4-methyl-2-morpholino-4-pentenamide (6b):** white prisms (from ethyl acetate/hexanes); mp 96.5−98.5 °C; yield 72%; $^1$H NMR $\delta$ 7.20−7.10 (m, 6H), 4.83 (s, 1H), 4.81 (s, 1H), 4.52−4.36 (m, 2H), 3.72−3.54 (m, 4H), 3.22 (t, $J$ = 7.2 Hz, 1H), 2.70−2.40 (m, 6H), 1.81 (s, 3H); $^{13}$C NMR $\delta$ 172.4, 143.3, 138.9, 129.1, 128.1, 127.9, 113.7, 67.8, 67.7, 50.8, 43.7, 36.5, 22.8. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.78; H, 8.66; N, 9.70.

**2-Morpholino-*N*-(1-phenylethyl)-4-pentenamide (6c).** Obtained as a mixture of two diastereomers in 3:1 ratio: white prisms (from ethyl acetate/hexanes); yield 73%; $^1$H NMR $\delta$ 7.36−7.20 (m, 6H), 5.87−5.81 (m, 1H), 5.20−4.94 (m, 3H), 3.69−3.61 (m, 4H), 2.99 (t, $J$ = 6.1 Hz, 0.25H, minor isomer), 2.93 (t, $J$ = 6.1 Hz, 0.74H, major isomer), 2.66−2.40 (m, 6H), 1.48 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR 171.1, 143.3, 135.2 (minor isomer), 134.9, 128.8, 127.5, 126.2, 117.6, 117.4 (minor isomer), 69.3, 67.3, 51.1, 50.9 (minor isomer), 48.4, 32.9, 32.4 (minor isomer), 22.1. Anal. Calcd for $C_{17}H_{24}N_2N_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.98; H, 8.68; N, 9.72.

**Methyl 4-(benzylamino)-2,2-dimethyl-3-morpholino-4-oxobutanoate (8a):** colorless needles (from $CH_2Cl_2$); mp 79−80 °C; yield 72%; $^1$H NMR $\delta$ 7.40−7.20 (m, 5H), 6.70 (brs, 1H), 4.46 (d, $J$ = 5.8 Hz, 2H), 3.69 (s, 3H), 3.60 (t, $J$ = 4.4 Hz, 4H), 3.50 (s, 1H), 2.68−2.45 (m, 4H), 1.32 (s, 3H), 1.29 (s, 3H); $^{13}$C NMR $\delta$ 177.9, 170.1, 138.4, 129.0, 128.1, 127.8, 74.7, 67.7, 52.5, 52.3, 45.7, 43.6, 24.2, 21.7. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.56; H, 7.84; N, 8.38. Found: C, 64.28; H, 8.16; N, 8.41.

***N*-Benzyl-2-morpholino-4-oxo-4-phenylbutanamide (8b):** white prisms (from ethyl acetate/hexanes); mp 121−122 °C; yield 63%; $^1$H NMR $\delta$ 8.01 (d, $J$ = 7.3 Hz, 2H), 7.57 (t, $J$ = 7.0 Hz, 1H), 7.47 (t, $J$ = 7.7 Hz, 3H), 7.39−7.22 (m, 5H), 4.50 (dd, $J$ = 15.3, 6.3 Hz, 1H), 4.42 (dd, $J$ = 15.3, 6.3 Hz, 1H), 4.18 (dd, $J$ = 7.3, 4.7 Hz, 1H), 3.80−3.56 (m, 5H), 2.97 (dd, $J$ = 16.7, 4.7 Hz, 1H), 2.58 (t, $J$ = 4.4 Hz, 4H); $^{13}$C NMR $\delta$ 198.6, 171.4, 138.5,

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137.2, 133.3, 128.9, 128.8, 128.4, 127.7, 127.6, 67.4, 65.0, 50.3, 43.6, 32.6. Anal. Calcd for $C_{21}H_{24}N_2O_3 \cdot 0.5H_2O$: C, 69.78; H, 6.97; N, 7.75. Found: C, 69.93; H, 6.86; N, 7.84.

**Methyl 2,2-dimethyl-3-morpholino-4-oxo-4-[(1-phenylethyl)amino]butanoate (8c):** colorless oil, obtained as a mixture of two diastereoisomers in 1:1 ratio; yield 62%; $^1$H NMR $\delta$ 7.50−7.20 (m, 5H), 6.75 (d, $J$ = 9.9 Hz, 0.5H, one isomer), 6.68 (d, $J$ = 8.1 Hz, 0.5H, other isomer), 5.22−5.06 (m, 1H), 3.69 (s, 0.5*3H, one isomer), 3.66−3.54 (m, 5.5H), 3.47 (s, 0.5H, one isomer), 3.41 (s. 0.5H, other isomer), 2.71−2.61 (m, 1H), 2.60−2.44 (m, 3H), 1.52 (d, $J$ = 6.9 Hz, 0.5 × 3H, one isomer), 1.44 (d, $J$ = 6.9 Hz, 0.5 × 3H, other isomer), 1.36−1.19 (m, 6H); $^{13}$C NMR $\delta$ 178.1, 169.3, 143.5, 143.3, 129.1, 127.9, 127.8, 126.6, 74.9, 74.8, 67.9, 67.8, 52.6, 48.9, 45.9, 45.5, 24.8, 24.5, 22.4, 22.1, 21.8, 21.6. Anal. Calcd for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.72; H, 8.52; N, 8.32.

**1-Benzyl-3,3-dimethyl-4-morpholinodihydro-1*H*-pyrrole-2,5-dione (9):** colorless oil; yield 54%; $^1$H NMR $\delta$ 7.37−7.25 (m, 5H), 4.62 (s, 2H), 3.61−3.57 (m, 4H), 3.13 (s, 1H), 2.74−2.62 (m, 2H), 2.53−2.40 (m, 2H), 1.25 (s, 3H), 1.23 (s, 3H); $^{13}$C NMR $\delta$ 182.0, 174.7, 136.0, 128.8, 128.7, 128.0, 72.7, 67.1, 51.3, 43.6, 42.0, 27.5, 18.1. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.12; H, 7.66; N, 9.55.

**(*E*)-4-Oxo-4-phenyl-*N*-(1-phenylethyl)-2-butenamide (10):** colorless needles (from ethyl acetate/hexanes); mp 155−156 °C; yield, 52%; $^1$H NMR $\delta$ 8.03 (d, $J$ = 15.0 Hz, 1H), 8.01 (d, $J$ = 6.9 Hz, 2H), 7.65 (t, $J$ = 7.5 Hz, 1H), 7.52 (t, $J$ = 7.2 Hz, 2H), 7.44−7.26 (m, 5H), 7.18 (d, $J$ = 15.0 Hz, 1H), 6.94 (d, $J$ = 7.5 Hz, 1H), 5.33 (dq, $J$ = 7.3, 7.3 Hz, 1H), 1.62 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR $\delta$ 190.1, 163.2, 142.6, 136.8, 135.7, 133.8, 133.2, 128.9, 128.8, 127.6, 126.3, 49.4, 21.7. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.01; H, 6.33; N, 5.14.

**7a-(2*H*-1,2,3-Benzotriazol-2-yl)-1-benzyl-3-morpholinooctahydro-2*H*-indol-2-one (13):** colorless plates (from ethyl acetate/hexanes); yield 30%; $^1$H NMR $\delta$ 7.77 (dd, $J$ = 6.6, 3.3 Hz, 2H), 7.34 (dd, $J$ = 6.6, 3.3 Hz, 2H), 7.04−6.92 (m, 5H), 4.53 (d, $J$ = 15.0 Hz, 1H), 4.13 (d, $J$ = 15.3 Hz, 1H), 3.86−3.76 (m, 1H), 3.66−3.54 (m, 4H), 3.37 (d, $J$ = 9.9 Hz, 1H), 3.34−3.24 (m, 1H), 3.16−3.02 (m, 2H), 2.84−2.72 (m, 2H), 1.98−1.20 (m, 7H); $^{13}$C NMR $\delta$ 171.9, 144.0, 136.9, 127.9, 127.8, 127.0, 126.8, 118.4, 83.8, 67.4, 67.1, 50.3, 43.5, 40.7, 32.8, 23.5, 20.9, 20.6. Anal. Calcd for $C_{25}H_{29}N_5O_2$: C, 69.58; H, 6.77; N, 16.23. Found: C, 69.14; H, 6.86; N, 16.32.

**1-Benzyl-3-morpholino-1,3,3a,4,5,6-hexahydro-2*H*-indol-2-one (14):** colorless oil; yield 27%; $^1$H NMR $\delta$ 7.40−7.15 (m, 5H), 4.88−4.81 (m, 1H), 4.77 (d, $J$ = 15.2 Hz, 1H), 4.48 (d, $J$ = 15.1 Hz, 1H), 3.77 (t, $J$ = 4.7 Hz, 4H), 3.32 (d, $J$ = 9.3 Hz, 1H), 2.96−2.85 (m, 2H), 2.84−2.68 (m, 3H), 2.24−1.94 (m, 3H), 1.93−1.81 (m, 1H), 1.62−1.34 (m, 2H); $^{13}$C NMR $\delta$ 172.6, 138.1, 136.4, 128.7, 127.4, 99.3, 70.5, 67.3, 50.1, 43.6, 36.1, 28.5, 23.1, 22.2; HRMS calcd for $C_{19}H_{25}N_2O_2$ 313.1916 (M + 1), found 313.1908.

**General Procedure for the Nucleophic Substitution of 4a with Organozinc Reagents.** A 1.0 M solution of zinc chloride (1.2 mL, 1.2 mmol) in THF was added to a flask containing a 1.0 M solution of the Grignard reagent (1.2 mL, 1.2 mmol) dissolved in 10 mL of THF at 0 °C. The reaction mixture was stirred at 20 °C for 45 min and then cooled to 0 °C again and **4a** (0.30 g, 1.0 mmol) dissolved in THF (10 mL) was added dropwise. The reaction mixture was stirred overnight at 25 °C, quenched with dilute $NH_4Cl$, and extracted with diethyl ether. The organic layer was washed with 5% $NaHCO_3$, brine, and dried ($Na_2SO_4$). The organic layer was filtered and evaporated in vacuo to give a residue. The residue was purified by column chromatography on $Al_2O_3$ (80−200 mesh) using hexanes/ethyl acetate (2:1) as eluent to afford **15a**−**c**.

***N*-Benzyl-2-morpholinoheptanamide (15a):** colorless oil; yield 52%; $^1$H NMR $\delta$ 7.36−7.26 (m, 5H), 7.15 (s, 1H), 4.47−4.44 (m, 2H), 3.65 (m, 4H), 2.85 (t, $J$ = 6.9 Hz, 1H), 2.59−2.44 (m, 4H), 1.71−1.62 (m, 2H), 1.43−1.28 (brs, 6H), 0.88 (t, $J$ = 6.3 Hz, 3H); $^{13}$C NMR $\delta$ 172.7, 138.4, 128.6, 127.5, 127.3, 69.6, 67.0, 50.8, 43.0, 31.9, 28.2, 26.0, 22.3, 13.9. Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.01; H, 9.27. Found: C, 70.78; H, 9.11.

***N*-Benzyl-2-morpholino-2-phenylacetamide (15b):**[17] colorless oil; yield 52%; $^1$H NMR $\delta$ 7.48−7.37 (m, 1H), 7.36−7.22 (m, 8H), 7.19−7.12 (m, 2H), 4.46 (dd, $J$ = 15.0, 6.3 Hz, 1H), 4.37 (dd, $J$ = 15.0, 6.0 Hz, 1H), 3.83 (s, 1H), 3.62 (t, $J$ = 4.5 Hz, 4H), 2.45−2.25 (m, 4H); $^{13}$C NMR $\delta$ 170.9, 138.3, 135.5, 128.8, 128.6, 128.3, 127.6, 127.4, 76.4, 66.8, 52.1, 43.1.

***N*-Benzyl-2-(4-methylphenyl)-2-morpholinoacetamide (15c):** white prisms (from ethyl acetate/hexanes); mp 109−110 °C; yield 32%; $^1$H NMR $\delta$ 7.34−7.26 (m, 4H), 7.22−7.20 (m, 4H), 7.15−7.12 (m, 2H), 4.51 (dd, $J$ = 14.7, 6.0 Hz, 1H), 4.42 (dd, $J$ = 15.0, 6.0 Hz, 1H), 3.83 (s, 1H), 3.72−3.58 (m, 4H), 2.45−2.36 (m, 4H), 2.34 (s, 3H); $^{13}$C NMR $\delta$ 171.4, 138.5, 138.4, 132.6, 129.6, 128.9, 128.8, 127.9, 127.3, 76.4, 67.1, 52.4, 43.4, 21.3; HRMS calcd for $C_{20}H_{25}N_2O_2$ 325.1916 (M + 1), found 325.1920.

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