Effective Amidation of Carboxylic Acids Using (4,5-Dichloro-6-oxo-6*H*-pyridazin-1-yl)phosphoric Acid Diethyl Ester

Seung-Beom Kang, Heung-Seop Yim, Ju-Eun Won, Min-Jung Kim, Jeum-Jong Kim, Ho-Kyun Kim, Sang-Gyeong Lee,* and Yong-Jin Yoon*

*Department of Chemistry & Environmental Biotechnology National Core Research Center, Research Institute of Natural Sciences, Graduate School for Molecular Materials and Nanochemistry, Gyeongsang National University, Jinju, Gyeongnam 660-701, Korea. *E-mail: yjyoon@gnu.ac.kr*

Received February 21, 2008

(4,5-Dichloro-6-oxo-6*H*-pyridazin-1-yl)phosphoric acid diethyl ester (**3a**) are efficient and selective coupling agents for the amidation of carboxylic acids. Amidation of aliphatic and aromatic carboxylic acids with aliphatic and aromatic amines using **3a** under mild condition gave chemoselectively the corresponding amides in good to excellent yield. Three protected-dipeptides were also synthesized from *N*-BOC-Phe and *O*-Me-amino acid hydrochlorides using **3a** under mild condition.

Key Words : (4,5-Dichloro-6-oxo-6*H*-pyridazin-1-yl)phosphoric acid diethyl ester, Coupling agent, Pyridazinone, Amidation, Dipeptide

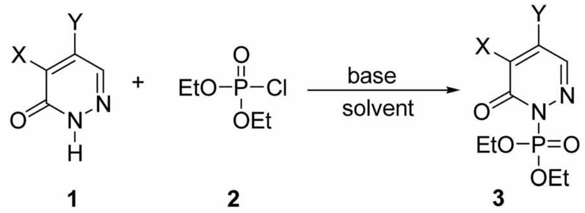
Introduction

Mild and effective amidation of carboxylic acids with amines is the most fundamental and important reactions in organic synthesis.[1] Common routes to amides mostly involve the treatment of activated derivatives of carboxylic acids such as acyl halides, acid anhydrides or esters with ammonia or amines.[2] However, these methods have some disadvantages such as formation of by-products, exthothermic reaction, and complicated conditions.[3] In order to overcome the problems, a variety of reagents have been developed,[4] and continuing efforts are being made to find an ideally selective and effective reagent. For direct amidation of carboxylic acid under mild conditions, carboxylic acid must be activated to more reactive species by using an activator.

In our previous paper,[5-7] we reported the synthesis of anhydrides and esters using 4,5-dichloro-2-[(4-nitrophenyl)sulfonyl]pyridazin-3(2*H*)-one as an activator. However, this activator requires two equivalents of carboxylic acid for the esterification.[6] Therefore, we developed (6-oxo-6*H*-pyridazin-1-yl)phosphoric acids diethyl ester as more effective coupling agent.[8] In this paper, we would like to report on mild and effective amidation of carboxylic acids with amines, and also synthesis of some dipeptides by using (4,5-dichloro-6-oxo-6*H*-pyridazin-1-yl)phosphoric acid diethyl ester in one port.

Results and Discussion

4,5-Disubstituted-pyridazin-3(2*H*)-ones were readily prepared by the reported methods.[9] According to the literature,[8] (4,5-disubstituted-6-oxo-6*H*-pyridazin-1-yl)phosphoric acid diethyl esters **3** were prepared in 79-96% yields *via* the reaction of 4,5-disubstituted-pyridazin-3(2*H*)-ones (**1**) with diethyl chlorophosphate (**2**) in the presence of triethylamine



1,3	X	Y	1, 3	X	Y
a	Cl	Cl	**d**	Cl	OPh
b	Cl	OMe	**e**	Cl	Br
c	Cl	N_3			

Scheme 1

in acetonitrile at room temperature.[8,9]

Initially, direct amidation of 4-nitrobenzoic acid (**4a**) with aniline (**5a**) using **3a** were studied in a variety of representative organic solvents and bases (Table 1, entries 1-10). Exclusive amidation in excellent yields was obtained in potassium carbonate/THF (or ethyl acetate) and triethylamine/THF. Among theses systems, we selected potassium carbonate/THF or ethyl acetate system for the direct amidation of carboxylic acid with amine using **3a**. The efficacy of **3b-3e** for amidation was evaluated using 4-nitrobenzoic acid (**4a**) and aniline (**5a**) in the presence of potassium carbonate in THF at room temperature (Table 1, entries 11-14).

Compounds **3a-3d** showed similar efficacy for the amidation under this condition. We selected compound **3a** as a novel coupling agent for the amidation of carboxylic acids with amines because **3b-3d** are prepared from **3a**.

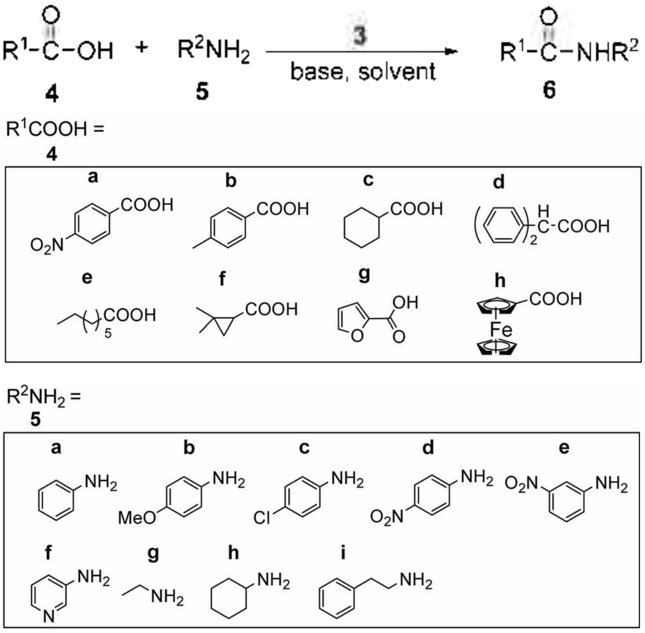
Amidation of 4-nitrobenzoic acid (**4a**) with various amines **5** using **3a** in the presence of potassium carbonate in THF at room temperature gave the corresponding amides **6b-6w** in good to excellent yields except for **6e** and **6f** (Table 2 and 3). When amines **5e** and **5f** are used, 4-nitrobenzoic anhydride was yielded as the by-product.

Treatment of some aliphatic or aromatic carboxylic acids **4**

Table 1. Amidation of 4-nitrobenzoic acid (**4a**) with aniline (**5a**) using **3** at r.t.

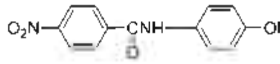
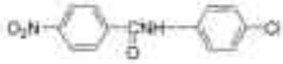
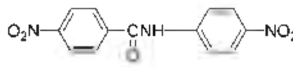
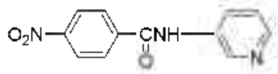
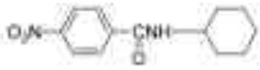
Entry	3	Base	Solvent	Time (h)	6a (%)[a]
1	**3a**	K_2CO_3	THF	3	96
2	**3a**	K_2CO_3	toluene	6	90
3	**3a**	K_2CO_3	EtOAc	3.5	95
4	**3a**	K_2CO_3	CH_3CN	6	91
5	**3a**	K_2CO_3	CH_2Cl_2	4	92
6	**3a**	K_2CO_3	$(Et)_2O$	34	74
7	**3a**	K_2CO_3	H_2O	19	–
8	**3a**	Et_3N	THF	1	94
9	**3a**	DMAP[b]	THF	1.5	85
10	**3a**	Resin[c]	THF	50	49[d]
11	**3b**	K_2CO_3	THF	6	90
12	**3c**	K_2CO_3	THF	4.5	87
13	**3d**	K_2CO_3	THF	4	94
14	**3e**	K_2CO_3	THF	2.5	83

[a]Isolated yield. Pyridazin-3(2*H*)-one derivatives were also isolated. [b]DMAP = *N,N*-dimethylaminopyridine. [c]Resin is Amberite-IRA66. [d]4-Nitrobenzoic acid was recovered.



Scheme 2

Table 2. Amidation of 4-nitrobenzoic acid (**4a**) with various amines **5** using **3a** in the presence of potassium carbonate in tetrahydrofuran at r.t.

Entry	R'NH$_2$, 5	Time (h)	Product	6 (%)[a]
1	**5b**	2.5		**6b** (98)
2	**5c**	3.5		**6c** (92)
3	**5d**	48		**6d** (80)
4	**5e**	7		**6e** (57)[b]
5	**5f**	7		**6f** (43)[b]
6	**5g**	3		**6g** (96)
7	**5h**	5		**6h** (98)
8	**5i**	2		**6i** (97)

[a]Isolated yield. 4,5-Dichloropyridazin-3(2*H*)-one was also isolated quantitatively. [b]The corresponding anhydride was isolated.

with an aromatic amine **5a** or an aliphatic amine **5g** using **3a** under same condition easily gave the corresponding amides **6j**-**6w** in excellent yields (Table 3). Selective amidation of mixed amines is also often required.

Therefore, we examined the selective amidation for a mixture of two amines such as 1°/2° amine and aromatic/aliphatic amine or bifunctional amines such as 2-mercaptoethanol and 4-aminophenol (Table 4). The amidation of benzoic acid (**7**) with ethylamine/diethylamine gave *N*-ethylbenzamide (**8a**) in excellent selectivity and in excellent yield (Table 4, entry 1). For the mixed amines such as cyclohexylamine/aniline and aniline/phenethylamine, aliphatic amine was also coupled with benzoic acid (**7**) under our conditions in excellent selectivity in high yield (Table 4, entries 2 and 3).

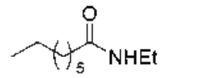
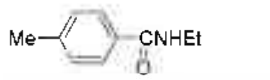
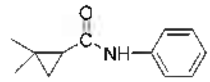
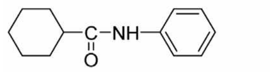
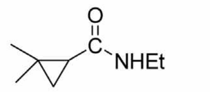
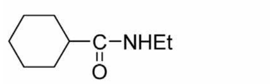
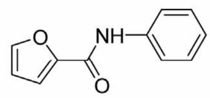
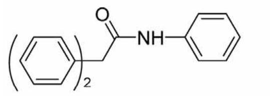
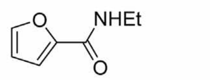
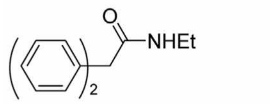
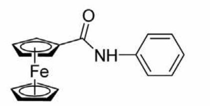
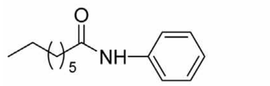
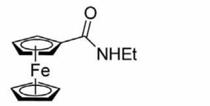
Amidation of aniline (**5a**)/benzenethiol with benzoic acid (**7**) gave chemoselectively the corresponding amide **8c** (82%) as major and thioester **8e** (6%) as minor (Table 4, entry 4). Reaction of 4-aminophenol (**5k**) with benzoic acid (**7**) under same condition also afforded chemoselectively the corresponding amide **8f** in 92% yield (Table 4, entry 5).

On the other hand, we attempted to synthesize dipeptide using coupling agent **3a** at room temperature. *N*-BOC-L-phenylalanine (1 equiv.) was coupled with *O*-methyl L-isoleucine hydrochloride (1 equiv.) using **3a** (1 equiv.) in the presence of triethylamine (2, 3 or 4 equiv.) in some organic solvent such as methylene chloride, acetonitrile, acetone, toluene and tetrahydrofuran at room temperature to give the corresponding dipeptides in 53 -81% yields (Table 5 entries 1-7).

From preliminary experiments (Table 5 entries 1-7), we selected *N*-BOC-amino acid (**9**, 1 equiv.)/*O*-methyl-amino acid.HCl (**10**, 1 equiv.)/**3a**(1 equiv.)/triethylamine (3 equiv.)/THF system as the optimum condition at room temperature for the synthesis of dipeptides. Treatment of *N*-BOC-L-phenylalanine (**10b**, 1 equiv.) was coupled with *O*-methyl L-phenylalanine hydrochloride (1 equiv.) or *O*-methyl L-tryptophan hydrochloride (**10c**, 1 equiv.) using **3a** (1 equiv.) in the presence of triethylamine (3 equiv.) in THF at room temperature to furnish the corresponding dipeptides **11b** (84%) or **11c** (70%) yield (Table 5 entries 8 and 9).

The structures of prepared compounds were established by

Table 3. Amidation of some carboxylic acids **4** with **5a** or **5g** using **3a** in the potassium carbonate in THF at r.t.

Entry	4	5	Time (h)	Product	6 (%)[a]	Entry	4	5	Time (h)	Product	6 (%)[a]
1	**4b**	**5a**	4		**6j** (97)	8	**4e**	**5g**	8		**6q** (92)
2	**4b**	**5g**	9		**6k** (96)	9	**4f**	**5a**	6.5		**6r** (97)
3	**4c**	**5a**	7		**6l** (98)	10	**4f**	**5g**	9		**6s** (88)
4	**4c**	**5g**	7		**6m** (89)	11	**4g**	**5a**	9		**6t** (89)
5	**4d**	**5a**	4		**6n** (98)	12	**4g**	**5g**	3.5		**6u** (90)
6	**4d**	**5g**	11		**6o** (98)	13	**4h**	**5a**	18		**6v** (93)
7	**4e**	**5a**	4.5		**6p** (98)	14	**4h**	**5g**	18		**6w** (95)

[a]Isolated yield. 4,5-Dichloropyridazin-3(2*H*)-one was also isolated.

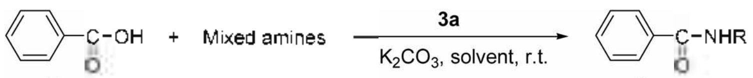
$$\mathrm{RCOOH} \xrightarrow[\text{- Pyridazinone}]{\textbf{3a}\text{/base}} \mathrm{RCOOP(=O)(OEt)_2} \xrightarrow[\text{- HOP(=O)(OEt)}_2]{\text{R'NH}_2\text{/base}} \mathrm{RCONHR'}$$

Scheme 3

IR, NMR and elemental analysis. In all the reactions described above, reusable 4,5-dichloropyridazin-3(2*H*)-one (**1a**) and phosphonic acid diethyl ester were also isolated.

On the other hand, acid anhydride as an intermediate was not detected during the amidation except for **5e** and **5f** by monitoring using TLC. Really, only one equivalent of carboxylic acid required for the amidation under these reaction condition. This amidation mechanism is different from it for the reaction using 4,5-dichloro-2-[(4-nitrobenzenesulfonyl)]pyridazin-3(2*H*)-one[6] as coupling agent. The amidation of carboxylic acid using compound **3a** may be proceeded *via* two steps; the formation of acyl phosphate in first step and then amine react with acyl phosphate to give the amide in second step. The reactivity of acyl phosphate

Table 4. Competition reaction of a mixture amines (or bifunctional amine) with **7** in the presence of potassium carbonate in THF at r.t.

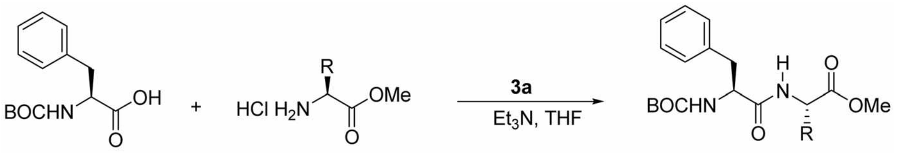


7 **8**

Entry	Mixed amines (5)	Reaction Time	Product	8 (%)[a]
1	$EtNH_2$ (**5g**)/Et_2NH (**5j**)	1 h	$C_6H_5CONHEt$	**8a** (90)
2	c-$C_6H_{11}NH_2$ (**5h**)/$C_6H_5NH_2$ (**5a**)	0.5 h	C_6H_5CONH-c-C_6H_{11}	**8b** (78)
			$C_6H_5CONHC_6H_5$	**8c** (8)
3	$C_6H_5(CH_2)_2NH_2$ (**5i**)/$C_6H_5NH_2$ (**5a**)	0.5 h	$C_6H_5CONH(CH_2)_2C_6H_5$	**8d** (72)
			$C_6H_5CONH\ C_6H_5$	**8c** (12)
4	$C_6H_5NH_2$ (**5a**)/C_6H_5SH	3 h	$C_6H_5CONHC_6H_5$	**8c** (82)
			$C_6H_5COSC_6H_5$	**8e** (6)
5	4-$H_2NC_6H_4OH$ (**5k**)	2.5 h	$C_6H_5CONHC_6H_4OH$-4	**8f** (92)

[a]Isolated yield. 4,5-Dichloropyridazin-3(2*H*)-one was also isolated.

Table 5. Synthesis of dipeptides **11** using **3a** in organic solvent at r.t.[a]



9 **10** **11**

Entry	Amino acid.HCl **10**	Et_3N (equiv.)	Reaction Condition	Disulfide 11 (yield %)[b]
1	*O*-Me-Leu (**10a**)	2	CH_2Cl_2, 48 h	*N*-BOC-Phe-Leu-*O*-Me (**11a**, 61)
2	*O*-Me-Leu (**10a**)	2	CH_3CN, 43 h	*N*-BOC-Phe-Leu-*O*-Me (**11a**, 69)
3	*O*-Me-Leu (**10a**)	2	Acetone, 33 h	*N*-BOC-Phe-Leu-*O*-Me (**11a**, 53)
4	*O*-Me-Leu (**10a**)	2	Toluene, 26 h	*N*-BOC-Phe-Leu-*O*-Me (**11a**, 66)
5	*O*-Me-Leu (**10a**)	2	THF, 24 h	*N*-BOC-Phe-Leu-*O*-Me (**11a**, 71)
6	*O*-Me-Leu (**10a**)	3	THF, 9 h	*N*-BOC-Phe-Leu-*O*-Me (**11a**, 81)
7	*O*-Me-Leu (**10a**)	4	THF, 9 h	*N*-BOC-Phe-Leu-*O*-Me (**11a**, 80)
8	*O*-Me-Phe (**10b**)	3	THF, 6 h	*N*-BOC-Phe-Phe-*O*-Me (**11b**, 84)
9	*O*-Me-Trp (**10c**)	3	THF, 5 h	*N*-BOC-Phe-Trp-*O*-Me (**11c**, 70)

[a]4,5-Dichloropyridazin-3(2*H*)-one was isolated. [b]Isolated yields.

with amine may be higher then it of carboxylate ion under our condition. Therefore, (4,5-dichloro-6-oxo-6*H*-pyridazin-1-yl)phosphoric acid diethyl ester (**3a**) is more effective coupling agent than 4,5-dichloro-2-[(4-nitrobenzenesulfonyl)]pyridazin-3(2*H*)-one[6] for amidation of carboxylic acid.

Conclusions

In conclusion, compound **3a** is an efficient and selective coupling agent for amidation of carboxylic acids with amines under the basic condition. It also has some advantages: i) the reaction condition is mild and basic, ii) this method shows good selectivity for primary or aliphatic amines in the presence of secondary or aromatic amines with high yields, iii) the coupling agent is easy to prepare, and iv) compound **1** can be recovered quantitatively for reuse. We also believe that these coupling agents should be particularly applicable to solid-phase synthesis, amidation of carboxylic acid and synthesis of peptides.

Experimental Section

General. Melting points were determined with a capillary apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrophotometer with chemical shift values reported in d units (ppm) relative to an internal standard (TMS). IR spectra were obtained on a IR spectrophotometer. Elemental analyses were performed with a CHNS-932 (Leco). Open-bed chromatography was carried out on silica gel (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent. The specific rotation values were determined by a Digital polarimeter (DIP-1000, Jasco). (4,5-Disubstituted-6-oxo-6*H*-pyridazin-1-yl)phosphoric acid diethyl esters **3** were synthesized by the literature method.[8]

Typical procedure for amidation of carboxylic acid. A solution of carboxylic acid **4** (1 equiv.), amine **5** (1.1 equiv.), base (1.1 equiv.), coupling agent **3** (1.5 equiv.) and solvent (30 mL) was stirred at room temperature until carboxylic acid disappeared by TLC monitoring. After filtering the mixture, the filtrate was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 × 11 cm). The column was eluted with methylene chloride or *n*-hexane/EtOAc (1:1, v/v). Fractions containing the amide were combined, and evaporated under reduced pressure to give the amide **6**. And fractions containing pyridazinone derivative were combined, and evaporated under reduced pressure to give pyridazinone derivative.

***N*-Phenyl-4-nitrobenzamide (6a).** Mp 213-214 °C (lit.[10] mp 211-212 °C). IR (KBr) 3350, 1660, 1600, 1540, 1500, 1440, 1360, 1330, 1270, 1110, 1020, 880, 860, 760 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.15 (t, 1H, J = 7.3 Hz), 7.39 (t, 2H, J = 8.0 Hz), 7.79 (d, 2H, J = 8.3 Hz), 8.19 (d, 2H, J = 8.8 Hz), 8.38 (d, 2H, J = 8.8 Hz), 10.57 ppm (s, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 121.0, 124.0, 124.6, 129.2, 129.7, 139.2, 141.1, 149.6, 164.3 ppm. Elemetal analysis calcd. for $C_{13}H_{10}N_2O_3$: C 64.46, H 4.16, N 11.56; found C 64.37, H 4.25, N 11.49.

***N*-(4-Methoxyphenyl)-4-nitrobenzamide (6b).** Mp 196-197 °C (lit.[11] mp 193-196 °C). IR (KBr) 3320, 1650, 1600, 1540, 1520, 1470, 1420, 1360, 1320, 1310, 1250, 1180, 1030, 830 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.76 (s, 3H), 6.96 (d, 2H, J = 9.0 Hz), 7.69 (d, 2H, J = 9.0 Hz), 8.18 (d, 2H, J = 8.8 Hz), 8.37 (d, 2H, J = 8.8 Hz), 10.45 ppm (s, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 55.7, 114.3, 122.5, 124.0, 129.5, 132.2, 141.2, 149.5, 156.3, 163.8 ppm. Elemental analysis calcd. for $C_{14}H_{12}N_2O_4$: C 61.76, H 4.44, N 10.29; found C 61.87, H 4.35, N 10.38.

***N*-(4-Chlorophenyl)-4-nitrobenzamide (6c).** Mp 228-229 °C (lit.[11] mp 227 °C) IR (KBr) 3450, 3150, 1690, 1610, 1540, 1520, 1500, 1400, 1360, 1340, 1310, 1250, 1090, 1010, 860, 840 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.44 (d, 2H, J = 8.8 Hz), 7.84 (d, 2H, J = 8.8 Hz), 8.19 (d, 2H, J = 8.8 Hz), 8.38 (d, 2H, J = 8.8 Hz), 10.68 ppm (s, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 122.4, 124.0, 128.3, 129.1, 129.7, 138.1, 140.7, 149.7, 164.4 ppm. Elemental analysis calcd. for $C_{13}H_9N_2ClO_3$: C 56.43, H 3.28, N 10.13; found C 56.32, H 3.37, N 10.30.

***N*-(4-Nitrophenyl)-4-nitrobenzamide (6d).** Mp 268-270 °C (lit.[12] mp 264-266 °C). IR (KBr) 3400, 3150, 1700, 1630, 1610, 1560, 1540, 1510, 1420, 1360, 1350, 1320, 1260, 1190, 1120, 860 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.06 (d, 2H, J = 9.2 Hz), 8.22 (d, 2H, J = 8.8 Hz), 8.30 (d, 2H, J = 9.2 Hz), 8.40 (d, 2H, J = 8.8 Hz), 11.10 ppm (s, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 120.6, 124.1, 125.3, 130.0, 140.3, 143.3, 145.4, 151.4, 165.2 ppm. Elemental analysis calcd. for $C_{13}H_9N_3O_5$: C 54.36, H 3.16, N 14.63; found C 54.48, H 3.08, N 14.54.

***N*-(3-Nitrophenyl)-4-nitrobenzamide (6e).** Mp 227-228 °C. IR (KBr) 3400, 3010, 3090, 1680, 1620, 1600, 1550, 1540, 1520, 1420, 1340, 1320, 1280, 1240, 1080, 1000 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.69 (t, 1H, J = 8.2 Hz), 8.00 (d, 2H, J = 8.2 Hz), 8.18-8.24 (m, 3H), 8.40 (d, 2H, J = 8.8 Hz), 8.79 (d, 1H, J = 1.9 Hz), 11.0 ppm(s, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 115.0, 119.1, 124.1, 126.7, 129.8, 130.6, 140.2, 140.3, 148.3, 149.6, 164.8 ppm. Elemental analysis calcd. for $C_{13}H_9N_3O_5$: C 54.36, H 3.16, N 14.63; found C 54.48, H 3.08, N 14.54.

***N*-(Pyridin-3-yl)-4-nitrobenzamide (6f).** Mp 137-138 °C. IR (KBr) 3200, 3140, 3100, 3000, 1680, 1590, 1540, 1520, 1470, 1440, 1350, 1320, 1150, 1090, 1000, 880 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.19-7.23 (m, 1H), 7.88 (t, 1H, J = 8.5 Hz), 8.19 (d, 1H, J = 8.4 Hz), 8.19 (d, 1H, J = 8.4 Hz), 8.23 (d, 2H, J = 8.8 Hz), 8.34 (d, 2H, J = 8.8 Hz), 8.42 (d, 1H, J = 4.8 Hz), 11.16 ppm (s, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 115.3, 120.7,, 123.9, 130.0, 138.7, 140.4, 148.5, 149.8, 152.3, 165.0 ppm. Elemental analysis calcd. for $C_{12}H_9N_3O_3$: C 59.26, H 3.73, N 17.28; found C 59.34, H 3.81, N 17.15.

***N*-Ethyl-4-nitrobenzamide (6g).** Mp 148-149 °C (lit.[13] mp 140-142 °C). IR (KBr) 3300, 3010, 3000, 2950, 2900, 1650, 1610, 1560, 1530, 1480, 1350, 1320, 1300, 1160, 1140, 1110 cm^{-1}. ^1H NMR ($CDCl_3$): δ 71.28 (t, 3H, J = 7.3 Hz), 3.48-3.57 (m, 2H), 6.43 (s, NH, D_2O exchangeable), 7.93 (d, 2H, J = 8.8 Hz), 8.26 ppm (d, 2H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$): δ 14.7, 35.3, 123.7, 128.1, 140.4, 149.5, 165.4 ppm. Elemental analysis calcd. for $C_9H_{10}N_2O_3$: C 55.67, H 5.19, N 14.43; found C 55.61, H 5.31, N 14.30.

***N*-Cyclohexyl-4-nitrobenzamide (6h).** Mp 205-206 °C (lit.[14] mp 207 °C). IR (KBr) 3350, 3150, 3100, 2970, 2890, 1650, 1610, 1560, 1530, 1470, 1360, 1340, 1330, 1300, 1160, 1120 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20-1.33 (m, 3H), 1.31-1.48 (m, 2H), 1.66-1.71 (m, 1H), 1.75-1.81 (m, 2H), 2.03-2.08 (m, 2H), 3.94-4.04 (m, 1H), 6.03 (s, NH, D_2O exchangeable), 7.91 (d, 2H, J = 8.9 Hz), 8.27 ppm (d, 2H, J = 8.9 Hz). ^{13}C NMR ($CDCl_3$): δ 24.8, 25.5, 33.1, 49.2, 123.8, 128.0, 140.7, 149.5, 164.6 ppm. Elemental analysis calcd. for $C_{13}H_{16}N_2O_3$: C 62.89, H 6.50, N 11.28; found C 63.02, H 6.61, N 11.33.

***N*-Phenylethyl-4-nitrobenzamide (6i).** Mp 213-214 °C IR (KBr) 3350, 3100, 1660, 1610, 1540, 1520, 1500, 1450, 1360, 1330, 1270, 1180, 1120, 1080, 1020, 920 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.95 (t, 2H, J = 7.5 Hz), 3.73 (q, 2H, J = 6.0, 6.8 Hz), 6.43 (s, NH, D_2O exchangeable), 7.21-7.35 (m, 5H), 7.83 (d, 2H, J = 8.8 Hz), 8.23 ppm (d, 2H, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6): δ 35.5, 41.4, 123.8, 126.8, 128.1, 128.7, 128.8, 138.5, 140.2, 149.5, 165.5 ppm. Elemental analysis calcd. for $C_{15}H_{14}N_2O_3$: C 66.66, H 5.22, N 10.36; found C 66.54, H 5.32, N 10.42.

***N*-Phenyl-4-methylbenzamide (6j).** Mp 144-145 °C (lit.[15] mp 145-147 °C). IR (KBr) 3370, 3070, 3050, 2970, 2930, 1660, 1620, 1600, 1530, 1520, 1450, 1380, 1330, 1300, 1270, 1250, 1200, 1120, 920, 890, 850, 840, 760, 700, 660 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H), 7.13 (t, 1H, J = 7.4 Hz), 7.26 (d, 2H, J = 7.9 Hz), 7.35 (t, 2H, J = 7.6 Hz), 7.63 (d, 2H, J = 8.2 Hz), 7.76 (d, 2H, J = 8.2 Hz), 7.86 ppm (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 21.5, 120.2, 124.4, 127.1, 129.1, 129.4, 132.2, 138.1, 142.3, 165.7 ppm. Elemental analysis calcd. for $C_{14}H_{13}NO$: C 79.59, H 6.20, N 6.63; found C 79.71, H 6.28, N 6.54.

***N*-Ethyl-4-methylbenzamide (6k).** Mp 90-92 °C (lit.[13] mp 90-93 °C). IR (KBr) 3290, 3100, 3000, 2950, 2900, 1640, 1560, 1520, 1480, 1360, 1310, 1290, 1270, 1200, 1150, 950 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (t, 3H, J = 7.3 Hz), 2.38 (s, 3H), 3.43-3.53 (m, 2H), 6.24 (s, NH, D_2O exchangeable), 7.20 (d, 2H, J = 8.2 Hz), 7.66 ppm (d, 2H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$): δ 14.9, 21.4, 34.9, 126.9, 129.1, 132.0, 141.6, 167.5 ppm. Elemental analysis calcd. for $C_{10}H_{13}NO$: C 73.59, H 8.03; N 8.58; found C 73.48, H 8.10, N 8.49.

***N*-Phenylcyclohexanamide (6l).** Mp 145-146 °C. IR (KBr) 3260, 3200, 3150, 3100, 2950, 2870, 1670, 1600, 1560, 1510, 1500, 1460, 1350, 1330, 1300, 1260, 1210, 1190 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.20-1.31 (m, 3H), 1.47-1.60 (m, 2H), 1.66-1.70 (m, 1H), 1.79-1.83 (m, 2H), 1.91-1.95 (m, 2H), 2.18-2.29 (m, 1H), 7.07 (t, 1H, J = 7.4 Hz), 7.28 (t, 2H, J = 8.3 Hz), 7.49 (s, NH, D_2O exchangeable), 7.53 ppm (d, 2H, J = 7.8 Hz) . ^{13}C NMR ($CDCl_3$): δ 25.6, 25.7, 29.7, 46.5, 119.9, 124.1, 128.9, 138.2, 174.6 ppm. Elemental analysis calcd. for $C_{13}H_{17}NO$: C 76.81, H 8.43, N 6.89; found C 76.92, H 8.52, 6.97.

***N*-Ethylcyclohexaneamide (6m).** Mp 96-97 °C (lit.[13] mp 84-88 °C). IR (KBr) 3330, 2950, 2880, 1650, 1560, 1460, 1400, 1340, 1270, 1230, 1160, 950, 920, 680 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.13 (t, 3H, J = 7.3 Hz), 1.18-1.32 (m, 3H), 1.37-1.49 (m, 2H), 1.65-1.68 (m, 1H), 1.76-1.87 (m, 4H), 2.00 - 2.11 (m, 1H), 3.23-3.32 (m, 2H), 5.59 ppm (D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 14.9, 25.7, 25.8, 29.7, 34.1, 45.6, 175.9 ppm. Elemental analysis calcd. for $C_9H_{17}ON$: C 69.93, H 11.04, N 9.02; found C 69.57, H 10.96, N 9.10.

***N*-Phenyl-2,2-diphenylacetamide (6n).** Mp 166-168 °C. IR (KBr) 3310, 3210, 3150, 3100, 3070, 1660, 1600, 1560, 1500, 1450, 1360, 1320, 1260, 1180, 1080, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.07 (s, 1H), 7.08 (t, 1H, J = 7.4 Hz), 7.23-7.37 (m, 12H), 7.40 (D_2O exchangeable), 7.44 ppm (d, 2H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$): δ 60.1, 119.9, 124.5, 127.5, 128.9, 129.0, 137.2, 137.7, 139.1, 170.1 ppm. Elemental analysis calcd. for $C_{20}H_{17}NO$: C 83.59, H 5.96, N 4.87; found C 83.61, H 6.01, N 4.90.

***N*-Ethyl-2,2-diphenylacetamide (6o).** Mp 134-135 °C IR (KBr) 3330, 3060, 3040, 2990, 2890, 1640, 1600, 1530, 1490, 1480, 1450, 1360, 1320, 1220, 1060, 1020 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75(t, 3H, J = 7.2 Hz), 3.24-3.37 (m, 2H), 4.89 (s, 1H), 5.73 (s, NH, D_2O exchangeable), 7.21-7.33 ppm (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.8, 34.7, 59.2, 127.2, 128.7, 128.9, 139.7, 171.7 ppm. Elemental analysis calcd. for $C_{19}H_{17}ON$: C 80.30, H 7.16, N 5.85; found C 80.35, H 7.24, N 5.93.

***N*-Phenyloctaneamide (6p).** Mp 50-51 °C IR (KBr) 3350, 3100, 2950, 2870, 1670, 1610, 1550, 1510, 1480, 1460, 1400, 1320, 1310, 1260, 1200, 1120, 1080, 970, 900 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 7.0 Hz), 1.22-1.38 (m, 8H), 1.70-1.77 (m, 2H), 2.34 (t, 2H, J = 7.7 Hz), 7.28 (s, NH, D_2O exchangeabale), 7.30 (t, 3H, J = 8.3 Hz), 7.51 ppm (d, 2H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.6, 25.6, 29.0, 29.2, 31.7, 37.8, 119.8, 124.1, 129.0, 138.0, 171.4 ppm. Elemental analysis calcd. for $C_{14}H_{21}ON$: C 76.67, H 9.65, N 6.39; found C 76.81, H 9.73, N 6.45.

***N*-Ethyloctaneamide (6q).** Liquid. IR (KBr) 3330, 3120, 2960, 2900, 1660, 1560, 1480, 1390, 1280, 1160 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.9 Hz), 1.13 (t, 3H, J = 7.3 Hz), 1.28-1.33 (m, 8H), 1.57-1.66 (m, 2H), 2.17 (t, 2H, J = 7.9 Hz), 3.23-3.32 (m, 2H), 6.27 ppm (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 13.9, 14.7, 22.5, 25.8, 29.0, 29.2, 31.6, 34.2, 36.7, 173.3 ppm. Elemental analysis calcd. for $C_{10}H_{21}ON$: C 70.12, H 12.36, N 8.18; found C 70.04, H 12.23, N 8.26.

***N*-Phenyl-2,2-dimethylcyclopropanecarboxamide (6r).** Mp 98-100 °C. IR (KBr) 3300, 3200, 3150, 3100, 3020, 2970, 2950, 2900, 1660, 1600, 1540, 1500, 1450, 1410, 1380, 1320, 1280, 1260, 1200, 1120, 1100, 1050, 990 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.19-1.27 (m, 2H), 1.16 (s, 3H), 1.23 (s, 3H), 1.40-1.45 (m, 1H), 7.05 (t, 1H, J = 7.0 Hz), 7.27 (t, 2H, J = 7.8 Hz), 7.51 (d, 2H, J = 6.7 Hz), 7.67 ppm (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 18.7, 20.7, 22.7, 27.1, 30.0, 119.7, 123.8, 128.9, 138.4, 170.1 ppm. Elemental analysis calcd. for $C_{12}H_{15}NO$: C 76.16, H 7.99, N 7.40; found C 76.22, H 8.08, N 7.51.

***N*-Ethyl-2,2-dimethylcycloproanecarboxamide (6s).** Liquid. IR (KBr) 3340, 3100, 2980, 2900, 1660, 1560, 1460, 1390, 1290, 1240, 1160, 1130, 1100, 980, 880 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.67-0.72 (m, 1H), 1.12 (s, 3H), 1.11-1.16 (t, 3H, J = 7.3 Hz), 1.17 (s, 3H), 1.21-1.27 (m, 1H), 3.25-3.34 (m, 2H), 5.82 (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 15.1, 18.7, 19.9, 21.1, 27.1, 29.0, 34.5, 171.3 ppm. Elemental analysis calcd. for $C_8H_{15}ON$: C 68.04, H 10.71, N 9.92; found C 68.11, H 10.64, 10.10.

***N*-Phenylfuran-2-carboxamide (6t).** Mp 122-123 °C (lit.[16] mp 123-124 °C). IR (KBr) 3280, 3150, 3050, 1660, 1600, 1580, 1520, 1500, 1480, 1440, 1380, 1320, 1310, 1270, 1230, 1170, 1120, 1080, 1010, 940, 910 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.51-6.53 (m, 1H), 7.13 (t, 1H, J = 7.4 Hz), 7.21 (d, 1H, J = 3.5 Hz), 7.34 (t, 2H, J = 8.4 Hz), 7.47-7.48 (m, 1H), 7.65 (d, 2H, J = 8.7 Hz), 8.19 (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 112.6, 115.3, 120.0, 124.6, 129.1, 137.4, 144.3, 147.8, 156.2 ppm. Elemental analysis calcd. for $C_{11}H_9ON$: C 70.58, H 4.85, N 7.48; found C 70.67, H 4.79, N 7.53.

***N*-Ethylfuran-2-carboxamide (6u).** Liquid. IR (KBr) 3350, 3150, 3100, 3020, 2970, 2900, 1660, 1600, 1590, 1540, 1490, 1460, 1400, 1320, 1240, 1200 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (t, 3H, J = 7.3 Hz), 3.41-3.50 (m, 2H), 6.47-6.48 (m, 1H), 6.60 (s, NH, D_2O exchangeable), 7.09 (d, 1H, J = 3.5 Hz), 7.42 ppm (t, 1H, J = 1.0 Hz). ^{13}C NMR ($CDCl_3$): δ 14.8, 34.0, 112.0, 113.8, 143.7, 148.1, 158.4 ppm. Elemental analysis calcd. for C_7H_9ON: C 60.42, H 6.52, N 10.07; found C 60.37, H 6.59, 10.16.

***N*-Phenylferrocene-2-carboxamide (6v).** Mp 206-207 °C. IR (KBr) 3300, 3100, 1640, 1600, 1520, 1460, 1430, 1380, 1310, 1300, 1260, 1240, 1130, 1020, 1000, 900 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.25 (t, 5H, J = 4.0 Hz), 4.42 (t, 2H, J = 1.9 Hz), 4.78 (t, 2H, J = 1.9 Hz), 7.12 (t, 1H, J = 4.7 Hz), 7.36 (t, 2H, J = 8.3 Hz), 7.39 (s, NH, D_2O exchangeable), 7.59 ppm (d, 2H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 68.3, 69.9, 70.8, 76.3, 119.8, 124.0, 129.1, 138.2, 168.5 ppm. Elemental analysis calcd. for $C_{16}H_{21}NOFe$: C 66.91, H 4.95, N 4.59; found C 67.02, H 5.02, N 4.64.

***N*-Ethylferrocene-2-carboxamide (6w).** Mp 157-159 °C. IR (KBr) 3310, 3120, 3000, 2960, 1640, 1560, 1480, 1430, 1400, 1320, 1240, 1200, 1160, 1120, 1070, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23 (t, 3H, J = 7.2 Hz), 3.42 (m, 2H), 4.20 (s, 5H), 4.33 (t, 2H, J = 7.2 Hz), 4.66 (t, 2H, J = 1.9 Hz), 5.72 ppm (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 15.3, 34.4, 68.0, 69.7, 70.3, 76.4, 170.1 ppm. Elemental analysis calcd. for $C_{13}H_{15}ONFe$: C 60.73, H 5.88, N 5.45; found C 60.82, H 5.94, 5.52.

Typical procedure for amidation of carboxylic acid with a mixed amines (or bifunctional amine). A solution of benzoic acid (7, 1 equiv.), a mixed amine (1:1 equiv.), potassium carbonate (1.1 equiv.), coupling agent **3a** (1.5 equiv.) and THF (30 mL) was stirred at room temperature until carboxylic acid disappeared by TLC monitoring. After filtering the mixture, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 × 10 cm). The column was eluted with ethyl acetate/methylene chloride (1:4, v/v). Fractions containing the amide were combined, and evaporated under reduced pressure to give the amide. And fractions containing pyridazinone derivative were combined, and evaporated under reduced pressure to give pyridazinone derivative.

***N*-Ethylbenzamide (8a).** Liquid. IR (KBr) 3350, 3100, 3000, 2950, 2900, 1650, 1620, 1560, 1500, 1460, 1390, 1370, 1320, 1060, 1120, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.89 (t, 2H, J = 7.3 Hz), 3.42 (q, 2H, J = 7.1, 7.0 Hz), 7.33 (t, 2H, J = 7.1 Hz), 7.43 (t, 1H, J = 7.3 Hz), 7.49 (s, NH, D_2O exchangeable), 7.77 ppm (d, 2H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 14.6, 35.1, 127.1, 128.4, 131.4, 134.1, 168.2 ppm. Elemental analysis calcd. for $C_9H_{11}ON$: C 72.46, H 7.43, N 9.39; found C 72.56, H 7.38, N 9.43.

***N*-Cyclohexylbenzamide (8b).** Liquid. IR (KBr) 3350, 1660, 1600, 1530, 1500, 1440, 1320, 1260, 750, 720, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.14-1.42 (m, 5H), 1.60 (1.65 (m, 1H), 1.70-1.77 (m, 2H), 1.99 (d, 2H, J = 12.0 Hz), 3.90-4.00 (m, 1H), 6.35 (D_2O exchangeable), 7.35-7.48 (m, 3H), 7.76 ppm (d, 2H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$): δ 25.0, 25.5, 33.1, 48.7, 126.9, 128.4, 131.2, 135.1, 166.7 ppm. Elemental analysis calcd. for $C_{13}H_{17}ON$: C 76.81, H 8.43, N 6.89; found C 76.90, , H 8.49, N 6.82.

***N*-Phenylbenzamide (8c).** Mp 144-145 °C (lit.[17] mp 134-135 °C). IR (KBr) 3270, 3100, 2970, 2900, 1640, 1580, 1500, 1470, 1350, 1320, 1280, 1100, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.15 (t, 1H, J = 7.4 Hz), 7.36 (t, 2H, J = 8.3 Hz), 7.44-7.54 (m, 3H), 7.64 (d, 2H, J = 7.6 Hz), 7.89 (d, 2H, J = 6.9 Hz), 7.92 ppm (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 120.3, 124.6, 127.1, 128.8, 129.1, 131.8, 135.0, 137.9, 165.8 ppm. Elemental analysis calcd. for $C_{13}H_{11}ON$: C 79.16, H 5.62, N 7.10; found C 79.09, H 5.68, 7.17.

***N*-Phenylethylbenzamide (8d).** Mp 118-120 °C (lit.[18] mp 119-120 °C) IR (KBr) 3360, 3070, 3050, 2950, 1650, 1610, 1580, 1550, 1500, 1490, 1460, 1320, 1300, 1200, 760, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.93 (t, 2H, J = 6.9 Hz), 3.71 (q, 2H, J = 6.1, 6.1 Hz), 6.24 (s, NH, D_2O exchangeable),, 7.22-7.26 (m, 3H), 7.30-7.42 (m, 4H), 7.47 (t, 1H, J =7.2 Hz), 7.79 ppm (d, 2H, J =6.9 Hz) . ^{13}C NMR ($CDCl_3$): δ 35.7, 41.2, 126.6, 126.8, 128.6, 128.7, 128.8, 131.4, 134.7, 138.9, 167.5 ppm. Elemental analysis calcd. for $C_{15}H_{15}ON$: C 79.97, H 6.71, N 6.22; found C 80.06, H 6.67, N 6.28.

***S*-Phenyl benzothiate (8e).** Mp 63-65 °C (lit.[19] mp 64-66 °C). IR (KBr) 3090, 1740, 1680, 1600, 1490, 1440, 1260, 1200, 1180, 1060, 1040, 900, 760, 690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.43-7.54 (m, 7H), 7.60 (t, 1H, J = 7.3 Hz), 8.03 ppm (d, 2H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 127.5, 128.6, 128.8, 129.3, 129.6, 130.2, 133.7, 135.1, 190.2 ppm. Elemental analysis calcd. for $C_{13}H_{10}SO$: C 72.87, H 4.70; found C 72.95, H 4.76.

***N*-(4-Hydroxyphenyl)benzamide (8f).** Mp 222-224 °C (lit.[20] mp 223-225 °C. IR (KBr) 3410, 3350, 1660, 1620, 1600, 1560, 1530, 1450, 1340, 1260, 1240, 1120, 840 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.27 (t, 2H, J = 6.3 Hz), 3.34 (s, OH, D_2O exchangeable), 3.84 (t, 2H, J = 6.2 Hz), 7.41 (t, 2H, J = 7.4 Hz), 7.54 (t, 1H, J = 7.5 Hz), 7.95 ppm (d, 2H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 31.7, 61.6, 127.3, 128.6, 133.6, 136.8, 192.3 ppm. Elemental analysis calcd. for $C_{13}H_{11}NO_2$: C 73.23, H 5.20, N 6.57; found C 73.31, H 5.24, N 6.62.

Typical procedure for synthesis of dipeptides. A solution of *N*-BOC-L-phenylalanine (**9**, 2.5 mmol, 1 equiv.), coupling agent **3a** (3.75 mmol, 1:5 equiv.), triethylamine (7.5 mmol, 3 equiv.), *O*-methyl-α-aminocarboxylate hydrochloride **10** (2.8 mmol, 1.1 equiv.) and methanol (30 mL) was stirred at room temperature until compound **9** disappeared by TLC monitoring. After filtering the mixture, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (3.5 × 16 cm). The column was eluted with ethyl acetate/*n*-hexane (1:1, v/v). Fractions containing the dipeptide were combined, and evaporated under reduced pressure to give the peptide **11**. And fractions containing pyridazinone derivative were combined, and evaporated under reduced pressure to give pyridazinone derivative.

***N*-BOC-Phe-Leu-*O*-Me (11a).** Mp 91-93 °C. $[\alpha]_D$ = + 42.85°. IR (KBr) 3345, 3340, 3100, 2990, 2900, 1760, 1700, 1660, 1550, 1460, 1440, 1400, 1380, 1280, 1260, 1180 cm^{-1}. ^1H NMR ($CDCl_3$): d 0.90 (t, 6H, J = 5.6 Hz), 1.41 (s, 9H), 1.44-1.61 (m, 3H), 3.07 (d, 2H, J = 6.7 Hz), 3.69 (s, 3H), 4.35 (d, 1H, J = 7.0 Hz), 4.53-4.61 (m, 1H), 5.02 (bs, NH, D_2O exchangeable), 6.29 (d, NH, D_2O exchangeable), 7.20-7.32 ppm (m, 5H). ^{13}C NMR ($CDCl_3$): δ 21.7, 22.7, 24.5, 28.2, 38.1, 41.5, 50.7, 52.2, 80.2, 126.9, 128.6, 129.4, 136.6, 155.4, 171.0, 172.8 ppm. Elemental analysis calcd. for $C_{21}H_{32}N_2O_5$: C 64.26, H 8.22, N 7.14; found C 64.33, H 8.29, N 7.21.

***N*-BOC-Phe-Phe-*O*-Me (11b).** Mp 119-121 °C. $[\alpha]_D$ = −7.10°. IR (KBr) 3350, 3340, 3080, 3050, 3000, 1750, 1700, 1670, 1530, 1500, 1450, 1390, 1370, 1350, 1300, 1250, 1220, 1170, 1040, 1020, 1010, 860, 750, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.39 (s, 9H), 2.98-3.09 (m, 4H), 3.66 (s, 3H), 4.33 (s, NH, D_2O exchangeable), 4.78 (q, 1H, J = 6.9, 6.1 Hz), 5.00 (s, NH, D_2O exchangeable), 6.37 (d, 1H, J = 7.4 Hz), 6.97-7.00 (m, 2H), 7.17-7.31 ppm (m, 8H). ^{13}C NMR ($CDCl_3$): δ 28.2, 38.0, 38.3, 52.3, 53.3, 55.7, 80.2, 127.0, 127.1, 128.7, 129.2, 129.4, 135.7, 136.6, 155.3, 170.8, 171.4 ppm. Elemental analysis calcd. for $C_{24}H_{30}N_2O_5$: C 67.59, H 7.90, N 6.57; found C 67.69, H 7.84, N 6.61.

***N*-BOC-Phe-Trp-*O*-Me (11c).** Mp 160-162 °C. $[\alpha]_D$ = −8.30°. IR (KBr) 3420, 3400, 3280, 1750, 1690, 1670, 1520, 1490, 1450, 1440, 1300, 1240, 1160, 640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (s, 9H), 3.02 (m, 2H), 3.23 (m, 2H), 3.59 (s, 3H), 4.37 (s, NH, D_2O exchangeable), 4.86 (q, 1H, J = 7.4 Hz), 5.04 (d, 1H, J = 7.9 Hz), 6.54 (d, 1H, J = 7.8 Hz), 6.84 (d, 1H, J = 7.4 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.12-7.30 (m, 7H), 7.36 (d, NH, D_2O exchangeable), 8.50 ppm (s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 27.7, 28.2, 38.4, 52.3, 53.1, 60.4, 80.1, 109.5, 111.4, 118.4, 119.5, 122.1, 123.1, 126.9, 127.5, 128.6, 129.4, 136.2, 136.6, 155.3, 171.0, 171.9 ppm. Elemental analysis calcd. for $C_{26}H_{31}N_3O_5$: C 67.08, H 6.71, N 9.03; found C 67.17, H 6.79, N 8.97.

Acknowledgments. This work was supported by a grant from the Korea Science and Engineering Foundation (KOSEF) to the Environmental Biotechnology National Core Research Center (grant #: R15-2003-012-02001-0).

References

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999; pp 494-564. (b) Mulzer, J. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 322-417.
2. Vogel, A. *Practical Organic Chemistry*. Longman Scientific & Technical and Wiley: New York, 1989; pp 708-710.
3. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001; pp 506-512.
4. For selected examples: (a) Kang, Y. J.; Chung, H. A.; Kim, J. J.; Yoon, Y. J. *Synthesis* **2002**, 733. (b) Wakasugi, K.; Nakamura, A.; Tanabe, Y. *Tetrahedron Lett.* **2001**, *42*, 7427. (c) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210. (d) Kondo,

K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843. (e) Yasuhara, T.; Nagaoka, Y.; Tomioka, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2233. (f) Blagbrough, I. S.; Geall, A. J. *Tetrahedron Lett.* **1998**, *39*, 439. (g) Kartrizky, A. R.; Yang, B.; Semenzin, D. *J. Org. Chem.* **1997**, *62*, 726. (h) Kartrizky, A. R.; Chang, H. X. *Synthesis* **1995**, 503. (i) Murahashi, S.-I.; Naota, T. *Synthesis* **1993**, 433. (j) Akikusa, N.; Mitsui, K.; Sakamoto, T.; Kikugawa, Y. *Synthesis* **1992**, 1058. (k) Kikukawa, Y.; Mitsui, K.; Sakamoto, T.; Kawase, M.; Tamiya, H. *Tetrahedorn Lett.* **1990**, *31*, 243. (l) Murahashi, S.-I.; Naota, T.; Nakajima, N. *Chem. Lett.* **1987**, 879. (m) Murahashi, S.-I.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* **1986**, *108*, 7846. (n) Atwell, G. L.; Denny, W. A. *Synthesis* **1984**, 1032. (o) Staab, H. A.; Walther, G. *Angew. Chem.* **1960**, *72*, 35.

5. Kim, J. J.; Park, Y. D.; Lee, W. S.; Cho, S. D.; Yoon, Y. J. *Synthesis* **2003**, 1517.
6. Kim, J. J.; Park, Y. D.; Kweon, D. H.; Kang, Y. J.; Kim, H. K.; Lee, S. G.; Cho, S. D.; Lee, W. S.; Yoon, Y. J. *Bull. Kor. Chem.* **2004**, *25*, 501.
7. Lee, S. G.; Kim, J. J.; Kim, H. K.; Kweon, D. H.; Kang, Y. J.; Cho, S. D.; Kim, S. K.; Yoon, Y. J. *Curr. Org. Chem.* **2004**, *8*, 1463.
8. Won, J. E.; Kim, H. K.; Kim, J. J.; Yim, H. S.; Kim, M. J.; Kang, S. B.; Chung, H. A; Lee, S. G.; Yoon, Y. J. *Tetrahedron* **2007**, *63*, 12720.
9. (a) Chung, H. A.; Kweon, D. H.; Kang, Y. J.; Park, J. W.; Yoon, Y. J. *J. Heterocylic Chem.* **1999**, *36*, 905. (b) Cho, S. D.; Choi, W. Y.; Yoon, Y. J. *J. Heterocyclic Chem.* **1996**, *33*, 1579.
10. Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, *72*(16), 6298.
11. Liley, M. J.; Johnson, T.; Gibson, S. E. *J. Org. Chem.* **2006**, *71*(4), 1322.
12. Fairfull-Smith, K. E.; Jenkins, I. D.; Loughlin, W. A. *Org. & Biomol. Chem.* **2004**, *2*(14), 1979.
13. Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, *23*(8), 1649.
14. Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*(35), 6137.
15. Wu, X.; Ekegren, J. K.; Larhed, M. *Orgnometallics* **2006**, *25*(6), 1434.
16. Gertzmann, R.; Guertler, C. *Tetrahedron Lett.* **2005**, *46*(39), 6659.
17. Khan, M. W.; Reza, A. F. G. M. *Tetrahedron* **2005**, *61*(47), 11204.
18. Ruan, Z.; Lawrence, R. M.; Cooper, C. B. *Tetrahedron Lett.* **2006**, *47*(43), 7649.
19. Bandgar, S. B.; Bandgar, B. P.; Korbad, B. L.; Sawant, S. S. *Tetrahedron Lett.* **2007**, *48*(7), 1287.
20. Kumar, A.; Narasimhan, B.; Kumar, D. *Bioorg. & Med. Chem.* **2007**, *15*(12), 4113.