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Alkylthio(4-methylpent-3-en-1-ynyl)carbenes: generation by the photolysis of 5-alkylthioethynyl-3,3-dimethyl-3*H*-pyrazoles and reactions with alkenes

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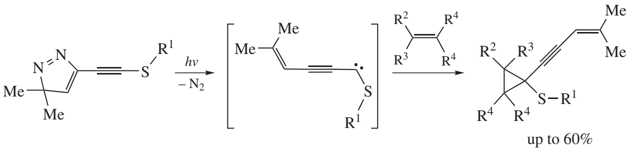
New singlet alkylthio(4-methylpent-3-en-1-ynyl)carbenes were generated by photolysis of corresponding 5-alkylthioethynyl-3,3-dimethyl-3*H*-pyrazoles and subsequently trapped by alkenes giving rise to 1-alkynyl-1-(alkylthio)cyclopropanes in yields up to 60%.



R^1 = Me, Et
R^2, R^3 = H, Me, Ph
$R^2 + R^3 = (CH_2)_4$
R^4 = H, Me

Strained organic molecules, especially cyclopropane derivatives, are of importance in modern chemistry. Compounds with a three-carbon ring are used as building blocks for the preparation of various acyclic, alicyclic and heterocyclic molecules[1–4] as well as demonstrate a broad range of biological activity.[5] Addition of alkynylcarbenes bearing a functional substituent at the carbenic center, such as halogen atom or ester moiety, to the double bond of alkenes represents a direct and effective synthetic route to functionalized alkynylcyclopropanes.[6–11] These cyclopropane derivatives find an application in various chemical transformations,[12–23] play an important role in biochemical processes and exhibit valuable pharmacological properties.[24–26] The highly reactive carbenic species are investigated not only to explore their reactivity towards various carbene acceptors, but also to determine their structure using instrumental methods along with quantum chemical calculations. Concerning alkynylcarbenes with functional substituents at the carbenic center, only one their representative, namely (chloroethynyl)chlorocarbene,[27] has been identified using matrix IR spectroscopy, which is most probably caused by the low availability of precursors necessary for generation of this type of carbenes.

The results of our previous works[28,29] on photolysis of 3,3-dimethyl-5-ethynyl-3*H*-pyrazole **1** have shown that upon irradiation this compound is initially converted into corresponding diazo compound, from which highly delocalized triplet 5-methylhexa-1,2,4-triene-1,3-diyl is formed after dinitrogen elimination. These results allowed us to propose that photodegradation of 5-alkynyl-3*H*-pyrazoles with functional substituents at the triple bond would be an efficient way for the generation of new (4-methylpent-3-en-1-ynyl)carbenes. This method would be suitable for carbene identification in low-temperature inert matrices as well as for application in organic synthesis. Examples of this new carbene type may be alkylthio(4-methylpent-3-en-1-ynyl)carbenes, whose analogues lacking vinyl fragment were previously generated by base-induced elimination of HCl from 1-chloro-3-alkylthiopropadienes.[9,10]

Initially we attempted to synthesize starting 3,3-dimethyl-5-methylthioethynyl-3*H*-pyrazole **2a** from 3,3-dimethyl-5-ethynyl-3*H*-pyrazole **1** by its lithiation in THF and subsequent reaction with dimethyldisulfide, reproducing the technique successfully used[30] for the methylthiolation of phenylacetylene. Unfortunately, only complex mixture was obtained using this approach, probably due to side reactions of lithium methylthiolate with a polarized triple bond in the ethynyl moiety. However, the one-pot procedure based on the oxidative addition of sulfur to lithiated terminal alkynes with subsequent reaction with methyl iodide[31] allowed us to synthesize the desired product **2a** from pyrazole **1** in 52% yield (Scheme 1).[†] Analogously, using ethyl iodide, the corresponding ethylthio derivative **2b** was obtained.

Room-temperature photolysis of pyrazoles **2a**,**b** in benzene for 2–3 h in the presence of 10- to 15-fold molar excess of alkene, such as 2,3-dimethylbut-2-ene, methylenecyclopentane or styrene, resulted in complete consumption of starting materials with the evolution of nitrogen gas. According to the NMR spectra, in all cases cyclopropanes **3** were formed as major products (see Scheme 1) isolated further by flash chromatography on silica

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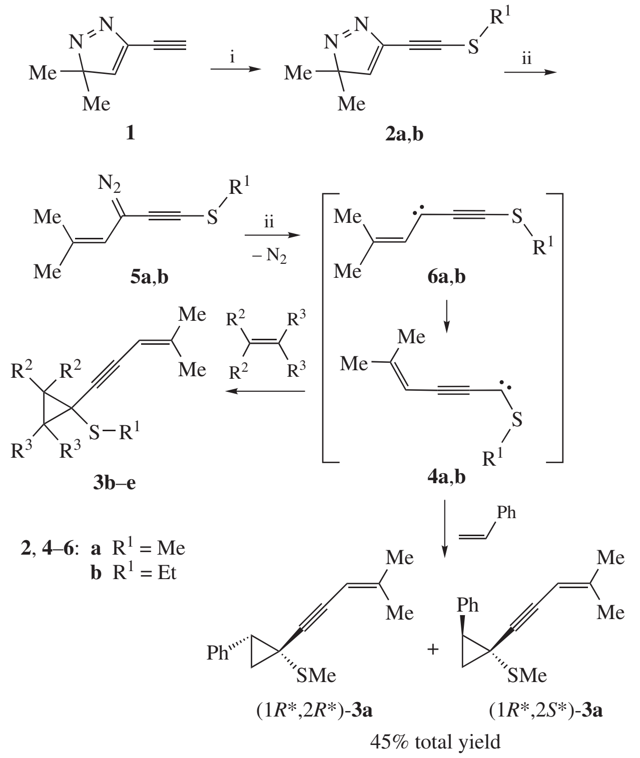
[†] *Synthesis of 3,3-dimethyl-5-methylthioethynyl-3*H*-pyrazole* **2a**. The 2.5 M solution of *n*-BuLi in hexanes (1.8 ml, 4.5 mmol) was added to the solution of diisopropylamine (460 mg, 4.6 mmol) in dry THF (3 ml), under argon atmosphere at 0 °C. The resulting mixture was stirred at the same temperature for 10 min, cooled down to the temperature range between –65 and –70 °C and then the solution of 3,3-dimethyl-5-ethynyl-3*H*-pyrazole **1** (500 mg, 4.17 mmol) in dry THF (2 ml) was added *via* a syringe. After stirring for 10 min, finely powdered sulfur (145 mg, 4.5 mmol) was added, resulting in fast change of color to dark-red. The temperature was gradually raised to the range of –40 to –30 °C, and after 30 min of stirring at this temperature, methyl iodide (710 mg, 5 mmol) was added in one portion. The mixture was slowly heated to room temperature and then diluted with an equal volume of water. The layers were separated, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the dark residue was washed twice with hot hexane with extensive stirring. Combined hexane extracts were concentrated and subjected to microdistillation *in vacuo* (bath temperature 80–100 °C, 1 Torr) to result in product **2a** as light-yellow liquid, which crystallized upon standing. Yield 358 mg (52%). ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 6H, 2Me), 2.50 (s, 3H, SMe), 6.88 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$) δ: 19.1 (SMe), 20.5 (2Me), 83.7, 86.9 (C≡C), 94.7 (*C*Me$_2$), 138.5 (=*C*C≡C), 146.3 (=CH). HRMS, *m/z*: 167.0640 $[M+H]^+$ (calc. for $C_8H_{10}N_2S$, *m/z*: 167.0637).

5-Ethylthioethynyl-3,3-dimethyl-3*H*-pyrazole **2b** was obtained by the same procedure using iodoethane instead of methyl iodide. Yield 41%. For its characteristics, see Online Supplementary Materials.



45% total yield

3b $R^1 = R^2 = R^3$ = Me (52%)
3c R^1 = Me, $R^2 + R^2 = (CH_2)_4$, R^3 = H (60%)
3d $R^1 = R^2$ = Me, R^3 = H (traces)
3e R^1 = Et, $R^2 + R^2 = (CH_2)_4$, R^3 = H (55%)

Scheme 1 *Reagents and conditions*: i, LDA, THF, hexanes, –70 °C, 10 min, then S_8, –70 to –30 °C, then R^1I; ii, *hv*.

gel in yields of 52–60%.[‡] As anticipated for reaction with styrene, 4 : 1 mixture of two diastereoisomers of cyclopropane **3a** was formed, and they were characterized without separation. It was also shown that benzene (taken in ratio ~1 : 1 by volume relative to alkene) led to substantial increase of the reaction rate. Thus, photolysis of pyrazole **2a** in pure 3-methylbut-2-ene resulted in ~90% conversion after 5 h, whereas the same reaction in the presence of benzene was almost complete within 2 h. This acceleration can probably be attributed to photosensitization effect of benzene.

Photolysis of pyrazole **2a** in the presence of 2-methylpropene gave only trace amount (< 10%) of the expected cyclopropane **3d**, which was identified by ^{1}H NMR in the reaction mixture from two doublets at 0.87 and 1.02 ppm corresponding to a methylene moiety in the cyclopropane ring. This points to the propensity of carbenes **4** to side reactions in the absence of an active trapping agent, possibly proceeding with participation of the enyne moiety. These results are in agreement with our previous observation[10] of poor reactivity of alkynyl(methylthio) carbenes towards 2-methylpropene.

An unexpected result was obtained in the competitive reaction of carbene **4a** with the mixture of 2,3-dimethylbut-2-ene and methylenecyclopentane. Reactivity ratio for these alkenes, calculated from amounts of corresponding cyclopropanes **3b** and **3c**, appeared to be 1 : 1.2 despite of higher nucleophilicity of double bond in 2,3-dimethylbut-2-ene in comparison with less sterically hindered methylenecyclopentane. This result may indicate the role of steric factor associated with a bulky sulfur atom at carbenic center, in contrast to the properties of well-known halocarbenes,[32] for which electron density on the double bond is the main factor determining the cycloaddition rate.

Generation of carbenes **4** proceeded *via* intermediate formation of diazo compounds **5** as the primary products of photoisomerization of pyrazoles **2**. However, we were unable to detect compounds **5** by NMR monitoring of the reaction mixtures. Obviously, under conditions used their formation was much slower than subsequent elimination of the nitrogen molecule.

Nevertheless, formation of compound **5a** was detected using matrix isolation technique. Photolysis of compound **2a** in an argon matrix at 10 K by ~350 nm light for ~1 h resulted in a decrease of the characteristic IR bands of compound **2a** at 2177.7 and 2174.8 cm^{-1} and gave rise to a new set of absorption bands, in particular a medium intensity band at 2150.4 cm^{-1} and a very strong band at 2033.5 cm^{-1}, which were assigned to symmetric and asymmetric C≡C and N≡N stretching vibrations, respectively, in the molecule of diazo compound **5a**. Experimental IR spectrum of product **5a** showed a good agreement with the calculated (B3LYP/aug-cc-pVTZ) one, indicating formation of this compound as the primary product upon irradiation of pyrazole **2a** (see Online Supplementary Materials).

On further photolysis, diazo compounds **5** eliminated nitrogen with formation of triplet carbenes **6**, in which the carbenic center was conjugated with alkynyl and 2,2-dimethylvinyl fragments. These alkynylvinylcarbenes are known to undergo easy isomerization accompanied by a shift of carbenic center to α-position to heteroatom,[6] and our calculations demonstrated that in this case the rearrangement **6** → **4** is thermodynamically favorable: ΔE calculated by G4MP2 method for transformation of triplet **6a** into singlet **4a** is –13.9 kcal mol^{-1}. This clarifies the selective formation of cyclopropanes **3** and the absence of isomeric products, which could arise from cycloaddition of initially

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[‡] *General procedure for the synthesis of 1-alkylthio-1-(4-methylpent-3-en-1-yn-1-yl)cyclopropanes* **3a**–**e** *from pyrazoles* **2a**,**b**. A solution of pyrazole **2** (0.4 mmol) in ~1 : 1 v/v mixture of benzene and corresponding alkene (1 ml) was subjected to photolysis in quartz cuvette by unfiltered light of a DRSh-500 high-pressure mercury lamp (500 W) at room temperature for 2.5–3 h. After ceasing of nitrogen gas evolution and full consumption of starting material (NMR control), solvent and an excess of alkene were evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel with hexane to give product **3**.

1-(4-Methylpent-3-en-1-yn-1-yl)-1-methylthio-2-phenylcyclopropane **3a** was prepared from pyrazole **2a** and styrene as a mixture of (1*R**,2*R**)- and (1*R**,2*S**)-isomers (1 : 4). Total yield 45%. HRMS, *m*/*z*: 243.1197 [M + H]$^+$, 265.1150 [M + Na]$^+$ (calc. for $C_{16}H_{18}S$, *m*/*z*: 243.1202; for $C_{16}H_{17}SNa$, *m*/*z*: 265.1019).

(1*R**,2*R**)-**3a**: ^{1}H NMR ($CDCl_3$) δ: 1.61 (dd, 1H, C*H*H, ^2J 5.3 Hz, ^3J 7.5 Hz), 1.76 (dd, 1H, CH*H*, ^2J 5.3 Hz, ^3J 8.9 Hz), 1.84, 1.94 (2 br. s, each 3 H, =CMe$_2$), 2.00 (s, 3 H, SMe), 2.85 (dd, 1H, PhC*H*, J 8.9, 7.5 Hz), 5.34 (br. s, 1H, CH=), 7.23–7.40 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ: 14.3 (SMe), 21.1, 24.8 (=C*Me*$_2$), 23.0 (CH_2), 24.3 (C≡C*C*), 34.9 (Ph*C*H), 76.3, 94.5 (C≡C), 105.1 (CH=), 126.9, 127.8, 129.2 (C^{2-6}, Ph), 135.8 (C^1, Ph), 148.3 (=*C*Me$_2$).

(1*R**,2*S**)-**3a**: ^{1}H NMR ($CDCl_3$) δ: 1.52, 1.71 (2 br. s, each 3 H, =CMe$_2$), 1.67 (dd, 1H, C*H*H, ^2J 5.3 Hz, ^3J 9.0 Hz), 1.74 (dd, 1H, CH*H*, ^2J 5.3 Hz, ^3J 7.0 Hz), 2.41 (s, 3 H, SMe), 2.65 (dd, 1H, PhC*H*, J 9.0, 7.0 Hz), 5.14 (br. s, 1H, CH=), 7.23–7.40 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ: 15.7 (SMe), 20.6, 25.0 (=C*Me*$_2$), 24.2 (CH_2), 25.0 (C≡C*C*), 36.0 (Ph*C*H), 83.4, 90.3 (C≡C), 105.0 (CH=), 126.7, 128.0, 128.5 (C^{2-6}, Ph), 137.1 (C^1, Ph), 148.1 (=*C*Me$_2$).

1-(4-Methylpent-3-en-1-yn-1-yl)-1-(methylthio)spiro[2.4]heptane **3c** was prepared from pyrazole **2a** and methylenecyclopentane. Yield 60%. ^{1}H NMR ($CDCl_3$) δ: 1.03 (d, 1H, C*H*H, ^2J 4.6 Hz), 1.21 (d, 1H, CH*H*, ^2J 4.6 Hz), 1.49–1.77 (m, 6 H, cyclo-C_5), 1.78, 1.87 (2 br. s, each 3 H, =CMe$_2$), 1.96–2.13 (m, 2 H, cyclo-C_5), 2.24 (s, 3 H, SMe), 5.30 (br. s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 15.3 (SMe), 21.0, 24.8 (=C*Me*$_2$), 26.7, 26.9, 31.1, 32.0, 34.4 (5 CH_2), 27.0 (C≡C*C*), 38.5 (quaternary C), 78.7, 92.7 (C≡C), 105.4 (CH=), 147.4 (=*C*Me$_2$). HRMS, *m*/*z*: 221.1362 [M + H]$^+$, 243.1183 [M + Na]$^+$ (calc. for $C_{14}H_{20}S$, *m*/*z*: 221.1358; for $C_{14}H_{19}SNa$, *m*/*z*: 243.1178).

For characteristics of compounds **3b** and **3e**, see Online Supplementary Materials.

formed carbenes **6**. Similar regioselectivity of cyclopropanation was observed previously[6] for the photolysis of 5-(bromoethynyl)-3,3-dimethyl-3*H*-pyrazole and 3,3-dimethyl-5-(methoxycarbonylethynyl)-3*H*-pyrazole in the presence of alkenes, resulting in 1-(4-methylpent-3-en-1-ynyl)-1-bromo- and 1-methoxycarbonyl-1-(4-methylpent-3-en-1-ynyl)cyclopropanes, respectively.

In summary, a photochemical approach to the generation of new alkylthio(alkynyl)carbenes has been developed, which seems promising for direct synthesis of functionalized alkynylcyclopropanes as well as for further investigation of these carbenic species by matrix IR spectroscopy.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.006.

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