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SONOGASHIRA COUPLING OFFERS A NEW SYNTHETIC ROUTE TO THIENO[2,3-*c*]PYRAZOLES

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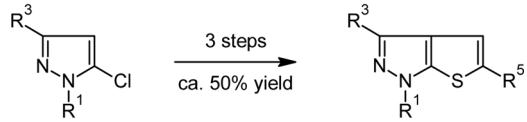
GRAPHICAL ABSTRACT



Abstract *1,3-Disubstituted-5-chloro-4-iodopyrazoles are selectively coupled with phenylacetylene under typical Sonogashira reaction conditions [$PdCl_2(PPh_3)_2$, CuI, Et_3N, dimethylformamide (DMF)] to obtain the corresponding 5-chloro-4-(phenylethynyl)pyrazoles in good yield. The latter are smoothly cyclized with Na_2S in DMF into the corresponding thieno[2,3-c]pyrazoles. Detailed spectroscopic investigations (^1H, ^{13}C, and ^{15}N NMR, mass, and infrared) of all compounds are reported.*

Keywords Fused-ring systems; NMR spectroscopy; palladium catalysis; pyrazoles

In continuation of our research on the reactivity of substituted pyrazoles toward palladium-catalyzed cross-coupling reactions,[1,2] we investigated the suitability of dihalopyrazole derivatives for a novel synthetic route to the thieno[2,3-*c*]pyrazole nucleus using the Sonogashira coupling.[3,4] This reaction provides an effective method for C–C bond formation and has also been applied as a key step in the synthesis of condensed heterocyclic systems.[5]

Starting from easily accessible and commercially available 1,3-disubstituted-5-chloro-1*H*-pyrazoles **1**, a second halogen substituent was introduced at position 4 of the pyrazole nucleus by a standard halogenation protocol (I_2/IO_3^-) to obtain the corresponding 5-chloro-4-iodopyrazoles **2** (Scheme 1). The latter were selectively linked to phenylacetylene in a Sonogashira cross-coupling reaction, yielding only the 4-(phenylethynyl)pyrazoles **3** in good yields (87–92%). The structures of

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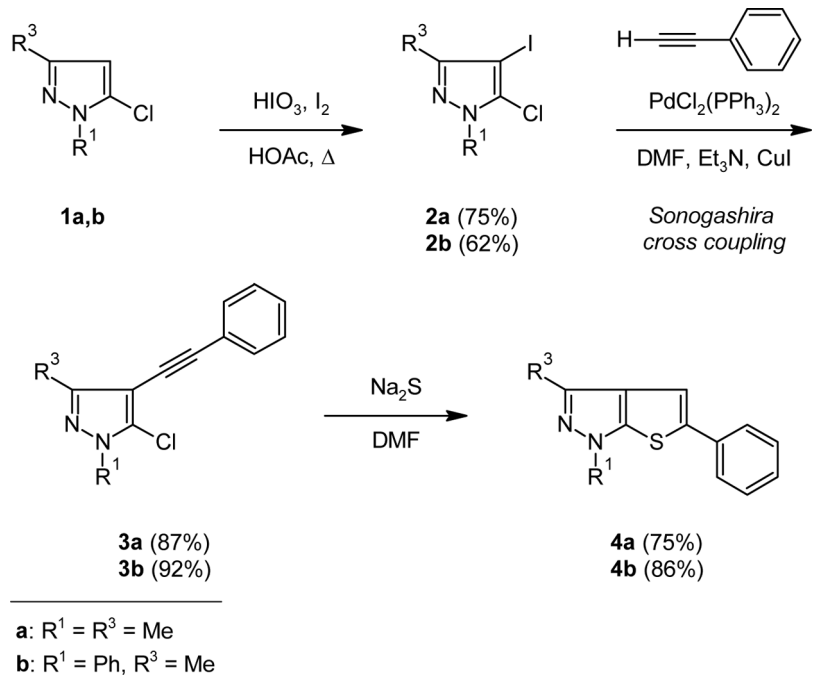

Scheme 1. Synthetic route to thieno[2,3-*c*]pyrazoles **4**.

compounds **3** were unambiguously confirmed by means of mass spectrometry (MS), multinuclear NMR spectroscopy, infrared (IR), and microanalysis.

From theoretical considerations, the selectivity in this key reaction is explainable. Although 5-iodopyrazoles are known to be more reactive for cross-couplings than 3- or 4-iodopyrazoles, the position of the halogen atom is by far less significant for the reactivity than the halogen's nature.[4,6,7] Among pyrazolyl-halides, a very clear preference in Sonogashira reactions for the iodides over the corresponding bromides and chlorides is evident. This effect is by far the dominating one and thus neutralizes and reverses the positional effect that would favor the substitution in position 5.

In the final reaction step, compounds **3** were reacted with sodium sulfide in dimethyl formamide to finally obtain the targeted fused heterocyclic ring system of compounds **4** (Scheme 1).

All the compounds prepared were thoroughly investigated with respect to their NMR spectra. Thus, unambiguous assignment of all proton, carbon, and nitrogen resonances was carried out by combined application of different standard NMR methods such as fully ^{1}H-coupled ^{13}C NMR spectra, APT, heteronuclear multiple quantum correlation (HMQC), gradient selected heteronuclear single quantum coherence (gs-HSQC), gradient selected heteronuclear multiple bond coherence (gs-HMBC), nuclear Overhauser effect spectroscopy (NOESY), and nuclear Overhauser effect (NOE)–difference spectroscopy.[8] Moreover, many ^{13}C and ^{1}H coupling constants could be unequivocally assigned using two-dimensional (2D) (δ, J) insensitive nuclei enhanced by polarization transfer (INEPT) spectra with selective excitation of unambiguously assigned ^{1}H resonances.[9]

The substitution pattern in compounds **3** (entry of alkyne substituent into the 4-position after reaction of **2** with phenylacetylene) can be clearly deduced considering the ^{13}C NMR spectrum of **3**. Whereas in compounds **2** the pyrazole C-4 resonance—easily assignable in the ^{1}H-coupled ^{13}C NMR spectrum because of a vicinal coupling ($^{3}J = 4.2$ Hz) to the methyl protons—receives a significant high-field shift as a result of the directly attached iodine atom (δ 60.8 and 64.6 ppm, respectively, heavy-atom effect[10]), the pyrazole C-4 signal in coupling products **3** (iodine atom replaced by an alkyne-C atom) exhibits a much larger chemical shift [δ 101.6 and 103.9 ppm, respectively; ^{3}J(C4, Me) = 3.5 Hz and 3.4 Hz, respectively]. The two alkyne-C signals in the ^{13}C NMR spectrum of **3** can be smoothly distinguished considering their coupling patterns: while the alkyne-C attached to pyrazole C-4 does not show couplings to any protons, the signal of C≡CPh is split into a triplet ($J = 5.3$ Hz and 5.4 Hz, respectively) because of a vicinal coupling to the phenyl protons 2 and 6.

In conclusion, we have demonstrated a hitherto unknown short synthetic route to thieno[2,3-*c*]pyrazoles from the corresponding 4,5-dihalopyrazoles.

EXPERIMENTAL

Instruments

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, MS) and on a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS). IR spectra were recorded on a Perkin-Elmer Fourier transform (FT)–IR 1605 spectrophotometer. Elemental analyses were performed at the Microanalytical Laboratory, University of Vienna. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The center of the solvent signal was used as an internal standard, which was related to tetramethylsilane (TMS) with δ = 7.26 ppm (^{1}H in $CDCl_3$) and δ = 77.0 ppm (^{13}C in $CDCl_3$). The digital resolutions were 0.2 Hz/data point in the ^{1}H NMR spectra and 0.4 Hz/data point in the ^{13}C NMR spectra (^{1}H broadband decoupling or gated decoupling). ^{15}N NMR spectra were obtained on a Bruker Avance 500 instrument with a "directly" detecting broadband observation probe and were referenced against external nitromethane. Systematic names were generated with ACD/Name[11] according to current International Union of Pure and Applied Chemistry (IUPAC) recommendations and were also checked manually to ensure the correct use of nomenclature within this publication.[12] Compound **1a** is commercially available from various suppliers (e.g., Alfa Aesar).

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole (1b)

This compound is commercially available from various suppliers (e.g., Alfa Aesar) or can be prepared from 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (bulk ware) and $POCl_3$. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.35–7.57 (5H, m, Ph), 6.18 (1H, s, H-4), 2.31 (3H, s, Me). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 149.7 (C-3), 138.2 (Ph C-1), 128.8 (Ph C-3,5), 127.8

(Ph C-4), 126.9 (C-5), 124.8 (Ph C-2,6), 106.2 (C-4), 13.9 (Me). Mass spectrum, m/z (I_{rel}, %): 194 $[M]^+$ (28), 192 $[M]^+$ (100), 157 (43), 116 (37), 77 (36), 51 (30).

5-Chloro-4-iodo-1,3-dimethyl-1*H*-pyrazole (2a)

The details of the synthetic preparation as well as the detailed characterization of this compound were published by our group recently.[13]

5-Chloro-4-iodo-3-methyl-1-phenyl-1*H*-pyrazole (2b)

Similar to a known procedure,[14] HIO_3 (0.176 g, 1 mmol) was added to a solution of **1b** (0.963 g, 5 mmol) in glacial acetic acid (5 ml). After stirring for 10 min, I_2 (1.014 g, 4 mmol) was added, and the resulting mixture was refluxed for 4 h. Then cold aq. Na_2SO_3 was added dropwise until the dark brown color disappeared, and the solution was then extracted three times with CH_2Cl_2. The organic layers were combined, washed with aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure to afford yellow crystals, which were recrystallized from methanol. Yield 1.004 g (62%), mp 59–60 °C (mp 60–62 °C [15]). IR spectrum (KBr), ν, cm^{-1}: 1598, 1508, 1407, 1352, 1056, 754, 688. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 7.51 (2H, m, Ph H-2,6), 7.48 (2H, m, Ph H-3,5), 7.40 (1H, m, Ph H-4), 2.34 (3H, s, Me). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm (J, Hz): 152.1 ($^2J_{C\text{-}3,Me} = 6.9$, C-3), 138.6 (Ph C-1), 131.1 (C-5), 129.0 (Ph C-3,5), 128.4 (Ph C-4), 124.7 (Ph C-2,6), 64.6 ($^3J_{C\text{-}4,Me} = 4.2$, C-4); 14.7 ($^1J = 128.6$, Me). ^{15}N NMR spectrum (50 MHz, $CDCl_3$), δ, ppm: −76.0 (N-2); −169.0 (N-1). Mass spectrum, m/z (I_{rel}, %): 320 $[M]^+$ (22), 318 $[M]^+$ (75), 150 (21), 104 (34), 77 (100), 51 (78), 50 (29).

5-Chloro-1,3-dimethyl-4-(phenylethynyl)-1*H*-pyrazole (3a)

Under Ar atmosphere, CuI (38 mg, 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol) were added to a solution of iodopyrazole **2a** (256 mg, 1 mmol), DMF (5 ml), Et_3N (5 mmol, 0.7 ml), and phenylacetylene (1.2 mmol, 123 mg). The reaction mixture was stirred in an oil bath at 50 °C for 10 min. After completion of the reaction, the mixture was cooled to rt, 20 ml of water were added, and the mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous. Na_2SO_4, filtrated, and concentrated on a rotary evaporator. Flash chomatography (silica gel, petrolether–ethyl acetate; 1:10 to 1:4) gave pure **3a** as a brownish liquid. Yield: 200 mg (87%). IR spectrum (KBr), ν, cm^{-1}: 2220 (C≡C), 1545, 1492, 1360, 1295, 755, 690. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.51 (2H, m, Ph H-2,6), 7.30–7.37 (3H, m, Ph H-3,4,5), 3.79 (3H, s, NMe), 2.33 (3H, s, CMe). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm (J, Hz): 150.5 ($^2J_{C\text{-}3,Me} = 6.9$, C-3), 131.4 (Ph C-2,6), 129.7 (C-5), 128.3 (Ph C-3,5), 128.1 (Ph C-4), 123.3 (Ph C-1), 101.6 ($^3J_{C\text{-}4,CMe} = 3.5$, C-4), 94.1 ($^3J_{\equiv C,Ph\text{-}2,6} = \sim 5.3$, C≡CPh), 78.8 (C≡CPh), 36.3 ($^1J = 141.1$, NMe), 13.0 ($^1J = 128.3$, CMe). ^{15}N NMR spectrum (50 MHz, $CDCl_3$), δ, ppm: −81.8 (N-2); −189.4 (N-1). Mass spectrum, m/z (I_{rel}, %): 232 $[M]^+$ (33), 230 $[M]^+$ (100), 189 (29), 174 (22), 148 (47), 139 (24), 113 (27), 57 (28), 43 (24). HRMS calcd. for $C_{13}H_{11}ClN_2$: 230.0611. Found: 230.0610.

5-Chloro-3-methyl-1-phenyl-4-(phenylethynyl)-1*H*-pyrazole (3b)

Under Ar atmosphere, CuI (10 mg, 1 mol %) and $PdCl_2(PPh_3)_2$ (105 mg, 3 mol%) were added to a solution of iodopyrazole **2b** (1.59 g, 5 mmol), DMF (10 ml), and Et_3N (10 ml). After stirring for 15 min, phenylacetylene (7.66 g, 7.5 mmol) was added, and the resulting reaction mixture was stirred in an oil bath at 80 °C for 3 h. After completion of the reaction, the mixture was cooled to rt, filtered through Al_2O_3, and concentrated on a rotary evaporator. Chromatography (silica gel, hexanes–ethyl acetate; 20:1) gave the pure product as colorless crystals. Yield 1.35 g (92%), mp 121–122 °C. IR spectrum (KBr), ν, cm^{-1}: 2223 (C≡C), 1598, 1556, 1506, 1440, 1411, 1360, 1070, 992, 757, 693. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.58 (2H, m, NPh H-2,6), 7.56 (2H, m, CPh H-2,6), 7.49 (2H, m, NPh H-3,5), 7.42 (1H, m, NPh H-4), 7.32–7.39 (3H, m, CPh H-3,4,5), 2.45 (3H, s, Me). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 151.8 ($^2J_{C\text{-}3,Me} = 6.9$, C-3), 137.9 (NPh C-1), 131.4 (CPh C-2,6), 129.3 (C-5), 129.0 (NPh C-3,5), 128.30 (CPh C-3,5), 128.29 (CPh C-4), 128.26 (NPh C-4), 124.7 (NPh C-2,6), 123.1 (CPh C-1), 103.9 ($^3J_{C\text{-}4,Me} = 3.4$, C-4), 95.1 ($^3J_{\equiv C,Ph\text{-}2,6} = 5.4$, C≡<u>C</u>Ph), 78.5 (<u>C</u>≡CPh), 13.1 ($^1J = 128.5$, Me). ^{15}N NMR spectrum (50 MHz, $CDCl_3$), δ, ppm: −79.6 (N-2); −172.5 (N-1). Mass spectrum, m/z (I_{rel}, %): 294 $[M]^+$ (32), 292 $[M]^+$ (94), 216 (41), 189 (52), 148 (44), 139 (31), 113 (56), 77 (100), 51 (77). Found, %: C, 73.82; H, 4.65; N, 9.51. $C_{18}H_{13}ClN_2$. Calculated, %: C, 73.85; H, 4.48; N, 9.57.

1,3-Dimethyl-5-phenyl-1*H*-thieno[2,3-*c*]pyrazole (4a)

A suspension of the alkyne **3a** (115 mg, 0.5 mmol), Na_2S (156 mg, 2 mmol), and DMF (5 ml) was stirred on an oil bath at 130 °C overnight. Then the mixture was diluted with cold H_2O and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous. Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. Flash chromatography (silica gel, petrolether–ethyl acetate; 1:4 to 1:2) gave pure **4a** as a pale solid. Yield: 86 mg (75%), mp 121–124 °C. IR spectrum (KBr), ν, cm^{-1}: 1545, 1498, 1476, 873, 761, 700. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.55 (2H, m, Ph H-2,6), 7.38 (2H, m, Ph H-3,5), 7.28 (1H, m, Ph H-4), 3.91 (3H, s, NMe), 2.46 (3H, s, CMe). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 140.3 ($^2J_{C\text{-}3,Me} = 6.9$, C-3), 140.6 ($^2J_{C\text{-}5,H\text{-}4} = 5.9$, C-5), 144.2 ($^3J_{C\text{-}6a,H\text{-}4} = 10.2$, $^3J_{C\text{-}6a,NMe} = 2.6$, C-6a), 135.2 (Ph C-1), 129.7 ($^2J_{C\text{-}3a,H\text{-}4} = 5.1$, $^3J_{C\text{-}3a,CMe} = 3.2$, C-3a), 128.9 (Ph C-3,5), 127.4 (Ph C-4), 125.5 (Ph C-2,6), 111.8 ($^1J = 167.7$, C-4), 37.9 ($^1J = 139.8$, NMe), 12.9 ($^1J = 127.7$, CMe). ^{15}N NMR spectrum (50 MHz, $CDCl_3$), δ, ppm: −65.8 (N-2); −208.4 (N-1). Mass spectrum, m/z (I_{rel}, %): 228 $[M]^+$ (100), 213 (49), 172 (34), 146 (24), 66 (26). Found, %: C, 68.13; H, 5.31; N, 12.14. $C_{13}H_{12}N_2S$. Calculated, %: C, 68.39; H, 5.30; N, 12.27.

3-Methyl-1,5-diphenyl-1*H*-thieno[2,3-*c*]pyrazole (4b)

A suspension of alkyne **3** (146 mg, 0.5 mmol), Na_2S (2 mmol), and DMF (15 ml) was stirred on an oil bath at 100 °C for 4 h. Then the mixture was diluted with cold H_2O and extracted three times with ethyl acetate. The combined organic layers were

washed with brine, dried over anhydrous Na_2SO_4, and concentrated to dryness under reduced pressure. The remaining solid was crystallized from methanol to afford **4b** as colorless crystals. Yield 125 mg (86%), mp 160–162 °C (mp 162–166 °C [16]). IR spectrum (KBr), ν, cm^{-1}: 1595, 1504, 1016, 761, 753, 697, 684. 665. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 7.79 (2H, m, NPh H-2,6), 7.61 (2H, m, CPh H-2,6), 7.51 (2H, m, NPh H-3,5), 7.41 (2H, m, CPh H-2,6), 7.31 (1H, m, CPh H-4), 7.25 (1H, m, NPh H-4), 7.21 (1H, s, H-4), 2.57 (3H, s, Me). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm (J, Hz): 142.8 ($^2J_{C\text{-}3,Me} = 6.9$, $^3J_{C\text{-}3,H\text{-}4} = 0.5$, C-3), 141.0 ($^2J_{C\text{-}5,H\text{-}4} = 6.0$, C-5), 140.6 ($^3J_{C\text{-}6a,H\text{-}4} = 10.5$, C-6a), 139.5 (NPh C-1), 134.7 (CPh C-1), 131.6 ($^2J_{C\text{-}3a,H\text{-}4} = 5.0$, $^3J_{C\text{-}3a,Me} = 3.2$, C-3a), 129.5 (NPh C-3,5), 129.0 (CPh C-3,5), 127.6 (CPh C-4), 125.6 (CPh C-2,6), 125.1 (NPh C-4), 117.3 (NPh C-2,6), 111.1 ($^1J = 168.4$, C-4), 13.1 ($^1J = 128.1$, Me). ^{15}N NMR spectrum (50 MHz, $CDCl_3$), δ, ppm: −71.9 (N-2); − 187.5 (N-1). Mass spectrum, m/z (I_{rel}, %): 290 $[M]^+$ (100), 146 (28), 145 (22), 121 (20), 102 (21), 77 (83), 51 (48). Found, %: C, 74.33; H, 5.09; N, 9.43. $C_{18}H_{14}N_2S$. Calculated, %: C, 74.45; H, 4.86; N, 9.65.

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