Synthesis of an Amide Library Based on the 6,8-Dioxa-3-azabicyclo[3.2.1]octane Scaffold by Direct Aminolysis of Methyl

Parallel Synthesis of an Amide Library Based on the 6,8-Dioxa-3-azabicyclo[3.2.1]octane Scaffold by Direct Aminolysis of Methyl Esters

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An efficient synthesis of unsubstituted and substituted amides based on the 6,8-dioxa-3-azabicyclo[3.2.1]-octane scaffold is described. The reaction, carried out at 60 °C in the absence of solvent, is characterized by its mildness and ease of workup. A library of amides, was synthesized by combination of methyl esters **1**−**6** with various amines. In addition, the microwave-assisted automated synthesis of the library was compared with the above conventional parallel synthesis. Microwave synthesis significantly decreased the reaction time from hours to minutes.

Introduction

The development of novel scaffolds is one of key tools for the generation of molecular diversity in combinatorial chemistry.[1,2] Recent communications from our group have described the synthesis of new 6,8-dioxa-3-azabicyclo[3.2.1]-octane-based scaffolds, named BTAa (bicycles from tartaric acid and amino acid),[3] from readily accessible tartaric acid derivatives and amino aldehydes or amino ketones.[4,5,6,7] These scaffolds are easy to prepare: they possess modulable stererochemistry and low molecular weight, and they present an unprecedented and fairly rigid core. Most important is their versatility for the generation of chemical diversity from up to six sites (Figure 1).[5]

BTAa's have been used for multiple applications[8] such as ordered homoligomers[9] and dipeptide isosters.[4] To enlarge their potential applications, we have decided to generate molecular diversity by choosing scaffolds substituted in positions C-2, N-3, C-4, and C-5 and to use the carboxylic function on C-7 for further elongation or functionalization. In this context, we planned to diversify the scaffolds through a new amide bond.

Because of the peculiar characteristics,[10,11,12] ubiquitous nature, biological, pharmacological,[13] and crop protection

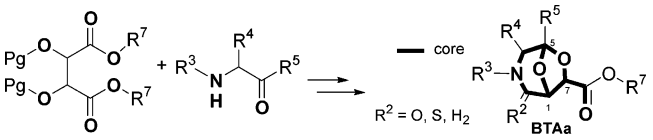

Figure 1.

properties[14] of molecules containing amide bonds, the amide bond[15] has stimulated a great deal of attention.[16,17,18] In addition, secondary amides are precursors of tertiary amines, which are an extremely important class of compounds from the drug discovery perspective.[19]

In this paper, we wish to report the results on the one-step parallel preparation of a series of more than one hundred BTAa amides, by direct aminolysis of the corresponding methyl esters.

Results and Discussion

Preliminary Assays. The direct transformation of esters to amides is an important synthetic tool. However, the application of this transformation to the parallel synthesis of amides is limited for a number of reasons. The aminolysis of esters, unless the esters have good leaving groups,[20] in general occurs under harsh conditions requiring high temperature and extended reaction times,[21,22] the use of high pressure,[23,24] or the use of strong alkali metal catalysts. These conditions[25−35] are not suitable for the synthesis of chemical libraries which require high-performing processes and final products in high purity.

Recently, our studies on BTAa's have shown the high reactivity of the methyl ester group of these scaffolds.[36] Thus, a methyl amide could be obtained easily by dropwise addition

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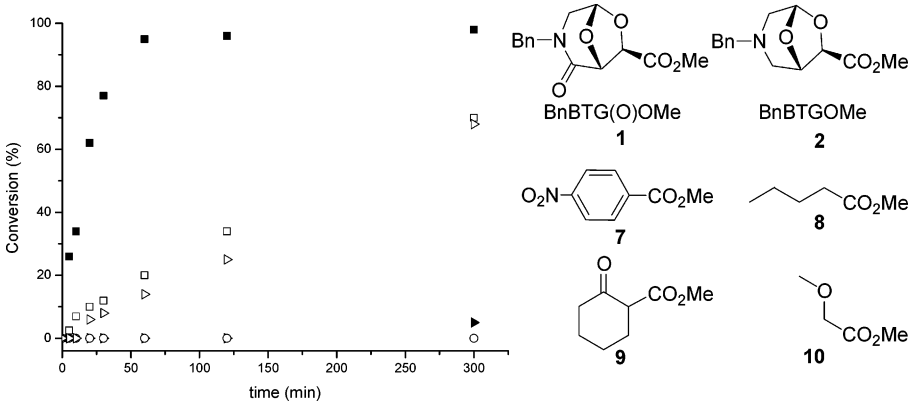


Figure 2. Time course of the ester aminolysis of BnBTG(O)Me **1** (filled square) and BTGOMe **2** (open square) compared with methyl pentanoate **8** (open circle), methyl *p*-nitrobenzoate **7** (filled triangle), and 2-methoxyacetic acid methyl ester **10** (open triangle) by piperidine, performed solvent free at 40 °C. The conversion of the reaction was monitored by ^{1}H NMR.

of an ethanol solution of methylamine to methyl ester **1**.[37] This result opened the possibility to devise a new methodology for the direct conversion of BTAa methyl ester into a variety of amide derivatives.

Initially, we assessed the reactivity of BTAa methyl esters by comparison with a series of methyl ester species (Figure 2). Direct solvent-free aminolysis experiments were set by heating of the methyl esters in the presence of excess of piperidine at 40 °C. The aminolysis of methyl pentanoate **8** and methyl cyclohexanone-2-carboxylate **9** in those conditions did not lead to any formation of the corresponding piperidine amide, even in case of prolonged reaction time (24 h). In case of methyl *p*-nitrobenzoate **7**,[38] the process was extremely slow. On the contrary, BTAa scaffolds **1** and **2** and their structurally similar α-methoxy methyl ester **10** showed high or complete conversion to the corresponding amide after few hours. These results showed the importance of the structure of the scaffold in the enhanced reactivity of the ester.

Because of this encouraging finding, scaffolds **1** and **2** were reacted against a series of amines with different nucleophilicities to understand the utility and limitation of the method.

Synthesis of the Library. The synthesis of the BTAa scaffold-based amide library was achieved by the reaction of a variety of substituted amines (Figure 3) with BTA methyl esters **1**−**6** at 60 °C over 16 h, in absence of solvent (Scheme 1). The conditions were set to pursue reaction completion for each amine-scaffold combination. The choice for the amine unit was based on its commercial availability, structural diversity, and melting point, which should be lower than the reaction temperature to give a homogeneous reaction mixture. A simple workup procedure was tailored on the basis of the nature of the amine. When volatile amines (boiling point less than 100 °C) were used, the crude reaction mixtures were concentrated under a gentle stream of nitrogen. For less volatile amines, when the scaffold was a lactam (R^2 = O), the reaction mixtures were diluted with MeOH and rapidly filtered through a short column of Amberlyst 15 H^+ ion-exchange resin to remove the excess amine. Otherwise, when the scaffold was an amine ($R^2 = H_2$), the reaction mixtures were filtered through a short pad of silica gel, eluted

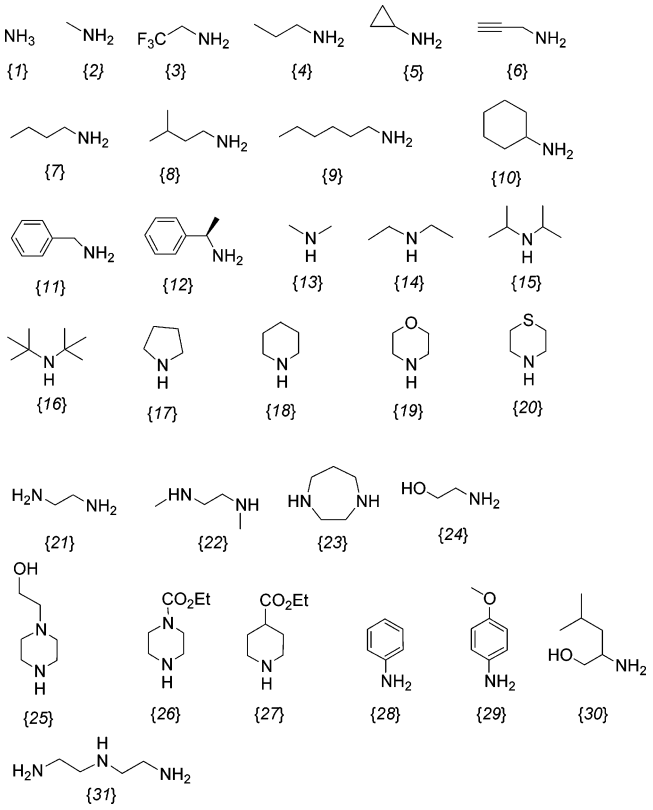


Figure 3. Set of amines {*1*−*31*} for the library.

with ethyl acetate; in this way, the amine reagents were rapidly removed from the final amide products. All the amides were obtained with excellent purities (based on HPLC or NMR analysis).

Secondary amides were synthesized according to Scheme 1 and analyzed by HPLC or NMR and MS. (Table 1). The reactions were carried out in parallel with different primary amines either linear or alpha-branched (cyclopropylamine, cyclohexylamine, and methylbenzylamine) or alpha-unsaturated (propargylamine). The purities of the resulting amides ranged from 67 to 99%, and the conversion was quantitative except in the case of trifluorethylamine **1**−**6**{*3*}, which showed low conversion and consequently low purity of the final products. The reasons were attributed to the low boiling

Scheme 1

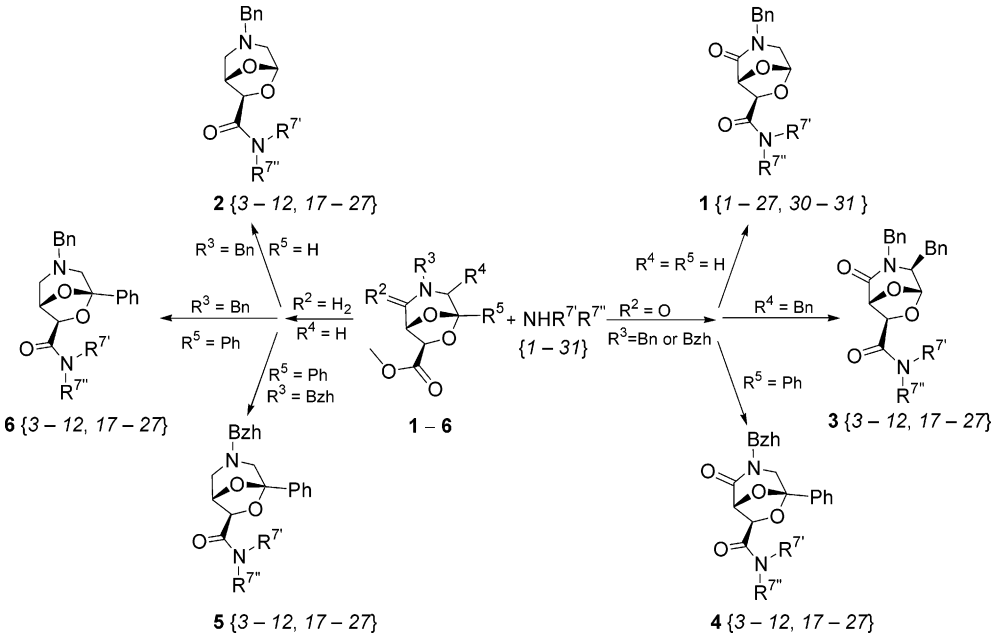


Table 1. Structure and Analytical Data for Secondary Amides Defined in the Library (Scheme 1)[a,d]

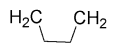
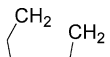
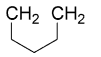
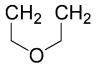
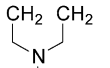
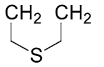
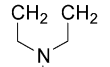
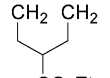
	R^2	R^3	R^4	R^5	$R^{7'}$	R_t (min)	purity[b] (conv)[c]		R^2	R^3	R^4	R^5	$R^{7'}$	R_t (min)	purity[b] (conv)[c]
1{*1*}	O	Bn	H	H	H	5.5	99	**3**{*12*}	O	Bn	Ph	H	MBn	15.5	70
1{*2*}	O	Bn	H	H	Me	6.5	97	**4**{*3*}	O	Bzh	H	Ph	TfE	16.0	69 (67)
1{*3*}	O	Bn	H	H	TfE	8.4	42 (36)	**4**{*4*}	O	Bzh	H	Ph	*n*Pr	16.2	91
1{*4*}	O	Bn	H	H	*n*Pr	9.3	99	**4**{*5*}	O	Bzh	H	Ph	Cyp	15.8	99
1{*5*}	O	Bn	H	H	Cyp	8.1	96	**4**{*6*}	O	Bzh	H	Ph	Prg	15.3	67
1{*6*}	O	Bn	H	H	Prg	5.8	99	**4**{*7*}	O	Bzh	H	Ph	*n*Bu	16.8	96
1{*7*}	O	Bn	H	H	*n*Bu	10.8	99	**4**{*8*}	O	Bzh	H	Ph	*i*Am	17.6	99
1{*8*}	O	Bn	H	H	*i*Am	11.9	92	**4**{*9*}	O	Bzh	H	Ph	Hex	18.2	99
1{*9*}	O	Bn	H	H	Hex	13.2	93	**4**{*10*}	O	Bzh	H	Ph	Cyh	17.9	82
1{*10*}	O	Bn	H	H	Cyh	12.1	95	**4**{*11*}	O	Bzh	H	Ph	Bn	6.5	49 (80)
1{*11*}	O	Bn	H	H	Bn	11.4	99	**4**{*12*}	O	Bzh	H	Ph	MBn	11.2	99
1{*12*}	O	Bn	H	H	MBn	12.0	99	**5**{*3*}	H	Bzh	H	Ph	TfE	–	– (40)
2{*3*}	H	Bn	H	H	TfE	5.7	23 (21)	**5**{*4*}	H	Bzh	H	Ph	*n*Pr	–	– (99)
2{*4*}	H	Bn	H	H	*n*Pr	5.6	76	**5**{*5*}	H	Bzh	H	Ph	Cyp	–	– (99)
2{*5*}	H	Bn	H	H	Cyp	5.6	88	**5**{*6*}	H	Bzh	H	Ph	Prg	–	– (50)
2{*6*}	H	Bn	H	H	Prg	5.4	99	**5**{*7*}	H	Bzh	H	Ph	*n*Bu	–	– (99)
2{*7*}	H	Bn	H	H	*n*Bu	7.6	89	**5**{*8*}	H	Bzh	H	Ph	*i*Am	–	– (99)
2{*8*}	H	Bn	H	H	*i*Am	8.2	99	**5**{*9*}	H	Bzh	H	Ph	Hex	–	– (99)
2{*9*}	H	Bn	H	H	Hex	5.7	73	**5**{*10*}	H	Bzh	H	Ph	Cyh	–	– (99)
2{*10*}	H	Bn	H	H	Cyh	5.6	82	**5**{*11*}	H	Bzh	H	Ph	Bn	–	– (80)
2{*11*}	H	Bn	H	H	Bn	6.4	90	**5**{*12*}	H	Bzh	H	Ph	MBn	–	– (99)
2{*12*}	H	Bn	H	H	MBn	7.4	68 (95)	**6**{*3*}	H	Bn	H	Ph	TfE	–	– (46)
3{*3*}	O	Bn	Ph	H	TfE	13.9	65 (52)	**6**{*4*}	H	Bn	H	Ph	*n*Pr	–	– (99)
3{*4*}	O	Bn	Ph	H	*n*Pr	14.4	86	**6**{*5*}	H	Bn	H	Ph	Cyp	–	– (54)
3{*5*}	O	Bn	Ph	H	Cyp	13.7	90	**6**{*6*}	H	Bn	H	Ph	Prg	–	– (99)
3{*6*}	O	Bn	Ph	H	Prg	13.4	83	**6**{*7*}	H	Bn	H	Ph	*n*Bu	–	– (99)
3{*7*}	O	Bn	Ph	H	*n*Bu	14.8	86	**6**{*8*}	H	Bn	H	Ph	*i*Am	–	– (99)
3{*8*}	O	Bn	Ph	H	*i*Am	11.2	90	**6**{*9*}	H	Bn	H	Ph	Hex	–	– (99)
3{*9*}	O	Bn	Ph	H	Hex	16.5	84	**6**{*10*}	H	Bn	H	Ph	Cyh	–	– (99)
3{*10*}	O	Bn	Ph	H	Cyh	15.9	67	**6**{*11*}	H	Bn	H	Ph	Bn	–	– (80)
3{*11*}	O	Bn	Ph	H	Bn	15.0	83	**6**{*12*}	H	Bn	H	Ph	MBn	–	– (99)

[a] Abbreviations: *i*Am, isoamyl; Bn, benzyl; *n*Bu, butyl; Bzh, benzhydryl; Cyp, cyclopentyl; Cyh, cyclohexyl; Hex, hexyl; MBn, (*S*)α-methylbenzyl; *n*Pr, propyl; Prg, propargyl; TFE, trifluoroethyl. For structural representations of all products, see the Supporting Information. [b] HPLC purities are given as area percent (UV) at 220 nm. For some C-5-substituted amides, HPLC data are not reliable and are not reported. See ref 6 for additional details. [c] Determined by ^{1}H NMR. Quantitative if not indicated. [d] Obtained by thermal heating.

point (37−38 °C) of {*3*}, likely to evaporate from reaction mixture under the conditions set for the aminolysis, and to the strong electron-withdrawing group effect of the trifluoroethyl group, which decreased the nucleophilicity[39] of {*3*}. Nevertheless, performance of the experiment at lower temperature resulted in no conversion.

Similar results were obtained with either acyclic or alicyclic secondary amines (Table 2), except when hindered

Table 2. Structure and Analytical Data for Tertiary Amides and Amides Derived from Multifunctionalised Amines Defined in the Library (Scheme 1)[a,d]

Compd	R^2	R^3	R^4	R^5	$R^{7'}$	$R^{7''}$	R_t (min)	Purity[b] (Conv)[c]	Compd	R^2	R^3	R^4	R^5	$R^{7'}$	$R^{7''}$	R_t (min)	Purity[b] (Conv)[c]
1{13}	O	Bn	H	H	Me	Me	7.3	94	**1**{22}	O	Bn	H	H		Me	6.6	78
1{14}	O	Bn	H	H	Et	Et	5.7	34(25)	**2**{22}	H	Bn	H	H		Me	6.8	77
1{15}	O	Bn	H	H	*i*Pr	*i*Pr	0	—(0)	**3**{22}	O	Bn	Bn	H		Me	12.0	56
1{16}	O	Bn	H	H	*t*Bu	*t*Bu	0	—(0)	**4**{22}	O	Bzh	H	Ph		Me	14.7	47
1{17}	O	Bn	H	H			9.0	99	**5**{22}	H	Bzh	H	Ph		Me	—	—(80)
2{17}	H	Bn	H	H			6.8	99	**6**{22}	H	Bn	H	Ph		Me	—	—(99)
3{17}	O	Bn	Bn	H			9.3	99	**1**{23}	O	Bn	H	H				73
4{17}	O	Bzh	H	Ph			16.2	91	**2**{23}	H	Bn	H	H				99
5{17}	H	Bzh	H	Ph			—	—(99)	**3**{23}	O	Bn	Bn	H			11.9	82
6{17}	H	Bn	H	Ph			—	—(99)	**4**{23}	O	Bzh	H	Ph			9.6	81
1{18}	O	Bn	H	H			10.8	96	**5**{23}	H	Bzh	H	Ph			—	99
2{18}	H	Bn	H	H			8.0	99	**6**{23}	H	Bn	H	Ph			—	99
3{18}	O	Bn	Bn	H			13.2	86	**1**{24}	O	Bn	H	H		H	16.5	51
4{18}	O	Bzh	H	Ph			17.0	85	**2**{24}	H	Bn	H	H		H	6.1	99
5{18}	H	Bzh	H	Ph			—	—(78)	**3**{24}	O	Bn	Bn	H		H	7.0	67
6{18}	H	Bn	H	Ph			—	—(99)	**4**{24}	O	Bzh	H	Ph		H	8.7	99
1{19}	O	Bn	H	H			7.4	99	**5**{24}	H	Bzh	H	Ph		H	—	—(99)
2{19}	H	Bn	H	H			3.9	83	**6**{24}	H	Bn	H	Ph		H	—	—(99)
3{19}	O	Bn	Bn	H			13.1	70	**1**{25}	O	Bn	H	H			6.02	99
4{19}	O	Bzh	H	Ph			15.3	99	**2**{25}	H	Bn	H	H			4.8	99
5{19}	H	Bzh	H	Ph			—	—(65)	**3**{25}	O	Bn	Bn	H			11.5	93
6{19}	H	Bn	H	Ph			—	—(99)	**4**{25}	O	Bzh	H	Ph			13.9	99(50)
1{20}	O	Bn	H	H			10.0	90	**5**{25}	H	Bzh	H	Ph			—	99(70)
2{20}	H	Bn	H	H			7.3	73	**6**{25}	H	Bn	H	Ph			—	99(65)
3{20}	O	Bn	Bn	H			16.4	72	**1**{26}	O	Bn	H	H			16.2	63
4{20}	O	Bzh	H	Ph			16.3	99	**2**{26}	H	Bn	H	H			8.5	99
5{20}	H	Bzh	H	Ph			—	—(82)	**3**{26}	O	Bn	Bn	H			9.5	99
6{20}	H	Bn	H	Ph			—	—(80)	**4**{26}	O	Bzh	H	Ph			14.4	60
1{21}	O	Bn	H	H		H	5.4	99	**5**{26}	H	Bzh	H	Ph			—	—(99)
2{21}	H	Bn	H	H		H	3.8	63	**6**{26}	H	Bn	H	Ph			—	—(99)
3{21}	O	Bn	Bn	H		H	11.3	99	**1**{27}	O	Bn	H	H			4.7	30
4{21}	O	Bzh	H	Ph		H	13.4	99	**2**{27}	H	Bn	H	H			7.9	99
5{21}	H	Bzh	H	Ph		H	—	—(99)	**3**{27}	O	Bn	Bn	H			9.7	99
6{21}	H	Bn	H	Ph		H	—	—(99)	**4**{27}	O	Bzh	H	Ph			10.9	75
1{30}	O	Bn	H	H	Leucinol	H	10.0	79	**5**{27}	H	Bzh	H	Ph			—	—(83)
									6{27}	H	Bn	H	Ph			—	—(74)

[a] For structural representations of all products, see the Supporting Information. [b] HPLC purities are given as area percent (UV) at 220 nm. For some C-5-substituted amides, HPLC data are not reliable and are not reported. See ref 6 for additional details. [c] Determined by ^{1}H NMR. Quantitative if not indicated. [d] Obtained by thermal heating.

secondary amines {*15, 16*} and aromatic amines {*28, 29*} were used. For aromatic amines, no reaction was achieved when the reaction was conducted at higher temperature (100−150 °C). The aminolysis with diamine {*21*−*23*} gave only the corresponding monoacetylated amide.

The complete analysis of amides contained in Tables 1 and 2 shows that 82% of the compounds had purities higher than 80% and the average purity was 87%. Analysis of the crude products by NMR indicated that the only contamination of the amide material was from the presence of the unreacted methyl ester.

As an alternative to this method, based on classical synthetic chemistry, microwave technology was sought as an important way to improve the direct aminolysis of BTAa methyl ester scaffolds. Over the past two decades, microwave-assisted organic synthesis (MAOS) has had a significant impact on synthetic chemistry[40] proving to be beneficial in a vast series of reactions including the aminolysis of ester.[41,42]

For comparison purposes and with the aim of simplification of the procedures, not only to reduce the reaction times but also to increase the conversion in the case of unreactive amines, we have therefore reinvestigated on a selected number of amines and scaffolds the runs under microwave irradiation using sealed-vessel technology.

The conditions we applied were different than the one used for conventional heating:[43] a solvent was added (methanol) and the temperature was higher (150−165 °C). Among different solvents, methanol was chosen because of its polarity (suitable for microwave use) and the absence of a potential transesterification reaction that may occur under these reaction conditions when other alcohols are used. In addition, methanol is easily removed from the reaction mixture.

Microwave (MW) heating using superheated methanol as a solvent led to the complete conversion of methyl esters to the corresponding amides, even in case of incomplete reaction using thermal heating (Table 3, entries 5, 9, 11, 19, and 23). The sterically encumbered diisopropyl {*15*} and

Table 3. Comparison of Thermal (Neat, 60 °C) versus Microwave Heating (Methanol, 160 °C) for the Aminolysis of **1**−**6**

			conversion (%)[a]	
entry	scaffold	amine	Δ	MW
1	**1**	*4*	100	100
2	**4**	*4*	100	100
3	**4**	*6*	100	100
4	**2**	*8*	100	100
5	**5**	*6*	50	100
6	**4**	*8*	100	100
7	**5**	*8*	100	100
8	**2**	*11*	100	100
9	**5**	*11*	80	100
10	**1**	*12*	100	100
11	**2**	*12*	95	100
12	**1**	*15*	0	0
13	**1**	*16*	0	0
14	**4**	*17*	100	100
15	**6**	*17*	100	100
16	**3**	*17*	100	100
17	**2**	*18*	100	100
18	**4**	*18*	100	100
19	**5**	*18*	78	100
20	**6**	*18*	100	100
21	**2**	*19*	100	100
22	**4**	*19*	100	100
23	**5**	*19*	65	100
24	**6**	*19*	100	100

[a] Determined by[1] HNMR and based on methyl ester.

diterbutyl {*16*} amines did not react at all (Table 3, entries 12 and 13), as well as the poor nucleophilic aniline{*28*}. With MW heating, the reaction time was dramatically reduced and the aminolysis of methyl ester **1**−**6** was completed in minutes (15−20 min).

Conclusions

In summary, we have developed a solvent-free (neat) synthetic method for the parallel synthesis of a set of secondary and tertiary amides based on the 6,8-dioxa-3-azabicyclo[3.2.1]octane scaffolds. The method is mild and compatible with sensitive functional groups on either the methyl ester scaffold or the amine unit. The library resulted in low levels of impurities using simple work up and purification procedures.

The amides obtained have low molecular weight (lower than 500) and variable structure. The availability of a wide variety of primary and secondary amines, diamines, and functionalized amines allows the synthesis of a large and highly diverse small molecule library based on the BTAa scaffolds. With the application of MW heating, the amides were obtained in a shorter time compared to that of conventional heating (15−20 min vs a typical 16 h) and with improved process efficiency.

Experimental Section

General Remarks. All amines were purchased from commercial sources and were used without further purification. Ammonia and methylamine were used as solutions in water (33 and 40%, respectively). Scaffolds **1**−**6** were prepared following our reported procedure and scaled up when necessary. NMR spectra ($CDCl_3$ solution, unless otherwise stated) were recorded on Varian Gemini 200 and Varian Mercury 400 (^{1}H, 200, 400 MHz) spectrometers. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$, 7.24 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; DMSO-d_6, 40.45 ppm for ^{13}C). Coupling constants, J (in Hz), refer to $^3J_{HH}$. EI mass spectra were carried out at 30 eV ionizing voltage by direct introduction on a QMD 1000 Carlo Erba instrument. Analytical reversed HPLC experiments were carried out on a Beckman System Gold instrument equipped, using a 5 μm (250 × 4.6 mm) C18 Vydac column monitored at 220 nm. The flow rates were 1 mL min^{-1}. The elution buffer included 0.1% TFA in H_2O (eluant A) and 0.1% TFA in CH_3CN (eluant B), and a linear gradient (30% of B in A to 90% of B in 15 min) was used.

Thermal Experiments. Thermal parallel solution-phase reactions were performed using an homemade laboratory synthesizer containing eight microreaction units supported with temperature control, magnetic stirring, and nitrogen streaming.

Microwave Irradiation Experiments. Microwave reactions were conducted using the Emrys Synthetiser (Biotage AB, Uppsala, Sweden). The microwave instrument comprises a monomode microwave cavity that operates at a frequency of 2.45 GHz with continuous microwave irradiation power from 0 to 300 W. The reaction vials are glass-based, conical, 5 mL closed tubes, sealed with Teflon septa and aluminum crimp tops. The reaction temperatures were measured with a built-in IR sensor and refer to total irradiation times.

Evaluation of Methyl Ester Reactivity. The time courses of the ester aminolysis of BnBTG(O)OMe (**1**) and BnBTGOMe (**2**), compared with methyl ester **7**−**10** by piperidine, were solvent free (1:10 molar ratio). Methyl ester and amine were mixed in a sealed microreaction vessel and immersed in a temperature-controlled bath at 40 °C for a definite time. Duplicate runs were performed if necessary. The conversion of the reaction was monitored by 400 MHz ^{1}H NMR integrating the appearance of the 7-H proton of amide scaffolds **1**{*18*} and **2**{*18*} (5.12 and 5.0 ppm respectively), while simultaneously integrating the disappearance of 1-H protons (4.74 and 4.82 ppm respectively) of ester scaffolds **1** and **2**, respectively. For methyl ester **10**, the disappearance of its C*H*$_2$CO protons (3.96 ppm) was integrated, while the appearance of the C*H*$_2$CO protons (4.05 ppm) of the corresponding 1-(methoxyacetyl)piperidine **11** was simultaneously integrated. Spectroscopic data for **11**. ^{1}H NMR (400 MHz): δ 4.05 (s, 2 H, C*H*$_2$CO), 3.51 (t, J = 5.6 Hz, 2 H, C*H*$_2$N), 3.38 (s, 3 H, C*H*$_3$), 3.35 (t, J = 5.6 Hz, 2 H, C*H*$_2$N), 1.64−1.56 (m, 2 H, Pip-H), 1.56−1.48 (m, 4 H, Pip-H). ^{13}C NMR: δ 167.0 (s, *C*═O), 71.7 (t, *C*H$_2$CO), 58.9 (q, *C*H$_3$), 45.9 (t, *C*H$_2$N), 42.8 (t, *C*H$_2$N), 26.4 (t, Pip-C), 25.5 (t, Pip-C), 24.4 (t, Pip-C). GC MS: *m*/*z* (%) 157 (M$^+$, 4), 127 (30), 112 (44), 69 (100). In case of benzoate methyl ester **7**, the aromatic protons and the disappearance of methyl ester protons were monitored.

General Procedure for Acylation of Volatile Amines. GP1. Methyl ester (0.014 mmol) and amine (0.14 mmol) were heated in a sealed microreaction vessel at 60 °C for 16

h. For the workup, the reaction mixture was treated under a stream of nitrogen to afford the final product mainly as a yellow oil.

Representative Analytical Data for Compounds Obtained with Procedure GP1 BnBTG(O)NHMe (1{*2*}). Yield: 3.9 mg, 100%. ^{1}H NMR: δ 7.39−7.15 (m, 5 H, Ph-*H*), 6.47 (bs, 1 H, N*H*), 5.80 (d, J = 2.2 Hz, 1 H, 5-H), 5.03 (s, 1 H, 7-H), 4.65 (s, 1 H, 1-H), 4.55 (s, 2 H, PhCH_2), 3.36 (dd, J = 2.2 and 12.1 Hz, 1 H, 4-H), 3.10 (d, J = 12.1 Hz, 1 H, 4-H), 2.85 (d, J = 4.8 Hz, 3 H, CH_3N). ^{13}C NMR: δ 168.9 (s, *C*═O), 165.8 (s, *C*═O), 135.4 (s, Ph−C), 128.9 (d, 2 C, Ph−C), 128.1 (d, 2 C, Ph−C), 127.9 (d, Ph−C), 99.9 (d, C-5), 79.4 (d, C-1), 77.5 (d, C-7), 50.9 (t, C-4), 48.3 (t, Ph*C*H_2), 26.0 (q, N*C*H_3). MS: *m*/*z* (%) 276 (M^+, 59), 218 ((M − CONHMe)$^+$, 14), 120 (79), 112 (61), 91 ((PhCH_2)$^+$, 100), 71 (90). Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276.29): C, 60.86; H, 5.84; N, 10.14. Found: C, 60.66; H, 5.58; N, 9.96.

BnBTG(O)Pip (1{*18*}). Yield: 4.7 mg, 100%. ^{1}H NMR: δ 7.17−7.37 (m, 5 H, Ph-*H*), 5.79 (d, J = 2.2 Hz, 1 H, 5-H), 5.12 (s, 1 H, 7-H), 4.89 (s, 1 H, 1-H), 4.68 (part A of AB system J = 13.9 Hz, 1 H, PhCH_2N), 4.44 (part B of AB system J = 13.9 Hz, 1 H, PhCH_2N), 3.66−3.28 (m, 5 H, 4-H, Pip-H), 3.08 (part B of AB system J = 12.1 Hz, 1 H, 4-H), 1.80−1.45 (m, 6 H, Pip-H). ^{13}C NMR: δ 166.6 (s, *C*═O), 165.0 (s, *C*═O), 135.4 (s, Ph−C), 128.8 (d, 2 C, Ph−C), 128.1 (d, 2 C, Ph−C), 127.8 (d, Ph−C), 99.6 (d, C-5), 77.9 (d, C-1), 76.6 (d, C-7), 51.2 (t, C-4), 48.4 (t, Ph*C*H_2), 46.4 (t, Pip-C), 43.3 (t, Pip-C), 26.3 (t, Pip-C), 25.4 (t, Pip-C), 24.5 (t, Pip-C). IR ($CHCl_3$): ν 1669 cm^{-1}. MS *m*/*z* (%): 330 (M^+, 30), 218 (5), 166 (25), 112 (100), 91 ((PhCH_2)$^+$, 95), 69 (55). Anal. Calcd for $C_{18}H_{22}N_2O_4$ (330.38): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.63; H, 6.38; N, 8.72.

BnBTGPip (2{*18*}). Yield: 4.5 mg, 100%. ^{1}H NMR: δ 7.30−7.26 (m, 5 H, Ph-*H*), 5.51 (s, 1 H, 5-H), 5.00 (s, 1 H, 7-H), 4.97 (s, 1 H, 1-H), 3.80−3.38 (m, 6 H, PhCH_2N, Pip-H), 2.82 (part A of AB system J = 12.6 Hz, 1 H, 2-H), 2.72 (part A of AB system J = 10.8 Hz, 1 H, 4-H), 2.55 (part B of AB system J = 10.8 Hz, 1 H, 4-H), 2.35 (part B of AB system J = 12.6 Hz, 1 H, 2-H), 1.75−1.51 (m, 6 H, Pip-H). ^{13}C NMR: δ 166.8 (s, *C*═O), 137.1 (s, Ph−C), 128.6 (d, 2 C, Ph−C), 128.3 (d, 2 C, Ph−C), 127.2 (d, Ph−C), 100.6 (d, C-5), 76.3 (d, C-1), 74.7 (d, C-7), 61.6 (t, Ph*C*H_2), 56.5 (t, C-4), 54.5 (t, C-2), 46.5 (t, Pip−C), 43.3 (t, Pip−C), 26.4 (t, Pip-C), 25.4 (t, Pip-C), 24.6 (t, Pip-C). IR ($CDCl_3$): ν 1631 cm^{-1}. MS *m*/*z* (%): 316 (M^+, 14), 204 (25), 158 (90), 152 (63), 91 (100). Anal. Calcd for $C_{18}H_{24}N_2O_3$ (316.40): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.01; H, 7.38; N, 8.59.

BnBTF(O)NH*n*Pr (3{*4*}). Yield: 5.5 mg, 100%. An analytical sample was obtained after chromatography on silica gel (EtOAc/hexane 2:3).^{1}H NMR: δ 7.44−7.31 (m, 8 H, Ph-*H*), 7.09−7.05 (m, 2 H, Ph-*H*), 6.35 (bs, 1 H, N*H*), 5.42 (s, 5-H), 5.41 (part A of AB system J = 15.4 Hz, 1 H, PhCH_2N), 5.04 (s, 1 H, 7-H), 4.61 (s, 1 H, 1-H), 4.00 (part B of AB system J = 15.4 Hz, 1 H, PhCH_2N), 3.34−3.07 (m, 4 H, PhCH_2CH, NCH_2CH$_2$ and 4-H), 2.82−2.70 (m, 1 H, PhCH_2CH), 1.50−1.42 (m, 2 H, CH$_2$CH_2CH$_3$), 0.88−0.84 (m, 3 H, CH$_2$CH_3). ^{13}C NMR: δ 168.1 (s, *C*═O), 166.0 (s, *C*═O), 136.0 (s, 2 C, Ph−C), 129.2 (d, 2 C, Ph−C), 129.0 (d, 2 C, Ph−C), 128.9 (d, 2 C, Ph−C), 128.0 (d, Ph−C), 127.9 (d, 2C, Ph−C), 127.2 (d, Ph−C), 101.0 (d, C-5), 79.7 (d, C-1), 77.6 (d, C-7), 60.5. (d, C-4), 45.7 (t, Ph*C*H_2N), 41.0 (t, *C*H_2NCO), 36.2 (t, Ph*C*H_2CH), 22.7 (t, *C*H_2CH$_3$), 11.2 (q, *C*H_3). MS *m*/*z* (%): 394 (M^+, 6), 303 (91), 160 (93), 91 (100). Anal. Calcd for $C_{23}H_{26}N_2O_4$ (394.46): C, 70.03; H, 6.64; N, 7.10. Found: C, 70.42; H, 6.88; N, 6.87.

General Procedure for Acylation of Nonvolatile Diamines and Monoamines with Aminoester Scaffolds. (GP2). Methyl ester (0.014 mmol) and amine (0.14 mmol) were heated in a sealed microreaction vessel at 60 °C for 16 h. For the workup, the reaction mixture was filtered through a pad of silica gel (Pasteur pipet filled with 5 cm of silica gel) and washed with 20 mL of EtOAc (for monoamines) or 20 mL of CH_2Cl_2/MeOH 10:1 (for diamines). Concentration of the solution under a stream of nitrogen afforded the final product mainly as yellow oil.

Representative Analytical Data for Compounds Obtained with Procedure GP2 BnBTKNHCH$_2$CH$_2$NH$_2$ (6{*21*}). Yield: 3.6 mg, 70%. ^{1}H NMR: δ 7.59−7.50 (m, 2 H, Ph-*H*), 7.42−7.36 (m, 3 H, Ph-*H*), 7.34−7.25 (m, 5 H, Ph-*H*), 6.74 (bs, 1 H, N*H*), 4.83 (s, 1 H, 7-H), 4.79 (s, 1 H, 1-H), 3.68 (part A of AB system J = 12.9 Hz, 1 H, PhCH_2N), 3.55 (part B of AB system J = 12.9 Hz, 1 H, PhCH_2N), 3.23 (part A of AB system J = 5.86 Hz, 1 H, CONCH_2), 3.18 (part B of AB system J = 5.86 Hz, 1 H, CONCH_2), 3.07 (part A of AB system J = 11.5 Hz, 1 H, 4-H), 2.93 (part A of AB system J = 11.9 Hz, 1 H, 2-H), 2.67 (m, 2 H, CH_2NH$_2$), 2.57 (part B of AB system J = 11.9 Hz, 1 H, 2-H), 2.41 (part B of AB system J = 11.5 Hz, 1 H, 4-H), 1.34 (bs, 2 H, NH_2). ^{13}C NMR: δ 171.8 (s, C═O), 137.8 (s, Ph−C), 137.2 (s, Ph−C), 129.0 (d, Ph−C), 128.8 (d, 2 C, Ph−C) 128.4 (d, 2 C, Ph−C), 128.3 (d, 2 C, Ph−C), 127.3-(d, Ph−C), 125.1 (d, 2 C, Ph−C), 107.9 (s, C-5), 78.6 (d, C-1), 78.5 (d, C-7), 61.3 (t, *C*H$_2$Ph), 60.8 (t, C-4), 54.0 (t, C-2), 41.9 (t, CONH*C*H$_2$), 41.3 (t, CH_2NH$_2$). IR ($CHCl_3$): ν 3414 (NH), 1667 cm^{-1}. MS *m*/*z* (%): 367 (M^+, 55), 338 (32), 247 (100). Anal. Calcd for $C_{21}H_{25}N_3O_3$ (367.44): C, 68.64; H, 6.86; N, 11.14. Found: C, 68.42; H, 6.97; N, 11.49.

BnBTGNHCH$_2$CH$_2$OH (2{*24*}). Yield: 3.8 mg, 92%. ^{1}H NMR: δ 7.29−7.26 (m, 5 H, Ph-*H*), 7.00 (s, 1 H, N*H*), 5.59 (s, 1 H, 5-H), 4.72 (s, 1 H, 7-H), 4.61 (s, 1 H, 1-H), 3.76−3.71 (m, 2 H, HOCH_2), 3.60−3.44 (m, 4 H, PhCH_2N, HNCH_2), 2.84 (d, J = 11.7 Hz, 1 H, 4-H), 2.85 (d, J = 11.0 Hz, 2 H, 2-H), 2.52 (part A of AB system J = 11.0 Hz, 1 H, 2-H), 2.32 (part B of AB system J = 11.7 Hz, 1 H, 4-H). ^{13}C NMR: δ 172.0 (*C*═O), 137.0 (s, Ph-*C*), 128.6 (d, 2 C Ph-*C*), 128.2 (d, 2 C, Ph-*C*), 127.2 (d, Ph-*C*), 101.0 (d, C-5), 77.2 (d, C-7), 76.6 (d, C-1), 61.2 (t, CH_2Ph), 60.9 (t, CH_2OH), 55.9 (t, C-4), 54.7 (t, C-2), 41.7 (t, *C*H$_2$NH$_2$). MS *m*/*z* (%): 292 (M^+, 5), 263 (32), 247 (34), 204 (37), 158 (87), 128 (70), 120 (88), 91 (100). Anal. Calcd for $C_{15}H_{20}N_2O_4$ (292.33): C, 61.63; H, 6.90; N, 9.58. Found: C, 61.79; H, 6.66; N, 9.29.

General Procedure for Acylation of Nonvolatile Monoamines with Amidoester Scaffolds. (GP3). Methyl ester

(0.014 mmol) and amine (0.14 mmol) were heated in a sealed microreaction vessel at 60 °C for 16 h. For the workup, the reaction mixture was then diluted with MeOH and rapidly filtered through a short column of Amberlyst 15 H^+ ion-exchange resin. Concentration of the solution under a stream of nitrogen afforded the final product mainly as a yellow oil.

Representative Analytical Data for Compounds Obtained with Procedure GP3 BnBTG(O)NHCH$_2$CH$_2$OH (1{*24*}). Yield: 3.8 mg, 88%. An analytical sample was obtained by crystallization from $CHCl_3$. White solid. ^{1}H NMR: δ 7.35−7.18 (m, 5 H, Ph-*H*), 6.85 (s, 1 H, N*H*), 5.83 (d, J = 2.6 Hz, 1 H, 5-H), 5.04 (s, 1 H, 7-H), 4.68 (s, 1 H, 1-H), 4.56 (s, 2 H, PhC*H*$_2$N), 3.74 (t, J = 5.2 Hz, 2 H, HNC*H*$_2$), 3.52−3.39 (m, 3 H, 4-H, HOC*H*$_2$), 3.12 (part B of AB system J = 12.2 Hz, 1 H, 4-H). ^{13}C NMR (DMSO-d_6): δ 172.6 (s, *C*═O), 167.6 (s, *C*═O), 137.0 (s, Ph−C), 129.1 (d, 2 C, Ph−C), 128.1 (d, 2 C, Ph−C), 127.9 (d, Ph−C), 110.3 (d, C-5), 80.3 (d, C-1), 78.6 (d, C-7), 58.5, (t, *C*H$_2$OH), 52.1 (t, C-4), 47.9 (t, PhCH$_2$), 42.2 (t, *C*H$_2$NH$_2$). MS *m*/*z* (%): 306 (M^+, 8), 218 (6), 120 (20), 91 (100). Anal. Calcd for $C_{15}H_{18}N_2O_5$ (306.31): C, 58.82; H, 5.92; N, 9.15. Found: C, 59.04; H, 5.62; N, 8.88.

BnBTF(O)Eip (3{*27*}). Yield: 5.1 mg, 74%. ^{1}H NMR: δ 7.38−7.25 (m, 8 H, Ph-*H*), 7.07−7.03 (m, 2 H, Ph-*H*), 5.47 (s, 1 H, 5-H), 5.28 (A part of AB system, J = 16.1 Hz, 1 H, PhC*H*$_2$N), 5.17 (s, 1 H, 7-H), 4.86 (s, 1 H, 1-H), 4.35−4.05 (m, 3 H, C*H*$_2$CH$_3$, PhC*H*$_2$N), 3.39−3.42 (m, 8 H, CH$_2$C*H*CO, PhC*H*$_2$CH, 4-H, N(C*H*$_2$)$_2$), 2.00−1.58 (m, 4 H, C(C*H*$_2$)$_2$), 1.36−1.18 (m, 3 H, C*H*$_3$). ^{13}C NMR: 174.0 (s, *C*═O), 166.8 (s, *C*═O), 165.5 (s, *C*═O), 136.1 (s, Ph−C), 135.9 (s, Ph−C), 129.2 (d, 2 C, Ph−C), 129.1 (d, 2 C, Ph−C), 129.0 (d, 2 C, Ph−C), 128.9 (d, Ph−C), 127.8 (d, 2 C, Ph−C), 127.1 (d, Ph−C), 100.9 (d, C-5), 78.4 (d, C-1), 77.6 (d, C-7), 61.1. (t, O*C*H$_2$CH$_3$), 60.7 (d, C-4), 46.2 (t), 44.7 (t), 41.4 (t), 36.5 (t), 29.7 (t, Eip-C), 14.1 (q, OCH$_2$*C*H$_3$). IR ($CHCl_3$): ν 1665 cm^{-1}. MS *m*/*z* (%): 492 (M^+, 5), 401 (95), 262 (39), 161 (48), 91 (100). Anal. Calcd for $C_{28}H_{32}N_2O_6$ (492.56): δ C, 68.28; H, 6.55; N, 5.69. Found: C, 67.89; H, 6.72; N, 5.38.

General Procedures for Microwave-Assisted Generation of Amide Library. Methyl ester (0.02 mmol) and amine (0.2 mmol) were dissolved in MeOH (600 μL) in a 5 mL conical microwave process vial. The vial was sealed with a Teflon septum and placed into the microwave cavity. After irradiation at 160 °C for 16 min and subsequent gas jet cooling (down to 40 °C), the reaction mixture was concentrated and treated, depending on the case, for the workup described above for the thermal prodedures.

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Supporting Information Available. Structures and ^{1}H NMR and MS data of all amides and ^{1}H NMR and MS spectra for amides **1**{*2*, *24*}, **3**{*4*, *27*}, **6**{*21*}, and **2**{*24*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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