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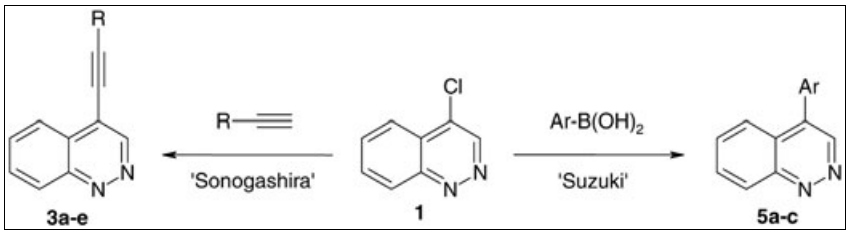

A series of 4-ethynylcinnolines **3a**–**e** was prepared by Sonogashira reaction of 4-chlorocinnoline (**1**) with appropriate alkynes. Moreover, Suzuki coupling of **1** with boronic esters gave the corresponding 4-arylcinnolines **5a**–**c**. Detailed NMR spectroscopic data including unambiguous chemical shift assignments of all ^{1}H, ^{13}C, and ^{15}N resonances of the obtained cinnoline derivatives are reported.

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INTRODUCTION

In contrast to the pyridazine system that is the core structure of a considerable number of drug molecules [1], benzo[*a*]pyridazine, i.e., cinnoline, is a rather rarely concerned system which has fallen somewhat into oblivion for medicinal chemists [2]. Thus, the antibacterial agent Cinoxacin (Fig. 1) is yet the only example of a drug molecule on the market incorporating a cinnoline nucleus [3].

In continuation of our studies on 4-substituted cinnolines [4, 5], we here report on investigations regarding functionalization of 4-chlorocinnoline (**1**) *via* Pd-assisted cross-coupling reactions. Such types of reactions have emerged to be one of the most powerful tools in modern synthetic organic chemistry, enabling not only carbon–carbon but as well carbon–nitrogen bond formation [6–9]. Also for the cinnoline system, commensurate couplings of 3- and 4-halocinnolines have been reported [10–14].

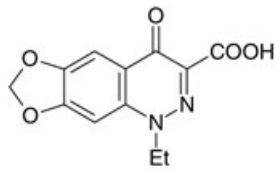
However, to the best of our knowledge, a systematic study concerning Sonogashira-type couplings with 4-chlorocinnoline (**1**) has not been published. The latter compound represents an ideal starting material due to its stability and its facile accessibility. Hence, we here report on the Sonogashira couplings with 4-chlorocinnoline (**1**) and on some arylations of the former using the Suzuki protocol. In addition, a substantiated NMR study with the obtained 4-substituted cinnolines including also ^{15}N-NMR chemical shifts is presented.

RESULTS AND DISCUSSION

The starting material **1** was obtained on treatment of cinnolin-4(1*H*)-one with phosphoryl chloride [4]. Initial attempts to react **1** with phenylacetylene in triethylamine in the presence of bis(triphenylphosphine)palladium(II) chloride showed a high degree of conversion. This hints to a sufficient reactivity of the chloro atom in compound **1** regarding Sonogashira-type reactions, for which a general reactivity I > OTf ~ Br > Cl is specified in the literature [15]—with a considerable number of cases known where chloroarenes do not react. In the following, **1** was reacted with a series of terminal alkynes **2a**–**e** to obtain the corresponding 4-alkynylcinnolines **3a**–**e** in moderate to good yields (Scheme 1). Of this series, only **3a** is a known compound that has been formerly prepared by reaction of 4-methylsulfonylcinnoline and phenylacetylene in the presence of a base [16].

In contrast, Suzuki couplings of 4-chlorcinnoline (**1**) with substituted phenyboronic acids have been already reported by Quéguiner and coworkers [13]. In addition, we reacted **1** with phenylboronic acid (**4a**), (2-formylphenyl)boronic acid (**4b**) and 3-thienylboronic acid (**4c**) to reach the corresponding 4-arylcinnolines **5a**–**c** (Scheme 1).

The obtained 4-substituted cinnolines of types **3** and **5** were subjected to detailed NMR spectroscopic investigations (concentrations of the used solutions ~ 0.15 M). Full and unambiguous assignment for all proton, carbon, and nitrogen resonances was achieved by combined application of standard NMR spectral techniques [17] such as fully ^{1}H-coupled ^{13}C-NMR spectra, APT, COSY, HMQC, HSQC, and HMBC. In special cases, for the unambiguous determination of long-range $^{13}C,^{1}H$ coupling constants 2D(δ,*J*) INEPT spectra with selective excitation were applied [18]. The ^{15}N-NMR spectra were mainly recorded using the gradient selected, sensitivity



Cinoxazin

Figure 1. Cinoxazin, an antibacterial agent containing a cinnoline nucleus.

enhanced HMBC sequence [19]. The obtained data show a high degree of consistency and are summarized for compound **3** in Table 1 (^{1}H-NMR, ^{13}C-NMR, and ^{15}N-NMR). The data of **5a–c** are given in the Experimental section.

In Figure 2, the chemical shifts (^{1}H, ^{13}C, and ^{15}N) for compound **3b**—as a representative example—are displayed. Moreover, selected ^{1}H,^{13}C correlations extracted from the HMBC spectra, being important for the unequivocal assignment of resonances, are marked by round arrows.

It should be mentioned that the ^{1}H-NMR chemical shifts of the cinnoline H-atoms frequently exhibit a notable dependence on the concentration. Thus, for instance, the ^{1}H-NMR spectrum of **3d** taken from a less concentrated solution (0.05*M*) shows 0.11–0.16 ppm larger chemical shifts for all cinnoline ring protons compared to those found with the 0.15*M* solution specified in Table 1. In contrast, the corresponding ^{13}C-NMR spectra do not manifest such explicit differences.

In conclusion, we have shown that 4-alkynylcinnolines are smoothly obtained by the Sonogashira coupling of 4-chlorocinnoline (**1**) with appropriate acetylenes. Compound **1** is an ideal starting material for Suzuki couplings as well, the latter leading to different 4-arylcinnolines.

EXPERIMENTAL

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Finnigan MAT 8230 instrument (ESI, HRMS). IR spectra were recorded on a Perkin-Elmer FTIR spectrum 1000 spectrophotometer. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna, using a Perkin-Elmer 2400 CHN Elemental Analyzer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 25°C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 298 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C) from deuterichloroform solutions. The centre of the solvent signal was used as an internal standard which was related to tetramethylsilane with δ 7.26 ppm (^{1}H) and δ 77.0 ppm (^{13}C). The ^{15}N-NMR spectra were obtained on a Bruker Avance 500 instrument with a "directly" detecting broadband observe probe and were referenced against external nitromethane. Column chromatographic separations were carried out using Silicagel60 (mesh) as stationary phase. 4-Chlorocinnoline (**1**) was prepared according to a procedure described in the literature [4]. Product yields were not optimized.

General procedure for the reaction of 4-chlorocinnoline (1) with terminal acetylenes 2 (Sonogashira reaction). Triethylamine (2.08 mL, 15 mmol), the appropriate acetylene **2** (4.5 mmol), Pd$(PPh_3)_2Cl_2$ (211 mg, 0.3 mmol), and CuI (114 mg, 0.6 mmol) were added to a solution of 4-chlorocinnoline (**1**) (494 mg, 3 mmol) in dry dimethylformamide (10 mL) under an argon atmosphere. The reaction mixture was stirred at 55°C under an argon atmosphere for 2 h, then it was poured into water (30 mL).The mixture was extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was evaporated, and the residue was treated as described below.

4-(Phenylethynyl)cinnoline (3a). Column chromatography (SiO_2, eluent ethyl acetate/light petroleum, 1:3 v/v) afforded 387 mg (56%) of brownish crystals, mp 106–107°C (EtOH) (lit. [16] mp 107.5–108°C); IR (KBr): 2203 (C C) cm^{-1}; ms: *m/z* 231 (M^+ + 1, 18), 230 (M^+, 61), 202 (30), 201 (30), 200 (48), 149 (24), 75 (21), 74 (29), 73 (29), 71 (43), 70 (25), 69 (80), 67 (27), 57 (100), 56 (35), 55 (85), 51 (21), 50 (26), 43 (94).

4-(3-Thienylethynyl)cinnoline (3b). Column chromatography (SiO_2, eluent ethyl acetate/light petroleum, 1:3 v/v) afforded 545 mg (77%) of brownish crystals, mp 87.5–89°C (EtOH); IR (KBr): 2198 (C C) cm^{-1}; ms: *m/z* 236 (M^+, 30), 163 (22), 85 (33), 83 (24), 73 (30), 71 (41), 69 (37), 57 (100), 56 (60), 55 (90), 43 (94). Anal. Calcd. for $C_{14}H_8N_2S$•0.1 H_2O: C, 70.62; H, 3.47; N, 11.77. Found: C, 70.65; H, 3.26; N, 11.56.

Scheme 1

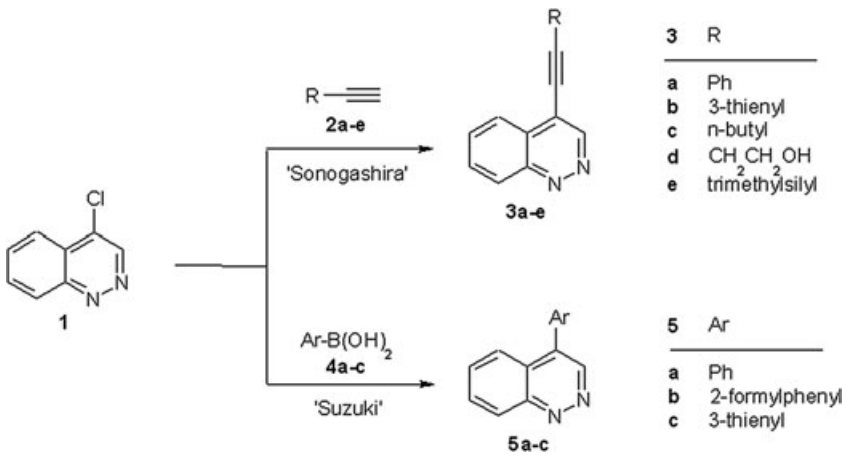


Table 1

^{1}H-NMR, ^{13}C-NMR, and ^{15}N-NMR data of compounds **3a–e** in deuteriochloroform.

Nuclei	**3a**	**3b**	**3c**	**3d**	**3e**
H-3[a]	9.36	9.31	9.27	9.13	9.29
H-5	8.26	8.2	8.16	8.02	8.17
H-6	7.8	7.76	7.77	7.65	7.79
H-7	7.86	7.82	7.84	7.75	7.85
H-8	8.52	8.49	8.53	8.41	8.51
H of R	7.67 (H2′,6′)	7.73 (H2′)[b]	2.60 (≡CCH$_2$)	2.88 (CH$_2$)	0.34 (Si(CH$_3$)$_3$)
	7.42 (H3′,5′)	7.29 (H4′)[b]	1.69 (CH$_2$)	3.99 (CH$_2$OH)	
	7.43 (H4′)	7.36 (H5′)[b]	1.54 (CH$_2$Me)	3.91 (OH)	
			0.98 (CH$_3$)		
N-1	36.1	35.6	–	30.9	37.8
N-2	29.6	29.4	–	25.6	29.8
C-3	146	145.9	146.6	146.3	146.3
	^{1}J = 186.3	^{1}J = 186.3	^{1}J = 186.1	^{1}J = 186.2	^{1}J = 186.4
C-4	119.2	118.9	119.9	119.6	118.5
		^{2}J(H3) = 5.5			
		^{3}J(H5) = 4.9			
C-4a	125.7	125.4	126.3	126	125.7
		^{3}J(H3) = 5.2			
C-5	124.8	124.8	124.9	124.8	124.9
C-6	131.5	131.5	131.3	131.4	131.7
C-7	131	130.9	130.9	131	131
C-8	130.1	130	130	129.6	130.1
C-8a	149.7	149.7	149.7	149.5	149.7
		^{4}J(H3) = 1.0			
Cinn-C≡	82.5	82.2	74.2	75.1	97.3
	^{3}J(H3) = 4.1	^{3}J(H3) = 4.1	^{3}J(H3) = 4.3	^{3}J(H3) = 4.3	^{3}J(H3) = 4.0
			^{3}J(CH$_2$) = 4.3	^{3}J(CH$_2$) = 4.3	
Cinn-C≡C	102.2	97	104.6	101.8	109.2
		^{3}J(H2′) = 3.8, ^{3}J(H4′) = 2.2			
C of R	121.6 (C1′)	131.1 (C2′)	19.6 (≡CCH$_2$)	24.4	–0.4 (SiCH$_3$)
	132.0 (C2′,6′)	^{1}J = 188.4, ^{3}J(H4′) = 8.4, ^{3}J(H5′) = 4.7	30.4 (≡CCH$_2$CH$_2$)	(≡CCH$_2$)	^{1}J = 120.4
	128.6 (C3′,5′)	120.6 (C3′)	22.1	^{1}J = 132.1	^{3}J = 2.0
	129.8 (C4′)	^{2}J(H2′) = 3.2	(CH$_2$CH$_3$)	60.6 (CH$_2$OH)	
		^{2}J(H4′) = 4.9	13.6 (CH$_3$)	^{1}J = 144.1	
		^{3}J(H5′) = 11.1			
		129.7 (C4′)			
		^{1}J = 174.6			
		^{2}J(H5′) = 4.6			
		^{3}J(H2′) =8.3			
		126.1 (C5′)			
		^{1}J = 187.9			
		^{2}J(H4′) = 7.1			
		^{3}J(H2′) = 5.8			

δ in ppm, *J* in Hz.
[a]H-3 always gives a singlet signal, signals of H-5 to H-8, and most H of R are multiplets.
[b]Thiophene system: ^{4}J(H2′,H4′) = 1.1 Hz, ^{4}J(H2′,H5′) = 3.0 Hz, ^{3}J(H4′,H5′) = 5.0 Hz.

4-(1-Hexyn-1-yl)cinnoline (3c). Flash chromatography (SiO_2, eluent ethyl acetate) and further purification by column chromatography (SiO_2, eluent dichloromethane) gave 353 mg (56%) of a tan oil; IR (KBr): 2223 (C C) cm^{-1}; ms: *m/z* 210 (M$^+$, 71), 167 (28), 166 (23), 165 (41), 154 (30), 153 (27), 152 (58), 140 (27), 139 (100), 126 (21), 75 (25), 74 (25), 63 (60), 51 (31), 50 (30), 43 (36). Anal. Calcd. for $C_{14}H_{14}N_2$•0.2 H_2O: C, 78.62; H, 6.79; N, 13.10. Found: C, 78.33; H, 6.39; N, 12.81.

4-(4-Cinnolinyl)-3-butyn-1-ol (3d). Column chromatography (SiO_2, eluent ethyl acetate/light petroleum, 1:1 v/v → ethyl acetate) afforded 297 mg (50%) of bright yellow crystals, mp 92.5–93.5°C (toluene); IR (KBr): 3353 (OH), 2225 (C C) cm^{-1}; ms: *m/z* 198 (M$^+$, 62), 140 (25), 139 (100), 77 (21), 74 (21), 69 (79), 67 (21), 63 (56), 62 (28), 57 (44), 51 (39), 50 (25), 43 (42). Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.47; H, 4.91; N, 14.00.

4-[(Trimethylsilyl)ethynyl]cinnoline (3e). The raw product was digested with light petroleum. Subsequent column chromatography (SiO_2, eluent ethyl acetate/light petroleum, 1:2 v/v) afforded 386 mg (57%) of a brownish oil which slowly solidified on standing; IR (KBr): 2155 (C C) cm^{-1}, ms: *m/z* 226 (M$^+$, 10), 211 (26), 154 (100), 126 (71), 87 (25), 76 (56), 75 (52), 74 (84), 73 (24), 69 (32), 63 (58), 62 (36), 61 (34), 51 (26), 50 (84), 43 (23). HRMS (ESI): Calcd. for $C_{13}H_{14}N_2NaSi$: 249.0824. Found: 249.0819.

General procedure for the reaction of 4-chlorocinnoline (1) with boronic acids 4 (Suzuki coupling). Anhydrous K_3PO_4 (1.27 g, 6 mmol), the appropriate arylboronic acid **4** (3.15 mmol),

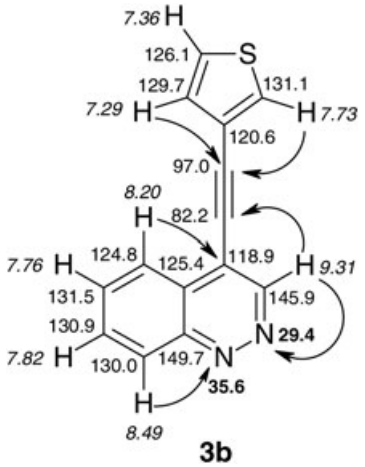


Figure 2. ^{1}H (in italics), ^{13}C, and ^{15}N (in bold) NMR chemical shifts and HMBC correlations (round arrows) for **3b** (in deuteriochloroform).

$Pd(PPh_3)_4$ (277 mg, 0.24 mmol), and KBr (393 mg, 3.3 mmol) were added to a solution of 4-chlorocinnoline (**1**) (494 mg, 3 mmol) in 1,4-dioxane (20 mL) under an argon atmosphere. After refluxing under an argon atmosphere for 4 h, the mixture was diluted with water (20 mL) and exhaustively extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. The residue obtained after evaporation of the solvent (reduced pressure) was further treated as described below.

4-Phenylcinnoline (5a). To remove a by-product, the residue was dissolved in 6*N* HCl (20 mL), the HCl-phase was extracted with diethyl ether (3 × 20 mL), the acidic layer was neutralized with 2*N* NaOH and exhaustively extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, and the solvent was evaporated. Column chromatography (SiO_2, eluent ethyl acetate/light petroleum, 1:2 v/v) afforded (248 mg, 40 %) of yellowish oil (lit. [20] mp 65.5–66°C).

^{1}H-NMR: δ 7.52–7.62 (m, 5H, Ph-H), 7.74 (m, 1H, H-6), 7.88 (m, 1H, H-7), 8.01 (m, 1H, H-5), 8.61 (m, 1H, H-8), 9.28 (s, 1H, H-3); ^{13}C-NMR: δ 124.5 (C-4a), 124.6 (C-5), 129.0 (Ph C-3,5), 129.2 (Ph C-4), 129.8 (Ph C-2,6), 130.2 (C-8), 130.4 (C-7), 131.2 (C-6), 134.2 (Ph C-1), 135.2 (C-4), 144.5 (C-3, ^{1}J = 183.4 Hz), 150.6 (C-8a); ^{15}N-NMR: δ 16.8 (N-2), 25.1 (N-1); ms: *m/z* 206 (M^+, 100), 178 (62), 177 (42), 176 (22), 152 (65), 151 (42), 150 (22), 78 (24), 77 (25), 76 (54), 75 (40), 74 (35), 63 (56), 62 (27), 57 (22), 52 (23), 51 (72), 50 (65). HRMS (ESI): Calcd. for $C_{14}H_{10}N_2Na$: 229.0742. Found: 229.0747.

2-(4-Cinnolinyl)benzaldehyde (5b). Column chromatography (SiO_2, eluent ethyl acetate/light petroleum, 1:2 v/v) afforded 344 mg (49%) of brownish crystals, mp 90–91°C (toluene); IR (KBr): 1688 (C O); ^{1}H-NMR: δ 7.44 (m, 1H, Ph H-3), 7.53 (m, 1H, H-5), 7.71 (m, 2H, H-6 and Ph H-5), 7.78 (m, 1H, Ph H-4), 7.88 (m, 1H, H-7), 8.13 (m, 1H, Ph H-6), 8.62 (m, 1H, H-8), 9.24 (s, 1H, H-3), 9.66 (s, 1H, CHO); ^{13}C-NMR: δ 124.2 (C-5), 125.5 (C-4a), 129.4 (Ph C-6), 129.9 (Ph C-5), 130.2 (C-8), 130.9 (C-7), 131.3 (Ph C-3), 132.1 (C-6), 132.5 (C-4), 134.1 (Ph C-4), 134.5 (Ph C-1), 136.3 (Ph C-2), 144.4 (C-3, ^{1}J = 183.4 Hz), 149.9 (C-8a), 190.1 (CHO, ^{1}J = 177.5 Hz); ^{15}N-NMR: δ 29.8 (N-2), 37.0 (N-1); ms: *m/z* 234 (M^+, 3), 206 (21), 205 (71), 176 (33), 152 (23), 151 (22), 149 (27), 77 (21), 76 (29), 75 (22), 74 (21), 71 (47), 67 (22), 63 (26), 57 (100), 51 (29), 43 (87). Anal. Calcd. for $C_{15}H_{10}N_2O$•0.1 H_2O: C, 76.32; H, 4.36; N, 11.87. Found: C, 76.30; H, 4.06; N, 11.63.

4-(3-Thienyl)cinnoline (5c). Column chromatography (SiO_2, eluent ethyl acetate/light petroleum, 1:2 v/v) afforded 413 mg (65%) of brownish crystals, mp 109–110.5°C (EtOH); ^{1}H-NMR: δ 7.40 (dd, 1H, *J* = 1.3, 5.0 Hz, Th H-4), 7.58 (dd, 1H, *J* = 3.0, 5.0 Hz, Th H-5), 7.65 (dd, 1H, *J* = 1.3, 3.0 Hz, Th H-2), 7.76 (m, 1H, H-6), 7.86 (m, 1H, H-7), 8.14 (m, 1H, H-5), 8.56 (m, 1H, H-8), 9.30 (s, 1H, H-3); ^{13}C-NMR: δ 124.5 (C-5 and C-4a), 126.6 (Th C-2, ^{1}J = 185.6 Hz, ^{3}J(C2,H4) = 8.7 Hz, ^{3}J(C2,H5) = 4.8 Hz), 127.3 (Th C-5, ^{1}J = 185.5 Hz, ^{2}J(C5,H4) = 5.3 Hz, ^{3}J(C5,H2) = 8.7 Hz), 128.4 (Th C-4, ^{1}J = 168.4 Hz, ^{2}J(C4,H5) = 5.3 Hz, ^{3}J(C4,H2) = 8.7 Hz), 130.1 (C-8), 130.7 (C-7), 130.9 (C-4), 131.6 (C-6), 134.4 (Th C-3), 143.7 (C-3, ^{1}J = 182.8 Hz), 150.3 (C-8a); ^{15}N-NMR: δ 22.0 (N-2), 27.7 (N-1); ms: *m/z* 213 (M^+ + 1, 17), 212 (M^+, 93), 184 (59), 183 (27), 152 (59), 140 (20), 139 (100), 79 (24), 75 (30), 74 (39), 69 (46), 63 (53), 62 (31), 58 (30), 57 (36), 51 (31), 50 (43), 45 (65). Anal. Calcd. for $C_{12}H_8N_2S$•0.2 H_2O: C, 66.77; H, 3.92; N, 12.98. Found: C, 66.79; H, 3.70; N, 12.62.

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