One-Pot Neat Reactions of Carboxylic Esters and Alkylenediamines for Efficient Preparation of *N*-Acylalkylenediamines

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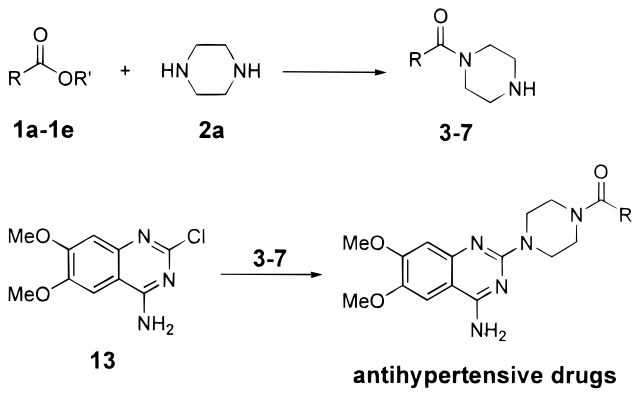
The amide unit is one of the most widely occurring functional groups. It is present as a key feature in many important natural products and man-made compounds.[1] For example (Scheme 1), *N*-acylalkylenediamines[2] are used to react with 4-amino-2-chloro-6,7-dimethoxyquinazolines to give a variety of antihypertensive agents.[3] Though the direct conversion of esters to amides has been reported, the previous application of this method is somewhat limited because it requires solvent and special reagents such as sodium methoxide,[4] sodium hydride,[5] sodium metal,[6] potassium amide,[7] butyllithium,[5] Grignard reagents,[8] lithium aluminum hydride,[9] and silicon tetrachloride,[10] which may interfere with other functional groups in the molecule. Milder catalysts such as 2-pyridone[11] and boron tribromide[12] have also been used; however, the generality of these reactions has not been examined. Another method using activated amines such as tin,[13] titanium[14] and aluminum[15] amides has been addressed; however, no practical technique is available

Scheme 1



for the synthesis of tertiary amides. Furthermore, there is no precedent synthesis of *N*-acylalkylenediamines by direct monoamidation of esters. Monoamidation of alkylenediamines with an acid chloride has been reported for the preparation of *N*-acylalkylenediamines; however, the reaction requires appropriately mask diamines such as monoacetates or hydrogen halides.[2,3] Otherwise, undesired diamidation can also occur. An alternative approach by conversion of esters to *N*-acylalkylenediamines is worthwhile. We report herein a convenient and efficient monoamidation, even for the preparation of tertiary amides, by one-pot neat reaction of carboxylic esters with a variety of alkylenediamines. The yields of *N*-acylalkylenediamines were thus greatly improved.

As shown in Table 1, we prepared *N*-acylalkylenediamine **3**, a useful precursor of the popular antihypertensive drug Doxazosin, in 94% yield by heating ethyl 2,3-dihydrobenzo[1,4]dioxin-2-carboxylate (**1a)** with piperazine (**2a**) under reflux for 3 h. Only 1 equiv of ethanol was released in this clean transformation. The amide **3** was readily obtained by simple acid−base extraction. No diamide was formed. A previous preparation of **3** (61% yield) requires a tedious procedure: (i) saponification of the ester **1a**, (ii) treatment of the resulting acid with $SOCl_2$ to give the acid chloride, and (iii) amidation with piperazine hydrobromide in MeOH. Our present method is obviously superior in terms of high yield and simple operation.

We also examined the effects of solvents and additives. However, no desired amidation occurred on treatment of the ester **1a** with piperazine in refluxing THF, CH_3CN, DMF, or benzene for several hours in the presence of sodium methoxide. Heating at higher temperature in a sealed tube for prolonged duration only caused saponification of **1a** to give the corresponding carboxylic acid. Thus, the amidation is best performed with neat substrates, without addition of any base, catalyst, or solvent.

To demonstrate the general utility of this procedure, we also prepared *N*-acylalkylenediamines **4**−**12** (Table 1) in satisfactory yields. Compounds **4**−**9** are especially useful in the synthesis of generic antihypertensive drugs, Prazosin, Terazosin, Neldazosin, Metazosin, Bunazosin,

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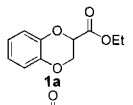
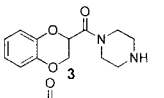
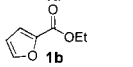
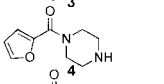
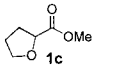
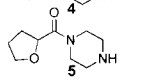
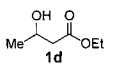
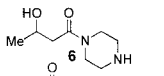
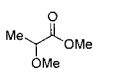
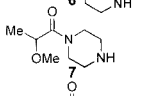
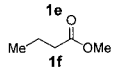
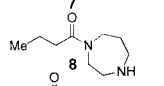
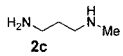
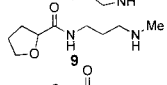
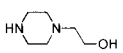
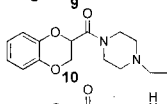
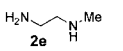
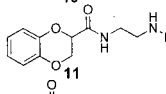
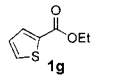
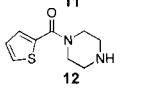
Table 1. Preparation of *N*-Acylalkylenediamines[a]

entry	ester	diamine	time (h)	amide	yield (%)
1	 **1a**	 **2a**	3	 **3**	94
2	 **1b**	**2a**	3	 **4**	89[b]
3	 **1c**	**2a**	5	 **5**	91
4	 **1d**	**2a**	10	 **6**	90
5	 **1e**	**2a**	6	 **7**	90
6	 **1f**	 **2b**	6	 **8**	92
7	**1c**	 **2c**	4	 **9**	83
8	**1a**	 **2d**	3	 **10**	98
9	**1a**	 **2e**	3	 **11**	99
10	 **1g**	**2a**	16	 **12**	60[b]

[a] The reaction was conducted by heating a mixture of ester and diamine at 110 °C for the indicated duration. No solvent is used. [b] A small amount of diamide (3−6%) was also produced.

and Alfuzosin. In each reaction, appropriate ester and diamine (1.2−2.0 equiv) were refluxed for several hours to give the desired *N*-acylalkylenediamines **4**−**12** in nearly pure form. The reactions proceeded smoothly with aliphatic or aromatic esters including the substrates bearing oxy substituents at the α- or *β*-positions. All of the examined acyclic and cyclic diamines were suitable to the monoamidation reactions, even the hydroxyl group on the side chain of piperazine did not interfere with this reaction (entry 8). The primary amine appeared to have higher reactivity than the secondary amine in the amidation (entries 7 and 9). A small amount of diamide (3−6%) could be formed in case a more reactive aromatic ester was used as the starting material (entries 2 and 10). Fortunately, the side product could be removed by simple extraction. Because ethyl thiophene-2-carboxylate did not mix well with piperazine even at a higher temperature (150 °C) in a sealed tube, the yield of amide **12** was not optimized (entry 10). It was noted that the four carbons on the piperazine ring of **4** or **12** underwent fast equilibrium in $CDCl_3$ solution at room temperature, presumably due to the restricted rotation of the amide bond. However, these carbons could be resolved when the ^{13}C NMR spectra were recorded at −50 °C.

In summary, we have demonstrated a general and efficient method of one-pot neat amidation. The operation is simple. The desired secondary and tertiary amides are prepared in high yields for further elaboration to antihypertensive agents.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Merck silica gel 60 F-254 sheets were used for analytical TLC. Column chromatography was conducted on silica gel 60 (Merck, 70−230 mesh ASTM). Melting points were uncorrected. Mass spectra were recorded at an ionizing voltage 70 eV. ^1H and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively.

Ester **1a** was prepared from catechol and ethyl 2,3-dibromopropionate according to reported procedure.[2a] Esters **1b** and **1c** were prepared by Fischer esterification of the corresponding carboxylic acids, other esters **1d**−**g** are commercially available.

***N*-(2,3-Dihydrobenzo[1,4]dioxin-2-carbonyl)piperazine (3).** Under a nitrogen atmosphere, ethyl 2,3-dihydrobenzo-[1,4]dioxin-2-carboxylate (**1a**) (31.20 g, 150 mmol) and piperazine (**2a**) (15.48 g, 180 mmol) were heated at 110 °C for 3 h. After cooling the reaction to room temperature, the mixture was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with water and then dried over Na_2SO_4. The extract was concentrated and chromatographed on a silica gel column (EtOAc/MeOH/Et_3N, 7:3:1) to give the amide **3** (34.96 g, 94%):[16] solid; mp 84−85 °C; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.32; IR (KBr) 3430, 1642 cm^{-1}; MS *m*/*z* (rel intensity) 248 (30, M^+), 111 (100); ^1H NMR ($CDCl_3$) δ 2.20 (s, 1 H, NH), 2.90−2.95 (m, 2 H), 2.95−3.00 (m, 2 H), 3.56−3.61 (m, 2 H), 3.75−3.82 (m, 2 H), 4.37 (dd, J = 11.9, 8.2 Hz, 1 H), 4.53 (dd, J = 11.9, 2.5 Hz, 1 H), 4.87 (dd, J = 8.2, 2.5 Hz, 1 H), 6.88−6.96 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 43.2 (t), 45.8 (t), 46.4 (t), 47.0 (t), 65.2 (t), 70.5 (d), 117.3 (d), 117.4 (d), 121.5 (d), 122.2 (d), 142.6 (s), 143.3 (s), 164.8 (s); HRMS for $C_{13}H_{16}N_2O_3$ calcd 248.1161, found 248.1152. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.73; H, 6.56; N,11.21.

***N*-(Furan-2-carbonyl)piperazine (4) and *N*,*N*′-Bis(furan-2-carbonyl)piperazine (4′).** Under a nitrogen atmosphere, ethyl furan-2-carboxylate (**1b**) (0.71 g, 5 mmol) and piperazine (**2a**) (1.29 g, 15 mmol) were heated at 110 °C for 3 h. After cooling the reaction to room temperature, the residue was extracted with CH_2Cl_2 and 0.5 N HCl. The aqueous layer was adjusted to pH 10 with saturated aqueous K_2CO_3, followed by extraction with $CHCl_3$. The organic layer was washed with water and then dried over Na_2SO_4. The extract was concentrated and chromatographed on a silica gel column (EtOAc/MeOH/Et_3N, 7:3:1) to give the amide **4** (0.80 g, 89%). The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and water and dried over Na_2SO_4. Concentration gave diamide **4′** (0.08 g, 6%). Amide **4**: solid; mp 68−69 °C (lit.[3a] mp 67−68 °C); TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.26; IR (KBr) 3442, 1620 cm^{-1}; MS *m*/*z* (rel intensity) 180 (54, M^+), 95 (100); ^1H NMR ($CDCl_3$) δ 2.27 (br s, 1 H, NH), 2.92−2.96 (m, 4 H), 3.79 (br s, 4 H), 6.49 (dd, J = 3.5, 1.8 Hz, 1 H), 7.00 (dd, J = 3.5, 0.8 Hz, 1 H), 7.50 (dd, J = 1.8, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, −50 °C) δ 43.3 (t), 45.7 (t), 46.3 (t), 47.7 (t), 111.4 (d), 116.4 (d), 144.2 (d), 146.8 (s), 159.2 (s); HRMS for $C_9H_{12}N_2O_2$ calcd 180.0899, found 180.0900. Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.81; H, 6.69; N, 15.48. Diamide **4′**: solid; mp 127−128 °C; TLC (EtOAc/hexane, 7:3) R_f 0.19; IR (KBr) 1628 cm^{-1}; MS *m*/*z* (rel intensity) 274 (5, M^+), 69 (100); ^1H NMR ($CDCl_3$) δ 3.90 (br s, 8 H), 6.51 (dd, J = 3.4, 1.8 Hz, 2 H), 7.08 (d, J = 3.5 Hz, 2 H), 7.51 (d, J = 1.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, −50 °C) δ 42.5 (t), 42.9 (t), 46.4 (t), 46.9 (t), 111.8 (d, 2 C), 117.6 (d, 2 C), 144.5 (d), 144.6 (d), 146.8 (s), 146.9 (s), 159.2 (s), 159.3 (s); HRMS for $C_{14}H_{14}N_2O_4$ calcd 274.0954, found 274.0943. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.35; H, 5.17; N, 10.15.

***N*-(Tetrahydrofuran-2-carbonyl)piperazine (5).** By a procedure similar to that for **3**, a mixture of methyl tetrahydrofuran-2-carboxylate (**1c**) (6.50 g, 50 mmol) and piperazine (**2a**) (5.16 g, 60 mmol) were heated at 110 °C for 5 h to give the amide **3** (8.37 g, 91%): oil; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.30; IR (neat) 3464, 1639 cm^{-1}; MS *m*/*z* (rel intensity) 184 (10, M^+), 71 (100); ^1H NMR ($CDCl_3$) δ 1.87−1.91 (m, 1 H), 1.93−2.07 (m, 2 H), 2.22−2.27 (m, 1 H), 2.45 (s, 1 H, NH), 2.85−2.91 (m, 4 H), 3.48−3.57 (m, 2 H), 3.60−3.69 (m, 2 H), 3.86−3.90 (m, 1 H), 3.93−3.99 (m, 1 H), 4.61 (dd, J = 7.3, 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.6 (t), 28.4 (t), 43.0 (t), 45.8 (t), 46.2 (t), 46.6 (t), 68.9 (t), 75. 6 (d), 169.8 (s); HRMS for $C_9H_{16}N_2O_2$ calcd 184.1212, found 184.1220. Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.20. Found: C, 58.46; H, 8.77; N, 15.29.

***N*-(3-Hydroxybutyryl)piperazine (6).** By a procedure similar to that for **3**, a mixture of ethyl 3-hydroxybutyrate (**1d**) (3.56

(16) For an actual application, the extract was concentrated and used in the subsequent coupling reaction for preparation to give Doxazosin. The U.S and R.O.C. patent applications are under review.

g, 27 mmol) and piperazine (**2a**) (3.44 g, 40 mmol) were heated at 110 °C for 10 h to give the amide **6** (4.18 g, 90%): yellow oil; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.18; IR (neat) 3412, 1624; MS *m/z* (rel intensity) 172 (8, M^+), 69 (100); ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 6.4 Hz, 3 H), 2.31 (dd, J = 16.4, 9.6 Hz, 1 H), 2.49 (dd, J = 16.4, 2.4 Hz, 1 H), 2.83−2.88 (m, 4 H), 3.08 (br s, 2 H, NH and OH), 3.40−3.44 (m, 2 H), 3.55−3.62 (m, 1 H), 3.61−3.67 (m, 1 H), 4.21 (ddq, J = 9.6, 6.4, 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.3 (q), 40.8 (t), 42.3 (t), 45.6 (t), 46.0 (t), 46.3 (t), 64.0 (d), 170.8 (s); HRMS for $C_8H_{16}N_2O_2$ calcd 172.1212, found 172.1217. Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.51; H, 9.42; N, 16.19.

***N*-(2-Methoxypropionyl)piperazine (7).** By a procedure similar to that for **3**, a mixture of methyl 2-methoxypropionate (**1e**) (1.18 g, 10 mmol) and piperazine (**2a**) (1.29 g, 15 mmol) were heated at 110 °C for 6 h to give the amide **7** (1.55 g, 90%): yellow oily solid; TLC (EtOAc/ MeOH/ Et_3N, 7:3:1) R_f 0.26; IR (neat) 3495, 1635 cm^{-1}; MS *m/z* (rel intensity) 172 (11, M^+), 59 (100); ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 6.8 Hz, 3 H), 2.00 (s, 1 H, NH), 2.89−2.98 (m, 4 H), 3.39 (s, 3 H), 3.64−3.70 (m, 4 H), 4.19 (q, J = 6.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.5 (q), 42.8 (t), 45.8 (t, 2 C), 46.1 (t), 56.6 (q), 76.8 (d), 170.4 (s); HRMS for $C_8H_{16}N_2O_2$ calcd 172.1212, found 172.1208. Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.57; H, 9.20; N, 16.33.

***N*-(Butyryl)homopiperazine (8).** By a procedure similar to that for **3**, a mixture of methyl butyrate (**1f**) (3.06 g, 30 mmol) and homopiperazine (**2b**) (4.51 g, 45 mmol) were heated at 110 °C for 6 h to give the amide **8** (4.69 g, 92%): yellow oil; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.35; IR (neat) 3427, 1628 cm^{-1}; MS *m/z* (rel intensity) 170 (100, M^+); ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 5.1 Hz, 3 H), 1.64−1.71 (m, 2 H), 1.75−1.84 (m, 2 H), 1.90 (s, 1 H, NH), 2.27−2.33 (m, 2 H), 2.85−2.89 (m, 2 H), 2.92−2.97 (m, 2 H), 3.46−3.50 (m, 1 H), 3.53−3.57 (m, 1 H), 3.58−3.64 (m, 2 H); ^{13}C NMR ($CDCl_3$) {the sample existed as a mixture of two rotatomers (1:1)} δ 13.9 (q, 2 C), 18.5 (t), 18.6 (t), 29.5 (t), 30.8 (t), 34.9 (t), 35.1 (t), 44.5 (t), 46.8 (t), 47.6 (t), 48.4 (t), 48.6 (t), 48.9 (t), 50.1 (t), 50.8 (t), 172.4 (s), 172.5 (s); HRMS for $C_9H_{18}N_2O$ calcd 170.1419, found 170.1422. Anal. Calcd for $C_9H_{18}N_2O$: C, 63.49; H, 10.66; N, 16.45. Found: C, 63.44; H, 10.70; N, 16.52.

***N*-[3-(Methylamino)propyl]tetrahydrofuran-2-carboxamide (9).** By a procedure similar to that for **3**, a mixture of methyl tetrahydrofuran-2-carboxylate (**1c**) (1.30 g, 10 mmol) and 3-(methylamino)propylamine (**2c**) (1.76 g, 20 mmol) were heated at 110 °C for 4 h to give the amide **9** (1.54 g, 83%): yellow oil; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.18; IR (neat) 3419, 1658 cm^{-1}; MS *m/z* (rel intensity) 186 (10, M^+), 71 (100); ^1H NMR ($CDCl_3$) δ 1.63−1.68 (m, 2 H), 1.73 (br s, 1 H, NH), 1.81−1.89 (m, 2 H), 1.98−2.05 (m, 1 H), 2.17−2.26 (m, 1 H), 2.39 (s, 3 H), 2.57−2.64 (m, 2 H), 3.26−3.34 (m, 2 H), 3.80−3.85 (m, 1 H), 3.86−3.91 (m, 1 H), 4.30 (dd, J = 8.4, 5.7 Hz, 1 H), 7.22 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 25.4 (t), 28.9 (t), 30.2 (t), 36.1 (q), 37.3 (t), 49.6 (t), 69.2 (t), 78.4 (d), 173.2 (s); HRMS for $C_9H_{18}N_2O_2$ calcd 186.1368, found 186.1360. Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 57.86; H, 9.68; N, 15.09.

***N*-(2,3-Dihydrobenzo[1,4]dioxin-2-carbonyl)-*N*′-(2-hydroxyethyl)piperazine (10).** By a procedure similar to that for **3**, a mixture of ethyl 2,3-dihydrobenzo[1,4]dioxin-2-carboxylate (**1a**) (2.08 g, 10 mmol) and 2-hydroxyethylpiperazine (**2d**) (1.56 g, 12 mmol) were heated at 110 °C for 3 h to give the amide **10** (2.86 g, 98%): solid; mp 61−62 °C; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.33; IR (KBr) 3449, 1646 cm^{-1}; MS *m/z* (rel intensity) 292 (6, M^+), 261 (100); ^1H NMR ($CDCl_3$) δ 1.62 (br s, 1 H, OH), 2.50−2.55 (m, 1 H), 2.56−2.64 (m, 5 H), 3.60−3.65 (m, 2 H), 3.66−3.70 (m, 2 H), 3.79−3.85 (m, 2 H), 4.33 (dd, J = 11.9, 8.1 Hz, 1 H), 4.48 (dd, J = 11.9, 2.2 Hz, 1 H), 4.83 (dd, J = 8.1, 2.2 Hz, 1 H), 6.85−6.93 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 42.0 (t), 45.7 (t), 52.5 (t), 53.2 (t), 57.9 (t), 59.4 (t), 65.2 (t), 70.6 (d), 117.3 (d), 117.4 (d), 121.5 (d), 122.2 (d), 142,5 (s), 143.3 (s), 164.8 (s); HRMS for $C_{15}H_{16}N_2O_4$ calcd 292.1423, found 292.1420. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.28; H, 5.62; N, 9.70.

***N*-[2-(Methylamino)ethyl]-2,3-dihydrobenzo[1,4]dioxin-2-carboxamide (11).** By a procedure similar to that for **3**, a mixture of ethyl 2,3-dihydrobenzo[1,4]dioxin-2-carboxylate (**1a**) (2.08 g, 10 mmol) and 3-(methylamino)ethylamine (**2e**) (0.89 g, 12 mmol) were heated at 110 °C for 3 h to give the amide **11** (2.34 g, 99%): solid; mp 60−61 °C; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.26; IR (KBr) 3382, 1677 cm^{-1}; MS *m/z* (rel intensity) 236 (2, M^+), 57 (100); ^1H NMR ($CDCl_3$) δ 1.90 (br s, 1 H, NH), 2.43 (s, 3 H), 2.72−2.81 (m, 2 H), 3.41−3.49 (m, 2 H), 4.23 (dd, J = 11.4, 7.2 Hz, 1 H), 4.55 (dd, J = 11.4, 2.7 Hz, 1 H), 4.71 (dd, J = 7.2, 2.7 Hz, 1 H), 6.89−6.94 (m, 3 H), 6.98−7.02 (m, 1 H), 7.16 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 35.9 (q), 38.4 (t), 50.3 (t), 65.3 (t), 73.2 (d), 117.2 (d), 117.5 (d), 121.8 (d), 122.2 (d), 141.7 (s), 143.2 (s), 167.3 (s); HRMS for $C_{12}H_{16}N_2O_3$ calcd 236.1161, found 236.1167. Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.86; H, 6.81; N, 11.81.

***N*-(Thiophene-2-carbonyl)piperazine (12) and *N*,*N*′-Bis-(thiophene-2-carbonyl)piperazine (12′).** By a procedure similar to that for **4** and **4′**, a mixture of ethyl thiophene-2-carboxylate (**1g**) (1.56 g, 10 mmol) and piperazine (**2a**) (1.72 g, 20 mmol) were heated at 110 °C for 16 h to give the amide **12** (1.18 g, 60%) and the diamide **12′** (0.10 g, 3%). Amide **12**: yellow oily solid; TLC (EtOAc/MeOH/Et_3N, 7:3:1) R_f 0.27; IR (neat) 3449, 1613 cm^{-1}; MS *m/z* (rel intensity) 196 (8, M^+), 111 (100); ^1H NMR ($CDCl_3$) δ 2.08 (s, 1 H, NH), 2.89−2.93 (m, 4 H), 3.70−3.74 (m, 4 H), 7.04 (dd, J = 5.1, 3.7 Hz, 1 H), 7.28 (dd, J = 3.7, 1.1 Hz, 1 H), 7.44 (dd, J = 5.1, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, −50 °C) δ 43.5 (t), 45.6 (t), 46.3 (t), 48.9 (t), 126.9 (d), 128.9 (d), 129.1 (d), 136.6 (s), 163.7 (s); HRMS for $C_9H_{12}N_2OS$ calcd 196.0670, found 196.0668. Anal. Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27. Found: C, 54.89; H, 6.36; N, 14.41. Diamide **12′**: solid; mp 177−178 °C; TLC (EtOAc/hexane, 7:3) R_f 0.32; IR (KBr) 1602 cm^{-1}; MS *m/z* (rel intensity) 306 (8, M^+), 111 (100); ^1H NMR ($CDCl_3$) δ_3.84 (br s, 8 H), 7.09 (dd, J = 4.8, 3.8 Hz, 2 H), 7.34 (d, J = 3.8 Hz, 2 H), 7.50 (d, J = 4.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, −50 °C) δ 42.5 (t), 43.1 (t), 47.6 (t), 48.2 (t), 127.2 (d), 127.3 (d), 129.4 (d), 129.5 (d), 129.8 (d), 130.0 (d), 136.2 (s, 2 C), 164.0 (s, 2 C); HRMS for $C_{14}H_{14}N_2O_2S_2$ calcd 306.0497, found 306.0511. Anal. Calcd for $C_{14}H_{14}N_2O_2S_2$: C, 54.88; H, 4.61; N, 9.14. Found: C, 54.89; H, 4.65; N, 9.05.

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Supporting Information Available: ^1H and ^{13}C spectra for compounds **3**−**12** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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