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Enantioselective Ethylation of N-(Amidobenzyl)benzotriazoles Catalysed by Chiral Aminoalcohols

Alan. R. Katritzky* and Philip A. Harris

Department of Chemistry and the Center for Heterocyclic Compounds, University of Florida, Gainesville, Florida 32611-2046

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Abstract: *In the presence of the chiral amino-alcohol (-) N,N-dibutylnorephedrine (DBNE), N-(amidobenzyl)benzotriazoles react with diethylzinc to give the corresponding amides with up to 76% ee.*

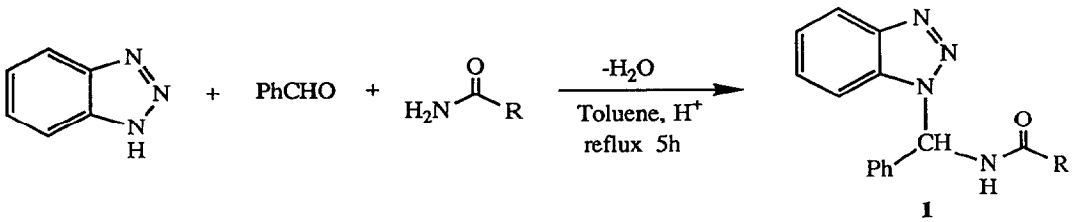
Although great advances have been made on the stereoselective addition of carbon nucleophiles to aldehydes, few examples of enantioselective alkylation of the imine function have been reported.[1] This reflects both the poor electrophilicity of the C=N bond and the tendency of imines to undergo deprotonation or isomerization to an enamine rather than addition. These problems can often be overcome by the use of activated imine derivatives such as iminium salts[2] or N-acyliminium ions.[3]

Recently, chiral ligand catalysts have been employed in alkylations of aldimines[4] and N-silylated imines[5] giving the corresponding optically active amines with moderate enantiomeric excess (ee). Asymmetric addition of dialkylzincs to aldehydes catalysed by chiral aminoalcohols has been intensively investigated in recent years and a variety of highly efficient catalysts have been reported.[6] However, imines or silylimines[5] are unreactive to diethylzinc even in the presence of a stoichiometric amount of aminoalcohol promotors at elevated temperatures.

In our laboratory we have studied the reactions of N-(amimoalkyl)benzotriazole Mannich bases, derived from benzotriazole, an aldehyde and an amine, with organometallics to give N-alkylated amines. The mechanism is thought not to be a substitution reaction but an elimination of benzotriazole or its anion followed by addition of nucleophile to the resulting imine or iminium cation.[7] We report here the use N-(amidobenzyl)benzotriazoles, acting as masked activated N-acylimines, as effective substrates for the enantioselective ethylation of the C=N double bond leading to optically active amides.

Of the wide range of ligands reported, sterically constrained β-dialkylamino alcohols such as (-)-N,N-dibutylnorephedrine (DBNE), prepared by alkylation of commercially available norephedrine,[8,9] have been shown to be efficient chiral catalysts for addition of diethylzincs to carbonyl substrates. Initially, we examined the Mannich base obtained from benzotriazole, benzaldehyde and the secondary amine morpholine in the reaction with diethylzinc and the chiral ligand DBNE. Reaction at -78°C in toluene gave the ethylated product, but with no selectivity, even with a stoichiometric amount of DBNE. Such N-(aminobenzyl)benzotriazoles were subsequently found to react smoothly with diethylzinc at -78°C even in the absence of a chiral promoter. This result prompted us to examine the corresponding Mannich derivatives obtained from amides which are known to be less reactive than their amine analogues[10] and a series of such N-(amidobenzyl)benzotriazoles **1** were prepared from various primary amides (see Table 1). The expected lower reactivity was confirmed by the observation that the acetamide derivative **1a** was unreactive to diethylzinc in toluene at 25°C.

Table 1. Preparation of N-(1-Benzotriazoyl-1-phenylmethyl)amides **1**.



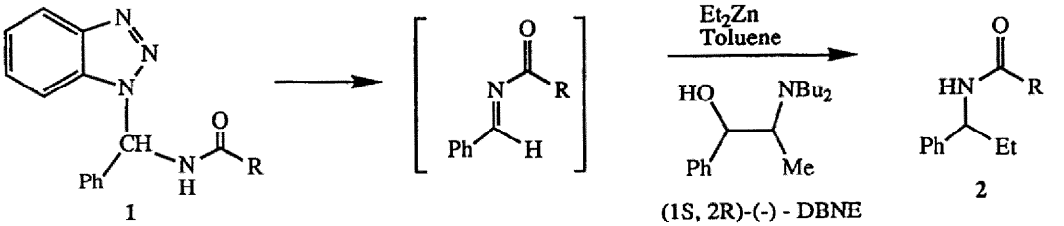
1

	R	Yield (%)	Molecular Formula	mp (°C)	Recrystallization Solvent	C(%) Required (Found)	H(%) Required (Found)	N(%) Required (Found)
1a	Me	61	$C_{15}H_{14}N_4O$	154.0-156.0	Toluene	67.65 (67.27)	5.30 (5.34)	21.04 (21.17)
1b	OMe	43	$C_{15}H_{14}N_4O_2$	85.0-85.5	Ethyl Acetate	63.82 (63.79)	5.00 (4.95)	19.85 (20.07)
1c	Et	54	$C_{16}H_{16}N_4O$	126.5-128.5	Toluene	68.55 (69.25)	5.75 (6.08)	19.99 (19.44)
1d	^{i}Pr	72	$C_{17}H_{18}N_4O$	160.0-161.5	Toluene	69.37 (69.03)	6.16 (6.27)	19.03 (18.27)
1e	^{t}Bu	71	$C_{18}H_{20}N_4O$	149.5-151.0	Toluene	70.11 (70.02)	6.54 (6.67)	18.17 (17.82)
1f	H	35	$C_{14}H_{12}N_4O$	135.0-138.0 (Lit[11] mp 141-142)	Ethanol			
1g	Ph	74	$C_{20}H_{16}N_4O$	165.0-167.0 (Lit[12] mp 188-190)	Toluene			

In the presence of DBNE, the N-(amidobenzyl)benzotriazoles **1** were ethylated with diethylzinc to give the corresponding N-(1-phenylpropyl)amides **2**. Initially, the reaction conditions giving the best selectivity were determined using acetamide **1a** as the representative benzotriazole derivative. Treatment of an equimolar mixture of **1a** and DBNE in toluene with two equivalents of diethylzinc at -78°C and slowly allowing the reaction to warm to room temperature before work-up gave the amide **2a** with 55% ee in 14% yield. The presence of one equivalent of DBNE was shown to be essential since use of a catalytic amount (0.2 equiv.) led to significantly reduced selectivity (13% ee). Lower enantioselectivities were also observed at higher temperatures such as 0°C (30% ee) and 25°C (19% ee). Also no ethylation occured if the reaction temperature was maintained at -78°C. An marked enhancement in both chemical yield (46%) and enantioselectivity (76% ee) was found when the amount of diethylzinc was increased to three equivalents.

The remaining N-(amidobenzyl)benzotriazoles **1b-f** were reacted under the optimum conditions found for **1a**, with the exception that the use of more than two equivalents of diethylzinc was found to have no effect on the chemical or optical yields for these derivatives. The results are summarised in Table 2. Only the formamide derivative **1f** did not yield the amide **2f** as expected, but a complex product of which the major component was that corresponding to reduction of the starting material. Enantiomeric excesses were determined by conversion of commercially available (S)-(-)-1-phenylpropylamine into the various optically pure amides **2**. The predominant enantiomers obtained from ethylation were found to possess the (R)-configuration.

Table 2. Preparation of N-(1-Phenylpropyl)amides 2.



	R	Yield (%)	$[\alpha]_D^{25}$ [a] (c = 1, $CHCl_3$)	$[\alpha]_D^{25}$ [b]	ee (%)	Molecular Formula	mp (°C)	C(%) Required (Found)	H(%) Required (Found)	N(%) Required (Found)
2a	Me	46	+101.2	-133.7	76	$C_{11}H_{15}NO$	108.0-109.0[c]	74.54 (74.73)	8.53 (8.71)	7.90 (7.89)
2b	OMe	5	+17.5	-82.8	21	$C_{11}H_{15}NO_2$	58.5-59.5[c]	68.37 (68.44)	7.82 (7.83)	7.25 (7.18)
2c	Et	51	+28.7	-121.5	24	$C_{12}H_{17}NO$	60.5-61.5[d]	75.35 (75.03)	8.96 (9.02)	7.32 (7.03)
2d	^{i}Pr	80	+48.4	-119.3	41	$C_{13}H_{19}NO$	70.5-72.5[d]	76.06 (76.23)	9.33 (9.39)	6.82 (6.77)
2e	^{t}Bu	96	0	-104.5	0	$C_{14}H_{21}N_4O$	122.5-124.0[d]	76.67 (76.61)	9.65 (9.87)	6.39 (6.39)
2f	H	0	—	-136.6	—	$C_{10}H_{13}NO$	oil			
2g	Ph	82	+12.3	-29.3	42	$C_{16}H_{17}NO$	119.0-119.5[e]	80.30 (79.97)	7.16 (7.02)	5.85 (5.69)

[a] Rotations for amides 2 obtained by Et_2Zn : DBNE ethylation of N-(amidobenzyl)benzotriazoles 1. [b] Rotations for optically pure amides 2 obtained from (-)-(1-phenylpropyl)amine. [c] Recrystallized from ethyl acetate. [d] Recrystallized from hexane. [e] Recrystallized from toluene.

The loss of selectivity with increase of the amide size on going from the isobutyramide **1d** to the pivalamide **1e** may be due to steric hindrance which prevents the chiral ligand from approaching the reaction site. Alternatively, this may reflect a change in the reaction mechanism going from an S_N1 reaction, with the N-acylimine as intermediate, to an S_N2 displacement of benzotriazole with subsequent inversion.

All N-(amidobenzyl)benzotriazoles **1** and N-(1-phenylpropyl)amides **2** were white crystalline solids (with the exception of the formamide derivative **2f**), and were characterized by their ^1H and ^{13}C NMR spectra (see Experimental and Tables 3 and 4) and confirmed by elemental analysis (Tables 1 and 2). Some aspects of the ^1H NMR spectra of the amides **2** are worthy of note. The benzylic proton appears as a quartet at about 4.9 ppm due to coupling to both the CH_2 of the ethyl group and the amide NH with similar coupling constants of about 7 Hz. The downfield amide NH appears as a broad doublet. The CH_2 of the ethyl group often appears as a multiplet at about 1.8 ppm since the protons are diastereotropic, however for amides **2d** and **2e** the diastereotropic protons overlap and the signals appear as quintets due to coupling to the methyl group and the benzylic proton.

In conclusion, the chiral N,N-dibutylnorephedrine catalyzed enantioselective additions of diethylzinc to N-(amidobenzyl)benzotriazoles **1**, acting as masked N-acylimines, give optically active secondary amides **2** with the (R)-configuration predominant. This represents the first extension of the well established enantioselective alkylation of aldehydes with dialkylzincs and chiral aminoalcohols to include addition to the imine function.

Table 3. ^{13}C-NMR Chemical Shifts (δ) for N-(1-Benzotriazoyl-1-phenylmethyl)amides **1** (d_6-DMSO).

	Benzotriazole	CHPh	Ph	CO	R
1a	110.7, 119.1, 123.8, 128.5, 131.8, 145.3	65.1	126.4, 127.2, 128.4, 136.2	169.8	22.1
1b	111.3, 119.4, 124.3, 128.9, 131.7, 145.5	68.3	126.7, 127.6, 128.7, 136.1	156.3	52.1
1c	110.0, 119.3, 123.8, 128.5, 132.2, 145.3	64.4	126.3, 127.2, 128.4, 136.2	174.0	9.0, 28.4
1d	109.9, 119.2, 123.8, 128.4, 132.3, 145.2	64.4	126.2, 127.2, 128.3, 136.2	177.2	18.8, 19.0, 34.2
1e	110.0, 120.2, 124.6, 129.4, 133.1, 145.9	64.9	126.6, 128.2, 129.3, 136.9	178.6	27.6, 39.2
1f	110.2, 119.7, 124.2, 129.0, 132.4, 145.7	63.1	126.5, 127.7, 128.8, 135.8	161.2	—
1g	109.7, 119.9, 124.4, 129.3, 132.7, 145.7	64.8	127.4, 128.0, 128.7, 136.4	166.9	126.4, 129.1, 132.4, 132.7

Table 4. ^{13}C-NMR Chemical Shifts (δ) for N-(1-Phenylpropyl)-amides **2** ($CDCl_3$).

	Et	CHPh	Ph	CO	R
2a	10.9, 23.0	55.1	126.7, 127.0, 128.4, 142.7	170.0	29.2
2b	10.6, 29.5	56.8	126.3, 127.2, 128.5, 142.5	156.4	52.0
2c	10.6, 29.0	54.6	126.4, 126.9, 128.2, 142.4	173.3	9.8, 29.4
2d	10.7, 29.1	54.5	126.5, 127.2, 128.5, 142.3	176.2	19.5, 19.7, 35.7
2e	11.0, 29.5	54.8	126.7, 127.4, 128.8, 142.8	177.9	27.8, 38.9
2f	10.6, 29.0	53.6	126.4, 127.2, 128.4, 141.6	160.6	—
2g	10.8, 29.0	55.3	126.6, 127.1, 128.5, 142.2	166.8	126.9, 128.3, 131.1, 134.6

Experimental

General: Column chromatography was carried out on MCB silica gel (230-400 mesh). Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 MHz spectrometer in $CDCl_3$ or d_6-DMSO using TMS for ^{1}H spectra and the solvent for ^{13}C NMR spectra as the internal reference (abbreviations used: s singlet; d doublet; t triplet; q quartet; m multiplet; bs broad singlet and bd broad doublet). Optical rotations were measured on a Perkin Elmer 241 polarimeter. Elemental analyses were performed on a Carlo Erba-1106 instrument under the supervision of Dr. D. Powell. High resolution mass measurements were recorded on an AEI MS-30 mass spectrometer. Toluene was predried and distilled from sodium. (-)-1-Phenylpropylamine was purchased from Schweizerhall Inc. (-) N,N-Dibutylnorephedrine (DBNE) was prepared according to the procedure of Soai *et. al.*.[9]

Preparation of N-(Amidobenzyl)benzotriazoles 1. A mixture of benzotriazole (11.9 g, 10 mmol), benzaldehyde (10.06 g, 10 mmol), the primary amide (10 mmol) and *p*-toluenesulfonic acid (250 mg) was refluxed in toluene (150 mL) for 5h with azeotropic removal of the water using a Dean-Stark collector. On completion of the reaction the solution was allowed to cool to room temperature. Benzotriazole derivatives **1a** and **1g** crystallized from the cooled toluene solution, whereas derivatives **1c-e** crystallized on addition of hexane (50 mL) to the reaction mixture and cooling in an ice bath. Derivative **1b** was obtained by removal of the toluene under reduced pressure and trituration of the resulting oil with ether/hexane (5:2) (100 mL). The solid N-(amidobenzyl)benzotriazoles **1** were filtered off and purified by recrystallization (see Table 1). The formamide derivative **1f** was prepared as described previously.[11]

^{1}H NMR spectra for the novel N-(amidobenzyl)benzotriazoles **1a-e** are listed below.

N-(1-Benzotriazoyl-1-phenylmethyl)acetamide (1a): δ 2.03 (s, 3 H), 7.30-7.55 (m, 7 H), 7.80-8.10 (m, 3 H), 9.80-9.90 (m, 1 H).

Methyl N-(1-benzotriazoyl-1-phenylmethyl)carbamate 1b: δ 3.71 (s, 3 H), 7.21-7.68 (m, 8 H), 8.09 (d, J = 8.4 Hz, 1 H), 8.80-8.90 (m, 1 H).

N-(1-Benzotriazoyl-1-phenylmethyl)propionamide (1c): δ 1.09-1.16 (m, 3 H), 2.22-2.40 (m, 2 H), 7.26-7.49 (m, 7 H), 7.71-8.05 (m, 3 H), 9.06-9.10 (m, 1 H).

N-(1-Benzotriazoyl-1-phenylmethyl)isobutyramide (1d): δ 1.03 (d, J = 6.8 Hz, 3 H), 1.16 (d, J = 6.8 Hz, 3 H), 2.52-2.70 (m, 1 H), 7.25-7.46 (m, 7 H), 7.69-8.02 (m, 3 H), 8.98 (d, J = 8.5 Hz, 1 H).

N-(1-Benzotriazoyl-1-phenylmethyl)trimethylacetamide (1e): δ 1.24 (s, 9 H), 7.21-7.50 (m, 8 H), 7.64 (d, J = 8.3 Hz, 1 H), 7.88 (d, J = 9.0 Hz, 1 H), 8.07 (d, J = 8.4 Hz, 1 H).

General Procedure for the Enantioselective Ethylation of N-(Amidobenzyl)benzotriazoles 1. A mixture of the chiral catalyst DBNE (2.63 g, 10mmol) and the N-(amidobenzyl)benzotriazole **1** (10 mmol) was placed under argon and dry toluene (40 mL) was added. The resulting suspension was stirred at room temperature for 30 min. and then cooled to -78°C. Diethylzinc (20 mL, 22 mmol, 1.1M solution in toluene) was added slowly and stirring continued for a further 12 h at -78°C. The reaction mixture was allowed to warm to room temperature over 12 h, and stirred for a further 6 h. The solution was quenched by the addition of dilute aqueous HCl (25 mL), the mixture extracted with ether (50 mL) and the extract dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was taken up in ether-hexane and filtered to remove remaining inorganic impurities. Amides **2a**, **2e** and **2g** solidified and were purified by recrystallization (see Table 2), whereas amides **2b-d** were subjected to flash column chromatography over silica gel (hexane/ethyl acetate). For the N-(amidobenzyl)benzotriazole **1a**, the same reaction conditions were used with the exception that three equivalents of diethylzinc (30 mL, 33 mmol, 1.1M solution in toluene) was employed.

(-)-N-(1-Phenylpropyl)acetamide 2a was obtained by refluxing a solution of (-)-1-phenylpropylamine (1.0 g, 5.8 mmol) in acetic anhydride (10 mL) for 1h. The acetic anhydride was removed under reduced pressure, the crude product partitioned between chloroform (25 mL) and water (25 mL), the chloroform layer separated, dried ($MgSO_4$) and evaporated to leave the amide **2a** as a white solid (1.02 g, 78% yield). ^{1}H NMR δ 0.86 (t, J = 7.3 Hz, 3 H), 1.71-1.87 (m, 2 H), 1.91 (s, 3 H), 4.78-4.88 (q, J = 7.6 Hz, 1 H), 6.95 (bd, J = 7.8 Hz, 1 H), 7.12-7.28 (m, 5 H).

(-)-Methyl N-(1-Phenylpropyl)carbamate 2b was prepared in 91% yield by treatment of (-)-1-phenylpropylamine with bis(trismethylsilyl)acetamide followed by methyl chloroformate according to the procedure of Raucher and Jones.[13] ^{1}H NMR 0.89 δ (t, J = 7.4 Hz, 3 H), 1.72-1.85 (m, 2 H), 3.63 (s, 3 H), 4.52-4.65 (m, 1 H), 5.1 (bs, 1 H), 7.24-7.38 (m, 5 H).

General Procedure for the Preparation of Optically Pure N-(1-phenylpropyl)amides 2c-e,g. (-)-N-(1-Phenylpropyl)amides **2c,d,e,g** were synthesized by treatment of (-)-1-phenylpropylamine (250 mg, 1.85 mmol) with the appropriate acid chloride (1.85 mmol) and pyridine (146 mg, 1.85 mmol) in chloroform (50 mL) for 2h at room temperature. On quenching the reaction mixture with water (30 mL), the organic phase was separated, washed with dilute HCl (30 mL), dried ($MgSO_4$) and evaporated to give the amide **2** as a white solid which was purified by recrystallization (see Table 2).

(-)-N-(1-Phenylpropyl)propionamide 2c: yield 73 %, ^{1}H NMR δ 0.88 (t, J = 7.4 Hz, 3 H), 1.14 (t, J = 7.6 Hz, 3 H), 1.76-1.85 (m, 2 H), 2.16-2.24 (m, 2 H), 4.89 (q, J = 7.5 Hz, 1 H), 5.81-5.83 (bd, J = 6.8 Hz, 1 H), 7.22-7.36 (m, 5 H).

(-)-N-(1-Phenylpropyl)isobutyramide 2d: yield 68%, ^{1}H NMR δ 0.89 (t, J = 7.4 Hz, 3 H), 1.12 (d, J = 6.9 Hz, 3 H), 1.16 (d, J = 6.9 Hz, 3 H), 1.77-1.86 (quintet, J = 7.3, 2 H), 2.34 (septet, J = 6.9 Hz, 1 H), 4.88 (q, J = 7.7 Hz, 1 H), 5.81 (bd, J = 6.6 Hz, 1 H), 7.22-7.35 (m, 5 H).

(-)-N-(1-Phenylpropyl)trimethylacetamide 2e: yield 57%, ^{1}H NMR δ 0.89 (t, J = 7.4 Hz, 3 H), 1.19 (s, 9 H), 1.81 (quintet, J = 7.4, 2 H), 4.86 (q, J = 7.5 Hz, 1 H), 5.9 (bd, 1 H), 7.23-7.31 (m, 5 H).

(-)-N-(Phenylpropyl)formamide 2f was obtained in 83% yield by refluxing a solution of (-)-1-phenylpropylamine (279.4 mg, 2.1 mmol) in ethyl formate (0.3 g) for 2h.[14] Removal of excess ethyl formate under reduced pressure and purification of the crude product by flash chromatography over silica gel eluting with chloroform gave the amide **2f** as an oil (280 mg, 83% yield). ^{1}H NMR δ 0.88 (t, J = 7.4 Hz, 3 H), 1.75-1.86 (m, 2 H), 4.91 (q, J = 7.8 Hz, 1 H), 6.70 (bd, J = 7 Hz, 1 H), 7.21-7.35 (m, 5 H), 8.10 (s, 1 H). High resolution mass spectrometry $C_{10}H_{13}NO$ (M^+) calc. 163.0997, requires 163.0997.

(-)-N-(1-Phenylpropyl)benzamide 2g: yield 76%, ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3 H), 1.84-1.96 (m, 2 H), 5.05 (q, J = 7.7 Hz, 1 H), 6.81 (d, J = 7.7 Hz, 1 H), 7.20-7.44 (m, 8 H), 7.76 (d, J = 7.5 Hz, 2 H).

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