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A new synthesis of ring-fused alkylidenecyclobutanes by ring-enlargement reaction of bicyclo[*n*.1.0]alkylidene derivatives

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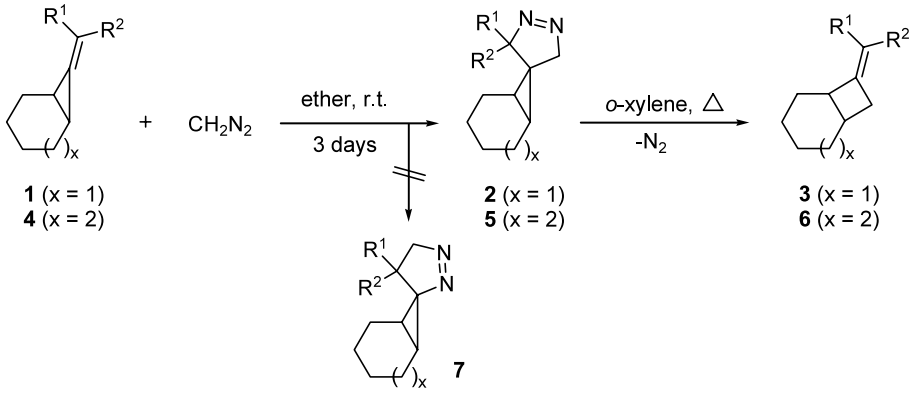
Abstract—Bicyclo[*n*.1.0]alkylidene derivatives (ring-fused alkylidenecyclopropanes) reacted with diazomethane to give spiro-pyrazolines regioselectively. Thermal decomposition of spiro-pyrazolines resulted in ring-enlargement and afforded ring-fused alkylidenecyclobutanes (bicyclo[*n*.2.0]alkylidene derivatives) in high yields. © 2003 Elsevier Science Ltd. All rights reserved.

Functionalized cyclobutanes and their derivatives are potentially valuable and attractive compounds for a variety of organic reactions.[1] Especially, much attention was paid to alkylidenecyclobutanes and -cyclobutenes because of their unique reactivity resulting from the presence of two reactive groups, the double bond and the cyclobutane ring, in the molecule.[2] Several methods have been reported for synthesis of alkylidenecyclobutene and -cyclobutane derivatives. Thus, electrocyclization of vinylallenes, for instance, is a straightforward method for direct preparation of alkylidenecyclobutenes from open-chain precursors.[3] It was also reported that alkylidenecyclobutanes could be prepared by conventional [2+2] cycloaddition of allenes with alkenes.[4] Methylene- and benzylidenecyclobutanes were prepared by intramolecular cyclization of 4-tributylstannylpent-4-enyl tosylates.[5] Alkylidenecyclobutanes could also be prepared by thermal decomposition of diazaspiro[4.2]heptanes (spiro-pyrazoline derivatives),[6] but the yield was low in the case of simple methylenecyclobutane.[6a] On the other hand, only a few methods for synthesis of ring-fused alkylidenecyclobutanes have been reported, i.e. intramolecular photocycloaddition of enones with optically active allenylsilane,[7] Cu(I)-mediated intramolecular conjugate addition of alkenylstannane function to α,β-alkynic esters,[8] and aluminum chloride promoted [2+2] cycloaddition of ethyl 2,3-butadienoate to olefins.[9]

Methylenecyclopropane and its derivatives are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[10]



Scheme 1.

Keywords: ring-enlargement; alkylidenecyclopropane; alkylidenecyclobutane; thermal decomposition; pyrazoline; diazomethane.

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We have already reported a facile synthesis of ring-fused alkylidenecyclopropanes by olefination reaction of bicyclo[*n*.1.0]alkanone *N*,*O*-hemiacetals with Wittig reagents.[11] As a part of our studies on the application of these highly strained molecules to organic synthesis, we recently found that ring expansion reaction of cyclopropane ring in the ring-fused alkylidenecyclopropanes readily proceeded to give ring-fused alkylidenecyclobutanes in high yields. Thus, 1,3-dipolar cycloaddition of diazomethane to alkylidenecyclopropanes **1** or **4** followed by thermolysis of the resulting spiro-pyrazolines **2** or **5** gave ring-enlarged alkylidenecyclobutanes **3** or **6** in high yields, respectively. We wish to report here a new and general method for an efficient synthesis of ring-fused alkylidenecyclobutanes (bicyclo[*n*.2.0]alkylidene derivatives) by the ring-enlargement reaction of ring-fused alkylidenecyclopropanes using 1,3-dipolar cycloaddition of diazomethane–thermolysis sequence (Scheme 1).

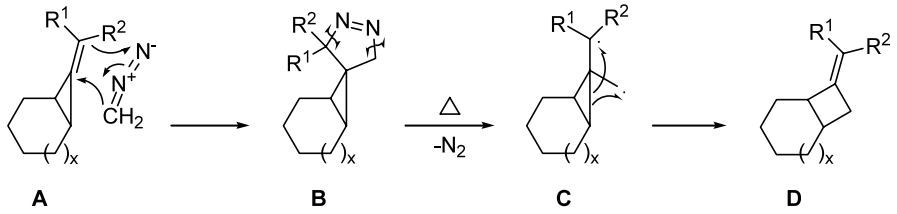
Addition of diazomethane to double bonds activated by a suitable electron-withdrawing group is an established route to pyrazolines.[12] Stirring of ring-fused alkylidenecyclopropanes **1** or **4** with diazomethane in ether at room temperature for 3 days afforded spiro-pyrazolines **2** or **5** in 95–99% yields[13] (Table 1). Bicyclo[4.1.0]hept-7-ylidene derivatives **1a–d** gave spiro-pyrazolines **2a–d** in the isolated yields of 97–99%. Similarly, bicyclo[5.1.0]oct-8-ylidene derivatives **4a–d** gave spiro-pyrazolines **5a–d** in 95–99% isolated yields. In both cases diazomethane was added stereospecifically from the less hindered *exo*-direction.[14] Determination of the stereochemistry of **5** was carried out by NMR spectroscopy including NOE experiments of **5c**. Irradiations at δ 4.49 and 4.56 showed enhancements at δ 1.10 (6.5%) and 1.11 (7.5%), respectively. Reverse irradiation at δ 1.10 showed enhancement at δ 4.50 (3.1%). These results indicate that the methylene protons of pyrazoline ring have NOE effects with cyclopropane protons, and it is possible when methylene group is in *exo*-position. This configuration of pyrazolines can be obtained when diazomethane attacks the bicyclo[*n*.1.0]-alkylidene derivatives from less hindered *exo*-direction only. Moreover, in both cases spiro-pyrazolines were formed regioselectively.[12] ^{1}H NMR spectrum of **5a**, for example, showed long-range coupling of CH_2 at δ 4.47 (d, $J=17.8$ Hz, 1H) and at δ 4.56 (dd, $J=17.8$ and 2.0 Hz, 1H) with that of CH at δ 5.26 (d, $J=2.0$ Hz, 1H) and no vicinal coupling was observed. These results indicate the formation of single isomer like **2** or **5** only but not **7** which would show vicinal coupling. Thermal decomposition[6,12a,b] of the prepared spiro-pyrazolines **2** or **5** were carried out in *o*-xylene and heated at 130°C until the evolution of nitrogen ceased. Ring-enlarged products, bicyclo[*n*.2.0]alkylidene derivatives **3** or **6** were produced in 85–99% yields.[16] Spiro-pyrazolines **2a–d** afforded bicyclo-[4.2.0]octylidene derivatives **3a–d** in 87–98% yields and spiro-pyrazolines **5a–d** afforded bicyclo[5.2.0]-nonylidene derivatives **6a–d** in 85–99% yields. ^{1}H NMR spectrum of **3b** is identical with that reported in the literature, indicating *E*-ethyl bicyclo[4.2.0]oct-8-ylideneacetate structure.[9] In all cases we isolated (*E*)-bicyclo[*n*.2.0]alkylidene derivatives and the results are summarized in Table 1.

Thermal decomposition of pyrazoline probably proceeds via diradical formation.[6,12a,b,17] In the present reaction, 1,3-dipolar cycloaddition of diazomethane to bicyclo[*n*.1.0]alkylidene derivatives **A** gives spiro-pyrazolines **B** which is the most obvious precursor of diradical. On heating in *o*-xylene **B** decomposes to give diradical **C** with the loss of a nitrogen molecule. Rearrangement of diradical **C** results in a rupture of cyclopropane ring due to its strain prior to further ring closure and ring-enlarged[6] products **D**, ring-fused alkylidenecyclobutanes (bicyclo[*n*.2.0]alkylidene derivatives), are produced as shown in Scheme 2.

Table 1. Preparation of bicyclo[*n*.2.0]alkylidene derivatives **3** and **6** by thermal decomposition[a] of pyrazolines **2** and **5** prepared by the reaction of ring-fused alkylidenecyclopropanes with diazomethane[b]

	Ring-fused alkylidenecyclopropane		Pyrazoline[c]	Ring-fused alkylidenecyclobutane[d]
x	R^1	R^2		
1	H	COOMe (**1a**)	**2a** (98)	**3a** (96)
1	H	COOEt (**1b**)	**2b** (97)	**3b** (96)
1	Me	COOMe (**1c**)	**2c** (99)	**3c** (98)
1	$CH_2CH{=}CH_2$	COOMe (**1d**)	**2d** (97)	**3d** (87)
2	H	COOMe (**4a**)	**5a** (99)	**6a** (92)
2	H	COOEt (**4b**)	**5b** (98)	**6b** (99)
2	Me	COOMe (**4c**)	**5c** (99)	**6c** (99)
2	$CH_2CH{=}CH_2$	COOMe (**4d**)	**5d** (95)	**6d** (85)

[a] **2** or **5** (5 mmol) in *o*-xylene (10 mL) was stirred at 130°C until the evolution of N_2 gas ceased (ca. 30 min).
[b] **1** or **4** (5 mmol) and diazomethane (25 mmol) in ether (25 mL) were stirred at room temperature for 3 days.
[c] Isolated yields of pyrazolines are shown in parentheses.
[d] Isolated yields of ring-fused alkylidenecyclobutanes are shown in parentheses.



Scheme 2.

Acknowledgements

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13. To a solution of 0.97 g (5 mmol) **4c** in 10 mL ether was added at rt to an ethereal solution of diazomethane prepared from 2.58 g (25 mmol) *N*-nitroso-*N*-methylurea.[15] The mixture was stirred for 3 days at rt and excess diazomethane was decomposed by addition of formic acid. Then the solution was washed with saturated sodium bicarbonate solution, water and brine, and dried over magnesium sulphate. Removal of solvent under vacuum gave a crude solid which on recrystallization from *n*-hexane at −10°C afforded pure spiro-pyrazoline **5c** (1.17 g, 99%). Selected data of **5c**: mp 55–56°C; IR (Nujol) ν 1742, 1556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (m, 1H), 1.02–1.17 (m, 3H), 1.17–1.32 (m, 3H), 1.55 (s, 3H), 1.68–1.90 (m, 4 H), 1.96 (m, 1H), 3.72 (s, 3H), 4.49 (d, J=18.3 Hz, 1H), 4.56 (d, J=18.3 Hz, 1H); ^{13}C NMR (67.5 MHz): δ 19.17, 25.18, 26.48, 27.61, 29.27, 29.56, 29.92, 31.59, 34.18, 52.47, 89.35, 91.26, 170.94; EIMS m/z (relative intensity) 236 (M^+, 0.4), 208 (9), 193 (20), 177 (33), 165 (53), 149 (54), 139 (100), 126 (60), 93 (64), 79 (69), 67 (60). Anal. calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 65.95; H, 8.65; N, 12.10.
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16. A solution of **5b** (1.18 g, 5 mmol) in *o*-xylene (10 mL) was heated at 130°C until the evolution of nitrogen gas ceased (ca. 30 min). The solution was cooled and evaporated in vacuo to remove xylene, and the product was purified by column chromatography on silica gel (ether:hexane, 1:1) to give ethyl bicyclo[5.2.0]non-9-ylideneacetate (**6b**) (1.03 g, 99% yield). Selected data of **6b**: IR (neat) ν 1719 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ

1.05–1.95 (m, 10H), 1.27 (t, $J=6.9$ Hz, 3H), 2.20–2.45 (m, 1H), 2.48–2.75 (m, 1H), 3.08–3.25 (m, 2H), 4.14 (q, $J=6.9$ Hz, 2H), 5.60 (q, $J=2.3$ Hz, 1H); ^{13}C NMR (67.5 MHz): δ 14.29, 28.63, 29.44, 30.01, 31.97, 32.58, 36.48, 36.82, 48.16, 59.46, 112.11, 166.79, 170.76; EIMS m/z (relative intensity) 208 (M^+, 89), 194 (17), 179 (45), 163 (57), 151 (37), 135 (100), 120 (44), 91 (71), 79 (62), 67 (46). Anal. calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.69; H, 9.64.

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