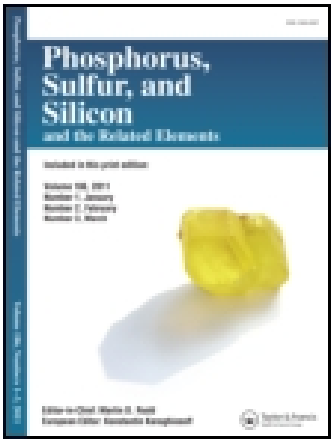

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Sequential One-Pot Reactions of Thioformamides with Organolithium and Zinc Reagents

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SEQUENTIAL ONE-POT REACTIONS OF THIOFORMAMIDES WITH ORGANOLITHIUM AND ZINC REAGENTS

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Abstract *Sequential one-pot reactions of thioformamides with organolithium and zinc reagents were carried out. As thioformamides, N,N-dimethylthioformamide and N-ethoxycarbonyl N′-thioformyl piperazine were used. A variety of organolithium reagents such as alkyl, aryl, and heteroaryllithiums were used to give the corresponding amines in moderate to high yields. The efficiency of the reaction was influenced by the substituents on the aromatic rings. Thienyllithium gave the product in good yield, whereas the reaction of furyllithium was less efficient. A similar reaction with lithium acetylides was not successful. As an alternative method, methyl iodide was added to the reaction mixture of thioformamides and lithium silylacetylide to form S,N-acetals as intermediates, and to this were added organozinc reagents to lead to propargylamines. For organozinc reagents, dialkyl zincs and 3-ethoxycarbonylpropylzinc bromide were used. The former reagents showed high efficiency when combined with several organolithium reagents, but the latter gave the corresponding product only when lithium silylacetylide was used as an initial reagent.*

Keywords Amines; organolithium reagents; organozinc reagents; piperazines; sequential reaction

INTRODUCTION

Sequential one-pot reactions are important processes in organic syntheses[1] because several components can be combined in a single operation without the need to isolate stable intermediates. For example, three-component reactions of aldehydes, amines, and terminal acetylenes mediated by metal catalysts have been widely developed to provide new methods for the synthesis of propargylamines.[2] During our studies[3] on thiocarbonyl compounds, we found a new approach to propargylamines via thioiminium salts derived from thioamides.[4] These salts undergo sequential reactions with lithium acetylides and Grignard reagents to lead to propargylamines with a tetra-substituted carbon atom adjacent to the nitrogen atom (Scheme 1). This protocol can be applied to thioiminium salts generated from thiolactams (Scheme 2).[5] These results have stimulated several groups to

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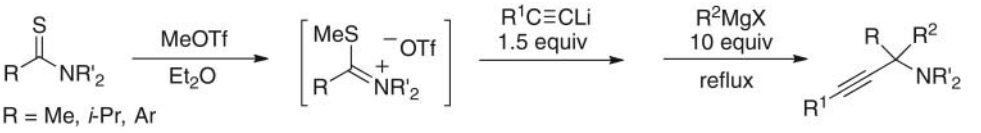
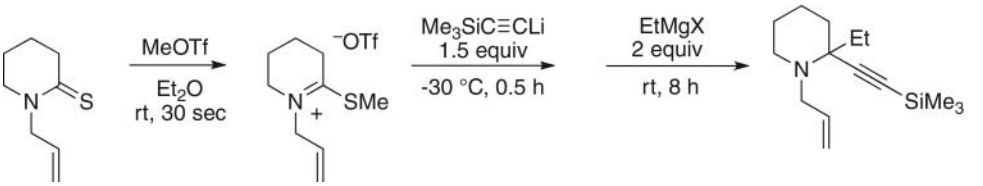
establish similar modified sequential reactions from thiolactams,[6] amides,[7] and lactams.[8] We further found that thioformamides can participate in sequential reactions with alkyl, aryllithiums, and Grignard reagents without their preactivation (Scheme 3).[9] The use of thioformamides enabled us to establish an addition reaction of two different Grignard reagents.[10] Organozinc reagents[11] have also been used for carbon–carbon bond-forming reactions and are considered to be milder reagents than Grignard regents. Therefore, some oxygen-containing functional groups can tolerate the reaction conditions with organozinc reagents. We then applied organozinc reagents to our sequential reactions, and the details of these reactions are reported here.



Scheme 1



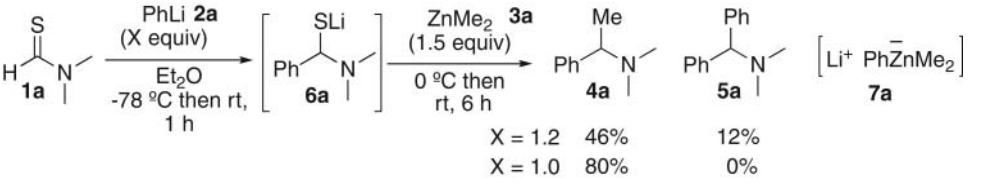
Scheme 2

Scheme 3

RESULTS AND DISCUSSION

Initially, to a diethyl ether solution of *N*,*N*-dimethyl thioformamide (**1a**) were added phenyllithium (**2a**) (1.2 equiv.) and dimethylzinc (**3a**) (1.5 equiv.) in this order (Scheme 4). As a result, amine **4a**, in which these two organometallic reagents were incorporated into **1a**, was obtained in 46% yield along with 12% of amine **5a**. Amine **5a** was formed by reacting **1a** with two molecules of **2a**, but the simple mixing of **1a** and excess **2a** under similar reaction conditions did not give **5a** at all. Therefore, the second addition of a phenyl group to lithium thiolate **6a** may be from lithium zincate[12] **7a** generated in situ from **2a** and **3a**. To avoid the formation of **5a**, **2a** (1 equiv.) was used to give **4a** in high yield.

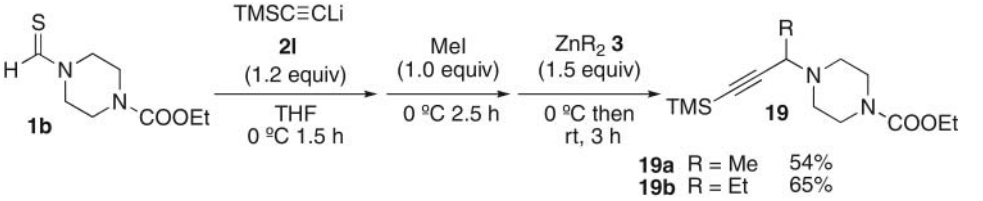
We then shifted our attention to thioformamides that were susceptible to the reaction with Grignard reagents. *N*-Ethoxycarbonyl *N*′-thioformyl piperazine (**1b**) was chosen, because *N*-alkoxylcarbonyl *N*-secondary alkyl piperazines are of biological interest and



Scheme 4

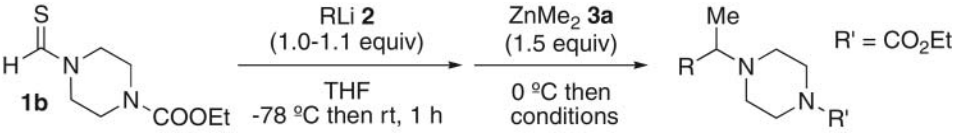
are used as key synthetic intermediates.[13] As in the reaction of thioformamide **1a**, **1b** was reacted with phenyllithium (**2a**) and **3a**, but the reaction with **3a** for 6 h gave no expected product (Table 1). The reaction with **3a** was then prolonged to 310 h to give the desired product **8** in only 34% yield (entry 1). The reaction with **3a** at higher temperature gave **8** in better yield (entry 2). A variety of organolithium reagents **2** were used for the reaction of **1b**. In the second step, the reaction with **3a** continued for 24 h under reflux in tetrahydrofuran (THF). The use of BuLi (**2**) followed by the addition of **3a** gave amine **9** (entry 3). However, in this case the reaction for a longer reaction time in the second step reduced the yield of the product **9** (entry 4). Furfuryllithium (**2c**) and thienyllithum (**2d**) participated in the reaction (entries 5–7), and the former gave amine **10** in lower yield. The reaction of 1-naphthyllithium **2e** and (2-methylphenyl)lithium (**2f**) gave amines **12** and **13** (entries 8 and 9). For the reaction of methoxyphenyllithiums **2g** and **2h**, the yields of the products **14** and **15** were influenced by the position of the methoxy group (entries 10 and 11). Ortho-substituted lithium **2g** gave **14** in lower yield than para-substituted lithium **2h**. The reaction of (4-trifluoromethylphenyl)lithium gave amine **15** in 85% (entry 12). Ferrocenyllithium could also be used as an organolithium reagent (entry 13).

In contrast to the successful results with alkyl and aryllithium reagents, the reaction of thioformamide **1b** with lithium acetylide and dimethylzinc (**3a**) did not give the desired products at all. To confirm whether the initial addition of lithium acetylides to **1** proceeded with high efficiency, methyl iodide was added to the reaction mixture of **1b** and lithium acetylides (Table 2). As a result, the reaction with lithium phenylacetylide (**2k**) gave *S*,*N*-acetal[14] **18a** in moderate to good yields (entries 1–3), and the reaction with lithium (trimethylsilyl)acetylide (**2l**) led to the product **18b** in high yield (entries 4 and 5), although isolation of the former product **18a** failed and gave a complex mixture. Methyl iodide was then added prior to the addition of organozinc reagents **3** in sequential reactions (Scheme 5). The reaction of **1b** with lithium acetylide **2l** and methyl iodide followed by the addition of **3** gave the desired products **19** in good yield, whereas the use of lithium acetylide **2k** did not give the corresponding products.



Scheme 5

Table 1 Sequential one-pot reaction of thioformamide **1b** with organolithium **2** and zinc reagents **3**



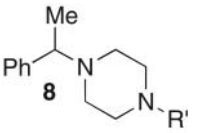
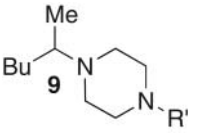
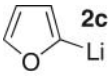
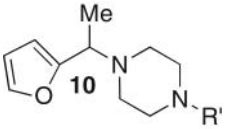
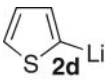
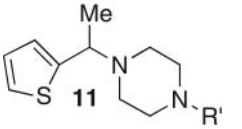
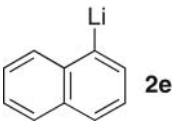
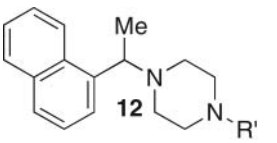
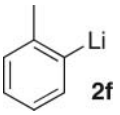
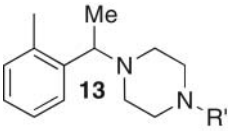
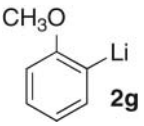
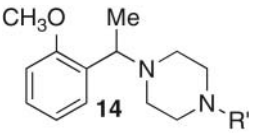
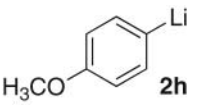
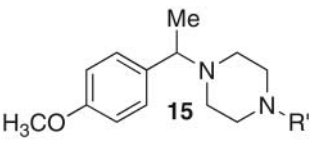
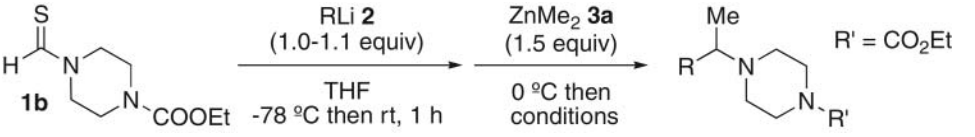
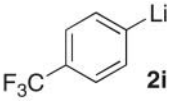
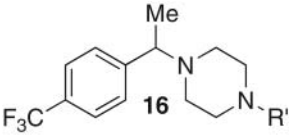
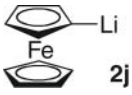
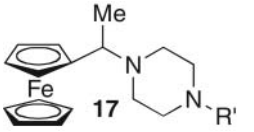
Entry	RLi **2**	Conditions	Yield	Product
1	PhLi	rt, 310 h	34%	
2	**2a**	reflux, 48 h	76%	
3	BuLi	reflux, 24 h	45%	
4	**2b**	reflux, 48 h	23%	
5		reflux, 24 h	<9%	
6[b]		reflux, 24 h	29%	
7		reflux, 24 h	53%	
8		reflux, 24 h	60%	
9		reflux, 24 h	74%	
10		reflux, 24 h	29%	
11		reflux, 24 h	59%	

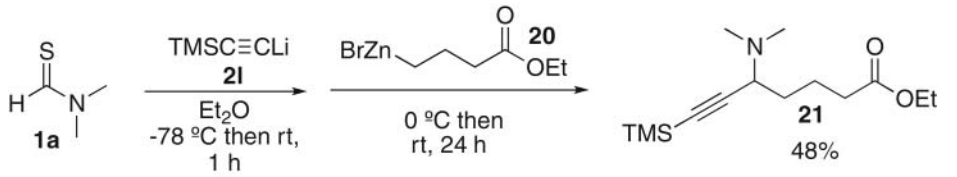
Table 1 Sequential one-pot reaction of thioformamide **1b** with organolithium **2** and zinc reagents **3** *(Continued)*



Entry	RLi **2**	Conditions	Yield	Product
12		reflux, 24 h	85%	
13		reflux, 24 h	43%	

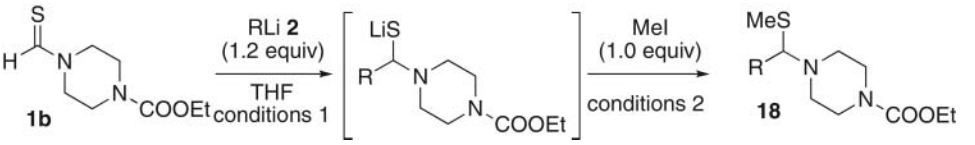
[a]Isolated yield. [b]Lithium reagent (1.5 equiv) was used.

Finally, organozinc reagents with a carbonyl group were used (Scheme 6). Several combinations of organolithium reagents and zinc reagent **20** were attempted. Among them, the sequential reaction of thioformamide **1a** with lithium silylacetylide **2l** and the reagent **20** gave propargylamine **21** in moderate yield.



Scheme 6

Table 2 Synthesis of *S,N*-acetals **8**.



Entry	RLi **2**	Conditions 1	Conditions 2	Product	NMR yield[a]
1	PhCE≡CLi	−78 °C then rt, 1h	0 °C then rt, 2.5 h	**18a**	30
2	**2k**	−18 °C 1.5 h	−15 °C, 2.5 h		61
3		0 °C 1.5 h	0 °C, 2.5 h		45
4	TMSC≡CLi	−78 °C then rt, 1h	0 °C then rt, 2.5 h	**18b**	86
5	**21**	0 °C 1.5 h	0 °C, 2.5 h		94

[a]1,1,2,2-Tetrachloroethane was used as an internal standard.

In summary, the sequential one-pot reaction of thioformamides with organolithium and zinc reagents has been demonstrated. The thioformamide with an ethoxycarbonyl group could be used as a starting material. As organolithium compounds, aliphatic and aromatic reagents were available, but the yields of the products depended on the substituents on the reagents. For organozinc reagents, dialkylzinc reagents were efficiently applied to the reaction, whereas the reaction with that having an ethoxycarbonyl group proceeded with medium efficiency.

EXPERIMENTAL

The infrared (IR) spectra were obtained on a JASCO FT/IR 410 spectrometer. ^{1}H NMR (399.7 MHz) and ^{13}C NMR (100.4 MHz) spectra were measured on a JNM-A400 spectrometer. The ^{1}H and ^{13}C chemical shifts are reported in δ values and refer to tetramethylsilane or $CDCl_3$ as an internal standard, respectively. All spectra were acquired in the proton-decoupled mode. The mass spectra (MS) and the high-resolution mass spectra (HRMS) were measured on JMS-700 mass spectrometers. Melting points were determined by using a Yanaco MP-S2 micro melting point apparatus (Seisakusho) and are uncorrected.

4-(1-Phenylethyl)-piperazine-1-carboxylic Acid Ethyl Ester (8)

To a 20-mL two-necked flask were added 1-ethoxycarbonyl-4-thioformylpiperadine (203 mg, 1.0 mmol) and THF (2 mL) under an Ar atmosphere, and to this was slowly added a 1.0 M solution of phenyllithium in cyclohexane-Et_2O (1.1 mL, 1.1 mmol) at -78°C. After the addition was complete, the mixture was stirred for 1 h at room temperature. To this was added a 1.0 M solution of dimethylzinc in n-hexane solution (1.50 mL, 1.5 mmol) at 0°C, and the mixture was stirred for 48 h under reflux. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl. After filtration, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc/Et_3N = 1:1:0.01) to afford the amine **8** (0.200 g, 76%) as a yellow oil: IR (neat) 2978, 2933, 2862, 2810, 2360, 2247, 1697, 1433, 1246, 1125, 997, 911, 732, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, J = 7.3 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H), 2.28–2.34 (br, 4H), 3.28–3.37 (brm, 5H), 4.18 (q, 2H), 7.18 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 14.6, 19.5, 43.8, 50.1, 61.1, 64.6, 127.0, 127.5, 128.2, 143.5, 155.4; MS (EI) m/z 262 (M^+); HRMS (EI) Anal. Calcd. for $C_{15}H_{22}N_2O_2$ (M^+) 262.1681; Found: 262.1667.

4-(1-Methylpentyl)-piperazine-1-carboxylic Acid Ethyl Ester (9)

A yellow oil: IR (neat) 2961, 1707, 1429, 1383, 1349, 1281, 1244, 1168, 1118, 1093, 1037, 996, 766, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.84 (t, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 1.14–1.28 (m, 9H), 2.30–2.51 (brm, 5H), 3.39 (brm, 4H), 4.07 (q, 2H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 14.1, 14.6, 22.8, 29.1, 33.1, 44.1, 48.0, 59.2, 61.1, 155.5; MS (EI) m/z 242 (M^+); HRMS (EI) Anal. Calcd. for $C_{13}H_{26}N_2O_2$ (M^+) 242.1994; Found: 242.2025.

4-(1-Furylethyl)-piperazine-1-carboxylic Acid Ethyl Ester (10)

A yellow oil: IR (neat) 3513, 2978, 2935, 2819, 1699, 1431, 1384, 1301, 1281, 1246, 1135, 995, 767, 739, 599 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, J = 6.8 Hz, 3H), 1.37 (d, J = 6.8 Hz, 3H), 2.36–2.43 (br, 4H), 3.43 (br, 4H), 3.73 (q, J = 6.8 Hz, 1H), 4.06 (q, J =

6.8 Hz, 2H), 6.10 (br, 1H), 6.27 (br, 1H), 7.32 (br, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.6, 15.5, 43.8, 49.1, 57.2, 61.2, 107.2, 109.7, 141.6, 155.1, 155.4; MS (EI) m/z 252 (M^+); HRMS (EI) Anal. Calcd. for $C_{13}H_{20}N_2O_3$ (M^+) 252.1474; Found: 252.1439.

4-(1-Thienylethyl)-piperazine-1-carboxylic Acid Ethyl Ester (11)

A yellow oil: IR (neat) 2976, 2813, 1699, 1431, 1382, 1302, 1280, 1245, 1122, 1086, 1044, 994, 850, 832, 766, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J = 6.8 Hz, 3H), 1.43 (d, J = 6.3 Hz, 3H), 2.46 (br, 4H), 3.47 (br, 4H), 3.91 (q, J = 6.8 Hz, 1H), 4.11 (q, J = 6.8 Hz, 2H), 6.86 (d, J = 3.4 Hz, 1H), 6.94 (dd, J = 3.4 Hz, 4.6 Hz, 1H), 7.32 (d, J = 3.4 Hz, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.6, 17.8, 43.9, 49.0, 59.4, 61.2, 124.2, 124.3, 126.2, 147.2, 155.4; MS (EI) m/z 312 (M^+); HRMS (EI) Anal. Calcd. for $C_{13}H_{20}N_2O_2S$ (M^+) 268.1245; Found: 268.1224.

4-(1-Naphthylethyl)-piperazine-1-carboxylic Acid Ethyl Ester (12)

A yellow oil: IR (neat) 3047, 2977, 2931, 2859, 2810, 1698, 1431, 1377, 1289, 1245, 1125, 995, 931, 802, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, J = 6.8 Hz, 3H), 1.46 (d, J = 6.8 Hz, 3H), 2.31–2.36 (m), 2.42 (br, 2H), 3.38 (q, J = 6.83 Hz, 1H), 3.44 (t, J = 4.9 Hz, 4H) 4.11 (q, J = 7.3 Hz, 2H), 7.21–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 14.6, 18.5, 43.9, 50.3, 61.1, 61.4, 124.0, 124.6, 125.3, 125.3, 125.4, 127.4, 128.9, 131.5, 134.0, 140.0, 155.4; MS (EI) m/z 312 (M^+); HRMS (EI) Anal. Calcd. for $C_{19}H_{24}N_2O_2$ (M^+) 312.1832; Found: 312.1827.

4-(2-Methylphenyl)-piperazine-1-carboxylic Acid Ethyl Ester (13)

A yellow oil: IR (neat) 2976, 2806, 1702, 1432, 1382, 1290, 1244, 1124, 994, 833, 761, 729, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J = 7.3 Hz, 3H), 1.28 (d, J = 6.4 Hz, 3H), 2.34 (br, 2H), 2.34 (s, 3H) 2.46 (br, 2H), 3.42 (br, 4H) 3.57 (q, J = 6.8 Hz, 1H), 4.12 (q, J = 7.3 Hz, 2H), 7.11–7.18 (m, 3H), 7.42 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.6, 18.2, 19.3, 43.8, 50.1, 60.2, 61.1, 125.9, 126.3, 126.5, 130.3, 135.7, 142.4, 155.3; MS (EI) m/z 276 (M^+); HRMS (EI) Anal. Calcd. for $C_{16}H_{24}N_2O_2$ (M^+) 276.1832; Found: 276.1829.

4-(2-Methoxyphenyl)-piperazine-1-carboxylic Acid Ethyl Ester (14)

A yellow oil: IR (neat) 3511, 2976, 2860, 2835, 2809, 2762, 1698, 1598, 1586, 1489, 1435, 1379, 1287, 1245, 1158, 1123, 1048, 1030, 994, 936, 755, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, J = 6.8 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 2.38 (br, 2H), 2.45 (br, 2H), 3.45 (br, 4H), 3.80 (s, 3H), 4.00 (q, J = 6.8 Hz, 1H), 4.10 (q, J = 6.8 Hz, 2H), 6.86 (d, J = 8.3 Hz, 1H), 6.95 (t, J = 7.3 Hz, 1H), 7.21 (t, J = 8.3 Hz, 1H), 7.40 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.6, 19.4, 43.8, 50.1, 55.3, 55.7, 61.1, 110.5, 120.5, 127.5, 127.6, 131.4, 155.4, 156.9; MS (EI) m/z 292 (M^+); HRMS (EI) Anal. Calcd. for $C_{16}H_{24}N_2O_3$ (M^+) 292.1787; Found: 292.1764.

4-(4-Methoxyphenyl)-piperazine-1-carboxylic Acid Ethyl Ester (15)

A yellow oil: IR (neat) 3537, 2974, 2934, 2809, 1700, 1612, 1510, 1432, 1378, 1294, 1246, 1172, 1124, 1036, 993, 936, 834, 766, 732, 552, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.23

(t, $J = 6.8$ Hz, 3H), 1.34 (d, $J = 6.8$ Hz, 3H), 2.34 (br, 2H), 2.40 (br, 2H), 3.45 (br, 4H), 3.45 (q, $J = 6.8$ Hz, 1H), 3.80 (s, 3H), 4.10 (q, $J = 6.8$ Hz, 2H), 6.85 (d, $J = 8.3$ Hz, 2H), 7.20 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 14.6, 19.3, 43.8, 49.9, 55.1, 61.1, 63.9, 113.5, 128.5, 135.3, 155.3, 158.8; MS (EI) m/z 292 (M^+); HRMS (EI) Anal. Calcd. for $C_{16}H_{24}N_2O_3$ (M^+) 292.1787; Found: 292.1792.

4-(4-Trifluoromethylphenyl)-piperazine-1-carboxylic Acid Ethyl Ester (16)

A yellow oil: IR (neat) 2979, 2812, 2762, 1702, 1618, 1432, 1379, 1325, 1245, 1163, 1124, 1068, 1016, 994, 935, 845, 767, 732, 610, 591, 541, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, $J = 7.1$ Hz, 3H), 1.35 (d, $J = 6.4$ Hz, 3H), 2.34 (br, 2H), 2.44 (br, 2H), 3.45 (br, 5H), 4.11 (q, $J = 7.1$ Hz, 2H), 7.43 (d, $J = 7.8$ Hz, 2H), 7.57 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.5, 19.2 (CH_3), 43.7, 50.0, 61.1, 64.1, 124 ($^1J_{C\text{-}F} = 272.1$ Hz), 125 ($^3J_{C\text{-}F} = 3.3$ Hz), 129 ($^2J_{C\text{-}F} = 33.1$ Hz), 148.1, 155.2, 155.4; MS (EI) m/z 330 (M^+); HRMS (EI) Anal. Calcd. for $C_{16}H_{21}F_3N_2O_2$ (M^+) 330.1555; Found: 330.1540.

4-(1-Ferrocenylethyl)-piperazine-1-carboxylic Acid Ethyl Ester (17)

A brown oil: IR (neat) 3534, 3093, 2978, 2815, 1698, 1433, 1383 1299, 1279, 1243, 1157, 1133, 1084, 1038, 999, 901. 819, 764, 732, 489, 480 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, $J = 7.3$ Hz, 3H), 1.44 (d, $J = 6.8$ Hz, 3H), 2.16 (br, 2H), 2.34 (br, 2H), 3.35 (br, 4H), 3.59 (q, $J = 6.8$ Hz, 1H), 4.02 (m, 2H), 4.08 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.6, 16.6, 43.9, 48.4, 58.9, 61.1, 66.8, 67.3, 68.6, 69.3, 86.9, 155.3; MS (EI) m/z 370 (M^+); HRMS (EI) Anal. Calcd. for $C_{19}H_{24}N_2O_2$ (M^+) 370.1344; Found: 370.1315.

4-(1-Methylthio-3-trimethylsilanyl-2-propynyl)-piperazine-1-carboxylic Acid Ethyl Ester (18b)

To a 20-mL two-necked flask were added 1-ethoxycarbonyl-4-thioformylpiperazine (**1b**) (203 mg, 1.0 mmol) and THF (1 mL) under an Ar atmosphere, and to this solution was slowly added lithium (trimethylsilyl)acetylide, prepared from (trimethylsilyl)acetylene (0.170 mL, 1.2 mmol) and 1.3 M solution of n-butyllithium in n-hexane (0.92 mL, 1.2 mmol) in THF (1 mL) at 0°C via a cannula. After the addition was complete, the mixture was stirred for 1.5 h at 0°C. To this mixture was added methyl iodide (0.62 mL, 1.0 mmol) at 0°C, and this mixture was stirred for 2.5 h at 0°C. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford the *S*,*N*-acetal **18b** (0.301 g, 94%) as a brown oil: IR (neat) 2959, 2919, 2862, 2826, 2165, 1700, 1633, 1432, 1384, 1323, 1301, 1279, 1246, 1170, 1134, 1079, 1051, 992, 844, 788, 762, 735, 646, 545 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.15 (s, 9H), 1.23 (t, $J = 7.1$ Hz, 3H), 2.16 (s, 3H), 2.54 (brm, 2H), 2.65 (brm, 2H), 3.47 (br, 4H), 4.10 (q, $J = 7.1$ Hz, 2H), 4.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 0.0, 14.7, 14.8, 43.5, 48.3, 61.4, 63.3, 68.0, 74.2, 93.2, 98.7, 155.5; MS (EI) m/z 314 (M^+); HRMS (EI) Anal. Calcd. for $C_{14}H_{26}N_2O_2SSi$(M^+) 314.1484; Found: 314.1492.

4-(1-Methyl-3-(trimethylsilyl)propynyl)-piperazine-1-carboxylic Acid Ethyl Ester (19a)

To a 20-mL two-necked flask were added 1-ethoxycarbonyl-4-thioformylpiperadine (**1b**) (203 mg, 1.0 mmol) and THF (1 mL) under an Ar atmosphere, and to this mixture was slowly added lithium (trimethylsilyl)acetylide, prepared from (trimethylsilyl)acetylene

(0.170 mL, 1.2 mmol) and 1.68 M solution of n-butyllithium in n-hexane (0.71 mL, 1.2 mmol) in THF (1 mL) at −78°C via a cannula. After the addition was complete, the mixture was stirred for 1.5 h at 0°C. To this mixture was added methyl iodide (0.62 mL, 1.0 mmol) at 0°C, and this mixture was stirred for 2.5 h at 0°C. To this was added a 1.0 M solution of dimethylzinc in n-hexane solution (1.50 mL, 1.5 mmol) at 0°C, and this mixture was stirred for 3 h under room temperature. The resulting mixture was poured into a saturated aqueous solution of NH_4Cl. After filtration, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc/Et_3N = 1:1:0.01) to afford the amine **19a** (0.153 g, 54%) as a brown oil: IR (neat) 2959, 2863, 2157, 1704, 1430, 1384, 1298, 1244, 1221, 1163, 1123, 1095, 1069, 1038, 992, 960, 891, 842, 760, 699, 633, 549 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.11 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H), 1.28 (d, J = 7.2 Hz, 3H), 2.36 (br, 2H), 2.56 (br, 2H), 3.39–3.53 (brm, 5H), 4.10 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 0.1, 14.6, 19.1, 43.6, 48.7, 52.5, 61.2, 89.4, 103.9, 155.5; MS (EI) m/z 282 (M^+); HRMS (EI) Anal. Calcd. for $C_{14}H_{26}N_2O_2Si$ (M^+) 282.1764; Found: 282.1754.

4-(1-Ethyl-3-(trimethylsilyl)propynyl)-piperazine-1-carboxylic Acid Ethyl Ester (19b)

A brown oil: IR (neat) 2964, 2820, 2159, 1705, 1430, 1384, 1326, 1279, 1243, 1216, 1158, 1123, 1045, 999, 958, 890, 842, 761, 699, 635, 543 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.58 (quint, J = 7.5 Hz), 2.34 (br, 2H), 2.52 (br, 2H), 3.17 (t, J = 7.4 Hz, 1H), 3.42 (brm, 4H) 4.10 (q, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 0.2, 11.1, 14.7, 26.2, 43.7, 48.9, 59.7, 61.2, 90.2, 103.2, 155.5; MS (EI) m/z 296 (M^+); HRMS (EI) Anal. Calcd. for $C_{15}H_{28}N_2O_2Si$ (M^+) 296.1920; Found: 296.1898.

5-Dimethylamino-7-trimethylsilanyl-hept-6-ynoic Acid Ethyl Ester (21)

To a solution of lithium (trimethylsilyl)acetylide (**2l**) prepared from (trimethylsilyl)acetylene (0.160 mL, 1.1 mmol) and a 1.55 M solution of n-butyllithium in n-hexane (0.71 mL, 1.1 mmol) in Et_2O (1 mL) at −78°C was slowly added *N*,*N*-dimethylthioformamide (**1a**) (87 μL, 1.0 mmol) via syringe. After the addition was complete, the mixture was stirred for 1 h at room temperature. To this was added a 0.3 M solution of 4-ethoxy-4-oxobutylzincbromide in THF (4.0 mL, 1.2 mmol) at 0°C, and this mixture was stirred for 6 h under room temperature. The resulting mixture was poured into an saturated aqueous solution of EDTA. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc/Et_3N = 1:1:0.01) to afford the amine **21** (0.107 g, 40%) as yellow oil: IR (neat) 2958, 2864, 2825, 2781, 2158, 1737, 1454, 1374, 1301, 1249, 1183, 1078, 1032, 997, 956, 928, 842, 760, 698, 620 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.11 (s, 9H), 1.19 (t, J = 7.2 Hz, 3H), 1.56 (quint, J = 7.6 Hz, 2H), 1.65–1.75 (m, 2H), 2.16 (s, 6H), 2.27 (t, J = 7.6 Hz, 2H), 3.24 (t, J = 7.2 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ: 0.1, 14.1, 21.9, 33.0, 33.9, 41.1, 57.8, 66.8, 90.0, 102.9, 173.3; MS (EI) m/z 269 (M^+); HRMS (EI) Anal. Calcd. for $C_{14}H_{27}NO_2Si$ (M^+) 269.1811; Found: 269.1814.

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