confirmed that all guest salts were rarely transported in the absence of carrier (transport rate $<0.3 \times 10^{-6}$ mol/h).

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Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for compounds **2c**, **7a**, **9a**, and **9d** (8 pages). Ordering information is given on any current masthead page.

N-[1-(Benzotriazol-1-yl)alkyl]amides, Versatile Amidoalkylation Reagents. 5. A General and Convenient Route to *N*-(α-Alkoxyalkyl)amides[1]

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N-[1-(Benzotriazol-1-yl)alkyl]amides **2**, easily prepared from benzotriazole **1**, an aldehyde, and an amide, react readily with a variety of primary and secondary alcohols under mild conditions to give *N*-(α-alkoxyalkyl)amides **3** in good yield.

N-(α-Alkoxyalkyl)amides are of importance both in natural product chemistry and in industrial synthesis. Pederin, a toxic principle isolated from *Paederus fuscipes* curt, contains an *N*-(α-methoxyalkyl)amide structural feature,[2] and *N*-(α-alkoxyalkyl)amide functionalities also occur in a number of synthetic herbicides.[3] *N*-(α-Alkoxyalkyl)amides are useful synthetic intermediates and have participated in the amidoalkylations of aromatics and of active methylene compounds.[4] They react with enol ethers, isonitriles, and phosphorus compounds to give useful products.[5] *N*-(α-Methoxyalkyl)amides are important starting materials for the preparation of hemithioaminals[6] and *N*-(haloalkyl)amides.[7] α-Methoxylated amides are easily transformed to unsaturated carbamates (enecarbamates) through elimination of methanol.[8]

Several synthetic routes to *N*-(α-alkoxyalkyl)amides **3** are known, but none is both general and convenient. Perhaps the most important method for their preparation is electrochemical:[5,9] anodic oxidation of *N*-alkylamides gave *N*-(α-alkoxyalkyl)amides when carried out in an alcoholic solution;[10] such oxidation in solutions of carboxylic acids gives *N*-(α-acyloxyalkyl)amides.[11] However, the anodic method is inconvenient in many laboratories and most of the results apply to methanol solution and hence to the *N*-(α-methoxyalkyl)amides (**3**: $R^3 = CH_3$).[12-14] Although some *N*-(α-alkoxyalkyl)-, and especially α-methoxylated, amides can be synthesized by conventional chemical methods, the types of α-alkoxylated amides obtainable are severely limited. Nucleophilic additions of alcohols to *N*-benzoylbenzaldimines, prepared by the pyrolysis of benzylidenebisbenzamides, afforded *N*-(α-alkoxybenzyl)benzamides;[15] however, the required *N*-acylimines are unstable;[16] furthermore, the bis-amides can be prepared only from aromatic aldehydes (without α-hydrogen), and finally 2-molar equiv of the amide must be used, so the utility of this route is restricted. Reactions of strongly electron-deficient aldehydes such as chloral or glyoxylic acid with amides form stable carbinol amides, which can be converted to *N*-(α-methoxyalkyl)amides.[6b]

Recently, Lokensgard and co-workers[17] claimed two general routes to *N*-(α-methoxyalkyl)amides from imidates: the first involves N-acylation of the imidate with an acyl chloride followed by reduction with sodium borohydride. In the second, an aldehyde is converted, via its methyl acetal, to an α-chloromethyl ether, which is used to alkylate the imidate, and further treatment with pyridinium chloride in dry DMSO gives the *N*-(α-methoxyalkyl)amide (yield of last step: 20-63%). However, both routes have

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Table I. Preparation of N-(α-Alkoxyalkyl)amides 3

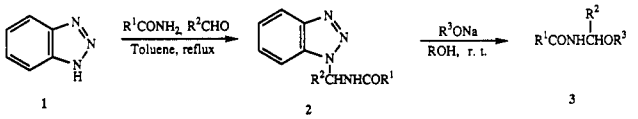
no.	R^1	R^2	R^3	yield (%)	mp (°C)	lit.[15] mp	molecular formula	calcd C	calcd H	calcd N	found C	found H	found N
3a	Ph	Ph	Me	91	98–100	102–104	$C_{15}H_{15}NO_2$	74.66	6.22	5.81	74.25	6.14	5.85
3b	Ph	Ph	Et	94	90–91	87–88	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.31	6.66	5.53
3c	Ph	Ph	*i*-Pr	69	117–119	117–118	$C_{17}H_{19}NO_2$	75.81	7.11	5.20	75.74	7.12	5.00
3d	Ph	4-$CH_3OC_6H_4$	Me	88	114–115	115–116	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	70.66	6.39	5.13
3e	Ph	4-$CH_3OC_6H_4$	Et	86	95–96		$C_{17}H_{19}NO_3$	71.57	6.71	4.91	71.99	6.82	4.96
3f	Ph	$PhCH_2$	Me	86	131–132		$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.37	6.61	5.59
3g	Ph	$PhCH_2$	Et	92	122–123		$C_{17}H_{19}NO_2$	75.81	7.11	5.20	76.19	6.95	5.35
3h	Me	4-ClC_6H_4	*i*-Pr	78	121–123		$C_{12}H_{16}ClNO_2$	59.63	6.63	5.79	59.23	6.46	5.51
3i	Me	4-ClC_6H_4	*i*-Bu	75	83–85		$C_{13}H_{18}ClNO_2$	61.06	7.05	5.46	60.79	7.02	5.27
3j	Me	4-$CH_3OC_6H_4$	*i*-Pr	56	100–102		$C_{13}H_{19}NO_3$	65.82	8.02	5.91	65.47	8.16	6.06
3k	Ph	H	*i*-Pr	64	liquid		$C_{11}H_{15}NO_2$	194.1181			194.1180		
3l	Ph	H	Et	67	41–43		$C_{10}H_{13}NO_2$	180.1024			180.1026		

obvious disadvantages: imidates and their acylated derivatives are neither very stable nor particularly readily available; three or four steps are needed from aldehydes, and the yields in each case are moderate (e.g., the reported yields for the sodium borohydride reduction in the first method ranged from 24 to 85%). Finally, for both routes only α-methoxylated amides (3: R^3 = Me) are reported.

A few further methods are available for *N*-(alkoxymethyl)amides (3: R^2 = H). The alkylation of secondary amides with halomethyl ethers under phase-transfer conditions[18] gave N-alkoxylated amides, but for the less acidic saturated aliphatic amides strongly basic amide alkylation conditions (e.g., in the presence of NaH, Na, or K) are often required.[19] *N*-Hydroxymethylamides condense with primary alcohols in acidic conditions to form *N*-alkoxymethyl amides.[20]

Recent work in this laboratory has shown the versatility of *N*-[α-(benzotriazolyl)alkyl]amides **2** in organic synthesis as a continuation of our exploitation of the synthetic auxiliary benzotriazole.[21] *N*-[α-(Benzotriazolyl)alkyl]-amides or thioamides have been advantageously employed in the preparation of alkylated amides[22,23] and thioamides.[24] Similar alkylation is also applicable for ureas and thioureas.[25] We have recently reported that *N*-[α-(benzotriazolyl)alkyl]amides **2**, in analogy to other frequently used amidoalkylation reagents,[4] are good precursors of the corresponding acyliminium cation because the benzotriazolate anion is a good leaving group. They have been successfully used in the amidoalkylation of alkylmalonates and other C–H acids,[26] active aromatic compounds,[27] and in the preparation of tri- and tetrasubstituted 4*H*-1,3-oxazines.[1] We also found that *N*-[1-(benzotriazol-1-yl)alkyl]amides react readily with a variety of thiols and sodium sulfide under mild conditions to give *N*-acylhemithioaminals in good yields.[28]

Scheme I[a]



[a] Key: R^1 = Ph, CH_3; R^2 = Ph, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, $PhCH_2$, H; R^3 = Me, Et, *i*-Pr, *i*-Bu.

The present paper reports a general and convenient route to *N*-(α-alkoxyalkyl)amides by the reaction of *N*-[α-(benzotriazol-1-yl)alkyl]amides with alcohols under mild conditions.

Results and Discussion

The amidoalkylation reagents, *N*-[α-(benzotriazol-1-yl)alkyl]amides **2**, were easily prepared by the previously described method from benzotriazole, an aldehyde, and an amide in toluene.[22,26] A variety of aldehydes and amides (both aliphatic and aromatic) were used, and all gave the expected stable products **2** (**2a**: R^1 = Ph, R^2 = Ph; **2b**: R^1 = Ph, R^2 = $CH_3OC_6H_4$; **2c**: R^1 = Ph, R^2 = $PhCH_2$; **2d**: R^1 = CH_3, R^2 = 4-ClC_6H_4; **2e**: R^1 = CH_3, R^2 = 4-$CH_3OC_6H_4$; **2f**: R^1 = Ph, R^2 = H) in good yields.

The *N*-[α-(benzotriazol-1-yl)alkyl]amides **2** react readily with sodium alkoxides to give the expected products. Thus, the benzotriazole derivative **2** was added to a slight excess of sodium metal in an appropriate alcohol and the solution was stirred at room temperature overnight. The essentially pure solid products, the *N*-(α-alkoxyalkyl)-amides **3a–3l**, were obtained simply by pouring the mixture into water followed by filtration. The byproduct, benzotriazole, remains as its soluble sodium salt in aqueous solution. The yields of the *N*-(α-alkoxyalkyl)amides formed are good to excellent (57–94%). Generally, methanol and ethanol gave the highest yields (all about 90%), and the secondary alcohols, such as 2-propanol and 2-butanol, afforded slightly lower yields of products. However, *tert*-butyl alcohol gave a complex mixture including only a very low yield of the desired product, presumably due to the steric hindrance and the high basicity of *tert*-butoxide. The reaction and the results are shown in Scheme I and Table I, respectively. Although highly successful for aliphatic alcohols, this method could not be extended to phenols. When a benzotriazole derivative **2** was similarly treated with sodium phenoxide in ethanol, the *N*-(α-ethoxyalkyl)amide was produced and a small amount of the starting material **2** remained even when 1 equiv of sodium metal was used. Evidently, the equilibrium between phenoxide and ethoxide allowed the more reactive ethoxide to attack **2**. Tetrahydrofuran was then used as the solvent instead of ethanol; however, the re-

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Table II. ^{1}H NMR Spectral Data (δ, J in Hz) of N-(α-Alkoxyalkyl)amides 3

no.	NH	CH	R^1	R^2	R^3
3a	6.63 (br)	6.38 (d, J = 9.3)	7.80 (d, J = 8.4, 2 H), 7.53–7.45 (m, 3 H)	7.41–7.32 (m, 5 H)	3.55 (s, OCH_3)
3b	6.73 (br)	6.46 (d, J = 9.6)	7.79 (d, J = 8.4, 2 H), 7.54–7.45 (m, 3 H)	7.40–7.30 (m, 5 H)	3.83 (m, 1 H), 3.69 (m, 1 H), 1.29 (t, 3 H)
3c	6.83 (d)	6.56 (d, J = 9.0)	7.79 (d, J = 8.2, 2 H), 7.49 (m, 3 H)	7.40–7.29 (m, 5 H)	4.02 (hept, 1 H), 1.26 (d, 6 H, Me_2)
3d	6.65 (d)	6.31 (d, J = 9.3)	7.80 (d, J = 7.2, 2 H), 7.52–7.45 (m, 3 H)	7.40 (d, 2 H), 6.90 (d, J = 8.7, 2 H), 3.80 (s, 3 H)	3.51 (s, OCH_3)
3e	6.71 (d)	6.41 (d, J = 9.3)	7.80 (d, J = 7.0, 2 H), 7.55 (m, 3 H)	7.41 (d, 2 H), 6.89 (d, J = 8.7, 2 H), 3.79 (s, 3 H)	3.82–3.74 (m, 2 H), 1.28 (t, CH_3)
3f	6.34 (D)	5.62 (dt, J = 9.6, 6)	7.70 (d, J = 8.2, 2 H), 7.48 (T, 1 H), 7.40 (t, 2 H)	7.32–7.23 (m, 5 H), 3.04 (d, 2 H, CH_2)	3.39 (s, OCH_3)
3g	6.42 (d)	5.69 (Dt, J = 9.6, 6)	7.69 (d, J = 8.3, 2 H), 7.48 (t, 1 H), 7.39 (t, 2 H)	7.30–7.20 (m, 5 H), 3.04 (d, 2 H, CH_2)	3.69 (m, 1 H), 3.55 (m, 1 H), 1.15 (t, 3 H)
3h	6.00 (br)	6.30 (d, J = 9.3)	2.05 (s, 3 H, CH_3CO)	7.38 (d, 2 H), 7.31 (d, 2 H)	3.93 (hept, 1 H), 1.27 (d, 3 H), 1.22 (d, 3 H)
3i	6.00 (br)	6.31 (d)	2.04 (s, 3 H, CH_3CO)	7.39 (d, 2 H), 7.32 (d, 2 H)	3.70 (m, 1 H), 1.22 (d, 3 H), 0.96 (t, 3 H)
3j	6.08 (br)	6.23 (d)	2.02 (s, 3 H, CH_3CO)	7.38 (d, 2 H), 6.88 (d, 2 H), 3.80 (s, 3 H, OCH_3)	3.95 (hept, 1 H), 1.25 (d, 3 H), 1.21 (d, 3 H)
3k	7.63 (br)	4.96 (d, 2 H, J = 6.6)	7.82 (d, J = 8.1, 2 H), 7.50–7.36 (m, 3 H)		3.96 (hept, 1 H), 1.17 (d, 3 H)
3l	7.26 (br)	4.95 (d, 2 H, J = 6.9)	7.83 (d, 2 H, J = 8.4), 7.58–7.47 (m, 3 H)		3.63 (q, 2 H), 1.21 (t, 3 H)

Table III. ^{13}C NMR Spectral Data (δ) of N-(α-Alkoxyalkyl)amides 3

no.	CO	CH	R^1	R^2	R^3
3a	167.3	81.8	133.7, 132.0, 128.7, 127.0	139.2, 128.9, 128.6, 125.8	56.2 (OCH_3)
3b	167.1	80.2	133.7, 131.9, 128.6, 127.1	139.7, 128.5, 128.4, 125.9	64.1 (OCH_2), 15.1 (CH_3)
3c	166.9	78.2	133.7, 131.7, 128.5, 127.0	140.1, 128.5, 128.4, 125.9	69.6 (OCH), 23.0 (CH_3), 21.8 (CH_3)
3d	167.2	81.6	133.7, 131.9, 128.6, 127.0	159.7, 131.5, 127.1, 113.9, 55.3 (OCH_3)	56.1 (OCH_3)
3e	167.1	80.3	133.8, 131.8, 128.6, 127.0	159.6, 131.8, 127.1, 113.9, 55.2 (OCH_3)	64.0 (OCH_2), 15.1 (CH_3)
3f	167.3	81.4	133.9, 131.8, 128.6, 126.9	135.8, 129.7, 128.4, 126.8, 41.6 (CH_2)	56.1 (OCH_3)
3g	167.1	80.0	133.0, 131.7, 128.6, 126.9	136.1, 129.7, 128.3, 126.7, 41.8 (CH_2)	66.0 (OCH_2), 15.0 (CH_3)
3h	167.2	77.4	23.5 (CH_3)	139.5, 134.1, 128.6, 127.4	69.7 (OCH), 23.0 (CH_3), 21.8 (CH_3)
3i	169.5	74.6	22.7 (CH_3)	139.0, 133.0, 127.6, 127.4	72.9 (OCH), 29.3, 19.1, 9.6
3j	169.8	77.6	23.5 (CH_3)	159.5, 132.4, 127.1, 113.8, 55.3 (OCH_3)	69.3 (OCH), 22.9 (CH_3), 21.9 (CH_3)
3k	167.9	68.3	133.8, 131.9, 128.5, 127.2		68.6 (OCH), 22.3
3l	167.9	70.4	133.9, 131.9, 128.6, 127.1		64.1 (OCH_2), 15.1 (CH_3)

action led to the decomposition of the starting material.

The N-(α-alkoxyalkyl)amides **3a–3l** prepared in this work, mostly new compounds, were characterized by their ^{1}H and ^{13}C NMR spectra, by elemental analyses, and where appropriate, by comparison with literature data. The ^{1}H and ^{13}C NMR chemical shifts of compounds **3a–3l** and their detailed assignments are summarized in Tables II and III. The ^{1}H NMR spectra of some N-(α-alkoxyalkyl)-amides, especially N-(α-methoxyalkyl)amides, have previously been reported.[6b,17] In the ^{1}H NMR spectra, NH signals of the amide group appeared at 6.34–6.83 ppm either as broad singlets or as doublets coupled with the adjacent CH protons which resonated at 5.62–6.56 ppm. Because the alkoxy group is attached to a chiral carbon (except where R^2 = H), the two protons of ethoxy methylene group are magnetically nonidentical (i.e., there is an ABX_3 system for OCH_2CH_3), and the two methyl groups in the isopropoxy derivatives **3c**, **3h**, **3j**, and **3k** are also nonidentical in both the ^{1}H and ^{13}C NMR spectra. In the ^{13}C NMR spectra, the carbonyl carbons appeared over a narrow range of 166.9–167.3 ppm and the methine carbons at from 78.2–81.6 ppm depending on the structure of the alkoxy functions.

In conclusion, an alternative procedure has been developed for the preparation of N-(α-alkoxyalkyl)amides. It is apparent that the present method is one of the simplest preparations for the target molecules. The reaction conditions are mild and nonacidic. N-[α-(Benzotriazol-1-yl)alkyl]amides are easily prepared from aldehydes and amides, and the advantages are evident if our method is compared with that of Lokensgard[22] from imidate and α-chloromethyl ether and with Breuer's route from benzylidenebisbenzamides.[15] The workup procedure is very simple, the products are easily purified, and the yields are mostly high.

Experimental Section

^{1}H NMR spectra were obtained at 300 MHz, and ^{13}C NMR spectra were determined at 75 MHz. N-[α-(Benzotriazol-1-yl)-alkyl]amides were prepared as previously reported.[22,26]

Preparation of N-(α-Alkoxyalkyl)amides 3, General Procedure. The N-[α-(benzotriazolyl)alkyl]amide **2** (10 mmol) was added in one portion to a solution of sodium (12 mmol) in the appropriate alcohol (30 mL) at room temperature. The mixture was stirred at room temperature overnight and poured into water (100 mL). The resulting precipitate was collected by filtration and dried (25 °C under vacuo) to give the pure product in most cases. **3c** was recrystallized from aqueous ethanol and **3j** from hexane. For products **3k** and **3l** no precipitate was formed when the reaction mixture was poured into water, so the aqueous solution was extracted with $CHCl_3$ (3 × 30 mL). The purification was by column chromatography (silica gel, $CHCl_3$). Compound **3l** solidified on standing. For data of compounds **3a–3l**, see Tables I–III.

Note Added in Proof. Some of the above compounds have recently been prepared by oxidation of N-acyl-α-amino acids.[29]

Registry No. **2a**, 117067-48-8; **2b**, 134004-79-8; **2c**, 134004-81-2; **2d**, 137570-70-8; **2e**, 134004-84-5; **2f**, 111184-75-9; **3a**, 10387-93-6; **3b**, 15563-54-9; **3c**, 10374-30-8; **3d**, 10374-25-1; **3e**, 137570-64-0; **3f**, 99355-57-4; **3g**, 137570-65-1; **3h**, 137570-66-2; **3i**, 137570-67-3; **3j**, 137570-68-4; **3k**, 137570-69-5; **3l**, 126317-94-0; methanol, 67-56-1; ethanol, 64-17-5; isopropyl alcohol, 67-63-0; isobutyl alcohol, 78-83-1.