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Highly Stereoselective Synthesis of Vinyl and Ethynylcyclopropane 1,1-Dicarboxylic Esters *via semi*-Stabilized Telluronium Ylides

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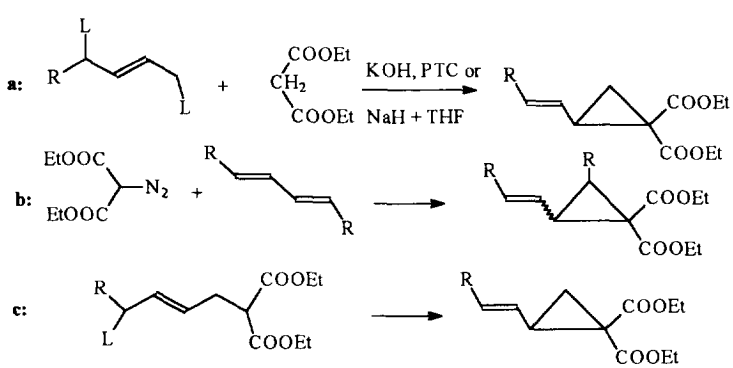
Abstract: Highly electron-deficient vinyl and ethynylcyclo-propane 1,1-dicarboxylic esters conveniently synthesized by the reaction of allylic diisobutyltelluronium ylides with alkylidene or arylmethy-lidene malonic esters with high yields and high stereoselectivity. The effects of the reaction media and bases used to produce the ylides on the stereoselectivity are studied.

Vinylcyclopropane 1,1-dicarboxylic esters are very useful in construction of cyclopentane skeleton[1] and seven-membered ring compounds containing a heteroatom.[2] Some of them were applied to the synthesis of several natural products such as prostanoid etc. [3] These compounds are often prepared from the following paths(**Scheme 1**): 1. Malonic esters condensation with bis allylic electrophiles;[2, 4] 2. Cyclopropanation reactions with carbenes;[1 b, 3, 5] 3. Multi-step methods utilizing 1,3-elimination reaction.[2] Only a few direct methods for the synthesis of them from readily available starting materials have been reported[2, 4, 5]. In our studies of the

Scheme 1

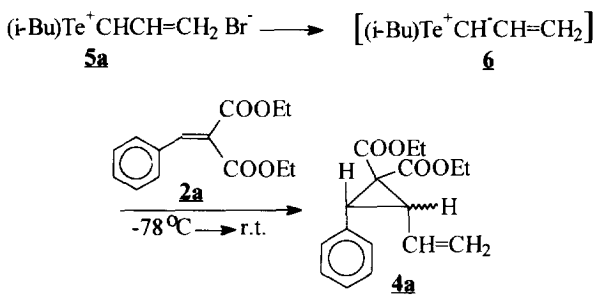


application of ylides to the preparation of small ring compounds, we documented a method to prepare *cis*-vinyloxiranes and ethynyloxiranes by the reaction of telluronium allylide and silylated propargylide with aldehydes and ketones.[6] We have also reported that these ylides were good reagents for

cyclopropanation of α,β-unsaturated esters and ketones.[7] All these findings enable us to be interested in developing a new method for synthesizing these compounds by utilizing the easily-prepared allylic ylides.

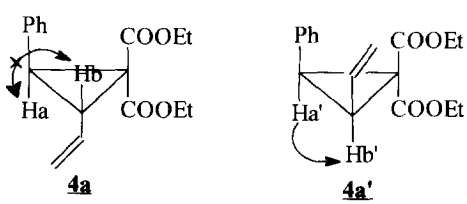
We found that upon treatment with base such as LiBr + $NaN(SiMe_3)_2$ in THF, the allyldiisobutyltelluronium bromide **5a** was transformed with proton abstraction to ylide **6a** which reacted smoothly with benzylidene malonic esters to produce vinylcyclopropane 1,1-dicarboxylic esters with high stereoselectivity(**Scheme 2**). Further studies showed that 3-silylated allyl, crotyl, cinnamyl, benzyl and 3-

Scheme 2



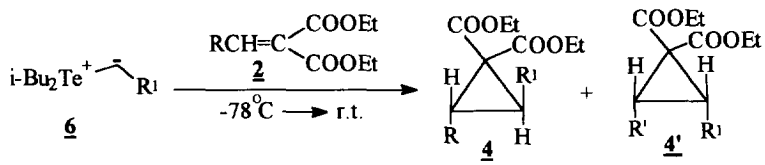
silylated propargyl telluronium ylide could also undergo cyclopropanation reactions with alkylidene malonic esters in excellent yield and with high *trans*-stereoselectivity(**Table 1**). It was noteworthy that the stereoselectivity of the above-described reaction was affected by the reaction media and base. When potassium bis(trimethylsilyl) amide was used instead of sodium bis(trimethylsilyl) amide to form the ylides, the ratio of **4** and **4'** was increased(entries 1 and 2 in **Table 1**). By the addition of lithium bromide, the *trans*-cyclopropane derivatives also increased obviously(entries 2 and 4 in **Table 1**). The mixed solvent of THF and toluene was found to be the better solvent for this reaction than sole THF(entry 3 in **Table 1**). Moreover, either alkylidene malonic esters(entries 6 and 11) or arylmethylidene malonic esters could readily react with these ylides.

The configuration of **4a**-**4h** was determined by ^1H NMR and ^1H-^1H NOESY spectra. In the ^1H NMR, the coupling constants of the two protons on the ring in cyclopropane derivatives **4** and **4'** were in the range of 7-8 Hz and 9-10Hz respectively. In general, the coupling constant between the two protons in *trans*-isomer is smaller than that in *cis*-isomer of cyclopropane ring.[8] Thus, we assigned that the two protons whose coupling constant between 7 and 8 Hz are oriented to *trans* each other. This assignment is consistent with the ^1H-^1H NOESY spectra of the mixture of **4a** and **4a'**. From this spectra, there exists strong NOE effect between



the two proton Ha' and Hb' in which the coupling constant is 9.4Hz, and no NOE effect was found between the two protons Ha and Hb of **4a** with this coupling constant 8.0Hz.

Table 1 The reaction of some *semi*-stabilized telluronium ylides with 2-ethoxycarbonyl-α,β-unsaturated ester



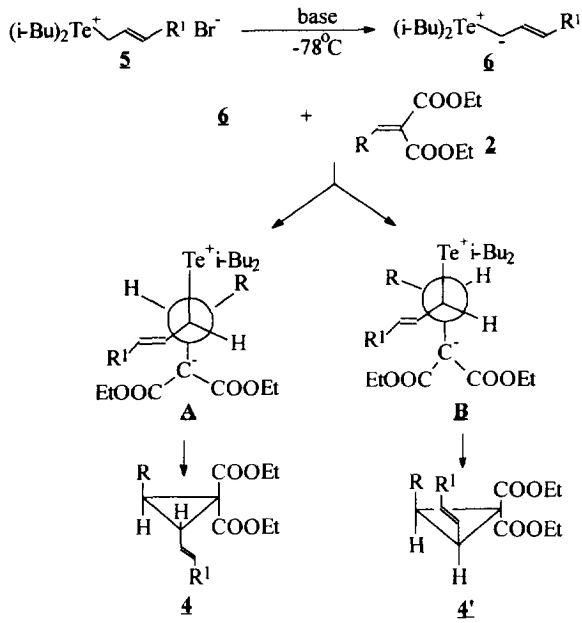
entry	R^1	R	base and solvent [a]	(4/4')[a, b]	yield(%)[c]
1	CH=CHSiMe$_3$ (**6b**)	p-CH$_3$-C$_6$H$_4$	KN(SiMe$_3$)$_2$, THF	82:18(**4b**)	92
2	CH=CHSiMe$_3$(**6b**)	p-CH$_3$-C$_6$H$_4$	NaN(SiMe$_3$)$_2$,THF	71:29(**4b**)	90
3	CH=CHSiMe$_3$(**6b**)	p-CH$_3$-C$_6$ H$_4$	KN(SiMe$_3$)$_2$, toluene+THF(10:1)	85:15(**4b**)	91
4	CH=CHSiMe$_3$(**6b**)	p-CH$_3$-C$_6$H$_4$	LiBr+NaN(SiMe$_3$)$_2$, toluene+ THF(10:1)	86:14(**4b**)	81
5	CH=CHSiMe$_3$(**6b**)	C$_6$H$_5$	KN(SiMe$_3$)$_2$, toluene+THF(10:1)	92:8(**4c**)	91
6	CH=CHSiMe$_3$(**6b**)	C$_6$H$_{13}$	KN(SiMe$_3$)$_2$, toluene+THF(10:1)	98:2(**4d**)	85
7	CH=CH$_2$(**6a**)	C$_6$H$_5$	LiBr +NaN(SiMe$_3$)$_2$, toluene+THF(10:1)	89:11(**4a**)	74
8	CH=CHCH$_3$(**6c**)	C$_6$H$_5$	LiBr+NaN(SiMe$_3$)$_2$, toluene +THF(10:1)	91:9(**4e**)	87
9	CH=CHPh(**6d**)	C$_6$H$_5$	KN(SiMe$_3$)$_2$, THF	98:2(**4f**)	93
10	Ph(**6e**)	C$_6$H$_5$	LiBr + NaN(SiMe$_3$)$_2$, THF	86:17(**4g**)	82
11	C≡CSiMe$_3$ (**6f**)	d	NaN(SiMe$_3$)$_2$, THF	/ (**4h**)	81

a. The configuration was determined by 300 MHz 1H NMR and ^{1}H-^{1}H NOESY spectra. b. The ratio of stereoisomers was determined by ^{1}H NMR. c. Isolated yields based on esters. d. Substrate is the diethyl isopropylidene malonate.

The possible mechanism for the formation of *trans*-isomers **4** may be similar to that of cyclopropanation between some arsonium[9] or sulfonium[10] ylides and Michael acceptors. And it was described in **Scheme 3**. Ylide **6** reacted with alkylidene malonic esters fastly to afford intermediate **A** and **B** and subsequent elimination furnished the cyclopropane derivatives **4** and **4'** respectively. Obviously, *trans*-isomer

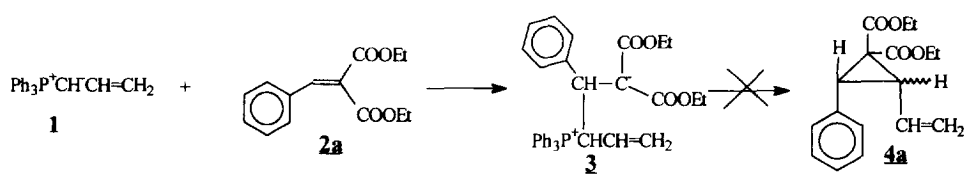
4 was the major product because the intermediate **A** is more stable than intermediate **B** and **A** is difficult to shift to unstable intermediate **B** .

Scheme 3



Although some stabilized sulfonium ylides such as $(CH_3)_2S^+OCH_2^-$ have been described to react readily with alkylidene malonic esters to form cyclopropane derivatives,[11] phosphorus allylide[12] or sulfonium 3,3-dichloroallylide[13] have proven not to be available since the intermediate **3** formed from the addition of ylides to alkylidene malonic esters is too stable to cyclize to form cyclopropane(**Scheme 4**).

Scheme 4



The above-described method demonstrates that allylic and propargylic telluronium ylides are promising reagents for the preparation of vinylcyclopropane 1,1-dicarboxylic ester derivatives. This facile and general method for the synthesis of the vinyl and ethynylcyclopropane 1,1-dicarboxylic esters is expected to be useful in organic synthesis after further transformations.[14]

Experimental Section

Infrared spectra were determined on IR 440 spectrometer. ^{1}H NMR spectra were measured at 300 MHz on AM-300 spectrometer and chemical shifts are reported in units relative to the tetramethylsilane(TMS) signal at 0.00 ppm. MS was determined on Finnigan 4021 spectrometer. HRMS was measured on Finnigan MAT 8430 spectrometer.

All reactions were carried out under N_2. All solvents for the reactions were purified before use. Sodium bis(trimethylsilyl)amide and potassium hydride were purchased from Aldrich and Fluka respectively and were used directly without further purification. Potassium bis(trimethylsilyl)amide and allyldiisobutyltelluronium bromide **5a**, 3-trimethylsilylprop-2-enyldiisobutyltelluronium bromide **5b**, crotyldiisobutyl telluronium bromide **5c**, cinnamyldiisobutyltelluronium bromide **5d**, benzyldiisobutyltelluronium bromide **5e**, and trimethylsilylpropynyldiisobutyltelluronium bromide **5f** were prepared as described in literatures 15 and 16 respectively.

General procedure: A solution of potassium bis(trimethylsilyl) amide (0.75mmol) in THF(0.75ml) was syringed to a solution of telluronium salt(0.75 mmol) in solvent(6.5ml) at -78°C under N_2. The mixture was stirred for 2 min. and a solution of α,β-unsaturated compound (0.5mmol) in solvent (1ml) was added. The reaction mixture was then allowed to warm to room temperature. After the reaction was completed, usual work-up and flash chromatography gave the pure product.

Diethyl *trans*-2-phenyl-3-vinylcyclopropane 1,1-dicarboxylate 4a ^{1}H NMR($CDCl_3$/TMS, 300MHz): 0.91(t, J=7.1Hz, 3H), 1.22(t, J=7.1Hz, 3H), 3.15(t, J=8.0Hz, 1H), 3.38(d, J=8.0Hz, 1H), 3.85(m, 2H), 4.31(m, 2H), 521(dd, J_1=1.0Hz, J_2=10.1Hz, 1H), 5.28(dd, J_1=1.0Hz, J_2=17.1Hz, 1H), 5.54(m, 1H), 7.05(m, 5H). M/Z(EIMS)(rel. intensity): 289(M^++1, 13), 288(M^+, 2), 243(M^+-OEt, 25), 242(M^+-OEt-1, 20), 214(M^+-COOEt+1, 69), 197(38), 196(25), 141(M^+-2xCOOEt+1, 100), 129(46), 128(40), 115(52), 91($PhCH^+$+1, 16), 77(Ph^+, 8). IR /cm^{-1}(neat): 1710(s), 1430(m), 1350(m), 1275(s), 1250(s), 1200(m), 1170(s), 1095(s), 1010(m), 830(m). HRMS for $C_{17}H_{20}O_4$: Found: 288.1316; Calcd. : 288.1362

Diethyl *trans*-2-tolyl-3-(2-trimethylsilylvinyl)cyclopropane 1,1-dicarboxylate 4b ^{1}H NMR(C_6D_6 TMS, 300MHz): 0.02(s, 9H), 0.88(t, J=7.0Hz, 3H), 1.23(t, J = 7.0Hz, 3H), 2.23(s, 3H), 3.12(dd, J_1 =J_2= 7.9Hz, 1H), 3.44(d, J=7.1Hz, 1H), 3.83(q, J= 7.0Hz, 2H), 4.12(q, J= 7.0Hz, 2H), 5.70(dd, J_1= 8.1Hz, J_2= 18..4Hz, 1H), 6.10(d, J=18.4Hz, 1H), 7.08(m, 4H). M/Z(EIMS)(rel. intensity): 374(M^+, 20), 313(M^+-$SiMe_3^+$-1, 29), 310(13), 256(32), 210(22), 183($C_{12}H_{11}Si^+$, 68), 142 ($C_{11}H_{10}^+$, 15), 77($C_6H_5^+$, 7), 73($SiMe_3^+$, 100), 58($SiMe_3^+$, 22). IR ν/cm^{-1}(neat): 2795 (m), 1725(s), 16610(m), 1515(m), 1460(m), 1440(m), 1365(s), 1250(brs, s), 1100(s), 1020(s), 835(s). HRMS for $C_{21}H_{30}O_4Si$: Found: 374.1925. Calcd.: 374.1926.

Diethyl *trans*-2-phenyl-3-(2-trimethylsilylvinyl)cyclopropane 1,1-dicarboxylate 4c ^{1}H NMR ($CDCl_3$ /TMS, 300MHz): 0.01(s, 9H), 0.90(t, J=7.1Hz, 3H), 1.28(t, J=7.2Hz, 3H), 3.10(dd, J_1=8.0Hz, J_2=8.09Hz, 1H), 3.22(d, J=8.0Hz, 1H), 3.89(m, 2H), 4.26(m, 2H), 5.76(dd, J_1=7.94Hz, J_2=18..4Hz, 1H),

6.11(d, J=18.4Hz, 1H), 7.24(m, 5H). M/Z(EIMS)(rel. intensity): 360(M^+, 15), 315(M^+-OEt, 3), 287(M^+-C_3H_9Si, 21), 242(26), 227(20), 169(47), 141(M^+-$C_{11}H_9^+$, 23), 128($C_{10}H_8^+$, 11), 115($C_9H_7^+$, 8), 103 $C_8H_7^+$, 24), 73($SiMe_3^+$, 100), 58($SiMe_3^+$, 8). IR ν/cm^{-1}(neat): 1720(s), 1280(s), 1240(s), 1210(m), 1180(m), 1200(m), 1100(m), 1020(m), 860(s). HRMS for $C_{20}H_{28}OSi$: Found: 360.1752; Calcd.: 360.1748.

Diethyl *trans*-2-n-hexyl-3-(2-trimethylsilylvinyl)cyclopropane 1,1-dicarboxylate 4d ^{1}H NMR ($CDCl_3$/TMS, 300MHz): 0.02(s, 9H), 0.82(t, J=6.9Hz, 3H), 1.31(m, 16H), 1.98(m, 1H), 2.38 (dd, J_1=7.9Hz, J_2=8.0Hz, 1H), 4.15(m, 4H), 5.55(ddd, J_1=0.9Hz, J_2=8.2Hz, J_3= 18.5Hz, 1H), 5.87(d, J=18.5Hz, 1H). M/Z (EIMS)(rel. intensity): 368(M^+, 0.3), 353(M^+-CH_3, 4), 323(M^+-OEt, 7), 295(M^+-$C_3H_9Si^+$, 10), 283(M^+-$C_4H_5O_2$, 10), 141(M^+-$C_6H_{13}^+$, 26), 208(26), 137($C_8H_{13}Si^+$, 10), 103(23), 89($C_6H_{13}^+$, 2), 73($SiMe_3^+$, 100), 58($SiMe_2^+$, 31). IR ν/cm^{-1}(neat): 1720(s), 1610(m), 1460(m), 1361(m), 1285(s), 1260(s), 1200(s), 1135(m), 1095(m), 990(m), 860(s), 840(s). Anal. ($C_{20}H_{36}O_4Si$) Found: C, 65.01, H, 9.96; Calcd.: C, 65.17, H, 9.84.

Diethyl *trans*-2-phenyl-3-propenylcyclopropane 1,1-dicarboxylate 4e ^{1}H NMR($CDCl_3$/TMS, 300MHz) 0.90(t, J=7.2Hz, 3H), 1.30(t, J=7.2Hz, 3H), 1.71(d, J=7.5Hz, 3H), 3.09(dd, J_1=8.1Hz, J_2=8.0Hz, 1H), 3.31(d, J=8.1Hz, 1H), 3.86(m, 2H), 4.29(m, 2H), 5.28(m, 1H), 5.81(m, 1H), 7.24(m, 5H). MS(EIMS) 303(M^++1, 100), 302(M^+, 11), 256(M^+-OEt-1, 62), 229(49), 211(M^+-COOEt, 63), 155(43), 91($PhCH^+$, 4), 77(Ph^+, 3). IR/cm^{-1}(rel. intensity) 1730(s), 1450(m), 1370(m), 1290(m), 1230(s), 1185(s), 1100(s), 1030(m), 965(m), 700(s). Anal.($C_{18}H_{22}O_4$) Found: C, 71.45; H: 7.63; Calcd. : C, 71.50; H, 7.33.

Diethyl *trans*-2-phenyl-3-(2-phenylvinyl)cyclopropane 1,1-dicarboxylate 4f ^{1}H NMR($CDCl_3$ /TMS, 300MHz) 0.86(t, J=7.1Hz, 3H), 1.25(t, J=7.1Hz, 3H), 3.43(dd, J_1=8.0Hz, J_2=8.6Hz, 1H), 3.56(d, J=8.0Hz, 1H), 3.89(m, 2H), 4.21(m, 2H), 6.05(dd, J_1=8.6Hz, J_2=15.3Hz, 1H), 6.29(d, J=1.53Hz, 1H), 7.35(m,10H). MS(EIMS) 365(M^++1, 5), 364(M^+, 7), 318(M^+-OEt-1, 100), 290(M^+-COOEt-1, 80), 217(M^+-2xCOOEt-1, 100), 202(26), 141(7), 115(20), 91($PhCH^+$, 15), 77(Ph^+, 6).IR/cm^{-1}(rel. intensity) 1720(s), 1640(m), 1380(m), 1362(m), 1210(m), 1095(m), 1010(m), 960 (m), 740(m). Anal.($C_{23}H_{24}O_4$) Found: C, 75.62; H, 6.53. Calcd.: C, 75.80; H: 6.64.

Diethyl *trans*-2-phenyl-3-phenylcyclopropane 1,1-dicarboxylate 4g ^{1}H NMR($CDCl_3$/TMS, 300 MHz) 0.91(t, J=7.1Hz, 3H), 1.29(t, J=7.0Hz, 3H), 3.82(s, 2H), 3.95(d, J=7.1Hz, 2H), 4.25(q, J=7.0Hz, 2H), 7.25(m, 10H). MS(EIMS) 339(M^++1, 17), 338(M^+, 2), 292(M^+-OEt-1, 62), 246(63), 203(100), 191(49), 145(7), 91($PhCH^+$+1, 18), 77(Ph^+, 12). IR/cm^{-1}(rel. intensity) 1730(s), 1638(s), 1500(m), 1450(m), 1372(m), 1290(s), 1260(s), 1220(s), 1010(m), 1025(m), 700(s). HRMS for $C_{21}H_{22}O_4$: Found: 338.1552; Calcd.: 338.1518

Diethyl 2, 2-methyl--3-(2-trimethylsilylacetylenyl)cyclopropane 1,1-dicarboxylate 4h ^{1}H NMR ($CDCl_3$/TMS, 300MHz) 0.01(s, 9H), 1.40(m, 12H), 2.33(s, 1H), 4.26(m, 4H).MS(EIMS) 311(M^++1, 4), 310(M^+, 4), 295(M^+-CH_3, 10), 265(M^+-3xCH_3, 17), 237(M^+-$SiMe_3$, 100), 193(16), 147(24), 119(36), 75(Me_3Si^+, 57). IR/cm^{-1}(rel. intensity) 2020(m), 1723(s), 1456(m), 1391(m), 1370(m), 1300(s), 1277(m),

1238(s), 1190(m), 1100(m), 1085(m), 1058(m), 840(s). Anal.($C_{16}H_{26}O_4Si$): Found: C, 61.77; H: 8.43. Calcd.: C, 61.90; H, 8.44.

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12. We found that phenylenemalonic esters disappeared immediately when 1.2eq. phosphorus allylide

was added into 1eq. phenylenemalonic esters in THF at -78°C. And no cyclopropane product was detected when the reaction mixture was allowed to rise at r.t. or reflux.

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