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PAPER

Pd(II)-Catalyzed Ligand Controlled Synthesis of Pyrazole-4-carboxylates and Benzo[*b*]thiophene-3-carboxylates

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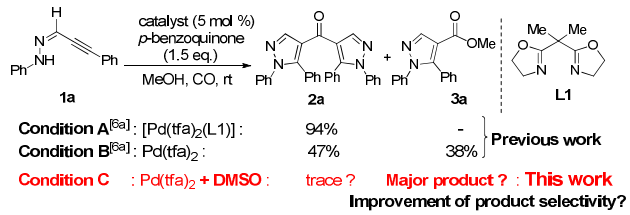
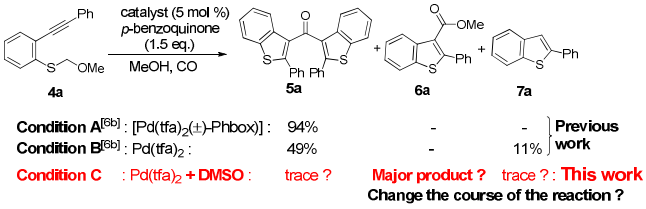
Cyclization-carbonylation of α,β-Alkynic hydrazones and (*o*-alkynylphenyl) (methoxymethyl) sulfides with $Pd(tfa)_2$ in DMSO / MeOH afforded methyl pyrazole-4-carboxylates and benzo[*b*]thiophene-3-carboxylates, respectively, in good yields. A simple change of ligand (solvent) allowed controlled, effective switching between cyclization-carbonylation-cyclization-coupling (CCC-coupling) reactions and cyclization-carbonylation reactions.

Introduction

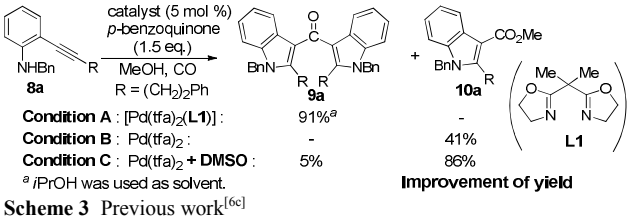
Pyrazoles and benzo[*b*]thiophenes are important classes of *N*- and *S*-heterocycles in pharmaceutical science.[1] They are found in a variety of drugs, pesticides and biologically active compounds, such as razaxaban (anticoagulant), zometapine (antidepressant), celecoxib (anti-inflammatory), fomepizole (antidote for methanol poisoning), cyenopyrafen (acaricide), raloxifene (selective estrogen receptor modulator used for treatment of osteoporosis) and penthiopyrad (fungicide).[2] Pyrazole-4-carboxylates also possess antitumor, antimicrobial and analgesic activities.[3] They can be synthesized by several methods: (i) thermal cycloaddition of sydnones with acetylenic esters,[4a] (ii) 1,3-dipolar cycloaddition of nitrile imines,[3a] (iii) condensation of β-enaminoketoesters or cyano ketene dithioacetals with hydrazines[4b,c] and (iv) Vilsmeier cyclization of hydrazones.[4d] Although α,β-alkynic hydrazones are good precursors for the synthesis of pyrazoles,[5] there is only one example of a cyclization-carbonylation reaction of α,β-alkynic hydrazones (Scheme 1, condition B).[6a] Recently, we reported that the cyclization-carbonylation-cyclization-coupling reaction (CCC-coupling reaction) of α,β-alkynic hydrazones **1** and (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** catalyzed by palladium(II)-bisoxazoline (box) complexes afforded bis(pyrazol-3-yl)methanones **2** and bis(benzothiophen-3-yl)methanones **5**, respectively, in good yields (Condition A in Schemes 1 and 2).[6a,b] In the absence of box ligand (Condition B in Schemes 1 and 2), dimeric ketones **2a** and **5a** were obtained in 47-49% yields along with low yields of pyrazole-4-carboxylate **3a** (38%) and benzo[*b*]thiophene **7a** (11%). In the case of condition B in Scheme 2, benzo[*b*]thiophene-3-carboxylate **6a** was not obtained. The course of the reaction can be switched by a simple change of ligand (or solvent), to afford pyrazole-4-carboxylate **3a** and benzo[*b*]thiophene-3-carboxylate **6a** selectively. Very recently, we reported[6c] palladium(II)-catalyzed ligand controlled synthesis of indole-3-carboxylates **10** and bis(indol-3-yl)methanones **9**; the box complex gave bis(indol-3-yl)methanone **9a** in good yield (Condition A in Scheme 3). In the absence of ligand (Condition B in Scheme 3), indole-3-carboxylate was obtained in 41% yield. Addition of DMSO (mixed solvent; DMSO-MeOH) improved the yield of indole-3-carboxylates. To



Scheme 1 CCC-coupling (previous work)[6a] versus cyclization-carbonylation (this work).



Scheme 2 CCC-coupling (previous work)[6b] versus cyclization-carbonylation (this work).



Scheme 3 Previous work[6c]

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investigate the generality of the effect of DMSO, we re-examined the Pd(II)-catalyzed carbonylation of α,β-alkynic hydrazones **1** and (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** by using mixed solvents. Consequently, we would like to report here a new method for the synthesis of pyrazole-4-carboxylate **3** and benzo[*b*]thiophene-3-carboxylates **6** (Condition C in Schemes 1 and 2).

Results and discussion

Initially, we selected **1a** as a standard substrate to search for potential catalysts and solvents (Table 1). The results of entries 1-5 in Table 1 have been reported previously.[6a] The reaction of **1a** with $Pd(tfa)_2$ (5 mol%) and *p*-benzoquinone (1.5 equiv.) in methanol under a carbon monoxide atmosphere (balloon) generated the bis(pyrazolyl)ketone **2a** in 47% yield along with a 38% yield of pyrazole-4-carboxylate **3a** (Table 1, entry 1). These products were easily separated by silica gel chromatography. The use of $[PdCl_2(PPh_3)_2]$ and a (2,2'-bipyridine)dichloro-palladium(II) complex also gave a mixture of the two products in low yields (Table 1, entries 2 and 3). The palladium(0)

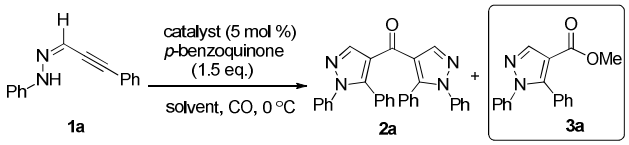


Table 1. Optimization of the reaction.[a] (synthesis of **3a**)

Entry	Catalyst	Solvent	Time (h)	Yield of **2a** (%)	Yield of **3a** (%)
1	$Pd(tfa)_2$	MeOH	46	47	38
2	$[PdCl_2(PPh_2)_2]$	MeOH	24	28	31
3	$[PdCl_2$(2,2'-bipy)]	MeOH	24	36	6
4	$Pd(PPh_3)_4$	MeOH	24	-	19
5	$[PdCl_2(CH_3CN)_2]$	MeOH	21	76	-
6	$Pd(tfa)_2$	DMF-MeOH (1/1)	24	15	28
7	$Pd(tfa)_2$	THF-MeOH (1/1)	24	18	37
8	$Pd(tfa)_2$	Toluene-MeOH (1/1)	24	22	22
9[b]	$Pd(tfa)_2$	DMSO-MeOH (1/1)	73	5	79
10[b]	$Pd(tfa)_2$	DMSO-MeOH (1/5)	49	41	54
11[b]	$Pd(tfa)_2$	DMSO-MeOH (5/1)	49	32	3
12[b]	$Pd(tfa)_2$	DMSO-MeOH (2.5/3)	72	trace	91
13[c]	$PdCl_2$	DMSO-MeOH (2.5/3)	72	12	-
14[d]	$Pd(OAc)_2$	DMSO-MeOH (2.5/3)	72	-	-

[a] The results of entries 1-5 have been reported in ref. 6a. [b] 0 ºC. [c] Recovery 34%. [d] Recovery 99%.

complex $Pd(PPh_3)_4$ was ineffective, affording **3a** in low yield (Table 1, entry 4). The use of $PdCl_2(CH_3CN)_2$ afforded **2a** as the sole product in increased yield (Table 1, entry 5). Next, we investigated the reaction in mixed solvents containing MeOH according to our previous findings.[6c] Although DMF-MeOH, THF-MeOH and toluene-MeOH were not suitable as solvents, the use of DMSO strikingly changed the course of the reaction, affording pyrazole-4-carboxylate **3a** as the major product (Table 1, entries 6-12). A large amount of DMSO (DMSO-MeOH = 5/1) led to decreased product yield, and the use of a small amount of DMSO (DMSO-MeOH = 1/5) gave almost the same result as that of entry 1(Table 1, entries 10 and 11). Eventually, the best result was obtained by using a 2.5/3 ratio of DMSO-MeOH, affording **3a** in 91% yields (Table 1, entry 12). In addition, $PdCl_2$ and $Pd(OAc)_2$ were not suitable catalysts (Table 1, entries 13–14), and the use of $CuCl_2$ instead of *p*-benzoquinone afforded **2a** in 30% yield along with recovery of substrate **1a** (34%).

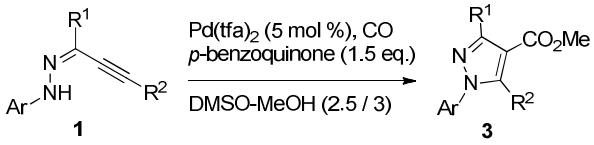


Table 2. Synthesis of pyrazole-4-carboxylates **3** via cyclization-carbonylation

Entry	R^1	R^2	Ar	Conditions	Yield of **3** (%)
1	H	Ph	Ph	0°C, 71h	**3a**: 91
2	H	4-MePh	Ph	0°C, 72h	**3b**: 82
3	H	4-MeOPh	Ph	0°C, 24h	**3c**: 80
4	H	3-thienyl	Ph	0°C, 21h	**3d**: 82
5	H	Octyl	Ph	0°C, 72h	**3e**: 76
6	H	Ph	4-BrPh	40°C, 22h	**3f**: 86
7	H	Ph	4-CF_3Ph	40°C, 72h	**3g**: 85
8	Me	Ph	Ph	-10°C, 23h	**3h**: 81
9	Phenethyl	Ph	Ph	0°C, 20h	**3i**: 83
10	Me	Ph	4-BrPh	0°C, 24h	**3j**: 87
11	Me	Ph	4-CF_3Ph	0°C, 17h	**3k**: 98
12	Me	Ph	4-NO_2Ph	0°C, 17h	**3l**: 90
13	Phenethyl	*n*-Hexyl	Ph	0°C, 18h	**3m**: 90
14	*i*-Pr	*n*-Butyl	Ph	0°C, 6h	**3n**: 93
15	Me	TMS	Ph	0°C, 47h	**3o**: 93

Having elucidated the optimum conditions for the reaction, we then employed several α,β-alkynic hydrazone derivatives in the cyclization-carbonylation reaction (Table 2). First, the reaction of substrates derived from α,β-alkynic aldehydes and $PhNHNH_2$ (R^1 = H, Ar = Ph) was investigated (Table 2, entries 1–7). The substrates **1b-1d**, bearing electron-donating substituents (R^2 = 4-MePh, 4-MeOPh) and a thiophene ring, gave good results which were similar to that of parent substrate **1a** (Table 2, entries 1–4). Replacement of the aryl groups at the alkyne terminus with an alkyl group afforded a slightly lower yield (76%) of **3e** (Table 2, entry 5). Both a Br substituent on the Ar moiety (Ar = 4-BrPh) and an electron-withdrawing group (R^2 = 4-CF_3Ph) were tolerated

(Table 2, entries 6 and 7). Next, the reactions of substrates derived from α,β-alkynic ketones (R^1 = alkyl) and $ArNHNH_2$ were investigated (Table 2, entries 8–15). For substrates **1h-l**, bearing a Ph group at the alkyne terminus, the reaction proceeded well (Table 2, entries 8–12). A Br substituent on an Ar moiety (Ar = 4-BrPh) was also tolerated (Table 2, entry 10). The substrates **1k** and **1l**, bearing electron-withdrawing groups on the Ar moiety (Ar = 4-CF_3Ph, 4-NO_2Ph), were transformed in 98% and 90% yields, respectively (Table 2, entries 11-12). Replacement of the Ph group at the alkyne terminus with alkyl groups also led to the desired **3m** and **3n** in good yields (Table 2, entries 13 and 14). It is noteworthy that the presence of a TMS group at the alkyne terminus was tolerated under the reaction conditions (Table 2, entry 15).

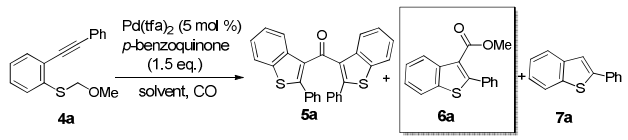


Table 3. Optimization of the reaction.[a] (Synthesis of **6a**)

Entry	Solvent	Temp (ºC) Time (h)	Yield of **5a** (%)	Yield of **6a** (%)	Yield of **7a** (%)
1[a]	MeOH	-20 ~ -10, 45	49	-	11
2	DMF-MeOH (2/1)	rt, 24	2	8	71
3	CH_2Cl_2-MeOH (2/1)	rt, 24	1	9	76
4	DMSO-MeOH (2/1)	rt, 24	9	74	-
5	DMSO-MeOH (1/1)	5, 28	45	37	-
6	DMSO-MeOH (5/1)	rt, 16	13	76	-
7[b]	DMSO-MeOH (5/1)	rt, 48	65	26	-
8[c]	DMSO-MeOH (5/1)	rt, 22	21	56	-
9	DMSO-MeOH (7/1)	5, 17	8	80	-

[a] The result was reported in ref. 6b. [b] $PdCl_2$ was employed. [c] $Pd(NO_3)_2$ was employed.

Next, we re-investigated the carbonylation of (*o*-alkynylphenyl) (methoxymethyl) sulfides **4a** by using mixed solvents (Table 3). As reported recently, the reaction in MeOH without ligand afforded bis(benzothiophen-3-yl)methanone **5a** in 49% yield along with cyclized product **7a**, ester product **6a** was not detected (Table 3, entry 1).[6b] When the reaction was performed in mixed-solvent, e.g., DMF-MeOH (2/1) and CH_2Cl_2-MeOH (2/1), **7a** was obtained as the major product (Table 3, entries 2 and 3). As in the case of Tables 1 and 2, the use of DMSO strikingly changed the course of the reaction, affording benzo[*b*]thiophene-3-carboxylate **6a** as the major product (Table 3, entry 4). Although an increased amount of MeOH led to decreased product selectivity, the best result was obtained in DMSO-MeOH (7/1) (Table 3, entries 5, 6 and 9). $PdCl_2$ and $Pd(NO_3)_2$ were not suitable for this reaction (Table 3, entries 7 and 8). Having elucidated the optimum conditions for the reaction, we then employed a variety of (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** in the cyclization-carbonylation reaction (Table 4). The substrates **1b-e**, bearing three kinds of halogen substituents (F, Cl, Br) and a methyl group on the phenyl ring, were tolerated under the reaction conditions: **6b-e** were obtained in similar yields as that of parent substrate **4a** (Table 4, entries 2-5). Replacement of the aryl groups at the alkyne terminus with a TMS group and an alkyl group also led to the desired **6f** and **6h**, respectively, in good yields (Table 4, entries 6 and 8). For substrate **4g**, bearing a methoxy group on an aromatic moiety, the reaction proceeded well (Table 4, entry 7).

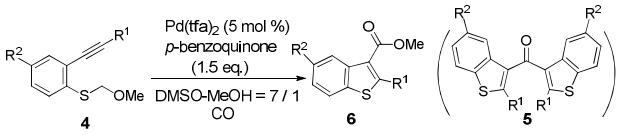


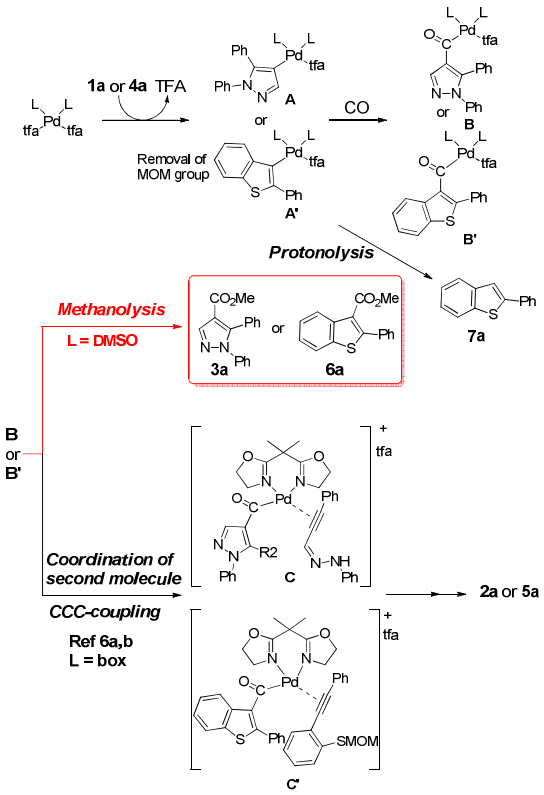
Table 4. Synthesis of benzo[*b*]thiophene-3-carboxylate **6** via cyclization-carbonylation

Entry	R^1	R^2	Temp (ºC), Time (h)	Yield %
1	Ph	H	5, 17	**6a**: 80
2	4-BrPh	H	5, 48	**6b**: 81
3	4-ClPh	H	5, 18	**6c**: 83
4	4-FPh	H	5, 17	**6d**: 82
5	4-MePh	H	0, 48	**6e**: 82
6	TMS	H	5, 96	**6f**: 86
7[a]	Ph	MeO	-20, 24	**6g**: 80
8	Phenethyl	H	0, 48	**6h**: 82

[a] DMSO-MeOH (2/1)

A plausible mechanism for the reaction of **1a** and **4a** is shown in Scheme 4. Nucleophilic attack by the nitrogen atom of **1a** at the electrophilically activated triple bond, produces the pyrazol-3-yl palladium intermediate **A**. In the case of **4a**, a similar intermediate **A'** is produced, accompanied by removal of the methoxymethyl group.[8] Insertion of carbon monoxide into intermediates **A** and **A'** leads to acyl palladium intermediates **B** and **B'**, while protonolysis of intermediate **A'** generates **7a**. As reported previously, we believe that the box ligand enhances the π-electrophilicity of palladium(II),[7] and thus promotes coordination of the second triple bond to the acyl palladium intermediates (**C** and **C'**), leading to a dimerization reaction. On the other hand, methanolysis of the acyl palladium intermediates **B** and **B'** gave the ester products **3a** and **6a** as a result of cyclization-carbonylation. Under condition C (Schemes 1-3), DMSO acts as a neutral ligand instead of the box (condition A) or MeOH (condition B),[6c] and it plays important roles for the production of esters **3a** and **6a**, namely, 1) stabilizing intermediates **A** and **A'** to prevent protonolysis, suppressing the formation of **7a**; 2) facilitating the methanolysis of the acyl palladium intermediates **B** and **B'**; and 3) impeding coordination of the second triple bond to the acyl palladium intermediates **B** and **B'**, suppressing the formation of dimeric ketones **2a** and **5a**.

Consequently, the ester products **3a** and **6a** should be produced



smoothly in the presence of DMSO as a mixed solvent.

Scheme 4 A plausible mechanism for the cyclization-carbonylation reaction **1a** and **4a**.

Conclusions

In conclusion, we investigated the carbonylation reactions of α,β-alkynic hydrazones **1** and (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** with $Pd(tfa)_2$ in mixed solvent, and found that DMSO-MeOH was very effective for controlling the reaction pathway. An effective switching between cyclization-carbonylation and cyclization-carbonylation-cyclization-coupling (CCC-coupling) reactions was achieved. At the same time a new method for the synthesis of pyrazole-4-carboxylates **3** and benzo[*b*]thiophene-3-carboxylates **6** was developed. These reactions were general for a wide range of substrates. We are currently investigating additional reactions based on this DMSO-MeOH strategy for cyclization-carbonylation in the synthesis of other types of heterocycles-carboxylates.

Experimental Section

General Information.

All melting points were determined on a microscopic melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometer using $CDCl_3$ as solvent and TMS as internal standard. In the case of CD_2Cl_2 or DMSO-d_6, solvent peaks were used as a reference (5.32 or 2.50 ppm for ^{1}H, and 53.8 or 39.5 ppm for ^{13}C). Coupling constants (J) are reported in hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br-s (broad singlet), d (doublet), br-d (broad doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectra were obtained using high-resolution EI or ESI-TOF mass spectrometers. Infrared spectra (IR) were recorded on a FT-IR spectrophotometer and are reported as wavelength numbers (cm^{-1}). All evaporations were performed under reduced pressure. For column chromatography, silica gel (63-200 mm) was employed. See Supporting Information for ^{1}H NMR and ^{13}C NMR spectra of all new compounds.

Preparation of substrates 1 and 4.

The α,β-alkynic hydrazones **1** were prepared by condensation of the corresponding α,β-alkynic aldehydes or ketones with $ArNHNH_2$ according to known literature procedures.[5c,d,6a] The (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** were prepared from known *o*-iodoanilines by the published procedure.[6b] All substrates were known compounds except **1k** and **4f**.

(*Z*)-1-(4-nitrophenyl)-2-(4-phenylbut-3-yn-2-ylidene)-hydrazine (1l)

Yellow solid; mp 137-138 ºC; ^{1}H NMR ($CDCl_3$): δ = 2.82 (3H, s), 7.08-7.12 (2H, m), 7.40-7.48 (3H, m), 7.54-7.57 (2H, m), 8.15-8.18 (2H, m), 8.63 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 22.4, 79.9, 102.4, 112.0, 120.7, 126.1, 128.6, 128.7, 130.0, 131.9, 140.5, 148.8; IR (KBr): 3306, 2173, 1596, 1499, 1478, 1330, 1272, 1144, 1114, 835, 752, 688 cm^{-1}; HRMS-EI:*m/z* [M^+] calcd for $C_{16}H_{13}N_3O_2$: 279.1008; found: 279.1008.

Methoxymethyl 2-(trimethylsilylethynyl)phenyl sulfide (4f)

Brown oil; ^{1}H NMR ($CDCl_3$): δ = 0.27 (9H, s), 3.43 (3H, s), 5.04 (2H, s), 7.10-7.14 (1H, m), 7.23-7.27 (1H, m), 7.43 (1H, br-d, J = 8.0 Hz), 7.56 (1H, br-d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 0.07 (3C), 56.2, 76.3, 100.6, 102.6, 123.2, 125.8, 128.4, 129.1, 132.9, 139.4; IR (KBr): 2945, 1697, 1681, 1456, 1354, 1225, 1010, 822, 755 cm^{-1}; HRMS-EI:*m/z* [M^+] calcd for $C_{13}H_{18}O_2SSi$: 250.0848; found: 250.0859.

General procedure for the cyclization-carbonylation reaction of α,β-alkynic hydrazones 1

A 30-mL two-necked round-bottom flask containing a magnetic stirring bar, substrate **1** (0.5 mmol), *p*-benzoquinone (81.1 mg, 0.75 mmol), DMSO (2 mL) and MeOH (6 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. A DMSO (1 mL) solution of $Pd(tfa)_2$ (8.3 mg, 0.025 mmol) was added to the stirred solution via syringe at the appropriate temperature. The remaining catalyst was washed in DMSO (1 mL) twice, and stirred for a set period of time. The reaction mixture was diluted with CH_2Cl_2 (60 mL), water (40 mL) and 5% NaOH (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane / EtOAc (25/1-10/1) afforded pyrazole-4-carboxylate **3**, and that eluted with hexane / EtOAc (3/1-2/1) afforded a small amount of bis(pyrazol-3-yl)methanones **2**.

Bis(1,5-diphenyl-1*H*-pyrazol-4-yl)methanone (2a)[6a]

Methyl 1,5-diphenyl-1*H*-pyrazole-4-carboxylate (3a)[6a]

Methyl 1-phenyl-5-(*p*-tolyl)-1*H*-pyrazole-4-carboxylate (3b)

Pale yellow solid; mp 116-117 ºC; ^{1}H NMR ($CDCl_3$): δ = 2.35 (3H, s), 3.75 (3H, s), 7.12-7.31 (9H, m), 8.16 (1H, s); ^{13}C NMR

($CDCl_3$): δ = 21.4, 51.2, 113.2, 125.3, 125.5, 127.8, 128.8, 130.3, 139.2, 139.3, 142.4, 145.7, 163.4; IR (KBr): 3035, 1718, 1563, 1504, 1445, 1382, 1293, 1225, 1130, 773, 693 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{18}H_{16}N_2O_2$ [M^+]: 292.1212; found: 292.1212.

Methyl 5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate (3c)

Colorless solid; mp 125-126 ºC; ^1H NMR ($CDCl_3$): δ = 3.76 (3H, s), 3.80 (3H, s), 6.83-6.87 (2H, m), 7.19-7.30 (7H, m), 8.16 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.2, 55.2, 113.0, 113.5, 120.6, 125.3, 127.8, 128.8, 131.8, 139.3, 142.4, 145.5, 160.2, 163.5; IR (KBr): 3054, 1717, 1506, 1447, 1226, 1130, 775 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{18}H_{16}N_2O_3$ [M^+]: 308.1161; found: 308.1159.

Methyl 1-phenyl-5-(thiophen-3-yl)-1*H*-pyrazole-4-carboxylate (3d)

Colorless solid; mp 97-98 ºC; ^1H NMR ($CDCl_3$): δ = 3.79 (3H, s), 6.96 (1H, dd, *J* = 5.2 Hz, *J* = 1.2 Hz), 7.22-7.27 (3H, m), 7.32-7.35 (3H, m), 7.39 (1H, dd, *J* = 2.8 Hz, *J* = 1.2 Hz), 8.15 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.3, 113.2, 125.0, 125.3, 127.9, 128.0, 128.2, 128.9, 128.9, 139.3, 140.7, 142.5, 163.3; IR (KBr): 3100, 1719, 1594, 1496, 1277, 1230, 1129, 1037, 973, 762, 690 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{15}H_{12}N_2O_2S$ [M^+]: 284.0619; found: 284.0621.

Methyl 5-octyl-1-phenyl--1*H*-pyrazole-4-carboxylate (3e)

Pale yellow oil; mp 99-100 ºC; ^1H NMR ($CDCl_3$): δ = 0.85 (3H, s), 1.17-1.27 (10H, m), 1.47-1.55 (2H, m), 2.90-2.94 (2H, m), 3.85 (3H, s), 7.38-7.40 (2H, m), 7.46-7.52 (3H, m), 8.01 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 14.0, 22.5, 24.9, 28.9, 28.9, 29.0, 29.2, 31.7, 51.1, 111.8, 125.9, 128.8, 129.2, 139.0, 141.9, 148.5, 163.9; IR (KBr): 2928, 2857, 1717, 1595, 1553, 1502, 1460, 1252, 1091, 978, 772, 696 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{19}H_{26}N_2O_2$ [M^+]: 314.1994; found: 314.1995.

Methyl 1-(4-bromophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate (3f)

Pale yellow solid; mp 112-113 ºC; ^1H NMR ($CDCl_3$): δ = 3.75 (3H, s), 7.05-7.09 (2H, m), 7.26-7.28 (2H, m), 7.34-7.42 (5H, m), 8.17 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.3, 113.8, 121.7, 126.6, 128.2, 128.4, 129.4, 130.3, 132.0, 138.2, 142.6, 145.5, 163.1; IR (KBr): 3056, 1722, 1551, 1498, 1291, 1223, 1130, 1068, 1014, 770, 697 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{17}H_{13}BrN_2O_2$ [M^+]: 356.0160; found: 356.0156.

Methyl 5-phenyl-1-((4-trifluoromethyl)phenyl)-1*H*-pyrazole-4-carboxylate (3g)

Pale yellow solid; mp 100-101 ºC; ^1H NMR ($CDCl_3$): δ = 3.75 (3H, s), 7.20-7.40 (7H, m), 7.48-7.55 (2H, m), 8.20 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.4, 114.2, 123.6 (q, J_{C-F} = 270.8 Hz), 125.1, 126.0 (q, J_{C-F} = 2.9 Hz), 128.3, 128.4, 129.6, 129.7 (q, J_{C-F} = 32.4 Hz), 130.3, 141.9, 142.9, 145.7, 163.0; IR (KBr): 3056, 1727, 1612, 1553, 1448, 1386, 1324, 1226, 1123, 1064, 846 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{18}H_{13}F_3N_2O_2$ [M^+]: 346.0929; found: 346.0929.

Methyl 3-methyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (3h)

Colorless solid; mp 122-123 ºC; ^1H NMR ($CDCl_3$): δ = 2.58 (3H, s), 3.69 (3H, s), 7.15-7.17 (2H, m), 7.22-7.37 (8H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.0, 111.6, 125.3, 127.6, 127.9, 128.7, 128.9, 129.7, 130.3, 139.1, 146.4, 151.7, 164.3; IR (KBr): 2946, 1712, 1595, 1548, 1502, 1311, 1238, 1101, 1091, 793, 693 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{18}H_{16}N_2O_2$ [M^+]: 292.1212; found: 292.1212.

Methyl 3-phenethyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (3i)

Pale yellow solid; mp 113-114 ºC; ^1H NMR ($CDCl_3$): δ = 3.01-3.05 (2H, m), 3.20-3.24 (2H, m), 3.62 (3H, s), 7.08-7.28 (15H, m); ^{13}C NMR ($CDCl_3$): δ = 30.6, 35.5, 51.0, 111.1, 125.3, 125.8, 127.6, 127.9, 128.3, 128.5, 128.7, 128.8, 129.7, 130.3, 139.1, 142.4, 146.5, 154.8, 164.0; IR (KBr): 3025, 2941, 1698, 1596, 1487, 1384, 1322, 1237, 1182, 1100 760, 696 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{25}H_{22}N_2O_2$ [M^+]: 382.1681; found: 382.1680.

Methyl 1-(4-bromophenyl)-3-methyl-5-phenyl-1H-pyrazole-4-carboxylate (3j)

Pale yellow solid; mp 99-100 ºC; ^1H NMR ($CDCl_3$): δ = 2.57 (3H, s), 3.68 (3H, s), 7.02-7.05 (2H, m), 7.21-7.24 (2H, m), 7.32-7.40 (5H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.0, 112.0, 121.3, 126.5, 128.1, 129.1, 129.4, 130.3, 131.9, 138.1, 146.4, 152.0, 164.1; IR (KBr): 3060, 1711, 1547, 1497, 1430, 1321, 1246, 1182, 1100, 1010, 700 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{18}H_{15}BrN_2O_2$ [M^+]: 370.0317; found: 370.319.

Methyl 3-methyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-carboxylate (3k)

Pale yellow solid; mp 113-114 ºC; ^1H NMR ($CDCl_3$): δ = 2.58 (3H, s), 3.69 (3H, s), 7.24-7.30 (4H, m), 7.34-7.43 (3H, m), 7.49-7.52 (2H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.1, 112.5, 122.3, 125.0, 125.9 (q, J_{C-F} = 30.4 Hz), 128.2, 129.36, 130.3 (q, J_{C-F} = 263.2 Hz), 130.2, 141.9, 146.6, 152.4, 164.0; IR (KBr): 2944, 1712, 1615, 1429, 1388, 1325, 1240, 1103, 844, 760, 697 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{19}H_{15}F_3N_2O_2$ [M^+]: 360.1086; found: 360.1086.

Methyl 3-methyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazol-4-carboxylate (3l)

Pale yellow solid; mp 127-128 ºC; ^1H NMR ($CDCl_3$): δ = 2.59 (3H, s), 3.70 (3H, s), 7.24-7.27 (2H, m), 7.32-7.44 (5H, m), 8.09-8.13 (2H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.2, 113.2, 124.3, 124.9, 128.5, 129.2, 129.6, 130.1, 144.0, 146.0, 146.8, 152.9, 163.8; IR (KBr): 2949, 1715, 1597, 1523, 1505, 1321, 1249, 1105, 763, 700 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{18}H_{15}N_3O_4$ [M^+]: 337.1063; found: 337.1064.

Methyl 5-hexyl-3-phenethyl-1-phenyl-1*H*-pyrazole-4-carboxylate (3m)

Pale yellow solid; mp 38 ºC; ^1H NMR ($CDCl_3$): δ = 0.84 (3H, t, *J* = 7.2 Hz), 1.14-1.28 (6H, m), 1.50-1.57 (2H, m), 2.85-2.90 (2H, m), 3.0-3.04 (2H, m), 3.19-3.23 (2H, m), 3.88 (3H, s), 7.18-7.22 (1H, m), 7.28-7.32 (4H, m), 7.35-7.39 (2H,m), 7.42-7.52 (3H, m); ^{13}C NMR ($CDCl_3$): δ = 13.9, 22.4, 25.5, 29.1, 29.1, 30.7, 31.1, 35.6, 50.9, 109.2, 125.8, 126.2, 128.2, 128.5, 128.7, 129.2, 139.0, 142.2, 149.7, 154.5, 164.5; IR (KBr): 2942, 2854, 1710, 1595, 1541, 1460, 1267, 1108, 758, 696 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{25}H_{30}N_2O_2$ [M^+]: 390.2307; found: 390.2308.

Methyl 5-butyl-3-isopropyl-1-phenyl-1*H*-pyrazole-4-carboxylate (3n)

Pale yellow solid; mp 45-46 ºC; ^1H NMR ($CDCl_3$): δ = 0.81 (3H, t, *J* = 7.2 Hz), 1.20-1.31 (2H, m), 1.32 (6H, d, *J* = 6.8 Hz), 1.46-1.54 (2H, m), 2.88-2.86 (2H, m), 3.52-3.62 (1H, m), 3.85 (3H, s), 7.36-7.49 (5H, m); ^{13}C NMR ($CDCl_3$): δ = 13.5, 21.9 (2C), 22.5, 25.4, 27.2, 31.4, 50.8, 108.5, 126.2, 128.6, 129.1, 139.2, 149.3, 160.4, 164.8; IR (KBr): 2967, 2870, 1698, 1539, 1448, 1281, 1174, 1106, 795, 697 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{18}H_{24}N_2O_2$

[M^+]: 300.1836; found: 300.1838.

Methyl 3-methyl-1phenyl-5-trimethylsilyl-1*H*-pyrazole-4-carboxylate (3o)

Colorless solid; mp 63-64 ºC; ^{1}H NMR ($CDCl_3$): δ = 0.05 (9H, s), 2.49 (3H, s), 3.85 (3H, s), 7.32-7.37 (2H, m), 7.42-7.45 (3H, m); ^{13}C NMR ($CDCl_3$): δ = 0.0 (3C), 13.7, 51.2, 121.1, 127.1, 129.1, 129.3, 142.3, 149.3, 151.5, 165.5; IR (KBr): 2996, 1705, 1596, 1501, 1261, 1110, 1008, 848, 774, 699 cm^{-1}; HRMS-EI:*m/z*calcd for $C_{15}H_{20}N_2O_2Si$ [M^+]: 288.1294; found: 288.1292.

General procedure for the cyclization-carbonylation reaction of (*o*-alkynylphenyl) (methoxymethyl) sulfides 4

A 30-mL two-necked round-bottom flask containing a magnetic stirring bar, substrate **1** (0.4 mmol), *p*-benzoquinone (65 mg, 0.6 mmol) and mixed solvent (5 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. A mixed solvent (1 mL) solution of $Pd(tfa)_2$ (6.7 mg, 0.02 mmol) was added to the stirred solution via syringe at the appropriate temperature. The remaining catalyst was washed in mixed solvent (1 mL) twice, and stirred for a set period of time. The reaction mixture was diluted with CH_2Cl_2 (60 mL), water (40 mL) and 5% NaOH (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane / Et_2O (200/1) afforded benzo[*b*]thiophene-3-carboxylate **6** and a small amount of bis(benzothiophen-3-yl)methanone **5**. In the case of entries 2 and 4 in Table 4, a small amount of ketone **5** contaminated ester **6**. Pure esters **6b** and **6d** were obtained in 81-82% yields after recrystallization (hexane).

Bis(2-phenylbenzo[*b*]thiophen-3-yl)methanone (5a)[6b]

Methyl 2-phenylbenzo[*b*]thiophen-3-carboxylate (6a)[9]

2-phenylbenzo[*b*]thiophene (7a)[10]

Methyl 2-(4-bromophenyl)benzo[*b*]thiophen-3-carboxylate (6b)

Orange solid; mp 80-81 ºC; ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s), 7.37-7.43 (3H, m), 7.46-7.51 (1H, m), 7.55-7.59 (2H, m), 7.82 (1H, br-d, *J* = 8.0 Hz), 8.36 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.6, 121.7, 123.1, 123.3, 124.7, 125.1, 125.5, 131.0, 131.3, 132.9, 138.3, 138.4, 150.4, 164.1; IR (KBr): 2945, 1697, 1681, 1456, 1354, 1225, 1010, 822, 755 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{16}H_{11}BrO_2S$ [M^+]: 345.9663; found: 345.9693.

Methyl 2-(4-chlorophenyl)benzo[*b*]thiophen-3-carboxylate (6c)

Orange solid; mp 64-65 ºC; ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s), 7.39-7.51 (6H, m), 7.82 (1H, br-d, *J* = 8.0 Hz), 8.38 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.6, 121.7, 123.1, 124.7, 125.1, 125.5, 128.3, 130.7, 132.4, 135.0, 138.3, 138.4, 150.4, 164.1; IR (KBr): 2946, 1698, 1429, 1355, 1224, 1091, 1018, 824, 768 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{16}H_{11}ClO_2S$ [M^+]: 302.0168; found: 302.0169.

Methyl 2-(4-fluorophenyl)benzo[*b*]thiophen-3-carboxylate (6d)

Orange solid; mp 78-80 ºC; ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s), 7.46-7.52 (3H, m), 7.38-7.42 (1H, m), 7.14-7.16 (2H, m), 8.35 (1H, br-d, *J* = 8.4 Hz), 7.82 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.6, 115.2 (d, $J_{C\text{-}F}$ = 21.9 Hz), 121.7, 123.0, 124.7, 125.1, 125.5, 129.9 (d, $J_{C\text{-}F}$ = 3.8 H), 131.2 (d, $J_{C\text{-}F}$ = 8.6 Hz), 138.3, 138.4, 150.8, 163.1 (d, $J_{C\text{-}F}$ = 248 Hz), 164.2; IR (KBr): 2924, 1715, 1701, 1457, 1203, 1159, 750 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{16}H_{11}FO_2S$ [M^+]: 286.0464; found: 286.0466.

Methyl 2-(4-methylphenyl)benzo[*b*]thiophen-3-carboxylate (6e)

Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 2.40 (3H, s), 3.77 (3H, s), 7.22-7.24 (2H, m), 7.34-7.47 (4H, m), 7.79 (1H, br-d, *J* = 8.4 Hz), 8.31 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 21.3, 51.5, 121.6, 122.5, 124.4, 124.8, 125.3, 128.9, 129.2, 130.9, 138.4, 138.5, 138.9, 152.1, 164.5; IR (KBr): 2944, 1497, 1350, 1159, 1019, 818, 740 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{17}H_{14}O_2S$ [M^+]: 282.0715; found: 282.0714.

Methyl 2-(4-trimethylsilyl)phenylbenzo[*b*]thiophen-3-carboxylate (6f)

Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 0.44 (9H, s), 3.98 (3H, s), 7.35-7.39 (1H, m), 7.43-7.47 (1H, m), 7.86 (1H, br-d, *J* = 8.4 Hz), 8.54 (1H, br-d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 0.18 (3C), 51.5, 121.9, 124.8, 124.8, 125.3, 132.5, 139.6, 142.8, 154.6, 164.5; IR (KBr): 2946, 1693, 1414, 1262, 1186, 1045, 965, 762 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{13}H_{16}O_2SSi$ [M^+]: 264.0640; found: 264.0641.

Methyl 5-methoxy-2-phenylbenzo[*b*]thiophen-3-carboxylate (6g)

White solid; mp 100-110 ºC; ^{1}H NMR ($CDCl_3$): δ = 3.76 (3H, s), 3.89 (3H, s), 7.08 (1H, dd, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.27 (1H, d, *J* = 2.4 Hz), 7.40-7.46 (3H, m), 7.47-7.52 (2H, m), 8.23 (1H, br-d, *J* = 9.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.5, 55.5, 104.0, 115.3, 122.3, 125.3, 128.1, 128.6, 129.4, 132.4, 134.0, 139.9, 149.3, 157.6, 164.4; IR (KBr): 2943, 1701, 1435, 1205, 1065, 827, 769 cm^{-1}; HRMS-EI:*m/z* calcd for $C_{17}H_{14}O_3S$ [M^+]: 298.0664; found: 298.0663.

Methyl 2-phenethylbenzo[*b*]thiophen-3-carboxylate (6h)

Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 3.03-3.07 (2H, m), 3.53-3.57 (2H, m), 3.94 (3H, s), 7.18-7.33 (6H, m), 7.38-7.43 (1H, m), 7.72 (1H, br-d, *J* = 8.4 Hz), 8.39 (1H, br-d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 32.7, 37.5, 51.4, 121.7, 122.2, 124.4, 124.5, 125.1, 126.2, 128.4, 128.5, 137.1, 138.3, 140.7, 156.7, 164; IR (KBr): 2940, 1497, 1275, 1236, 1180, 759 cm^{-1}; HRMS-EI:*m/z*calcd for $C_{18}H_{16}O_2S$ [M^+]: 296.0871; found: 296.0871.

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