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Cyclization-Carbonylation-Cyclization Coupling Reaction of (ortho-Alkynyl Phenyl) (Methoxymethyl) Sulfides with Palladium(II)-Bisoxazoline Catalyst

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A cyclization-carbonylation-cyclization coupling reaction (CCC-coupling reaction) of (o-alkynylphenyl) (methoxymethyl) sulfides, catalyzed by (box)PdII complexes, afforded symmetrical ketones bearing two benzo[b]thiophene groups in good to excellent yields. This method is applicable to a broad range of substrates.

Introduction

Benzo[b]thiophenes have been recognized as an important class of S-heterocycles in pharmaceutical sciences.[1] They exhibit various interesting biological properties, such as antitumor,[2a] antipsychotic,[2b] anti-inflammatory,[2c] antiallergic,[2d] and antimicrobial activities[2e] and inhibition of tubulin polymerization[2f] (Fig. 1). Diarylketones are also frequently found in natural products and pharmaceuticals,[3] e.g., suprofen (non-steroid anti-inflammatory), raloxifene (selective estrogen receptor modulator used for treatment of osteoporosis), benz bromarone (antiasthmatic) and amiodarone (antiarrhythmic). A variety of heterocycles can be synthesized by transition-metal-catalyzed cyclization of unsaturated systems.[4] Among these, ortho-alkynyl phenyl sulfides are good precursors for the synthesis of benzo[b]thiophenes.[5]

Fig. 1 Structures of biologically active benzo[b]thiophenes and diarylketones.

Recently, we reported that the cyclization-carbonylation-cyclization coupling reaction (CCC-coupling reaction) of propargylic compounds using palladium(II)-bisoxazoline (box) complexes afforded symmetrical ketones bearing two oxazoles, cyclic orthoesters, oxabicyclic groups, quinolines, benzofurans, oxazolines and pyrazoles (Scheme 1).[6] The CCC-coupling is a two-components (three molecules) coupling reaction based on double intramolecular cyclization of propargylic compounds bearing nucleophiles in conjunction with incorporation of carbon monoxide. Two C-X bonds and two C-C bonds are formed in one-step reactions. In this transformation, the box ligand plays an important role for the coordination of a second molecule in intermediate A, and methanolysis of the acyl palladium should be suppressed by coordination of this second molecule. To extend the generality of the CCC-coupling reaction, we investigated the (box)PdII-catalyzed carbonylation reaction of (o-alkynylphenyl) (methoxymethyl) sulfides 1 (Tables 1 and 2).

Scheme 1 Cyclization-carbonylation-cyclization-coupling reaction (CCC-coupling reaction) of propargylic compounds.

Results and discussion

The (o-alkynylphenyl) (methoxymethyl) sulfides 1 were prepared from known o-iodoanilines by a modification of the published
Having elucidated the optimum conditions for the reaction, we then employed a variety of (o-alkynylphenyl) (methoxymethyl) sulfides 1 in the CCC-coupling reaction (Table 2). First, the reaction of substrates derived from (o-iodophenyl) (methoxymethyl) sulfides and ArC=CH (R₁= Ar, R₂=R₃=H) was investigated (Table 2, entries 1-8). The substrates 1b-1d, bearing both electron-donating and electron-withdrawing substituents, gave good results, similar to that of parent substrate 1a (Table 2, entries 2-4). Three kinds of halogen substituents (F, Cl, Br) on the phenyl ring and a thiophene ring in the alkyne terminus were tolerated under the reaction conditions (Table 2, entries 5-8).
of the triple bond of a second molecule induces the second cyclization, and reductive elimination then leads to the formation of a ketone bearing two heterocyclic groups. 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 intermediate A, leading to the dimerization reaction.

Scheme 2 A plausible mechanism for the Cyclization-carbonylation-cyclization-coupling reaction of \((\alpha\text{-alkynylphenyl})(\text{methoxymethyl})\) sulfides 1.

Conclusions

In conclusion, we carried out cyclization-carbonylation-cyclization coupling reactions (CCC-coupling reaction) of \((\alpha\text{-alkynylphenyl})(\text{methoxymethyl})\) sulfides 1 catalyzed by \((\text{box})\text{Pd}^{II}\) complexes. Symmetrical ketones possessing two benzo[\(b\)]thiophene groups were obtained in good to excellent yields. The reaction was general for a wide range of \((\alpha\text{-alkynylphenyl})(\text{methoxymethyl})\) sulfides 1. We are currently investigating additional cascade reactions based on the cyclization-carbonylation-cyclization strategy presented here for the synthesis of other types of ketone containing two heterocyclic groups.

Experimental Section

General Information.

See Supporting Information for general experimental details as well as procedures for the preparation and characterization of all precursors and products.

Preparation of box-palladium complexes.

The box ligands \(\text{L1-L3}\) and palladium complexes \([\text{Pd}(\text{tfa})_2(2,2'-bipy)]\), \([\text{Pd}(\text{tfa})_2(\text{L2})]\), \([\text{Pd}(\text{tfa})_2(\text{L3})]\) and \([\text{PdCl}_2(\text{L3})]\) were prepared according to the literature.\(^{[6a,6d,10]}\)

General procedure for the CCC-coupling reaction of \((\alpha\text{-alkynylphenyl})(\text{methoxymethyl})\) sulfides 1

A 30-mL two-necked round-bottom flask containing a magnetic stirring bar, \((\alpha\text{-alkynylphenyl})(\text{methoxymethyl})\) sulfides 1 (0.4 mmol), \(p\)-benzoquinone (65 mg, 0.6 mmol) and MeOH (3 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 MeOH (1 mL) suspension of \([\text{Pd}(\text{tfa})_2(\text{L3})]\) (13.3 mg, 0.02 mmol) was added to the stirred solution via syringe at an appropriate temperature. The remaining catalyst was washed in MeOH (1 mL) twice, and stirred for the period of time. In most cases, the dimeric ketones precipitated from the reaction mixture. The resulting precipitate was collected by filtration and washed with cold MeOH (1.5 mL × 2) to yield dimeric ketones 2. As small amounts of 2 (and 3a, see Table 1) still remained in the filtrate, the filtrate was diluted with CH\(_2\)Cl\(_2\) (50 mL) and washed with 5% NaOH (40 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (25 mL) and 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 (100/1) afforded small amounts of dimeric ketones 2 (and monomeric ester 3a (only hexane)).
7.63 (2H, br-d, J = 8.0 Hz), 8.28 (2H, br-d, J = 8.0 Hz); 13C NMR (100 MHz, CDCl3) δ 21.1 (2C), 121.3 (2C), 123.7 (2C), 124.7 (2C), 125.4 (2C), 128.2 (4C), 129.0 (4C), 129.8 (2C), 132.5 (2C), 138.3 (2C), 138.5 (2C), 140.1 (2C), 150.9 (2C), 189.6; IR (KBr) 1643, 1531, 676 cm⁻¹; HRMS-El: m/z: [M⁺] calcd for C31H24O5S 547.9928, found 547.9929.

Bis(2-phenylenbenzophenone)[thiophen-3-yl]methanone 2i. 95% yield (95.5 mg), Yellow oil, 1H NMR (400 MHz, CDCl3) δ 2.83-2.93 (4H, m), 3.04-3.12 (4H, m), 6.92-6.95 (4H, m), 7.10-7.19 (6H, m), 7.24 (2H, dd, J = 1.2, 8.0 Hz), 7.31 (2H, dd, J = 1.2, 7.2 Hz), 7.57 (2H, br-d, J = 8.0 Hz), 7.80 (2H, br-d, J = 8.0 Hz); 13C NMR (100 MHz, CDCl3) δ 31.9 (2C), 37.9 (2C), 122.0 (2C), 123.3 (2C), 124.7 (2C), 125.2 (2C), 125.3 (4C), 130.1 (4C), 132.0 (2C), 138.3 (2C), 138.5 (2C), 140.3 (2C), 151.4 (2C), 188.3; IR (KBr) 2923, 1636, 1455, 1432, 1188, 745, 698 cm⁻¹; HRMS-El: m/z: [M⁺] calcd for C31H24O5S 502.1425, found 502.1425.

Bis(2-octylbenzophenone)[thiophen-3-yl]methanone 2j. 80% yield (83.0 mg), Pale yellow oil, 1H NMR (400 MHz, CDCl3) δ 0.85 (6H, t, J = 7.5 Hz), 1.13-1.26 (20H, m), 1.59-6.0 (4H, m), 2.78 (4H, t, J = 7.5 Hz), 7.23-7.31 (4H, m), 7.64 (2H, br-d, J = 7.5 Hz), 7.78 (2H, br-d, J = 7.5 Hz); 13C NMR (100 MHz, CDCl3) δ 14.1 (2C), 22.6 (2C), 29.1 (2C), 29.1 (2C), 29.4 (2C), 29.7 (2C), 31.8 (2C), 32.0 (2C), 121.9 (2C), 123.1 (2C), 124.5 (2C), 125.1 (2C), 133.6 (2C), 137.7 (2C), 138.4 (2C), 151.4 (2C), 188.7; IR (KBr) 2924, 2853, 1637, 1457, 1433, 1188 cm⁻¹; HRMS-El: m/z: [M⁺] calcd for C31H24O5S 518.2677, found 518.2675.

Bis(cyclopentybenzophenone)[thiophen-3-yl]methanone 2k. 86% yield (64.4 mg), White solid, mp 260-262 °C; 1H NMR (400 MHz, CDCl3) δ 0.82-0.89 (4H, m), 2.13-2.20 (2H, m), 2.77-3.33 (4H, m), 7.70-7.74 (2H, m), 7.80-7.84 (2H, m); 13C NMR (100 MHz, CDCl3) δ 11.9 (4C), 12.0 (2C), 121.8 (2C), 123.0 (2C), 124.5 (2C), 125.2 (2C), 134.7 (2C), 136.3 (2C), 138.8 (2C), 157.2 (2C), 188.6; IR (KBr) 2923, 1629, 1515, 1447, 1358, 734 cm⁻¹; HRMS-El: m/z: [M⁺] calcd for C31H26O5S 374.0799, found 374.0794.

Bis[2-(9-hydroxybenzophenone)[thiophen-3-yl]methanone 2l. 87% yield (100.6 mg), Yellow oil, 1H NMR (400 MHz, CDCl3) δ 1.15-1.32 (22H, m), 1.49-1.60 (6H, m), 1.77 (2H, br-s), 2.79 (4H, t, J = 7.8 Hz), 3.60 (4H, t, J = 6.6 Hz), 7.23-7.32 (4H, m), 7.63 (2H, br-d, J = 7.2 Hz), 7.78 (2H, br-d, J = 7.2 Hz); 13C NMR (100 MHz, CDCl3) δ 131.9 (2C), 132.0 (2C), 132.1 (2C), 125.4 (2C), 125.5 (2C), 125.9 (2C), 130.4 (4C), 130.8 (4C), 131.4 (2C), 133.1 (2C), 138.3 (2C), 139.8 (2C), 149.2 (2C), 188.8; IR (KBr) 1654, 1627, 465 cm⁻¹; HRMS-El: m/z: [M⁺] calcd for C31H26O5S 578.2889, found 578.2888.

Bis(benzophenone)[thiophen-3-yl]methanone 2m. 80% yield (47 mg), White solid, mp 167-168 °C; 1H NMR (400 MHz, CDCl3) δ 7.44-7.54 (4H, m), 7.91 (2H, br-d, J = 8.0 Hz), 8.08 (2H, s), 8.57 (2H, br-d, J = 8.0 Hz); 13C NMR (100 MHz, CDCl3) δ 122.4 (2C), 125.0 (2C), 125.7 (2C), 125.7 (2C), 136.4 (2C), 136.8 (2C), 137.3 (2C), 140.2 (2C), 184.9; IR (KBr) 1627, 1189, 1065, 1550, 677 cm⁻¹; HRMS-El: m/z: [M⁺] calcd for C31H24O5S 294.0173, found 294.0175.

Bis(2-chloro-2-phenoxybenzophenone)[thiophen-3-yl]methanone 2n. 83% yield (85.6 mg), White solid, mp 209-211 °C; 1H NMR (400 MHz, CDCl3) δ 6.91-6.98 (8H, m), 7.04-7.09 (2H, m), 7.34 (2H, dd, J = 2.0, 8.4 Hz), 7.54 (2H, dd, J = 8.4 Hz, 8.4 Hz), 8.34 (2H, d, J = 8.0 Hz); 13C NMR (400 MHz, CDCl3) δ 122.5 (2C), 123.4 (2C), 125.6 (2C), 127.7 (4C), 129.0 (2C), 129.2 (2C), 131.8 (2C), 132.1 (2C), 136.4 (2C), 141.0 (2C), 152.7 (2C), 188.5; IR (KBr) 1622, 1423, 1150, 1071, 747 cm⁻¹; HRMS-El: m/z: [M⁺] calcd for C31H24O5S 514.0020, found 514.0021.

Bis[2-(4-tolylphenyl)-1,3-dihydro-2H-benzofuro[3,2-b]pyridine]thiophen-3-yl]methanone 2o. 86% yield (108.0 mg), White solid, mp 280-
281 °C; 1H NMR (400MHz, CDCl3) δ = 1.13 (18H, s), 6.89 (8H, s), 7.33 (2H, dd, J = 2.0, 8.4 Hz), 7.50 (2H, br-d, J = 8.4 Hz), 8.30 (2H, br-d, J = 2.0 Hz); 13C NMR (100MHz, CDCl3): δ = 30.9 (6C), 34.4 (2C), 122.3 (2C), 123.2 (2C), 124.5 (4C), 125.3 (2C), 129.0 (4C), 129.2 (2C), 131.9 (2C), 132.0 (2C), 136.3 (2C), 141.2 (1C), 152.2 (2C), 152.8 (2C), 188.9; IR (KBr) 2975, 1642, 1627, 1549, 1426, 1079, 675 cm⁻¹; HRMS-ESI m/z [M+Na]+ Caled for C35H26Na2O2S: 649.1331 found 649.1340.

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**Notes and references**


See the Electronic Supplementary Information.

