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FULL PAPER

Palladium-catalyzed highly regioselective synthesis of 3-(hetero)arylpropynamides from *gem*-dibromoalkenes and isocyanides

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Abstract. An alternative method related to the formation of 3-(hetero)arylpropynamides using palladium/Cs_2CO_3, the regiochemically-controlled coupling of isocyanides with 1,1-dibromo-1-alkenes is described.

Keywords: 3-Propynamides; Cross-coupling reaction; Isocyanides; 1,1-Dibromo-1-alkenes, Palladium acetate; Tandem reaction

Introduction

Substituted acetylenes are considered as organic structures owing to their occurrence in several natural products. Since they are well known as the main building blocks for a number of organic syntheses, chemical and biological processes, and in the field of material sciences,[1] finding new routes for the synthesis of alkynyl compounds has attracted the significant attention of organic chemists.

It has been found that 1,2-disubstituted acetylenes are excellent substrates for a number of reactions, including cycloisomerization,[1] palladium-mediated coupling reactions,[2] ring-closing,[3] and cycloadditions,[4] as well as for many other useful transformations. 1,1-Dibromo-1-alkenes, which are easily derived from aldehydes or ketones with CBr_4/PPh_3, *are extremely versatile* precursors and are often used for synthesizing diverse molecules.[5] Applications of these building block molecules have been extended to the generation of acetylene derivatives, including alkynylphosphonates,[6] ynol ethers,[7] symmetric and asymmetric 1,3-diynes,[8] ynamides,[9] 1,2-diarylacetylenes,[10] ynoate esters,[11] and ynsilanes.[12] Piguel *et al*. proposed a method for copper-catalyzed, C_2-directed alkynylation of 3*H*-imidazo[4,5-*b*]pyridine derivatives using 1,1-dibromo-1-alkenes.[13] Bach *et al*. reported the synthesis of propynamides by utilizing *gem*-dibromoalkenes and isocyanate under harsh, multi-step conditions,[14] whereas Xu *et al*. established a process for the selective synthesis of 1,2-heterodisubstituted alkenes *via* nucleophilic *β*-addition to *gem*-dibromoalkenes followed by a cross-coupling reaction.[15]

Further, the synthesis of 2-ynamides by transition metal-catalyzed aminocarbonylation of alkynes (bromoalkynes, alkynes, and propynoic acids) with amines that utilize carbon monoxide sources, such as CO gas and $Co_2(CO)_8$, has been discovered.[16]

Recently, Zhang *et al*. reported the Co(II)/DPE-phos/Ag(I)-catalyzed insertion reaction of isocyanide to terminal alkynes based on the formation of alkynamide derivatives.[17] Further, in this context, one of the common and practical method for the synthesis of terminal alkynes (Corey-Fuchs reaction)[18,19a] as well as bromoacetylenes[19] is the reaction from aldehydes and CBr_4/PPh_3 to form 1,1-

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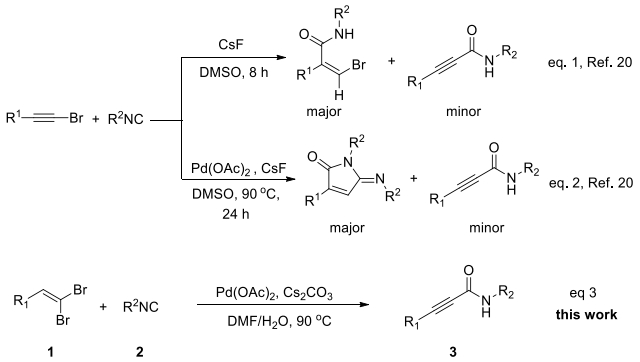
dibromo-1-alkenes followed by treatment with base. Therefore, if a compound which can be prepared from either **a**) the reaction of 1,1-dibromo-1-alkene or **b**) reaction of terminal alkyne and bromoacetylene, it is more logical to follow pathway **a**, since some steps are avoided as well as complying with the *green chemistry principles*.

Recently, the synthesis of substituted 5-iminopyrrolones by utilizing palladium(II)/CsF-catalyzed nucleophilic *β*-addition in sequential cross-coupling reactions that involve bromoalkynes and isocyanides was reported by Jiang *et al.* (Scheme 1, eq. 2).[20] They also observed that propynamides were produced in the form of byproducts during this process.[20]

Inspired by their work and based on our continued interest in exploring the reactivity and synthetic applications of isocyanides,[21] we speculated that the increased reactivity of the C–Br bond in 1,1-dibromo-1-alkenes **1** made this class of compounds more susceptible to cross-coupling C–C bond formation with isocyanides **2**, especially in the presence of a palladium catalyst. The propynamides **3** that would be generated from this reaction could be achieved through the subsequent HBr elimination processes (Scheme 1, eq. 3).

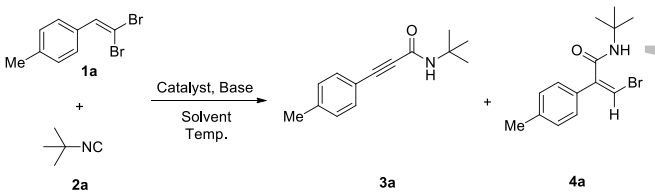


Scheme 1. Selective metal-catalyzed cross-coupling reactions using 1-bromo-1-alkynes and 1,1-dibromo-1-alkenes

Results and Discussion

First, we carried out the reaction of 1-(2,2-dibromovinyl)-4-methylbenzene (**1a**) with *tert*-butyl isocyanide (**2a**) under the same conditions as those proposed in Scheme 1, eq. 1 (1.5 equiv. of CsF in DMSO at 90 °C for 5 h). 3-Bromo-*N*-(*tert*-butyl)-2-(*p*-tolyl)acrylamide (**4a**) was isolated in a 60% yield, and *N*-(*tert*-butyl)-3-(*p*-tolyl)propynamide (**3a**) was isolated in less than 25% yield (Table 1, entry 1). These results were in agreement with those reported by Jiang *et al*. for 1-(bromoethynyl)-4-methylbenzene **4a** formation[20] and was indicative of a two-step reaction mechanism in which HBr elimination initially occurred and was followed by the *β*-addition of isocyanide to obtain the desired bromoalkynes. Formation of **3a** as a byproduct in a 25% yield under this condition revealed that *α*-addition to the proposed bromoalkyne followed by second HBr elimination is also possible. When changes were made to the reaction conditions, such as the use of DMF as the solvent and Cs_2CO_3 as the base, it was noted that the yield of **4a** diminished (Table 1, entries 2 and 3). Additionally, using CsF in the presence of a catalytic amount of $Pd(OAc)_2$ in DMSO generated **3a** in 50% yield; however, the results that were obtained when the reaction was conducted in DMF at 90 ºC were uninspiring (Table 1, entries 6 and 7). Fortunately, **3a** could be isolated in a 90% yield in the presence of Cs_2CO_3 with $Pd(OAc)_2$ in DMF (Table 1, entry 9). Reactions that were focused on optimizing the palladium catalyst, base, and solvent revealed that the best conditions for the formation of 3a were $Pd(OAc)_2$ (5 mol%) and Cs_2CO_3 (1 equiv.) in DMF at 90 °C (Table 1). It should be noted that using an excess amount of isocyanide (up to 3 equiv.) only increased the rate of the reaction and resulted in no new products.

Table 1. Optimization of the reaction conditions[a]



Entry	Catalyst	Base	Solvent	Isolated yield (%)	
				3a	**4a**
1	-	CsF	DMSO	25	60
2	-	CsF	DMF	-	40
3	-	Cs_2CO_3	DMSO	-	5
4	-	Cs_2CO_3	DMF	-	5
5	-	K_2CO_3	DMF	-	-
6	$Pd(OAc)_2$	CsF	DMSO	50	-
7	$Pd(OAc)_2$	CsF	DMF	22	-
8	$Pd(OAc)_2$	Cs_2CO_3	DMSO	17	10
9	$Pd(OAc)_2$	Cs_2CO_3	DMF	90	-
10	$PdCl_2$	Cs_2CO_3	DMF	20	-
11	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	15	-
12	CuI	Cs_2CO_3	DMF	-	-

13	$Pd(OAc)_2$	Na_2CO_3	DMF	-	-
14	$Pd(OAc)_2$	K_2CO_3	DMF	10	-
15	$Pd(OAc)_2$	MeONa	DMF	20	-
16	$Pd(OAc)_2$	AcONa	DMF	30	-
17	$Pd(OAc)_2$	*t*-BuONa	DMF	73	-
18	$Pd(OAc)_2$	Et_3N	DMF	5	-
19	$Pd(OAc)_2$	Cs_2CO_3	toluene	trace	-
20	$Pd(OAc)_2$	Cs_2CO_3	CH_3CN	trace	-

[a]Reaction conditions: 1-(2,2-Dibromovinyl)-4-methylbenzene (1.0 mmol), *tert*-butyl isocyanide (1.3 equiv.), catalyst (5 mol%), base (1 equiv.) and 0.5 mL of H_2O in 5.0 mL of solvent at 90 °C for 4 h.

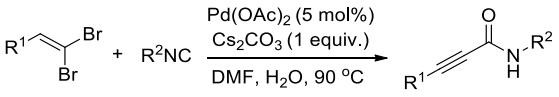
After achieving optimal reaction conditions, we examined the reactivity between a variety of substituted dibromoalkenes **1** and isocyanides **2**; the results are summarized in Table 2. It was found that 1,1-dibromo-1-alkenes that contained *para*-, *meta*-, and *ortho*-electron donating and/or electron-withdrawing substituents were all easily converted to their corresponding 3-arylpropiolamides **3a**–**h** in good to excellent yields. Interestingly, the presence of electron-withdrawing groups seemed to increase the reaction efficiency and reduce the reaction time (as seen in the case of compound **3b** and **3h**, Table 2). Of all the tested reactions, the desired product was produced in ≥ 75% yield; this indicated that the coupling reaction was not very sensitive to sterically-hindered compounds.

2-Chloroquinolines-bearing dibromoalkene were also evaluated under optimal reaction conditions. These substrates proved to be a challenge, especially when it came to reaction selectivity. This is attributed to the presence of the reactive Cl at position 2. The reaction of 2-chloro-3-(2,2-dibromo vinyl)quinoline with cyclohexyl isocyanide directly produced **3i** in an isolated yield of 75% with quinoline's ring remaining inactive at position 2 (Table 2). When other quinolines bearing Me, Cl, and OMe substituents were employed in reactions with aliphatic and aromatic isocyanides, the corresponding compounds **3i**–**3p** were obtained.

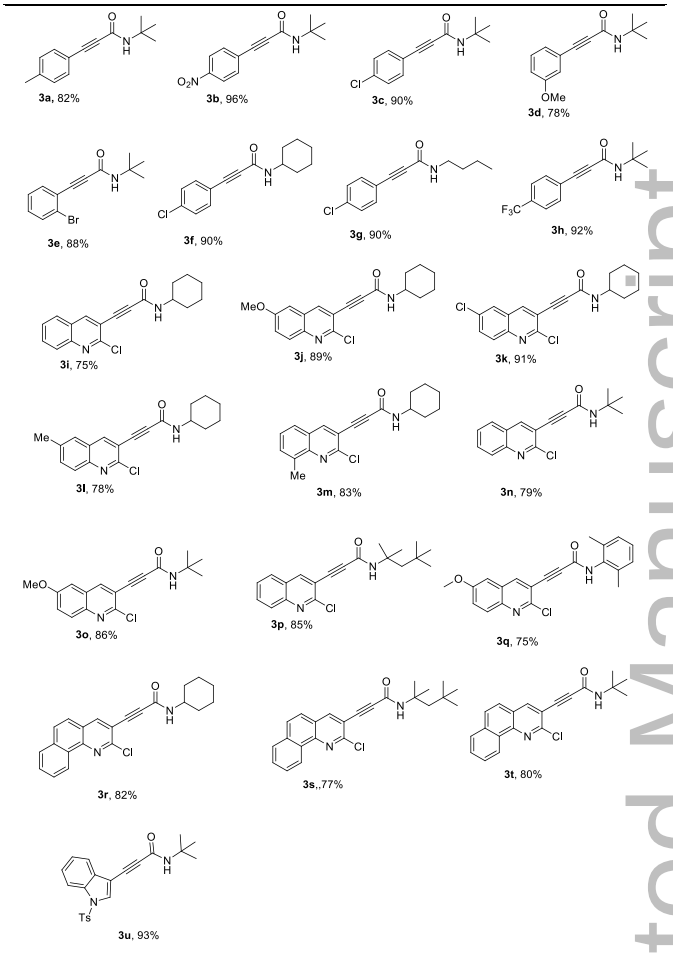
When R^2 replaced by aromatic moiety the reactions gave efficiently corresponding amide **3q** in 75% yield (Table 2).

The scope of the reaction was also expanded to include benzoquinoline 1,1-dibromo-1-alkene coupling partners; these produced compounds **3p**–**3s** in 75%–82% yields with a variety of isocyanides (Table 2).

Table 2. Synthesis of various 3-arylpropynamides **3**[a]



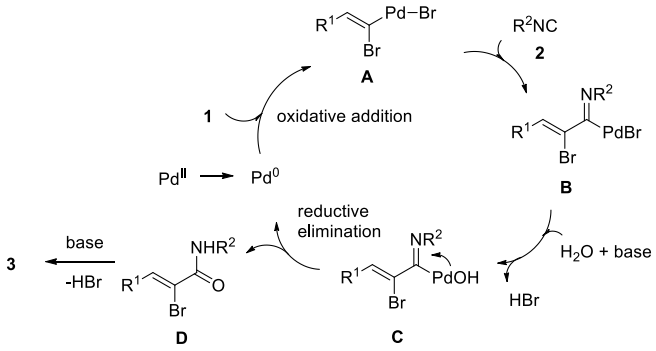
1 **2** **3**



[a]All reactions were carried out using 1,1-dibromo-1-alkenes (1.0 mmol), isocyanides (1.3 mmol), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (1 mmol) and 0.5 mL of H_2O in 5.0 mL of DMF at 90 °C for 2-5 h.

Scheme 2 highlights a plausible mechanism for this Pd-catalyzed coupling reaction of isocyanides with 1,1-dibromo-1-alkenes **1**. In the absence of palladium, the formation of bromoalkynes in base media becomes more favorable, after which the addition of isocyanide at the β-position yields **4**.[20] However, the existence of palladium in the basic media appears to activate the C–Br bond in compound **1**, thereby forming intermediate **A**. Subsequently, isocyanide was inserted into **A** to produce **B**. The base-mediated replacement of OH by X resulted in the formation of **C**.[22] This step is crucial because the reaction will not proceed well in the

absence of water even under an O_2 atmosphere. A subsequent reductive elimination of palladium results in amide **D** (Scheme 2). Finally, the elimination of HBr using a base enables **D** to be converted to the desired product **3** (Scheme 2).[7b,9a]



Scheme 2. Possible pathways involved in the Pd-catalyzed cross-coupling of 1,1-dibromo-1-alkenes with isocyanides

Conclusion

Thus, we developed a highly selective and straightforward protocol for the synthesis of 3-(hetero)arylpropynamides from *gem*-dibromo alkenes and isocyanides by utilizing $Pd(OAc)_2$ and Cs_2CO_3. Further, one of the challenging methodologies for synthesizing propynamides is the transition metal-catalyzed aminocarbonylation of alkynes (bromoalkynes, alkynes, and propynoic acid) by utilizing CO and amines.[16] However, we used isocyanide, which was safer than CO and which acted simultaneously as both carbonyl and amines source. Therefore, this method is operationally simple and works well with an extensive range of aromatic and aliphatic isocyanides and 1,1-dibromo-1-alkene coupling partners.

General Remarks. The solvents and chemicals purchased from Merck and Aldrich chemical companies. Unless otherwise mentioned they were used without further purification. The 1,1-dibromoalkenes were prepared according to the reported procedures.[23] Melting points are taken on an Electrothermal 9100 apparatus and are uncorrected. FT-IR spectra were recorded on a Shimadzu Infra-Red Spectroscopy IR-435. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE Spectrometer (300, 400, 500 MHz for ^{1}H, 75, 100, 125 MHz for ^{13}C) in DMSO-d_6 and $CDCl_3$ as a solvent. Mass spectra recorded on Agilent Technology (HP) 5973 Network Mass Selective Detector operating at an ionization potential of 70 eV and a Leco CHNS, model 932 was used for elemental analysis.

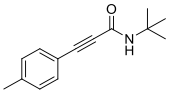
Experimental Section

General procedure for the synthesis of 3-(hetero)arylpropynamides 3a-3s

To the mixture of *gem*-dibromo alkenes **1** (1.0 mmol), $Pd(OAc)_2$ (5 mol%), Cs_2CO_3 (1.0 mmol) and 0.5 mL of H_2O in 5.0 mL of DMF (5.0 mL), isocyanide **2** (1.3 mmol) was added. Then the mixture was stirred at 90 °C for 2-5 hours. Upon completion, to the reaction mixture, water (20 mL) was added then extracted with CH_2Cl_2 (3×10 mL), and the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography using *n*-hexane-ethyl acetate (9:1) to obtain products **3** in pure form.

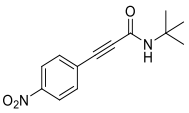
Characterization Data for All Prepared Compounds

***N-tert*-Butyl-3-(*p*-tolyl)propynamide (3a)**



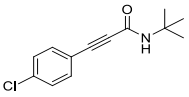
Yield: 176 mg (82%). White solid. MP = 98-100 °C. FT-IR (KBr): 3286, 3030, 2969, 2204, 1629, 1532, 1473, 816 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.76 (s, 1H), 2.36 (s, 3H), 1.41(s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.7, 140.3, 132.3, 129.2, 117.3, 83.7, 82.9, 52.3, 28.6, 21.6 ppm. MS (EI) m/z: calcd for $C_{14}H_{17}NO$, 115.13, found, 115. Anal. calcd. For $C_{14}H_{17}NO$; C, 78.10; H, 7.96; N, 6.51%; Found; C, 78.20; H, 8.12; N, 6.42%.

***N-tert*-Butyl-3-(4-nitrophenyl)propynamide (3b)**



Yield: 236 mg (96%). Light yellow solid. MP = 160-163 °C. FT-IR (KBr): 3291, 3055, 2967, 2928, 2221, 1643, 1596, 1221, 855 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.22 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 5.84 (s, 1H), 1.42 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 151.5, 148.1, 133.1, 127.2, 123.7, 87.9, 79.8, 52.8, 28.6 ppm. MS (EI) m/z: calcd for $C_{13}H_{14}N_2O_3$; 246.10, found, 246. Anal. calcd. For $C_{13}H_{14}N_2O_3$; C, 63.40; H, 5.73; N, 11.38%, Found; C, 63.19; H, 5.55; N, 11.22%.

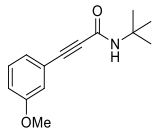
***N-tert*-Butyl-3-(4-chlorophenyl)propynamide (3c)**



Yield: 212 mg (90%). White solid. MP = 120-123 °C. FT-IR (KBr): 3288, 3041, 2971, 2929, 2221, 1629, 1543, 1363,

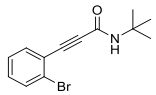
1220, 828 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 5.79 (s, 1H), 1.41 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.2, 136.1, 133.6, 128.9, 118.9, 84.9, 81.3, 52.5, 28.6 ppm. MS (EI) m/z: calcd for $C_{13}H_{14}ClNO$; 235.08, found, 235. Anal. calcd. For $C_{13}H_{14}ClNO$; C, 66.24; H, 5.99; N, 5.94%; Found; C, 66.13; H, 5.83; N, 5.77%.

***N*-*tert*-Butyl-3-(3-methoxyphenyl)propynamide (3d)**



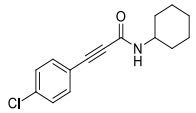
Yield: 180 mg (78%). Light yellow solid. MP = 108-112 ºC. FT-IR (KBr): 3293, 3055, 2969, 2932, 2215, 1636, 1601, 1536, 1364, 1223, 876, 784, 687 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.17 (t, *J* = 6.2 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 6.88 (d, *J* = 7.8 Hz,, 1H), 5.70 (s, 1H), 3.72 (s, 3H), 1.34 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4, 152.5, 129.6, 124.9, 121.4, 117.1, 116.6, 83.8, 82.5, 55.3, 52.5, 28.7 ppm. MS (EI) m/z: calcd for $C_{14}H_{17}NO_2$; 231.13, found, 231. Anal. calcd. For $C_{14}H_{17}NO_2$; C, 72.70; H, 7.41; N, 6.06%; Found; C, 72.63; H, 7.30; N, 6.11%.

3-(2-Bromophenyl)-*N*-(*tert*-butyl)propynamide (3e)



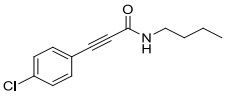
Yield: 245 mg (88%). Light yellow solid. MP = 61-65 ºC. FT-IR (KBr): 3274, 3055, 2969, 2928., 2219, 1634, 1541, 1221, 1120, 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59 (dd, *J* = 1.0 Hz, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 1.5 Hz, *J* = 7.5 Hz, 1H), 7.31-7.23 (m, 2H), 5.82 (s, 1H), 1.42 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.1, 134.4, 132.6, 126.0, 122.9, 87.8, 80.6, 52.5, 28.6 ppm. MS (EI) m/z: calcd for $C_{13}H_{14}BrNO$; 279.03, found, 279. Anal. calcd. For $C_{13}H_{14}BrNO$; C, 55.73; H, 5.04; N, 5.00%; Found; C, 55.48; H, 5.19; N, 4.85%.

3-(4-Chlorophenyl)-*N*-cyclohexylpropynamide (3f)



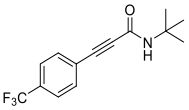
Yield: 235 mg (90%). White solid. MP =155-159 ºC. FT-IR (KBr): 3269, 3059, 2929, 2854, 2220, 1625, 1539, 1486, 1291.31, 1089, 826, 706 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 5.83 (d, *J* =10.5 Hz, 1H), 3.91-3.85 (m, 1H), 2.01-1.18 (m, 10H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 152.2, 136.3, 133.6, 128.9, 118.8, 84.1, 82.9, 49.0, 32.8, 25.4, 24.8 ppm. MS (EI) m/z: calcd for $C_{15}H_{16}ClNO$; 261.09, found, 261. Anal. calcd. For $C_{15}H_{16}ClNO$; C, 68.83; H, 6.16; N, 5.35%; Found; C, 68.71; H, 6.22; N, 5.39%.

***N*-Butyl-3-(4-chlorophenyl)propynamide (3g)**



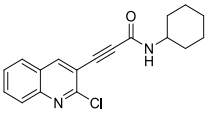
Yield: 212 mg (90%). White solid. MP = 131-134 ºC. FT-IR (KBr): 3289, 3057, 2957, 2924, 2854, 2222, 1627, 1540, 1298, 1219, 1090, 830, 722 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (d, *J* =8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 5.94 (s, 1H), 3.38-3.34 (m, 2H), 1.59-1.53 (m, 2H), 1.43-1.36 (m, 2H), 0.95 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 153.1, 136.3, 133.7, 128.9, 118.8, 83.9, 83.2, 39.7, 31.4, 20.0, 13.6 ppm. MS (EI) m/z: calcd for $C_{13}H_{14}ClNO$; 235.08, found, 235. Anal. calcd. For $C_{13}H_{14}ClNO$; C, 66.24; H, 5.99; N, 5.94%; Found; C, 66.14; H, 6.12; N, 5.75%.

N-(tert-butyl)-3-(4-(trifluoromethyl)phenyl) propiolamide (3h)



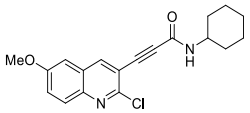
Yield: 245 mg (92%). White crystal. MP =117-122 ºC. FT-IR (KBr): 3240, 3058, 2924, 2854, 2229, 1634, , 1558, 1328, 841 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (s, 4H), 5.74 (s, 1H), 1.35 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.0, 132.7, 131.3, 125.5 (q, *J* = 3.75 Hz) , 124.3, 121.8, 85.8, 80.7, 52.7, 28.6 ppm. MS (EI) m/z: calcd for $C_{14}H_{14}F_3NO$, 269.10 found, 369. Anal. calcd. For $C_{14}H_{14}F_3NO$; C, 62.45; H, 5.24; N, 5.20. Found; C, 62.30; H, 5.14; N, 5.11%.

3-(2-Chloroquinolin-3-yl)-*N*-cyclohexylpropynamide (3i)



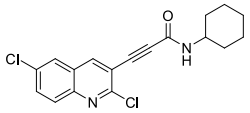
Yield: 224 mg (75%). White solid. MP = 211-213 ºC. FT-IR (KBr): 3263, 3050, 2926, 2851, 2212, 1626, 1584, 1446, 1247, 1137, 803, 746 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.89 (d, *J* = 7.6 Hz, 1H), 8.86 (s, 1H), 8.11-8.06 (m, 1H), 8.02-7.99 (m, 1H), 7.93-7.89 (m, 1H), 7.76-7.72 (m, 1H), 3.68-3.61 (m, 1H), 1.80-1.19 (m, 10H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 151.1, 149.4, 146.8, 144.7, 133.1, 128.74. 128.72, 128.4, 126.4, 115.1, 90.0, 78.4, 48.9, 33.8, 32.5, 25.6, 25.1 ppm. MS (EI) m/z: calcd for $C_{18}H_{17}ClN_2O$; 312.10, found, 312. Anal. calcd. For $C_{18}H_{17}ClN_2O$; C, 69.12; H, 5.48; N, 8.96%; Found; C, 68.99; H, 5.54; N, 9.05%.

3-(2-Chloro-6-methoxyquinolin-3-yl)-*N*-cyclohexylpropynamide (3j)



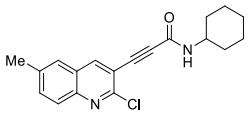
Yield: 304 mg (89%). White solid. MP = 222-224 ºC. FT-IR (KBr): 3264, 3068, 2922, 2853, 2225, 1625, 1578, 1317, 1284, 1128, 834, 707cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.93 (d, *J* = 7.6 Hz, 1H), 8.72 (s, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.49 (s, 1H), 3.93 (s, 3H), 3.66 (s, 1H), 1.82-1.23 (m, 10H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 158.8, 151.2, 146.7, 143.1, 142.8, 129.8, 127.7, 125.2, 115.2, 106.4, 90.0, 78.5, 56.3, 48.9, 32.5, 25.6, 25.1 ppm. MS (EI) m/z: calcd for $C_{19}H_{19}ClN_2O_2$; 342.11, found, 342. Anal. calcd. For $C_{19}H_{19}ClN_2O_2$; C, 66.57; H, 5.59; N, 8.17%; Found; C, 66.42; H, 5.67; N, 7.89%.

_N_-Cyclohexyl-3-(2,6-dichloroquinolin-3-yl)propynamide (3k)



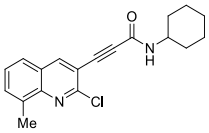
Yield: 315 mg (91%). White solid. MP = 242-247 ºC. FT-IR (KBr): 3251, 3058, 2931, 2853, 2221, 1625, 1546, 1477, 1284, 974, 885, 714, 618cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.92 (d, *J* = 7.6 Hz, 1H), 8.81 (s, 1H), 8.23-8.20 (m, 1H), 8.05-8.02 (m, 1H), 7.93-7.90 (m, 1H), 3.66-3.61 (m, 1H), 1.80-1.18 (m, 10H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 150.5, 149.4, 144.7, 143.3, 132.8, 132.5, 130.0, 126.8, 118.4, 115.7, 90.0, 77.4, 48.4, 31.9, 25.0, 24.5 ppm. MS (EI) m/z: calcd for $C_{18}H_{16}Cl_2N_2O$; 346.06, found, 346. Anal. calcd. For $C_{18}H_{16}Cl_2N_2O$; C, 62.26; H, 4.64; N, 8.07%; Found; C, 62.12; H, 4.73; N, 8.19%.

3-(2-Chloro-6-methylquinolin-3-yl)-_N_-cyclohexylpropynamide (3l)



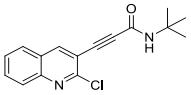
Yield: 254 mg (78%). White solid. MP = 220-222 ºC. FT-IR (KBr): 3255, 3057, 2924, 2853, 2221, 1624, 1580, 1352, 1200, 889, 762 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.93 (d, *J* = 7.6 Hz, 1H), 8.77 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 3.66 (d, *J* = 4.8 Hz, 1H), 1.82-1.23 (m, 10H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 151.1, 148.5, 145.4, 143.9, 138.6, 135.2, 128,1, 127.2, 126.4, 115.0, 89.9, 78.5, 48.8, 32.5, 25.5, 25.1, 21.6 ppm. MS (EI) m/z: calcd for $C_{19}H_{19}ClN_2O$; 326.12, found, 326. Anal. calcd. For $C_{19}H_{19}ClN_2O$; C, 69.83; H, 5.86; N, 8.57%; Found; C, 69.73; H, 5.77; N, 8.41%.

3-(2-Chloro-8-methylquinolin-3-yl)-_N_-cyclohexylpropynamide (3m)



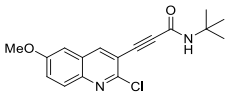
Yield: 270 mg (83%). White solid. MP = 218-221 ºC. FT-IR (KBr): 3257, 3056, 2918, 2852, 2220, 1630, 1579, 1390, 1282, 1152, 893, 769, 611 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.91 (t, *J* = 8.1 Hz, 1H), 8.83 (s,1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.67-7.60 (m, 1H), 3.69-3.62 (m, 1H), 2.52 (s, 3H), 1.83-1.57 (m, 5H), 1.37-1.10 (m, 5H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 151.2, 148.4, 145.8, 144.9, 136.2, 133.0, 128..4, 126.5, 114.9, 90.0, 78.5, 48.8, 32.5, 25.6, 25.1, 17.7 ppm. MS (EI) m/z: calcd for $C_{19}H_{19}ClN_2O$; 326.12, found, 326. Anal. calcd. For $C_{19}H_{19}ClN_2O$; C, 69.83; H, 5.86; N, 8.57%; Found; C, 70.94; H, 5.95; N, 8.67%.

_N_-(_tert_-Butyl)-3-(2-chloroquinolin-3-yl)propynamide (3n)



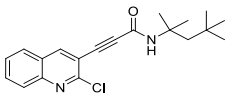
Yield: 226 mg (79%). White solid. MP = 215-218 ºC. FT-IR (KBr): 3273, 3051, 2926, 2851, 2215, 1625, 1578, 1549, 1239, 1135, 813, 747 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.84 (s, 1H), 8.59 (s,1H), 8.09-8.06 (m, 1H), 8.02-7.99 (m, 1H), 7.93-7.89 (m, 1H), 7.76-7.71 (m, 1H), 1.32 (s, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 151.0, 146.2, 144.1, 143.3, 132.5, 128.2, 128.1, 127.8, 125.9, 114.8, 90.1, 76.5, 51.5, 28.2 ppm. MS (EI) m/z: calcd for $C_{16}H_{15}ClN_2O$, 286.09, found, 286. Anal. calcd. For $C_{16}H_{15}ClN_2O$; C, 67.02; H, 5.27; N, 9.77%; Found; C, 67.21; H, 5.38; N, 9.85%.

_N_-(_tert_-Butyl)-3-(2-chloro-6-methoxyquinolin-3-yl)propynamide (3o)



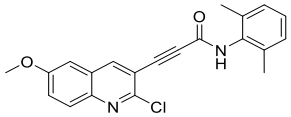
Yield: 272 mg (86%). White solid. MP = 172-176 ºC. FT-IR (KBr): 3281, 3039, 2969, 2935, 2217, 1620, 1533, 1360, 1222, 1184, 832, 744, 639 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.67 (s, 1H), 8.58 (s, 1H), 7.93-7.89 (m, 1H), 7.55-7.51 (m, 1H), 7.47-7.45 (m, 1H), 3.91 (s, 3H), 1.32 (s, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 158.3, 151.0, 146.2, 142.4, 142.2, 129.3, 127.2, 124.6, 114.9, 105.9, 90.1, 76.6, 55.8, 51.5, 28.2 ppm. MS (EI) m/z: calcd for $C_{17}H_{17}ClN_2O_2$; 316.10, found, 316. Anal. calcd. For $C_{17}H_{17}ClN_2O_2$; C, 64.46; H, 5.41; N, 8.84%; Found; C, 64.33; H, 5.57; N, 9.02%.

3-(2-Chloroquinolin-3-yl)-_N_-(2,4,4-trimethylpentan-2-yl)propynamide (3p)



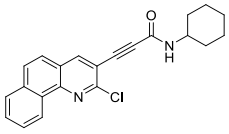
Yield: 291 mg (85%). White crystal. MP = 186-189 ºC. FT-IR (KBr): 3280, 3046, 2955, 2223, 1647, 1534, 1481, 1359, 1277, 1132, 958, 771 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.84 (s, 1H), 8.49 (s, 1H), 8.10-8.07 (m, 1H), 8.02-7.99 (m, 1H), 7.93-7.88 (m, 1H), 7.76-7.71 (m, 1H), 1.76 (s, 2H), 1.35 (s, 6H), 0.99 (s, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 151.0, 148.9, 146.2, 144.0, 132.5, 128.3, 128.2, 127.8, 125.9, 114.8, 90.3, 76.3, 55.2, 49.5, 31.4, 31.1, 29.1 ppm. MS (EI) m/z: calcd for $C_{20}H_{23}ClN_2O$; 342.15, found, 342. Anal. calcd. For $C_{20}H_{23}ClN_2O$; C, 70.06; H, 6.76; N, 8.17%; Found; C, 70.21; H, 6.82; N, 8.33%.

3-(2-Chloro-6-methoxyquinolin-3-yl)-N-(2,6-dimethylphenyl) propiolamide (3q)



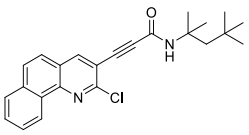
Yield: 273 mg (75%). White solid. MP = 186-188 ºC. FT-IR (KBr): 3239, 3009, 2950, 2922, 2217, 1641, 1622, 1496, 1381, 1228, 710 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ = 10.38 (s, 1H), 8.80 (s, 1H), 7.94 (d, *J* = 10.0 Hz, 1H), 7.57 (d, *J* = 10.0 Hz, 1H). 7.52-7.50 (m, 1H), 7.17-7.11 (m, 3H), 3.93 (s, 3H), 2.21 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ̄ = 158.9, 150.5, 146.8, 143.4, 142.9, 135.6, 134.1, 129.9, 128.6, 128.4, 127.8, 127.7, 125.3, 115.0, 106.6, 89.7, 79.5, 56.3, 18.5 ppm. MS (EI) m/z: calcd for $C_{21}H_{17}ClN_2O_2$, 364.10, found, 364. Anal. calcd. For $C_{21}H_{17}ClN_2O_2$; C, 69.14; H, 4.70; N, 7.68%; Found; C, 69.10; H,4.60; N, 7.65%.

3-(2-Chlorobenzo[h]quinolin-3-yl)-*N*-cyclohexylpropynamide (3r)



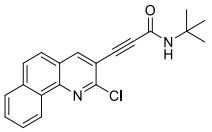
Yield: 297 mg (82%). White solid. MP = 216-218 ºC. FT-IR (KBr): 3268, 3050, 2935, 2853, 2219, 1621, 1534, 1438, 1342, 1283, 1150, 817, 753 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 9.02-9.00 (m, 1H), 8.97-8.95 (m, 1H), 8.89 (s, 1H), 8.13-8.12 (m, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.87-7.84 (m, 2H), 3.68-3.64 (m, 1H), 1.83-1.22 (m, 10H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 151.2, 149.2, 145.4, 144.6, 144.0, 134.6, 130.3, 129.6, 129.5, 128.8, 128.4, 125.0, 124.6, 115.8, 90.5, 78.4, 48.9, 32.5, 25.6, 25.1 ppm. MS (EI) m/z: calcd for $C_{22}H_{19}ClN_2O$; 362.12, found, 362. Anal. calcd. For $C_{22}H_{19}ClN_2O$; C, 72.82; H, 5.28; N, 7.72%; Found; C, 73.01; H, 5.17; N, 7.59%.

3-(2-Chlorobenzo[h]quinolin-3-yl)-*N*-(2,4,4-trimethylpentan-2-yl)propynamide (3s)



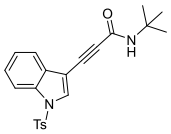
Yield: 302 mg (77%). Light yellow crystal. MP = 179-182 ºC. FT-IR (KBr): 3243, 3055, 2956, 2937, 2221, 1635, 1546, 1465, 1389, 1291, 1220, 1143, 887, 759 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 9.01-8.99 (m, 1H), 8.85 (s, 1H), 8.51 (s, 1H), 8.11-8.09 (m, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.85-7.82 (m, 2H), 1.77 (s, 2H), 1.36 (s, 6H), 1.00 (s, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 151.1, 148.7, 144.8, 143.3, 134.1, 129.7, 129.1, 129.0, 128.3, 127.9, 124.5, 124.4, 124.0, 115.5, 90.8, 76.3, 55.2, 49.5, 31.4, 31.1, 29.1 ppm. MS (EI) m/z: calcd for $C_{24}H_{25}ClN_2O$; 392.17, found, 392. Anal. calcd. For $C_{24}H_{25}ClN_2O$; C, 73.36; H, 6.41; N, 7.13%; Found; C, 73.19; H, 6.58; N, 7.19%.

***N*-(*tert*-Butyl)-3-(2-chlorobenzo[h]quinolin-3-yl)propynamide (3t)**



Yield: 269 mg (80%). White solid. MP = 212-216 ºC. FT-IR (KBr): 3233, 3051, 2966, 2926, 2220, 1632., 1547, 1399, 1291, 1219, 1143, 877, 751 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 9.01-8.98 (m, 1H), 8.85 (s, 1H), 8.62 (s, 1H), 8.11-8.10 (m, 1H). 8.07 (d, *J* = 9.2 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.85-7.82 (m, 2H), 1.33 (s, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ = 151.0, 148.6, 144.9, 143.4, 134.1, 129.8, 129.1, 129.0, 128.3, 127.9, 124.4, 124.0, 115.4, 90.7, 76.5, 51.5, 28.2 ppm. MS (EI) m/z: calcd for $C_{20}H_{17}ClN_2O$; 336.10, found, 336. Anal. calcd. For $C_{20}H_{17}ClN_2O$; C, 71.32; H, 5.09; N, 8.32%; Found; C, 71.22; H, 5.17; N, 8.43%.

N-(tert-butyl)-3-(1-tosyl-1H-indol-3-yl)propiolamide (3u)



Yield: 370 mg (94%). White solid. MP = 114-119 ºC. FT-IR (KBr): 3230, 3050, 2969, 2926, 2212, 1623, 1540, 1451, 1381, 1117, 810, 740 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 8.45 (s, 1H), 8.36 (s, 1H), 7.99 (t, *J* = 8.4 Hz, 3H), 7.77 (d, *J* = 7. 5 Hz, 1H), 7.50-7.38 (m, 4H), 2.34 (s, 3H), 1.33 (s, 9H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ̄ = 152.0, 146.7, 134.0, 133.8, 132.5, 130.9, 130.2, 127.5, 126.6, 124.8, 120.9, 113.9, 102.5, 89.6, 73.8, 51.8, 28.8, 21.5 ppm. MS (EI) m/z: calcd for $C_{22}H_{22}N_2O_3S$, 394.14, found, 394. Anal. calcd. For $C_{22}H_{22}N_2O_3S$; C, 66.98; H, 5.62; N, 7.10%; Found; C, 66.9; H, 5.5; N, 7.05%.

Acknowledgements

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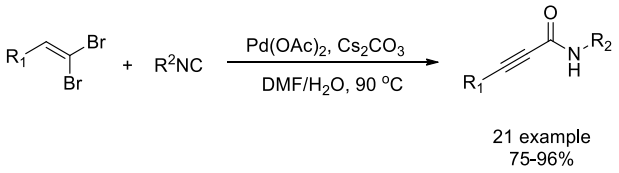
FULL PAPER

Palladium-catalyzed highly regioselective synthesis of 3-(hetero)arylpropynamides from *gem*-dibromoalkenes and isocyanides



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