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(α-Aminoacyl)amino-Substituted Heterocycles and Related Compounds

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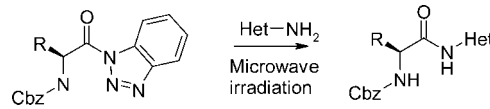

N-Protected-(aminoacyl)benzotriazoles **1a**−**e**,**g**,**i**,**j**,**1a′**−**c′** convert heterocyclic amines of the following series: thiazoles (**3a** and **3a′**), benzothiazoles (**3b** and **3b′**), benzimidazoles (**3c** and **3c′**), thiadiazoles (**3d**), pyrimidones (**9a**,**b**,**a′**), pyrazoles (**11a**,**b**), and pyridines (**13a**−**g**, **13d′**) under microwave irradiation, into N-substituted amides in yields of 40−98% (average 76%). N-Protected peptidoylbenzotriazoles **6a**,**b** similarly afforded C-terminal N-protected dipeptidoyl amides **7a**,**b** (52−60%).

Introduction

N-Substituted heterocycles show anti-inflammatory,[1] antiproliferative,[2] antithrombotic,[3] antifungal,[4] and antineurological biological activities.[5] Such units occur in diverse pharmacologically active molecules including cell adhesion inhibitors,[6] platelet-activating factor (RAF), or angiotensin II antagonists,[7] mitogen-activated protein (MAP) kinase,[8] and mitotic kinesin KSP inhibitors.[9] (α-Aminoacyl)amino-substituted heterocycles are useful synthetic intermediates (Figure 1) for endomorphin-2 (EM-2) analogues (**1**),[10] bacterial RND efflux pump inhibitors (EPIs) such as MC-04,124 (**2**)[11] and MC-02,595 (**3**),[12] γ-secretase inhibitor LY411575 (**4**),[13] and inhibitors of tumor necrosis factor-α converting enzyme (TACE) GW 3333 (**5**).[14]

N-Acylbenzotriazoles[15] have been employed for (i) N-acylation[16] in the preparation of primary, secondary, tertiary,[17] and Weinreb amides;[18] (ii) C-acylation for the preparation of β-ketosulfones[19] primary and secondary α-cyanonitriles,[20] α-nitroketones,[21] ketones,[22] and α-ketoazines;[23] and (iii) O-acylation of aldehydes[24] and of steroids[25] to give esters.

N-(Boc-aminoacyl)benzotriazoles and chiral amines give *N*-(Boc-α-amino)amides with no detectable racemization.[26] Numerous N-(protected-α-aminoacyl)benzotriazoles couple with unprotected amino acids in mixed organic/aqueous solution with complete

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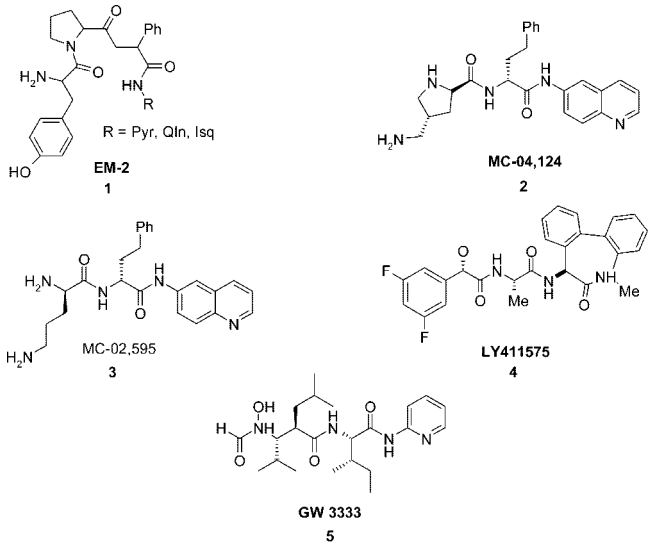

FIGURE 1. Biologically active (α-aminoacyl)amino-substituted heterocycles.

preservation of the original chirality.[27] In continuation of this research, we now report the synthesis of N-substituted amides **3a**−**d**, **3a′***−**c′**, **9a**,**b**, **9a′**, **11a**,**b**, **13a**−**g**, **13d′** and N-protected dipeptidoyl amides **7a**,**b** by treatment of the corresponding N-(protected-aminoacyl)benzotriazoles **1a**−**e**,**g**,**i**,**j**, **1a′**−**c′**, *N*-acylbenzotriazoles **1f**,**h** or N-(protected-peptidoyl)benzotriazoles **6a**,**b** with heterocyclic amines under microwave irradiation.

Result and Discussions

I. Preparation of Acylaminothiazoles, -benzothiazoles, -benzimidazoles, and -thiadiazoles. The starting N-(protected-aminoacyl)benzotriazoles **1a**−**d**, **1a′**, **1b′**, **1c′** were prepared from N-protected amino acids following our published one-step procedure.[28,29]

Treatment of 2-aminothiazole (**2a**), 2-amino-6-methoxybenzothiazole (**2b**), *N*-benzyl-2-aminobenzimidazole (**2c**), and 5-amino-3-methoxy-1,2,4-thiadiazole (**2d**) and N-(protected-α-aminoacyl)benzotriazoles **1a**−**d**, **1a′**, **1b′**, **1c′** under microwave irradiation at 70 °C for 30 min (150 min for **2d** with **1d**) gave the N-substituted amides **3a**−**d**, **3a′**, **3b′**, and **3c′** in 50−98% yields (Scheme 1 and Table 1).

The enantiopurity of compounds **3a**−**c** was confirmed by HPLC analysis. As expected, HPLC analysis of enantiopure **3a**−**c** gave a single peak for each compound. In contrast, two peaks were observed for the corresponding racemic N-substituted heterocycles **3a′**, **3b′**, and **3c′** (Table 1).

As a further application of this synthetic approach, Cbz-L-Met-L-Trp-OH (**5a**) (prepared as reported[27b] by coupling of Cbz-L-Met-Bt (**1e**) with unprotected L-Ala (**4a**) in aqueous acetonitrile) was treated with benzotriazole and $SOCl_2$ to provide N-(protected-dipeptidoyl)benzotriazole Cbz-L-Met-L-Trp-Bt (**6a**). Compound **6a** was reacted with **2a** under microwave irradiation (100 W) in DMF at 70 °C for 30 min to give dipeptidoyl amide **7a** in 60% yield (Scheme 2). Dipeptidoyl amide **7b** was prepared by coupling of 6-methoxybenzothiazol-2-amine (**2b**) with Cbz-L-Phe-L-Ala-Bt (**6b**) as described above in 52% (Scheme 2).

Few literature reports describe the preparation of carboxamides of type **3**. Kraus et al.[30,31] investigated the coupling reaction between amino acids and weakly nucleophilic heteroaromatic amines including substituted 2-aminothiazole and substituted 2-aminobenzothiazole using four different coupling reagents such as (i) DCC/HOBt, (ii) EDC, (iii) HBTU, (iv) benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), and (v) phosphorus oxychloride $POCl_3$/pyridine. Use of the uronium coupling reagent HBTU failed. The best literature yields (41−93%) were achieved with the $POCl_3$ in pyridine. These authors conclude[30] "the N-acylation of weakly nucleophilic heterocyclic amines by protected amino

SCHEME 1

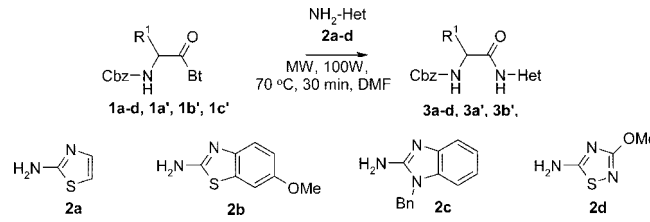

TABLE 1. Preparation of Acylaminothiazoles, -benzothiazoles, -benzimidazoles, and -thiadiazoles

Entry	Reactant	Product	Yield[a] (%)	Mp (°C)	$[\alpha]^{25}_D$	R.T. (min)
1	Cbz-*L*-Trp-Bt **1a**	Cbz-L-Trp- **3a**	81	94-96	-39.8	3.57
2	Cbz-*DL*-Trp-Bt **1a'**	Cbz-DL-Trp- **3a'**	66	103-105	racemic	3.52 and 5.36
3	Cbz -*L*-Ala-Bt **1b**	Cbz-L-Ala- **3b**	98	90-92	-49.8	3.41
4	Cbz -*DL*-Ala-Bt **1b'**	Cbz-DL-Ala- **3b'**	78	83-85	racemic	3.46 and 4.01
5	Cbz -*L*-Val-Bt **1c**	Cbz-L-Val- **3c**	98	70-72	-44.6	3.39
6	Cbz -*DL*-Val-Bt **1c'**	Cbz-DL-Val- **3c'**	82	131-133	racemic	2.97 and 3.56
7	Cbz-*L*-Phe-Bt **1d**	Cbz-L-Phe- **3d**	50 (27)[b]	150-152	-63.9	

[a] Isolated yield. [b] From ref 32.

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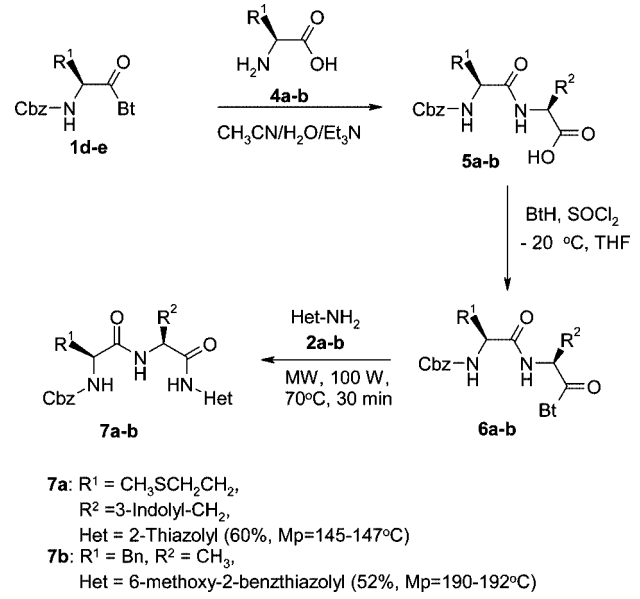
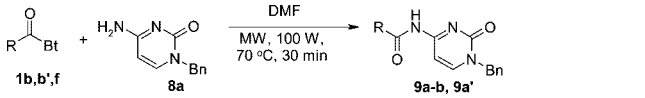
SCHEME 2



7a: $R^1 = CH_3SCH_2CH_2$, R^2 =3-Indolyl-CH_2, Het = 2-Thiazolyl (60%, Mp=145-147°C)
7b: R^1 = Bn, $R^2 = CH_3$, Het = 6-methoxy-2-benzthiazolyl (52%, Mp=190-192°C)

SCHEME 3



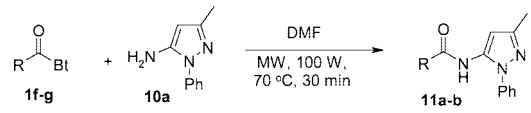
9a: R = Cbz-NHCHCH$_3$ (97%, Mp = 198-200 °C)
9a': R = Cbz-*DL*-NHCHCH$_3$ (76%, Mp = 194-196 °C)
9b: R = 4Cl-Ph (98%, Mp = 253-255 °C)

acids is not a straight-forward reaction which could be achieved under any standard coupling conditions". Other literature methods utilizing DCC/HOBt[32] or EDC[14] as coupling reagents reported yields of 27−36% and reaction times of 4−16 h.

II. Preparation of (Acylamino)pyrimidones. Procedures similar to those of Section I above coupled Cbz-L-Ala-Bt **1b**, Cbz-DL-Ala-Bt **1b′**, and 4-ClPhCOBt **1f**, with 4-amino-1-benzylpyrimidin-2-one (**8a**) under microwave irradiation to give novel **9a**,**b** and **9a′** in 76−98% yields (Scheme 3). The structures of compounds **9a**,**b** and **9a′** were supported by spectroscopic data together with microanalyses. The ^{13}C NMR and ^1H NMR spectra of N-substituted amides **9a**,**b** and **9a′** showed characteristic signals in the regions of 165.9−175.2 and 10.94−11.31 ppm which were assigned to the *N*-heteroaryl amide carbonyl carbon and the proton of the NH, respectively.

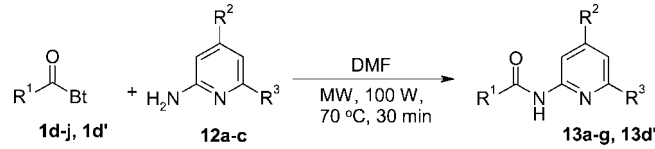
Previous preparations of N-substituted aminopyrimidones reported yields of 19−79% and reaction times of 17−40 h using carbodiimide-based reagents such as DCC,[33] 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDAC),[34] or (1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI)[35] in the presence of HOBt. Kenner et al.[36] acylated 3-methylcytosine with benzoyl chloride in pyridine at 100 °C (1.5 h) in 65% yield.

SCHEME 4



11a: R = 4Cl-Ph (75%, Mp = 151-153°C) (no lit. yield stated)[37a]
11b: R = Cbz-NHCH$_2$ (40%, Mp = 152-153°C) (lit. Yield 72%)[4]

SCHEME 5



12a: R^2=R^3=H
12b: R^2=R^3=CH_3
12c: R^2=CH_3, R^3=H

For structural designation of **1d-j, 1d'** and **13a-g, 13d'** see Table 2

III. Acylation of Aminopyrazoles. N-Substituted pyrazoles were prepared in yields of 23−89% and reaction times of 5−10 h from activated aromatic acids and N-protected amino acids via isolated intermediates utilizing acyl chlorides[37] or N-protected aminoacyl chlorides[4] (not easily storable and sensitive to degradation and racemization.[38] Literature couplings without isolation of intermediates include activation by (HCTU)/(HATU),[39] EDC/HOBt,[39] or phosponate anhydrides (T3P)[39] in yields ranging of up to 42% in reaction times up to 16 h.

We successfully coupled 4-ClPhCOBt **1f** and Cbz-Gly-Bt **1g** with 5-amino-3-methyl-1-phenylpyrazole (**10a**) in DMF under microwave irradiation (100 W, 70 °C) during 30 min (Scheme 4) to obtain **11a**,**b** (40 and 75%, respectively). Our *N*-(aminoacyl)benzotriazoles are stable, easy to handle reagents and can be stored at 20 °C for months.

IV. Preparation of (Acylamino)pyridines. Microwave irradiation of **1f** and 2-aminopyridine (**12a**) at 70 °C for 30 min gave *N*-(4-chloropyridin-2-yl)benzamide (**13a**) in 94% yield (heating **1f** and **12a** in DMF at 100 °C for 6 h gave **13a** in 75%). The microwave conditions were applied to the reactions of *N*-acylbenzotriazoles **1d**,**e**,**g**−**j** and **1d′** with 2-aminopyridine (**12a**), 2-amino-4-methylpyridine (**12b**), and 2-amino-4,6-dimethylpyridine (**12c**), thus providing 55−98% of the corresponding heteroaryl carboxamides **13b**−**g** and **13d′** (Scheme 5 and Table 2).

The absence of racemization was confirmed for **13d** by HPLC analysis, which showed a single peak at 3.66 min, while two peaks of equal intensity at retention times 3.63 and 5.74 min were observed for the racemic Cbz-*DL*-Phe-NHPy-2 (**13d′**).

This methodology is advantageous compared to several recent approaches to (α-aminoacyl)amino-substituted pyridines in yields from unreported to 77% and reaction times from unreported to 54 h, using (i) *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole HOBt,[40] (ii) 1-ethyl-3-(3-

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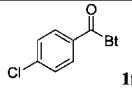
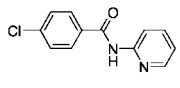
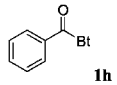
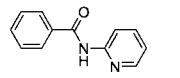
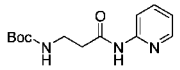
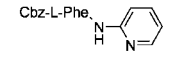
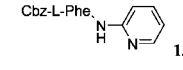
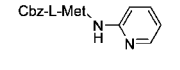
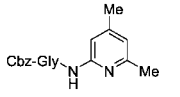
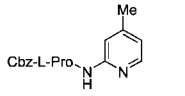
TABLE 2. Preparation of (Acylamino)pyridines from *N*-Acyl and *N*-(Aminoacyl)benzotriazoles

Entry	Reactant	Product	Yield[a] (%)	Mp (°C)	$[\alpha]^{25}_D$
1	 **1f**	 **13a**	94 (30[d])	130-131	Non chiral
2	 **1h**	 **13b**	82 (66[e])	76-78	Non chiral
3	Boc-β-Ala-Bt **1i**	 **13c**	82	122-123	Non chiral
4	Cbz-*L*-Phe-Bt[b] **1d**	 **13d**	55 (60[f])	129-131	-18.3
5	Cbz -*DL*-Phe-Bt[c] **1d'**	 **13d'**	70	51-53	Racemic
6	Cbz -*L*-Met-Bt **1e**	 **13e**	68	oil	-24.0
7	Cbz -Gly-Bt **1g**	 **13f**	76 (77[g])	108-110	Non chiral
8	Cbz -*L*-Pro-Bt **1j**	 **13g**[h]	98 (N/A[h])	125-126	-92.5

[a] Isolated yield. [b] HPLC for **13d**: 3.66 min. [c] HPLC for **13d′**: 3.63 and 5.74 min. [d] From ref 44a. [e] From ref 44b. [f] From ref 10. [g] From ref 42. [h] No yield stated from ref 43.

dimethylaminopropyl)carbodiimide (EDC) and HOBt,[41] (iii) 1,1′-carbonyldiimidazole (CDI),[42] (iv) ethyl chloroformate,[43] (v) phosphorus trichloride (PCl_3),[10] and (vi) acid chloride method.[44]

Our approach provides known compounds **13a**,**b**,**d**,**f**,**g** in better or comparable yields to those reported in the literature (Table 2) and afforded previously unreported N-substituted amides **13c**, **13d′**, **13e**, and **7b** in isolated yields of 52−98%. The method quoted in ref 42, that is, activating the corresponding N-protected amino acids with CDI followed by treatment with 2-amino-4,6-dimethylpyridine is advantageous for N-substituted amides from 2-amino-4,6-dimethylpyridine, and we prepared **13f** (68%, cf. 77%) by this procedure. However, similar treatment of 2-amino-4-methylpyridine failed to yield compound **13g**, which was prepared in high yield (98%) by our alternative methodology, demonstrating the wide scope of the benzotriazole approach.

Conclusions

In summary, a general and convenient route has been developed for the preparation of N-substituted amides derived from diverse heterocyclic amines and carboxylic acids under simple reaction conditions.

Experimental Section

General Procedure for the Preparation of N-Substituted Amides 3a−d, 3a′−c′, 9a,b, 9a′, 11a,b, 13a−g, 13d′, and Dipeptide Amides 7a,b. A dried heavy-walled Pyrex tube containing a small stir bar was charged with benzotriazole adduct (0.25 mmol) and aminoheterocycle **1** (0.25 mmol) dissolved in DMF (1 mL). The reaction mixture was exposed to microwave irradiation (100 W) for 30 min at a temperature of 70 °C. The mixture was allowed to cool through an inbuilt system until the temperature had fallen below 30 °C (ca. 10 min). The reaction mixture was quenched with water and extracted with EtOAc (3 × 25 mL). The extracts were washed with (10%) Na_2CO_3 (3 × 50 mL) and water (3 × 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was subjected to silica gel column using EtOAc/hexane (1:1) as an eluent to give the corresponding N-substituted amide.

Benzyl *N*-[(1*S*)-1-(1*H*-indol-3-ylmethyl)-2-oxo-2-(1,3-thiazol-2-ylamino)ethyl]carbamate (3a): White microcrystals (81%), mp 94−96 °C, $[\alpha]^{25}_D = -39.8$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84−4.86 (m, 1H), 3.21−3.35 (m, 2H), 5.06 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.90 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 2H), 6.95 (t, *J* = 7.1 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.19−7.32 (m, 7H), 7.45 (d, *J* = 7.6 Hz, 1H), 8.00 (s, 1H), 11.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 55.6, 67.2, 109.5, 111.2, 113.7, 118.4, 119.7, 122.3, 123.0, 127.1, 128.0, 128.2, 128.5, 135.9, 136.9, 156.1, 158.3, 170.0. Anal. Calcd for $C_{22}H_{20}N_4O_3S$: C, 62.84; H, 4.79; N, 13.32. Found: C, 62.65; H, 4.74; N, 13.14.

Benzyl {(*S*)-1-[(*S*)-1-(6-Methoxybenzothiazol-2-ylcarbamoyl)-ethylcarbamoyl]-2-phenylethyl}carbamate (7b): White prisms (52%), mp 190−192 °C, $[\alpha]^{25}_D = -68.8$ (*c* 2.3, $CHCl_3$); ^{1}H NMR δ 12.05 (br s, 1H), 8.15 (d, *J* = 8.9 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.27−7.23 (m, 6H), 7.03−7.00 (m, 5H), 6.86 (dd, *J* = 8.9, 2.3 Hz, 1H), 5.42−5.35 (m, 2H), 5.12 (d, *J* = 12.6 Hz, 1H), 5.03 (dd, *J* = 16.2, 8.4 Hz, 1H), 3.85 (s, 3H), 3.13−2.98 (m, 2H), 1.49 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR δ 172.8, 170.7, 156.8, 156.7, 156.0, 142.5, 136.6, 136.0, 133.2, 129.3, 128.3, 127.8, 127.7, 126.9, 121.9, 115.1, 103.9, 103.3, 66.9, 56.5, 55.7, 48.7, 39.9, 19.2. Anal. Calcd for $C_{28}H_{28}N_4O_5S$: C, 63.14; H, 5.30; N, 10.52. Found: C, 62.77; H, 5.34; N, 10.34.

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Supporting Information Available: Compound characterization data for **3b−d**, **3a′−c′**, **7a**, **9a**,**b**, **9a′**, **11a**,**b**, **13a−g**, **13d′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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