Synthesis of New 3*H*-Pyrazoles and Cyclopropenyl Alcohols Directly from Propargyl Alcohols

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The 1,3-dipolar cycloaddition of 2-diazopropane (**1**) to propargylic alcohols is regioselective and leads to 3*H*-pyrazoles **3** in good yield. The surprising formation of the tetrasubstituted 3*H*-pyrazole **4c** from $HC{\equiv}CCH_2OH$ and **1** can be explained by formation of an initial 1,3-dipolar cycloadduct intermediate followed by a second cycloaddition of **1** to the C=C bond and loss of dinitrogen. Photolysis of the antibacterial 3*H*-pyrazoles **3** and **4** selectively gives α- and β-methylcyclopropenyl alcohols **5** and **6**, respectively.

Introduction

Three-membered strained-ring systems are an attractive class of molecules as synthetic intermediates.[1–3] Among them, the rigid, unsaturated cyclopropenes are the key to selective useful transformations,[4,5] such as regioselective additions of organometallics[6–8] or cycloadditions.[9,10] Three-membered cyclic derivatives also have potential biological activity since their structural feature is included in valuable natural products such as phorbol and chrysanthemic acid.[11,12] An approach for the synthesis of cyclopropene derivatives is offered by the formation of cyclopropenyllithium, which is generated from 2,2-dibromo-1-chlorocyclopropane.[13] The metal-catalyzed addition of carbene sources to alkynes constitutes the most direct access to cyclopropene derivatives,[14] most of which involve rhodium[15,16] and copper[17] catalysts. However, the metal-catalyzed addition of a diazoalkane is not always satisfactory with bulky and functional alkynes. The carbene easily inserts into heteroatom–hydrogen bonds[18] and the insertion of the triple bond into the metal–carbene bond is in competition with cyclopropenation.[19]. The initial regioselective 1,3-dipolar addition of a diazoalkane to functional alkynes, followed by photochemical elimination of dinitrogen,[20–23] constitutes an alternative for the preparation of cyclopropenes with an α functional group on the condition that carbene insertion into the heteroatom–hydrogen bond can be prevented. Moreover, when the functional group of alkynes controls the regioselectivity of diazoalkane 1,3-cycloaddition, this approach allows a simple access to functional 3*H*-pyrazoles with potential biological properties.[24]

We now report the synthesis of new antibacterial 3*H*-pyrazoles by regioselective 1,3-dipolar cycloaddition of the versatile 2-diazopropane to nonprotected disubstituted propargyl alcohols and that the unsubstituted propargyl alcohol allows the double addition of 2-diazopropane and gives a 3*H*-pyrazole with formal insertion of the dimethylcarbene into a carbon–carbon bond. We also show that the photolysis of the 3*H*-pyrazoles leads to new alcohols containing the cyclopropenyl unit.

Results and Discussion:

Preparation and Properties of 3*H*-Pyrazoles 3 and 4

Whereas the $Rh_2(OAc)_4$-catalyzed addition of diazoalkanes to propargyl alcohols readily gives the insertion of the carbene into the O–H bond, with only a small amount of cyclopropenation of the resulting propargylic ether,[18] the 2-diazopropane **1** reacts with 1,1-diphenyl-2-propyn-1-ol (**2a**) in dichloromethane at 0 °C to give exclusively, after 10 h of reaction, only the adduct **3a**, which was isolated in 75% yield and corresponds to the regioselective 1,3-dipolar cycloaddition of the 2-diazopropane to the alkyne C≡C bond (Scheme 1).

The structure of compound **3a** was determined by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum shows singlets at δ = 1.45 ppm for the methyl protons and at δ = 4.17 and 6.30 ppm for the hydroxylic and the ethylenic protons, respectively. The addition regioselectivity in the formation of **3a** was established by ^1H-^{13}C HMBC 2D NMR spectroscopy, which shows the C^5–C^4–C^3–Me linkages. The ethylenic proton correlates only with carbon atoms C^6, C^5, and C^3. The methyl protons correlate with C^3 and with the

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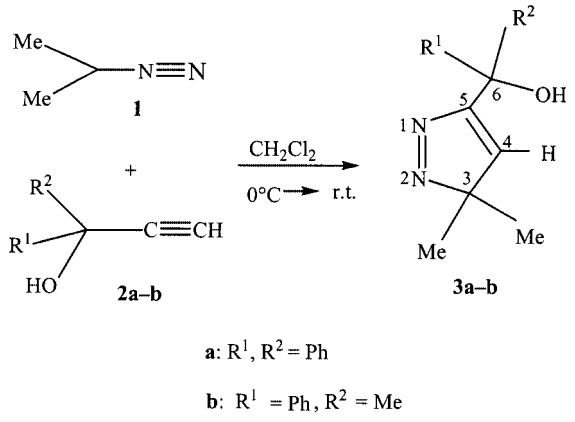


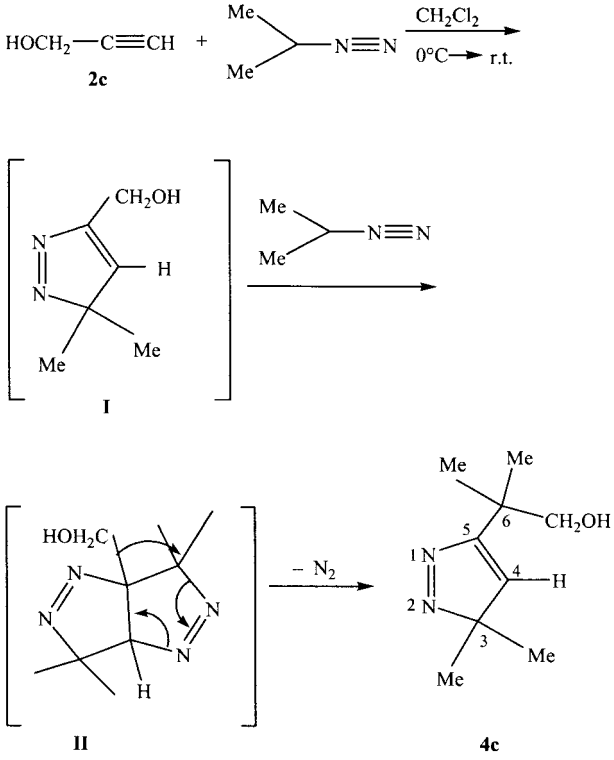
Scheme 1. Synthesis of 3*H*-pyrazoles **3**.

ethylenic carbon C^4, consistent with the neighboring C^3–C^4 connection. The NOESY spectrum shows a nOe cross peak between the ethylenic and the aromatic protons. Whereas the addition of diazoalkane to alkynes is not usually regioselective, the cycloaddition of diazopropane to **2a** leads only to derivative **3a**, with the linkage of the nitrogen atom with the unsaturated carbon connected to the functional group, and corresponds to that observed for the 1,3-dipolar cycloaddition reaction of simple diazoalkanes with α,β-unsaturated ketones.[25]

Analogously, the 1,3-dipolar cycloaddition reaction of 2-diazopropane with propargyl alcohol **2b**, performed at 0 °C in dichloromethane, was completed in less than 10 hours and led to a monoadduct **3b** with the same regioselective addition mode of **1** to the triple bond (Scheme 1). The HMBC spectrum shows correlations between the ethylenic proton and the carbons C^3 and C^5, and between the methyl protons and the carbons C^3 and C^4.

In contrast, the unsubstituted propargylic alcohol **2c** reacts with an excess of 2-diazopropane and in 10 hours at 0 °C to surprisingly give the tetrasubstituted 3*H*-pyrazole **4c**, which was isolated in 73% yield (Scheme 2). The ^{1}H NMR spectrum of **4c** shows the presence of two equivalent exocyclic and two different intracyclic methyl groups, and singlets at δ = 4.01 ppm for the OH group, δ = 4.86 ppm for the methylenic protons, and δ = 6.70 ppm for the ethylenic protons. The formation of **4c**, which includes the incorporation of two CMe_2 groups arising from the diazoalkane, can be explained by the formation of the expected cycloadduct intermediate **I**, followed by a second cycloaddition of diazoalkane to the remaining C=C double bond to give the intermediate **II**. The later is not stable at room temperature, and it loses dinitrogen and undergoes a rearrangement of the carbon skeleton to give **4c**.

It is noteworthy that the addition of an excess of 2-diazopropane to the alkynes **2a**,**b** does not give the corresponding bisadduct of diazoalkane. It is likely that the bulkiness of the CR^1R^2OH group, which is close to the C=C bond in intermediate **I**, prevents the second addition of diazopropane that is allowed by the smaller propargyl alcohol CH_2OH group.



Scheme 2. Synthesis of the tetrasubstituted 3*H*-pyrazole **4c**.

The antibacterial activity of the obtained 3*H*-pyrazoles **3a**,**b** and **4c** was studied. They were tested against a pathogenic bacterial stump and show antibacterial activity against *Staphyloccocus aureus*. The 3*H*-pyrazole **3b** has the strongest antibacterial activity.[26]

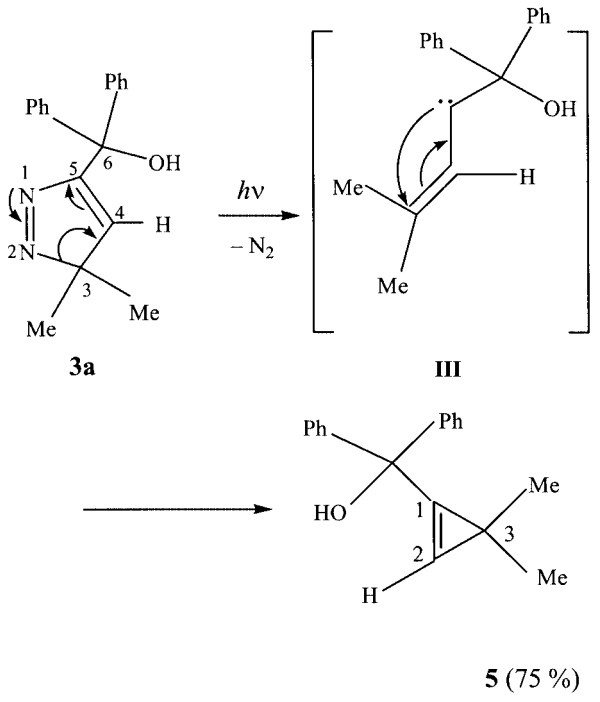
Photochemical Transformation of the Obtained 3*H*-Pyrazoles into Cyclopropene Derivatives

A photochemical study of 3*H*-pyrazoles was performed in the search for a route to tertiary cyclopropenyl alcohols. Irradiation of **3a** in dry dichloromethane at 300 nm and at room temperature for 0.5 h led to the exclusive formation of the *gem*-dimethylcyclopropene **5** (Scheme 3). The formation of cyclopropene **5** arises from the loss of N_2 and cyclization of the vinylcarbene intermediate **III**.

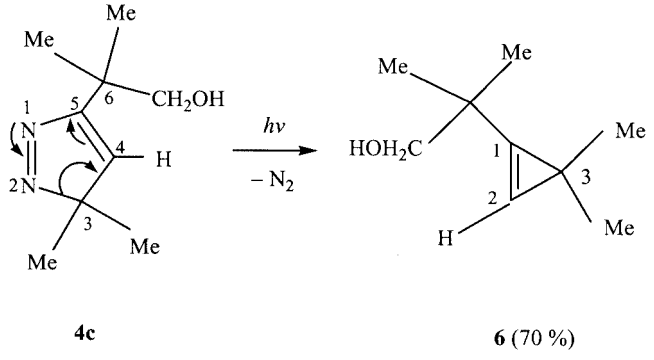
The structure of **5** was determined by a detailed one- and two-dimensional NMR study. In the ^{13}C NMR spectrum a signal at δ = 20.3 ppm corresponds to the methyl groups and the $=C^2$-H carbon appears at δ = 142.3 ppm. The *gem*-dimethylcyclopropene structure of **5** is consistent with an analysis of the ^{1}H-^{13}C HMBC spectrum.

The analogous photochemical reaction (300 nm) of 3*H*-pyrazole **4c** in dichloromethane at room temperature led to cyclopropene derivative **6**, which possesses a β-hydroxy group, in 70% yield (Scheme 4).

The above two consecutive transformations give a straightforward access, from propargyl alcohols, to cyclopropene derivatives with an α- or β-hydroxy group directly. This simple method is complementary to the route to 3-hydroxymethylcyclopropenes by $Rh_2(OAc)_4$-catalyzed ad-



Scheme 3. Preparation of α-hydroxycyclopropene **5**.



Scheme 4. Preparation of β-hydroxycyclopropene **6**.

dition of diazoacetate to alkynes followed by reduction of the ester group, a route that is restricted to the access of primary cyclopropenyl alcohols,[27] and is an alternative to the use of 2,2-dibromo-1-chlorocyclopropane via the cyclopropenyllithium salt.[13]

Conclusions

This study demonstrates that the addition of 2-diazopropane to the triple bond of propargyl alcohols is regioselective and affords new antibacterial 3*H*-pyrazoles. The photochemical reaction of these 3*H*-pyrazoles selectively leads to α- and β-hydroxy cyclopropenes. The overall transformation constitutes a simple straightforward route to substituted cyclopropenyl alcohols without initial protection of the propargyl alcohol hydroxyl group.

Experimental Section

General Remarks: NMR spectra were recorded at room temperature on a AC 300 MHz in $CDCl_3$. Chemical shifts are expressed in ppm downfield from $SiMe_4$ (^1H and ^{13}C). The IR spectra were recorded on a Bruker FT-IR IFS 28 in the region between 4000 and 400 cm^{-1} (KBr).

Mass spectra were obtained with a Hewlett–Packard 5880 A Spectrometer. In this case electron impact techniques were employed. Melting points were determined on a Büchi apparatus and are uncorrected. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator. Column chromatography was carried out with silica gel 60.

Cycloaddition Reaction of 2-Diazopropane with Propargyl Alcohols 2a–c. Synthesis of 3*H*-Pyrazoles 3a,b and 4c: A freshly prepared (at –60 °C) 2.6 M diethyl ether solution of 2-diazopropane (10 mL) was added, in small fractions, to a stirred solution containing alkyne **2a**–**c** (1 g) in 40 mL of anhydrous dichloromethane at 0 °C. The reaction was followed by TLC (hexane/ethyl acetate, 1:1) and the reaction was allowed to proceed until the alkyne had totally disappeared. The solution was allowed to react for a further 10 h at 0 °C and the solvent was then evaporated under reduced pressure. The obtained 3*H*-pyrazole was purified either by filtration through a column of silica or by recrystallization from a mixture of dichloromethane and petroleum ether.

Compound 3a: Yield: 75%; m.p. 163 °C. MS: *m*/*z* (%) = 261 (41.5) [M^+ – OH]. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 6 H, CH_3); 4.17 (s, 1 H, OH), 6.35 (s, 1 H, =C–H), 7.28–7.38 (m, 10 H, H^{arom}) ppm.^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.3 (CH_3), 77.3 (C^6), 93.7 (C^3), 142.4 (C^5), 127.1–144.3 (C^{arom}), 160.4 (C^4) ppm. IR (KBr): ν_{OH} = 3293, $\nu_{C=C}$ = 1599 cm^{-1}. HMBC spectrum (see Figure 1). $C_{18}H_{18}N_2O$: calcd. C 77.67, H 6.52, N 10.06; found C 77.6, H 6.4, N 10.4.

Compound 3b: Yield: 75%. MS: *m*/*z* (%) = 199 (13.2) [M^+ – OH]. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 6 H, CH_3); 1.90 (s, 3 H, CH_3); 3.93 (s, 1 H, OH), 6.61 (s, 1 H, =C–H), 7.24–7.33 (m, 10 H, H^{arom}) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.2 (CH_3), 29.2 (CH_3), 87.5 (C^6), 93.5 (C^3), 145.3 (C^5), 124.8-159.8 (C^{arom}), 161.4 (C^4). IR (KBr): ν_{OH} = 3397, $\nu_{C=C}$ = 1492 cm^{-1}. $C_{13}H_{16}N_2O$: calcd. C 72.19, H 7.46, N 12.95; found C 72.2, H 7.7, N 12.8.

Compound 4c: Yield: 73%. MS: *m*/*z* (%) = 168 (19.8) [M^+]. 153 [M – CH_3]$^+$, 95 [M – $CMe_2CH_2OH^+$]. ^1H NMR (300 MHz, $CDCl_3$): δ =1.30 (s, 6 H, C*Me*$_2$CH$_2$OH),1.80 (s, 3 H, Me), 1.90 (s, 3 H, Me), 4.81 (CH_2), 4.00 (s, 1 H, OH), 6.70 (s, 1 H, CH) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.4 (C*Me*$_2$CH$_2$OH), 25.2 (NC*Me*$_2$), 31.25 (C_6), 57.9 (CH_2OH), 93.8 (C^3), 141.5 (CH), 160.5 (C^4) ppm. IR (KBr): ν_{OH} = 3280, $\nu_{C=C}$ = 1580 cm^{-1}. $C_9H_{16}N_2O$: calcd. C 64.25, H 9.59, N 16.65; found C 64.1, H 9.4, N 16.5.

Typical Procedure for the Synthesis of Cyclopropenyl Alcohols 5 and 6: 3*H*-Pyrazole **3** or **4c** (500 mg) was diluted in 100 mL of dry dichloromethane and irradiated at 300 nm in a Rayonet apparatus for 30 min. The starting colorless solution became dark red during the reaction. The solvent was then removed under reduced pressure and the crude product was purified by column chromatography on silica with dichloromethane as eluent to provide **5** or **6**, respectively.

Compound 5: Yield: 75%; m.p. 145 °C. MS: *m*/*z* = 250 [M^+], 235 [M – CH_3]$^+$, 183 [M – CPh_2OH]$^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 6 H, CH_3); 3.93 (s, 1 H, OH), 6.33 (s, 1 H, =C–H), 7.28–7.38 (m, 10 H, H^{arom}) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.3 (CH_3), 77.3 (*C*Ph$_2$), 93.8 (C^3), 127.0–144.2 (C^{arom}), 142.3 (C^2), 160.4 (C^1). HMBC: correlations C^1/C^2H; C^3/C^2H. IR (KBr): ν_{OH} = 3381, $\nu_{C=C}$ = 1499 cm^{-1}.

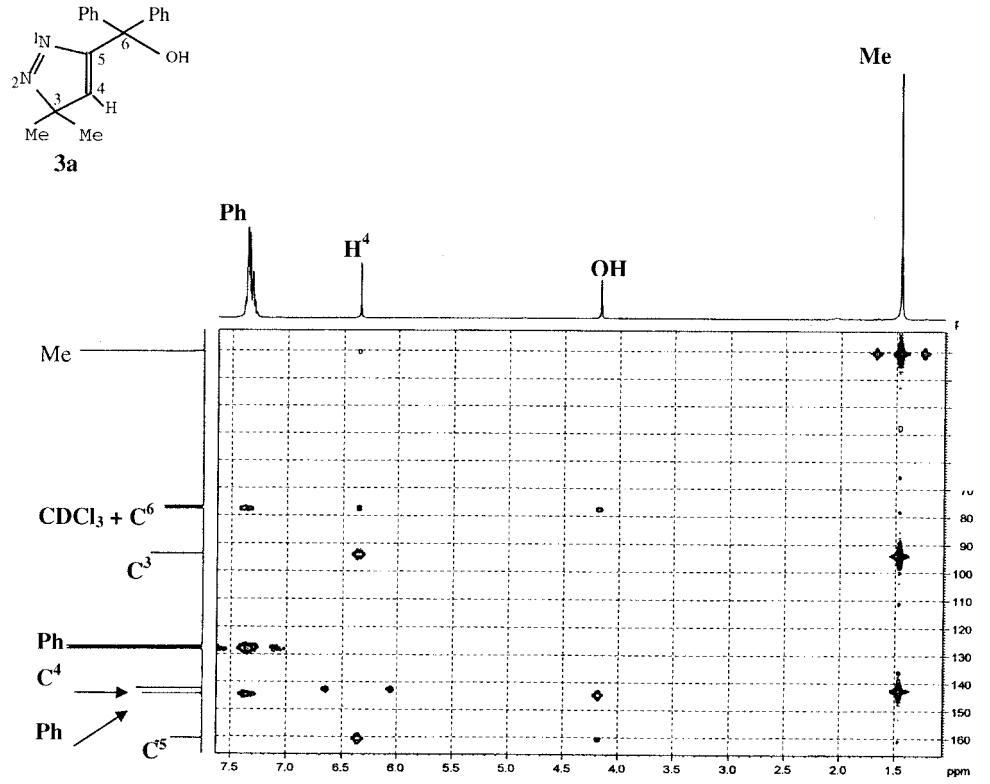


Figure 1. ^{1}H-^{13}C HMBC spectrum of compound **3a**.

Compound 6: Yield: 70%. MS: *m/z* (%) = 140 $[M]^+$, 125 $[M - CH_3]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 6 H, CMe_2-CH_2OH), 1.79 (s, 3 H, CH_3), 1.92 (s, 3 H, CH_3). 6.40 (s, 1 H, OH), 4.82 (s, 2 H, CH_2), 6.70 (s, 1 H, CH) ppm. IR (KBr): ν_{OH} = 3418, $\nu_{C=C}$ = 1443 cm^{-1}.

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