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NEW HETEROCYCLES: 4-METHYL-2*H*-PYRANO[6,5-*f*]CYCLOALKA-[2,1-*b*]2*H*-CHROMEN-2-ONES

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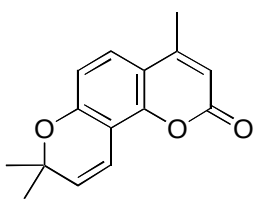
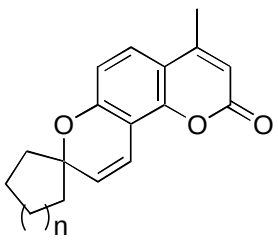
Abstract –A synthesis of the new heterocycles, 4-methyl-2*H*-pyrano[6,5-*f*]cycloalka[2,1-*b*]2*H*-chromen-2-ones (**3**) was described, *via* the unexpected intermediates 2-chloro-1-chloroethenylidenecycloalkanes (**6**) from the reaction of 1-ethynylcycloalkanols with thionyl chloride. The mechanism of some steps was discussed.

INTRODUCTION

4,8,8-Trimethyl-2*H*-pyrano[6,5-*h*]2*H*-chromen-2-one (**1**) was the key intermediate to synthesize 4-methyl-DCK(4-methyl-3',4'-di-O-(-)-camphanoyl-(+)-*cis*-khellactone), which showed excellent anti-HIV activity (EC_{50}=1.57×10^{-7}μM and TI>10^{9}, AZT: EC_{50}=0.15 μM and TI=12500).[1] In our previous initial research works,[2] we had found that the substituents at 8-position might have considerable effects on the anti-HIV activities of this class of compounds. This prompted us to further synthesize the analogs of **1** with different substitutes at 8-position and explore their SAR. Interestingly, when we tried to introduce cycloalkanyl group into the 8-position according to the reported method for synthesizing DCK[3] instead of the desired 4-methylspiro[2*H*-pyrano[6,5-*h*]2*H*-chromene-8,1'-cycloalkan]-2-ones (**2**), a series of new tetracyclic heterocycles, 4-methyl-2*H*-pyrano[6,5-*f*]cycloalka[2,1-*b*]2*H*-chromen-2-ones (**3**) were obtained.



1



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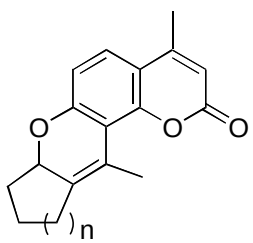
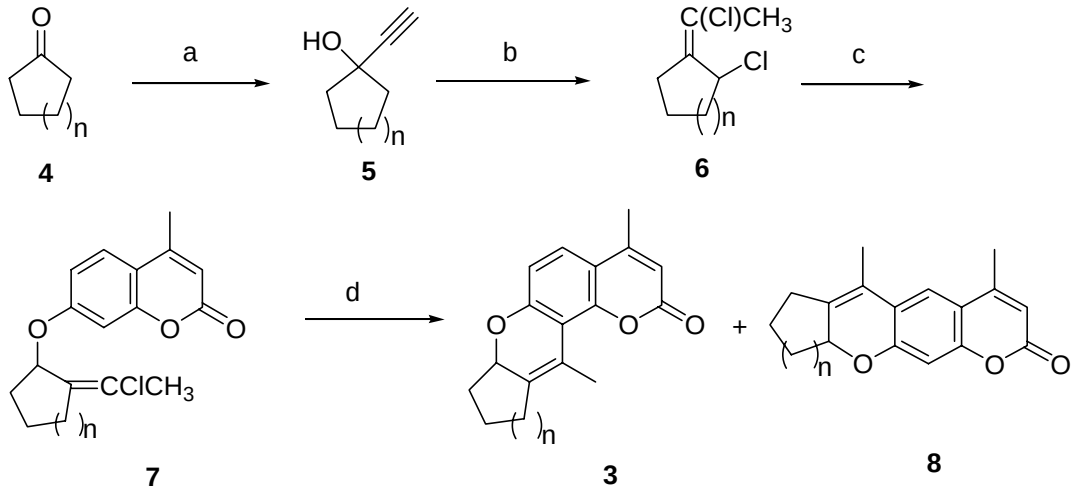


3

In this paper, we will discuss the synthesis and the proposed mechanism for the formation of this new class of heterocycles.

RESULTS



Compounds: a, n=1; b, n=2; c, n=3

a. monopotassium acetylide / THF b. $SOCl_2$ / ether
c. 7-hydroxy- 4-methylcoumarin / K_2CO_3, KI, acetone d. DMF / reflux

Scheme 1

As shown in **Scheme 1**, cyclic ketones (**4**) reacted with monopotassium acetylide to obtain alkynols (**5**), which were transferred further into unexpected chlorination products, 2-chloro-(1-chloroethylidene)cyclo-alkanes (**6**) by treatment with thionyl chloride. Because of difficulty in purification, the structure of **6** was determined by the ^{1}H NMR, MS spectrum, elemental analysis and X-Ray diffraction of its derivative (**7**). As an example, the X-Ray crystal structure of **7a** was showed in **Figure 1**.

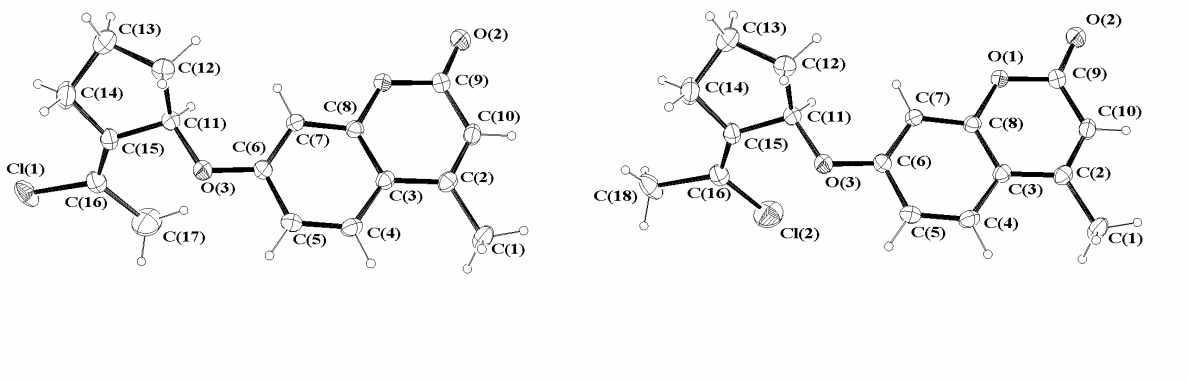
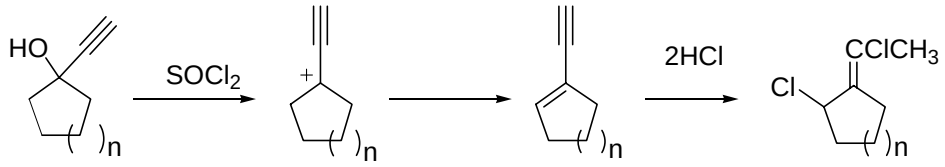


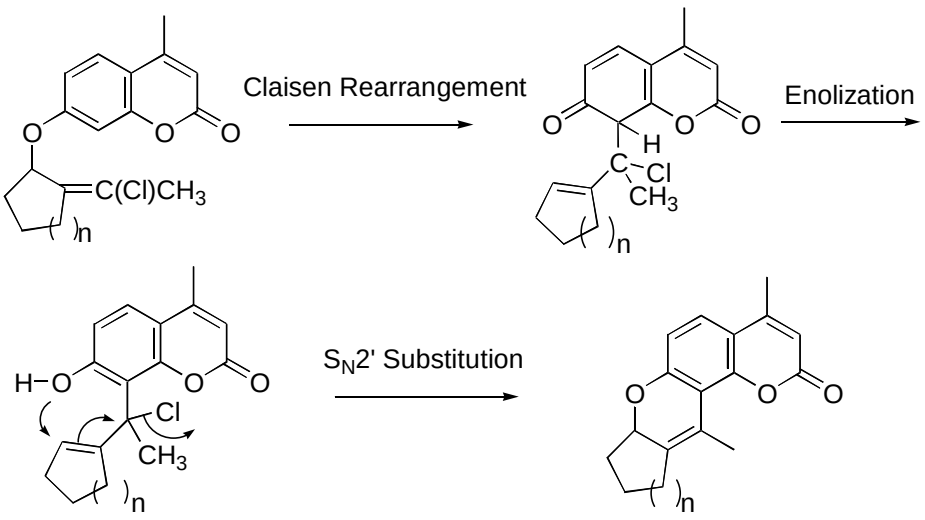
Figure 1:*The X-Ray diffraction of* ***7a****, which was a mixture of Z- and E-configurations.*

Hennion and Lynch Jr. have reported their studies on the chlorination of 1-ethynylcyclohexanol with thionyl chloride and indicated the complication and difficulty to separate the products. By the analysis of IR spectra of the crude distillates they revealed the structures of the more than five kinds of products.[4] However the type of dichloro-product (**6**) was not mentioned. Although the exact mechanism for the formation of **6** was not clear, it seems to proceed *via* elimination and twice addition of HCl, generated *in situ*, to the conjugated enyne (**scheme 2**).



Scheme 2

7-[2-(Chloroethylidene)cycloalkanyloxy]-4-methyl-2*H*-chromen-2-ones (**7**) were refluxed in DMF to give 2*H*-pyrano[6,5-*f*]cycloalka[2,1-*b*]2*H*-chromen-2-ones (**3**) and 2*H*-pyrano[5,6-*g*]cycloalka[2,1-*b*]2*H*-chromen-2-ones (**8**) in a ratio of about 13:1, that indicated the ring closure preferentially occurred at 8-position of coumarin. We proposed the ring closure reaction took place *via* Claisen rearrangement followed by ketone-phenol tautomerization and a S_N2' *O*-alkylation (**Scheme 3**).



Scheme 3

EXPERIMENTAL

General Procedure for Synthesis of 5: Acetylene gas was bubbled into a solution of *t*-BuOK (22.45 g, 0.20 mol) in 200 mL of THF under N_2 at 0 ºC for about 1 h and the reaction mixture became white paste. To the mixture a solution of 0.15 mol of cycloalkanone in 100 mL of THF was added dropwise. The mixture was stirred at 0 ºC for 45 min and warmed up to rt. NH_4Cl was added to adjust the pH to 7. The

mixture was extracted with EtOAc and the organic layer was washed with 40% aq. $NaHSO_3$, water and brine successively. After dried over anhydrous Na_2SO_4, filtered and concentrated, a yellow oil was obtained and solidified gradually at 4 ºC.

1-Ethynylcyclopentanol (5a)

mp 24-26ºC (lit.,[5] 27ºC), 16.50 g (99.9%).

^{1}H-NMR($CDCl_3$, 300 MHz) δ: 2.49 (s, 1H, -C≡C**H**), 2.00 -1.74 (m, 9H, -C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$- and -O**H**); MS *m/z* (%): 109 (M^+-1, 26), 68 [M^+-(OH+C≡CH), 80], 67 [M^+-1-(OH+C≡CH), 82]

1-Ethynylcyclohexanol (5b)

mp 28-31ºC (lit.,[6] 31-33ºC), 18.50 g (99.3%).

^{1}H-NMR($CDCl_3$, 300 MHz) δ: 2.48 (s, 1H, -C≡C**H**), 1.25-2.00 (m, 11H, -C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$- and –O**H**); MS *m/z* (%): 123 (M^+-1, 11), 81 [M^+-1-(OH+C≡CH), 100]

1-Ethynylcycloheptanol (5c)

mp 35-37ºC, n^{25}_D 1.5041 (lit.,[6] n^{20}_D 1.4898), 20.00 g (96.5%).

^{1}H-NMR($CDCl_3$, 300 MHz) δ: 2.48 (s, 1H, -C≡C**H**), 1.58-2.06 (m, 13H, -C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$- and -O**H**); MS *m/z* (%): 137 (M^+-1, 6)

General Procedure for Synthesis of 6: $SOCl_2$ (10.95 mL 0.15 mol) was dropped into a solution of 0.15 mol of 1-ethynylcycloalkanol (**5**) in 30 mL of ether, and the mixture was stirred at rt for 3 h. A colorless liquid was collected *via* vacuum distillation and directly used in next reaction without further purification.

General Procedure for Synthesis of 7: 2-Chloro-(1-chloroethenylidene)cycloalkane (**6**) (51.00 mmol) was added to a mixture of 7-hydroxyl-4-methylcoumarin (5.00 g, 28.38 mmol), K_2CO_3 (50.00 g, 354.75 mmol) and KI (4.70 g, 28.38 mmol) in 340 mL of acetone dropwise and the mixture was refluxed for 65 h under N_2. Filtration and removal of solvent gave an oil residue. Flash column chromatography (Silica H, petroleum: AcOEt=10:1) gave colorless sheet crystals.

7-[2-(Chloroethylidene)cyclopentyloxy]-4-methyl-2*H*-chromen-2-one (7a)

mp 110-111ºC, yield 6.88 g, 79.5%

^{1}H-NMR($CDCl_3$, 300 MHz) δ: 2.12 (s, 3H, =C(Cl)C**H**$_3$), 2.39 (s, 3H, 4-C**H**$_3$), 1.87-2.41 (m, 6H, -C**H**$_2$C**H**$_2$C**H**$_2$-), 5.17 (m, 1H, 2'-C**H**), 6.12-6.15 (m, 1H, 3-H), 6.86-6.93 (m, 2H, 6 and 8-H), 7.48-7.53

(dd, 1H, J_1=9.1 Hz, J_2=2.5 Hz, 5-H); MS *m/z* (%): 305 (M^++1, 100),307 (33); Anal. Calcd for $C_{17}H_{17}O_3Cl$: C, 67.00; H, 5.62; Cl, 11.63; Found: C, 67.12; H, 5.66; Cl, 11.60.

7-[2-(Chloroethylidene)cyclohexyloxy]-4-methyl-2*H*-chromen-2-one (7b)

mp 146-148ºC, yield 6.50 g, 71.8%

^{1}H-NMR($CDCl_3$, 300 MHz) δ: 2.26 (s, 3H, =C(Cl)C**H**$_3$), 2.39 (s, 3H, 4-C**H**$_3$), 1.36-2.87 (m, 8H, -C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$-), 5.23 (m ,1H ,2'-**H**), 6.14 (s, 1H, 3-**H**); 6.77, 6.78 (d, 1H, J=2.5 Hz, 8-**H**); 6.83-6.87 (dd, 1H, J_1=8.8 Hz, J_2=2.5 Hz, 6-**H**); 7.47, 7.50 (d, 1H, J=8.8 Hz, 5-**H**); MS *m/z* (%): 319 (M^++1, 100), 321 (38); Anal. Calcd for $C_{18}H_{19}O_3Cl$: C, 67.82; H, 6.01; Cl, 11.12; Found: C, 67.65; H, 6.23; Cl, 11.16.

7-[2-(Chloroethylidene)cycloheptyloxy]-4-methyl-2*H*-chromen-2-one (7c)

mp 102-104ºC, yield 6.00 g, 63.5%

^{1}H-NMR($CDCl_3$, 300 MHz) δ: 2.22 (s, 3H, =C(Cl)C**H**$_3$), 2.39 (s, 3H, 4-C**H**$_3$), 1.49-2.70 (m, 10H, -C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$-), 5.19 (m, 1H, 2'-**H**), 6.13 (s, 1H, 3-**H**), 6.74, 6.75 (d, 1H, J=2.5 Hz, 8-**H**), 6.81-6.85 (dd, 1H, J_1=8.8 Hz, J_2=2.5 Hz, 6-**H**), 7.47, 7.50 (d, 1H, J=8.8 Hz, 5-**H**); MS *m/z* (%): 333 (M^++1, 100), 335 (36); Anal. Calcd for $C_{19}H_{21}O_3Cl$: C, 68.57; H, 6.36; Cl, 10.65; Found: C, 68.40; H, 6.38; Cl, 10.39.

General Procedure for Synthesis of 3 and 8: **7** (7.87 mmol) was dissolved in 80 mL of DMF and refluxed for 48 h. DMF was removed by vacuum distillation. Compounds (**3**) and (**8**) were obtained *via* column chromatography (petroleum: AcOEt=15:1) in turn.

4,11-Dimethyl-8,9,10,7a-tetrahydro-2*H*-pyrano[6,5-*f*]cyclopenta[2,1-*b*]2*H*-chromen-2-one (3a)

mp 165-167ºC, yield 730 mg, 34.6%

^{1}H-NMR($CDCl_3$ 300 MHz) δ: 2.27 (s, 3H, 11-C**H**$_3$), 2.38 (s, 3H, 4-C**H**$_3$), 1.55-2.65 (m, 6H, -C**H**$_2$C**H**$_2$C**H**$_2$-), 4.76 (m, 1H, 7a-**H**), 6.12 (s, 1H, 3-**H**), 6.83, 6.86 (d, 1H, J=8.6 Hz, 6-**H**), 7.32, 7.35 (d, 1H, J=8.6 Hz, 5-**H**); ^{13}C-NMR($CDCl_3$) δ: 17.432 (11-CH_3), 19.004 (4-CH_3), 21.726, 27.634, 32.580 (-$CH_2CH_2CH_2$-), 79.487 (7a-CH), 111.745 (3-CH), 112.884 (6-CH), 123.586 (5-CH), 114.728, 115.292 (10a,11-C), 121.255 (4-C), 137.806, 150.847, 152.886, 158.185 (C in benzene), 160.784 (2-C); MS *m/z* (%): 268 (M^+, 51), 253 (M^+-CH_3, 100), 240 (M^+-CO, 92); HR-MS: Calcd for $C_{17}H_{16}O_3$ 268.1099, Found 268.1100; Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; Found: C, 75.88; H, 6.02.

4,6-Dimethyl-7,8,9,9a-tetrahydro-2*H*-pyrano[5,6-*g*]cyclopenta[2,1-*b*]2*H*-chromen-2-one (8a)

mp 198-200ºC, yield 56 mg, 2.7%

^{1}H-NMR($CDCl_3$, 300 MHz) δ: 1.68-2.57 (m×4, 6H, 7,8,9-C**H**$_2$), 1.96 (s, 3H, 6-C**H**$_3$), 2.41 (s, 3H, 4-C**H**$_3$), 4.91 (m, 1H, 9a-**H**), 6.13 (s, 1H, 3-**H**), 6.79 (s, 1H, 11-**H**), 7.25 (s, 1H, 5-**H**); MS *m/z* (%): 268 (M^+, 50), 253 (M^+-CH_3, 70), 240 (M^+-CO, 100); Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01; Found: C, 76.33; H, 5.98.

4,12-Dimethyl-8,9,10,11,7a-pentahydro-2*H*-pyrano[6,5-*f*]cyclohexa[2,1-*b*]2*H*-chromen-2-one (3b)

mp 169-170ºC, yield 575 mg, 25.9%

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.35 (s, 3H, 12-C**H**$_3$), 2.38 (s, 3H, 4-C**H**$_3$), 1.26-3.00 (m, 8H, -C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$-), 4.69 (m, 1H, 7a-**H**), 6.11 (s, 1H, 3-**H**), 6.74, 6.76 (d, 1H, J=8.7 Hz, 6-**H**), 7.31, 7.33 (d, 1H, J=8.7 Hz, 5-**H**); MS *m/z* (%): 282 (M^+, 77), 267 (M^+-CH_3, 44), 253 (M^+-1-CO, 100); HR-MS: Calcd for $C_{18}H_{18}O_3$ 282.1256, Found 282.1239; Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.34; H, 6.40.

4,6-Dimethyl-7,8,9,10,10a-pentahydro-2*H*-pyrano[5,6-*g*]cyclohexa[2,1-*b*]2*H*-chromen-2-one (8b)

mp 196-198ºC, yield 36 mg, 1.6%

^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.25-1.93 (m×4, 6H, 8,9,10-C**H**$_2$), 2.19-2.20, 2.87-2.91 (m×2, 2H, 7-C**H**$_2$), 2.00 (s, 3H, 6-C**H**$_3$), 2.39 (s, 3H, 4-C**H**$_3$), 4.89-4.90 (m, 1H, 10a-**H**), 6.09 (s, 1H, 3-**H**), 6.64 (s, 1H, 12-**H**), 7.19 (s, 1H, 5-**H**); MS *m/z* (%): 282 (M^+, 26), 267 (M^+-CH_3, 27), 253 (M^+-1-CO, 100); Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.46; H, 6.40.

4,13-Dimethyl-8,9,10,11,12,7a-hexahydro-2*H*-pyrano[6,5-*f*]cyclohepta[2,1-*b*]2*H*-chromen-2-one (3c)

mp 150-152ºC, yield 532 mg, 22.82%

^{1}H-NMR($CDCl_3$, 500 MHz) δ: 2.30 (s, 3H, 13-C**H**$_3$), 2.39 (s, 3H, 4-C**H**$_3$), 1.57-2.70 (m, 10H, -C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$-), 4.66 (m, 1H, 7a-**H**), 6.13 (s, 1H, 3-**H**), 6.82, 6.84 (d, 1H, J=8.6 Hz, 6-**H**), 7.34, 7.35 (d, 1H, J=8.6 Hz, 5-**H**); MS *m/z* (%): 296 (M^+, 30), 281 (M^+-CH_3, 18), 253 (100); HR-MS: Calcd for $C_{19}H_{20}O_3$ 296.1412, Found 296.1406; Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; Found: C, 77.16; H, 6.94.

4,6-Dimethyl-7,8,9,10,11,11a-hexahydro-2*H*-pyrano[5,6-*g*]cyclohepta[2,1-*b*]2*H*-chromen-2-one (8c)

mp 206-210ºC, yield 46 mg, 1.98%

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.88-2.66 (m, 10H, 7,8,9,10,11-C**H**$_2$), 2.04 (s, 3H, 6-C**H**$_3$), 2.41 (d, 3H, J=1.1 Hz, 4-C**H**$_3$), 4.86 (m, 1H, 11a-**H**), 6.11 (d, 1H, J=1.1 Hz, 3-**H**), 6.74 (s, 1H, 13-**H**), 7.27 (s, 1H, 5-

H); MS m/z (%): 296 (M^+, 14), 281 (M^+-CH_3, 9); Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; Found: C, 76.82; H, 6.83.

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