Pergamon

Tetrahedron Letters, Vol. 38, No. 52, pp. 9005-9008, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10406-3

Reactions of Methylenecyclopropanes with a Diethylzinc-Bromoform System, and the Utilization for Synthesis of a Novel Cyclopropylidene-Nucleoside

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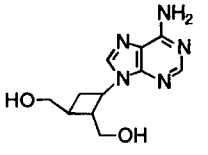
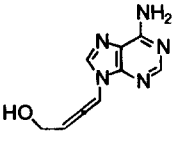
Abstract: The reactions of substituted methylenecyclopropane with diethylzinc-bromoform gave bromospiro[2.2]pentane derivatives, bromoform-addition compounds, an oxabicyclo-compound and adjacent dibromo-compound, and the last product was derived to a novel α, β-unsaturated nucloside.

Carbocyclic oxetanocins[1] and allene-nucleosides[2] are effective for HIV and other viruses, but cyclopropyl- and cyclopropylmethyl-nucleosides[3] are ineffective. For study of the structure-activity relationships and in new drug design, syntheses of novel cyclopropylidene and/or spiro[2.2]pentyl-nucleosides are considered to be of prime importance.



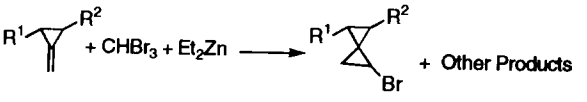
Carbocyclic oxetanocin-A



Adenallene

Akhachinskaya showed stereoselective additions of dihalocarbenes to 2-substituted methylenecyclopropanes to give dihalospiro[2. 2] pentane derivatives.[4] Miyano et al. also reported monobromocyclopropanation reactions between simple olefins and a bromocarbenoid intermediate which was generated from a diethylzinc bromoform system.[5] In the course of our work to synthesize novel carbocyclic nucleosides, we first examined some reactions of substituted methylenecyclopropanes **1**, **2**, **3**, **4** with a diethylzinc-bromoform system to prepare the key intermediates of substituted bromospiro[2.2]pentanes and dibromocyclopropanes as shown in Scheme 1 and Table 1.

Thus, the reaction of dimethyl 3-methylene-cyclopropane-trans-1, 2-dicarboxylate **1** (Feist's diester)[6]-$CHBr_3$-Et2Zn system (1:7:6) was carried out at 68°C in nitrogen atmosphere to afford the target molecule, dimethyl 4-bromospiro[2.2] pentane-trans-1, 2-dicarboxylate **5**[7], in 12% yield after column chromatography(1:5 ethyl acetate/hexane), and the isomer ratio was 8:3 (by ^{1}H NMR spectrum). A similar mixture was then reacted in air atmosphere which was reported to have accelerated generation of the bromocarbenoid reagent from diethylzinc and bromoform.[5] At the low temperature, the reaction did not give the target molecule, upon heating the reaction mixture to 68℃, we obtained unexpectedly, dimethyl 3-bromo-3-(2, 2-dibromoethyl)cyclopropane-trans-1,2-dicarboxylate **6**[8] in

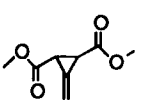
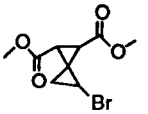
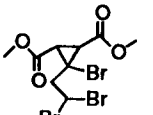
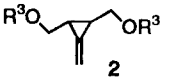
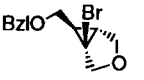
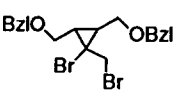
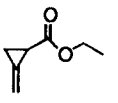
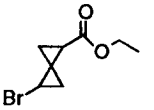
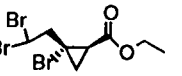


R^1, R^2: Alkoxycarbonyl or Alkoxymethyl
Scheme 1

61% yield. **6** may be a radical-fission adduct of bromoform to **1**. Changing of the solvents, molecular ratio and catalysts gave no better result for the spiro-compound.

Carbenes or carbenoids usually act as electrophilic reagents when they are added to olefins, so it is reasonable for the yield of the spiro-compound to be low as **1** has two electron-withdrawing groups in the three-membered ring. In order to increase electron density of the double bond on the substrates, compound **1** was reduced by $LiAlH_4$ to give Feist's diol[9], and the diol was derived to the corresponding TMS and TBDMS ethers **2**[10] and benzyl ether **3**.[11]

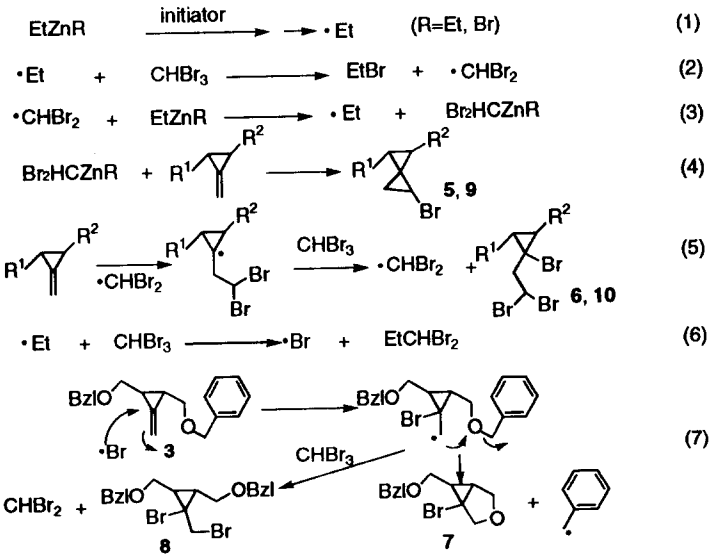
Table 1. Reactions of Substituted Methylenecyclopropanes-Diethylzinc-Bromoform Systems and the Products

Starting Materials	Products and Yields		
 1	 5 12%	 6 61%	
 2	No products were isolated		
 3	 7 15%	 8 12%	
 4	 9 46%	 10 8%	

R^3: TMS, TBDMS

Compound **2** was consumed but gave no meaningful products under several conditions. On the other hand, the same treatment of compound **3** at 68°C gave 6-benzyloxymethyl-1-bromo-3-oxabicyclo[3.1.0] hexane **7**[12] and 1-bromo-1-bromomethyl-trans-2, 3-di(benzyloxymethyl)cyclopropane **8**[13] in 15% and 12% yields, respectively, after column chromatography (1:10 ethyl acetate/ hexane). These results suggest the existence of some radical competing reactions. Compound 2 might be charged with radical fission at the electron-rich silylether bonds.

Finally, monosubstituted compound **4** was subjected to the reaction at 60 °C to give the target molecule, ethyl 4-bromo-spiro[2.2] pentane-1-carboxylate **9**[14], in 46% yield, whose isomer ratio was 2:1, in addition to ethyl 2-bromo-2-(2, 2-dibromoethyl)cyclopropane-1-carboxylate **10**[15] (8% yield). The whole reaction mechanism is inferred as shown in Scheme 2 and it agrees with Miyano's inference.[5]



Scheme 2

Compounds **5**, **8**, **9** were subjected to coupling with adenine in the presence of K_2CO_3, and only **8** afforded a cyclopropylidenemethylenyladenine **11**[16] in 65% yield. The structure of crystal **11** was confirmed as Figure 1 by X-ray analysis. **11** was deprotected by 6 eq. BCl_3 at -20°C to give a novel α, β-

unsaturated nucleoside, trans-3',4'-di(hydroxymethyl)cyclopropylidenemethylenyladenine **12**[17], in 91% yield as shown in Scheme 3.

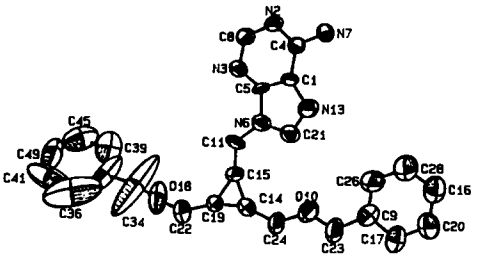
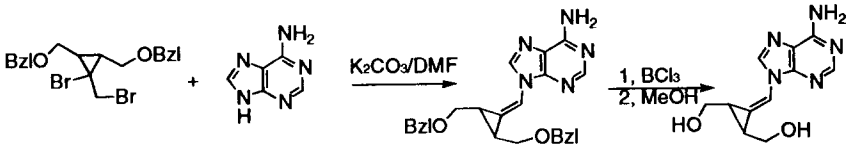


Figure 1, Molecular structure of **11** crystal



8 **11** **12**

Scheme 3

Other trials of coupling reactions between spiro-compounds, etc. and bases, and the interesting anti-HIV-1 activity data of the cyclopropylidene nucleosides will be reported in our next paper.

References and notes

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7. All new compounds gave satisfactory spectral data. **5a**: ^{1}H NMR(400MHz, CDCl3) δ:3.74(s, 6H), 3.36(dd, 1H, J=4.4Hz, 7.6Hz), 2.80(d, 1H, J=4.0Hz), 2.65(d, 1H, J=4.0Hz), 1.86(t, 1H, J=7.6Hz), 1.45(dd, 1H, J=4.4Hz, 7.6Hz); ^{13}C NMR(100MHz, CDCl3) δ:52.64, 52.56, 30.45, 28.99, 28.65, 20.14, 16.56, 170.53, 170.35; MS(m/z): 262 M^+, 264 $(M+2)^+$. **5b**:^{1}H NMR (400MHz, CDCl3) δ:3.70(s, 6H), 3.50 (dd, 1H, J=4.4Hz, 7.6Hz), 2.87(d, 1H, J=4.0Hz), 2.74(d, 1H, J=4.0Hz), 1.65(t, 1H, J=7.6Hz), 1.59(dd, 1H, J=4.4Hz, 7.6Hz); ^{13}C NMR(100MHz, CDCl3) δ:169.12, 167.52, 52.39, 52.31, 30.96, 28.20, 20.41, 19.73, 14.11; MS(m/z): 262 M^+, 264 $(M+2)^+$.
8. **6**: ^{1}H NMR(400MHz, CDCl3) δ:6.00(t, 1H, J=7.2Hz), 3.81(s, 6H), 3.11(ddd, 2H, J=7.2Hz, 7.2Hz,

14.0Hz), 2.87(d, 1H, J=7.2Hz), 2.65(d, 1H, J=7.2Hz); ^{13}C NMR(100MHz, $CDCl_3$)δ:168.52, 166.93, 52.84, 52.81, 48.35, 41.71, 39.37, 33.77, 33.37; MS(m/z): 389 $(M-CH_3O)^+$, 391 $(M+2-CH_3O)^+$, 393 $(M+4-CH_3O)^+$, 395 $(M+6-CH_3O)^+$.

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12. **7**: ^{1}H NMR(400MHz, $CDCl_3$) δ:7.33(m, 5H), 4.56(s, 2H), 4.08(d, 1H, J=8.0Hz), 3.88(dd, 1H, J=8.0Hz, 3.2Hz), 3.85(d, 1H, J=8.6Hz), 3.78(d, 1H, J=8.6Hz), 3.65(d, 2H, J=7.2Hz), 1.71(dd, 1H, J=3.2Hz, 4.8Hz), 1.41(dt, 1H, J=4.8Hz, 7.2Hz); ^{13}C NMR(100MHz, $CDCl_3$) δ:138.45, 130.00, 128.73, (2C), 128.03(2C), 75.70, 73.33, 70.83, 69.49, 38.75, 30.45, 24.86; MS(m/z): 282 $(M)^+$, 284 $(M+2)^+$
13. **8**: ^{1}H NMR(400MHz, $CDCl_3$) δ:7.31(m, 10H), 4.57(q, 2H, J=11.6Hz), 4.50(q, 2H, J=11.6Hz), 3.86(q, 2H, J=11.6Hz), 3.70(m, 4H), 1.76(dd, 1H, J=7.2Hz, 12.6Hz), 1.35(dd, 1H, J=7.2Hz, 12.6Hz); MS(m/z): 360 $(M-C_7H_8)^+$, 362 $(M+2-C_7H_8)^+$, 364 $(M+4-C_7H_8)^+$. **8** also was quantitatively obtained by bromination of **3**.
14. **9a**: ^{1}H NMR(400MHz, $CDCl_3$) δ:4.13(ddq, 2H, J=8.8Hz, 8.8Hz, 14.0Hz), 3.33(dd, 1H, J=4.0Hz, 2.8Hz), 2.21(dd, 1H, J=8.0Hz, 5.2Hz), 1.70(dd, 1H, J=6.8Hz, 4.0Hz), 1.59(dd, 1H, J=8.0Hz, 5.2Hz), 1.52(dd, 1H, J=8.0Hz, 5.2Hz), 1.38(dd, 1H, J=6.8Hz, 2.8Hz), 1.25(t, 3H, J=8.8Hz); MS(m/z): 218 M^+, 220 $(M+2)^+$. **9b**: ^{1}H NMR(400MHz, $CDCl_3$) δ:4.15(ddq, 2H, J=8.8Hz, 8.8Hz, 14.0Hz), 3.45(dd, 1H, J=4.4Hz, 6.8Hz), 2.21(dd, 1H, J=8.4Hz, 4.8Hz), 1.83(t, 1H, J=4.8Hz), 1.68(t, 1H, J=7.2Hz), 1.60(dd, 1H, J=8.4Hz, 4.8Hz), 1.43(dd, 1H, J=7.2Hz, 4.4Hz), 1.25(t, 3H, J=8.8Hz); MS(m/z): 218 M^+, 220 $(M+2)^+$.
15. **10**: ^{1}H NMR(400MHz, $CDCl_3$) δ:5.98(t, 1H, J=7.2Hz), 4.18(ddq, 2H, J=7.2Hz, 7.2Hz, 14.4Hz), 3.06(ddd, 2H, J=7.2Hz, 7.2Hz, 14.0Hz), 2.36(t, 1H, J=8.4Hz), 1.71(ddd, 2H, J=8.4Hz, 8.4Hz, 10.8Hz), 1.28(t, 3H, J=7.2Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ:164.56, 61.50, 47.87, 42.97, 37.20, 29.02, 23.54, 14.23; MS(m/z): 375 M^+, 377 $(M+2)^+$, 379 $(M+4)^+$, 381 $(M+6)^+$.
16. **11**: ^{1}H NMR(400MHz, $CDCl_3$) δ: 8.79(s, 1H), 8.37(s, 1H), 7.58(t, 1H, J=2.0Hz), 7.30(m, 10H), 4.56(m, 4H), 3.88(dd, 1H, J=9.6Hz, 5.6Hz), 3.62(dd, 1H, J=10.4Hz, 6.0Hz), 3.42(dd, 1H, J=10.4Hz, 7.6Hz), 3.33(t, 1H, J=9.6Hz), 2.07(dddd, 1H, J=9.6Hz, 5.6Hz, 5.0Hz, 2.0Hz), 1.94(dddd, 1H, J=7.6Hz, 6.0Hz, 5.0Hz, 2.0Hz); ^{13}C NMR(100MHz, $CDCl_3$) δ:155.34, 153.21, 149.00, 138.53, 138.06, 137.68, 128.53(2C), 128.48(2C), 128.40, 127.86(2C), 127.78(2C), 127.73, 119.00, 116.59, 112.03, 73.20, 72.82, 71.39, 71.15, 22.99, 20.08; Anal. calcd for $C_{25}H_{25}N_5O_2$ C 70.26, H 5.85, N 16.39, found C 69.92, H 5.85, N 16.09; MS(m/z): 427 M^+. The X-ray data of **11** will be fully presented in our other paper.
17. **12**: ^{1}H NMR(400MHz, CD_3OD) δ:8.86(s, 1H), 8.42(s, 1H), 7.58(t, 1H, J=2.0Hz), 3.84(dd, 1H, J=12.0Hz, 6.8Hz), 3.62(d, 2H, J=6.8Hz), 3.56(dd, 1H, J=12.0Hz, 6.8Hz), 2.14(ddt, 1H, J=6.8Hz, 5.0Hz, 2.0Hz), 2.00(ddt, 1H, J=6.8Hz, 5.0Hz, 2.0Hz); ^{13}C NMR(100MHz, CD_3OD) δ:151.98, 148.92, 146.50, 143.18, 123.78, 119.73, 112.42, 64.17, 64.00, 26.37, 23.87; MS(m/z): 247 M^+; HRMS calcd for $C_{11}H_{13}N_5O_2$ 247.1071, found 247.1111.

(*Received in Japan* 1 *September* 1997; *revised* 8 *October* 1997; *accepted* 14 *October* 1997)