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Heteropoly metallophosphoric acid-catalyzed Prins-type cyclizations in the synthesis of functionalized 8-oxabicyclo[5.4.0]undecanes

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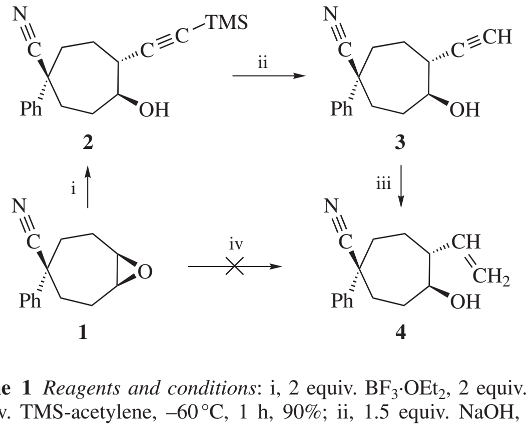
Heteropoly metallophosphoric acid-catalyzed microwave-assisted Prins cyclizations of 4-cyano-4-phenyl-7-vinylcycloheptanol with carbonyl compounds affords functionalized 8-oxabicyclo[5.4.0]undecanes in good yields and with high stereoselectivity.

Synthesis of diastereo- and enantiomerically pure tetrahydropyran derivatives from readily available starting materials[1] is topical since mono- and polycyclic compounds containing tetrahydropyran structural subunit are common components of natural products and their analogues which possess biological activities.[2]

The Prins cyclization of homoallylic alcohols with carbonyl compounds under acidic conditions is one of the most efficient means to create tetrahydropyran core.[3,4] Many types of Lewis acids have been used in the Prins cyclization, but there are only a few interesting examples of oxygenated nucleophiles incorporated in the resulting tetrahydropyran cycle, including OAc from $BF_3\cdot OEt_2$/AcOH/TMSOAc catalytic system[5] and OH indirectly from trifluoroacetic acid[6] and heteropoly metal acid salts.[7] Although a large number of versions and modifications of the Prins cyclization have been developed, it still remains strongly substrate dependent.[3]

Previously,[8] we reported preparation of diastereomerically pure epoxycycloheptanecarbonitrile **1**. Herein we describe its conversion into the homoallylic alcohol and its further utilization in the Prins cyclization leading to new polycyclic tetrahydropyran derivatives.



Scheme 1 *Reagents and conditions*: i, 2 equiv. $BF_3\cdot OEt_2$, 2 equiv. BuLi, 1 equiv. TMS-acetylene, –60 °C, 1 h, 90%; ii, 1.5 equiv. NaOH, EtOH, 20 °C, 3 h, 100%; iii, ethyl acetate, Lindlar catalyst, H_2 (1 atm.), 20 °C, 8 h, then 20 °C, 100%; iv, conditions similar to those in ref. 9.

Attempted access to compound **4** by epoxide ring opening with vinyl cuprates[9] under mild conditions was unsuccessful and led to mixtures of the target product **4** with undetectable byproducts. To alleviate this problem, we focused on epoxide opening with acetylene derivatives followed by partial catalytic hydrogenation[10] of formed triple bond of compound **3**. However, reaction of epoxide **1** with commercially available lithium acetylide–ethylenediamine complex in DMSO at different temperatures[11] was non-reproducible and afforded homopropargylic alcohol derivative **3** in moderate to low yields. Luckily, use of lithium TMS-acetylide in the presence of $BF_3\cdot OEt_2$ in THF for the ring opening of epoxide **1** under reduced temperature conditions[12] gave compound **2** in practically quantitative yield. Mild desilylation of **2** with slight excess of NaOH in methanol at room temperature[13] resulted in the desired **3**. Further partial reduction of its triple bond quantitatively afforded key intermediate **4** (Scheme 1),[†] which was accomplished by the Lindlar hydrogenation[14] in ethyl acetate.[15]

The Prins–Ritter cyclization of enol **4** and benzaldehyde **5a**, acetone **5b** or 1N-(cbz)-4-piperidone **5c** was initially performed with chlorosulfonic acid in acetonitrile (this solvent was trapped by the formed tetrahydropyranyl carbocation).[16] LC/MS monitoring showed the presence of diastereomers **6a**,**b** when the reaction was performed at room temperature. Cyclization at much lower temperature allowed us to obtain pure diastereomers **6a**,**b** in good yields (Scheme 2).[‡] In the case of **5c**, only single spiro diastereomer **6e** was isolated in moderate yield. The relative stereochemistry of compounds **6a**,**b**,**e** was determined from 2D ^{1}H NMR experiments.

We commenced our studies of the Prins cyclization (Scheme 2 and Table 1) by examining the reaction of intermediate **4** with carbonyl compounds **5a–c** in the presence of the $BF_3\cdot OEt_2$/AcOH/TMSOAc catalytic system. At different temperatures, and irrespective of equivalents of catalytic system used, no target

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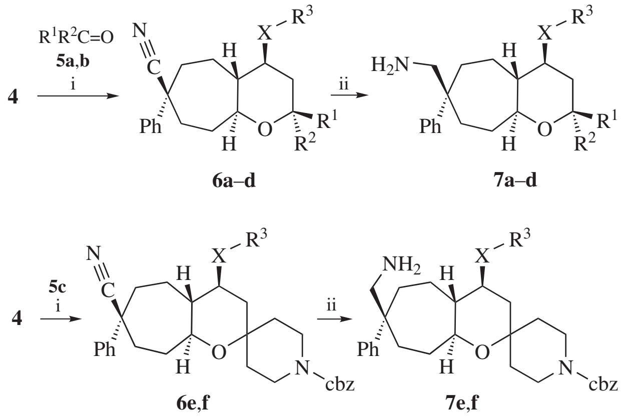
[†] For synthesis and characteristics of compounds **2**–**4**, see Online Supplementary Materials.

[‡] *Compounds* **6a**,**b**,**e** *(general procedure)*. Chlorosulfonic acid (1.5 ml, 22 mmol) was added dropwise to a vigorously stirred solution of compound **4** (4.8 g, 20 mmol) and carbonyl compound **5a**–**c** (22 mmol) in dry MeCN (70 ml) at –40 °C under inert atmosphere. The rusulting mixture was stirred over 1 h at this temperature and allowed to warm to room temperature. Then, 10 wt% K_2CO_3 water solution (300 ml) was added and the mixture was stirred vigorously over 0.5 h. The organic layer was separated and the water layer was extracted with DCM (2×200 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (eluent, ethyl acetate) to give compounds **6a**,**b**,**e**, respectively.

11-Acetylamino-4,9-diphenyl-8-oxabicyclo[5.4.0]undecane-4-carbonitrile **6a**: yield 5.6 g (72%), white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: –1.30 (m, 2H), 1.50 (m, 1H), 1.75 (m, 3H), 1.85 (m, 1H), 2.00 (m, 3H), 2.10 (m, 1H), 2.25 (m, 2H), 2.40 (m, 1H), 3.50 (ddd, 1H, *J* 9.7, 6.6 and 4.9 Hz), 3.75 (tdd, 1H, *J* 12.0, 8.7 and 4.2 Hz), 4.51 (d, 1H, *J* 7.5 Hz), 7.25 (m, 1H), 7.28 (m, 5H), 7.38 (t, 2H, *J* 8.5 Hz), 7.50 (d, 2H, *J* 8.5 Hz), 7.75 (d, 1H, *J* 5.0 Hz). MS, *m/z*: 389.4 [M+H]$^+$. Found (%): C, 77.28; H, 7.30; N, 7.35. Calc. for $C_{25}H_{28}N_2O_2$ (%): C, 77.29; H, 7.26; N, 7.21.

For characteristics of compounds **6b**,**e** see Online Supplementary Materials.



5a $R^1 = Ph, R^2 = H$
5b $R^1 = R^2 = Me$
5c $R^1 + R^2 = (CH_2)_2N(cbz)(CH_2)_2$

6,**7** **a** $R^1 = Ph, R^2 = H, R^3 = Ac, X = NH$
b $R^1 = R^2 = Me, R^3 = Ac, X = NH$
c $R^1 = Ph, R^2 = H, R^3 = H, X = O$
d $R^1 = R^2 = Me, R^3 = H, X = O$
e $R^3 = Ac, X = NH$
f $R^3 = H, X = O$

Scheme 2 *Reagents and conditions*: i, see Table 1; ii, Raney-Ni, MeOH/NH_3, H_2 (2–3 atm.), 20 °C, 18 h, ~100%.

tetrahydropyran products were obtained, whereas decomposition of the starting material **4** occurred. The use of trifluoroacetic acid in DCM provided compound **6c** in a low yield. The **4** + **5b** cyclization under TFA-catalytic conditions gave product **6d** in a very low yield. In the meantime, on using catalytic amounts of heteropoly acids $H_3PMo_{12}O_{40}$ or $H_3PW_{12}O_{40}$ under reflux conditions products **6c**,**d** were formed in moderate yields.[§] These yields were significantly raised by conducting the cyclization under microwave irradiation at 120–140 °C in a water–dioxane media. Also, molybdophosphoric acid provided better results than its tungsten analogue (see Table 1). Unfortunately, ketone **5c** on using heteropoly acids gave compound **6f** in trace amounts only. The structure and configuration of products **6c**,**d** was confirmed by 2D ^{1}H NMR experiments.

The further transformation of nitrile groups in compounds **6a**–**e** is a simple access to a variety of versatile 4-hydroxy tetrahydropyranyl containing bicyclo[5.4.0]undecane derivatives building blocks.[17] Both acidic and basic hydrolyses were attempted to obtain the corresponding carboxylic acids, but only complex mixtures of unidentified compounds were obtained. Mild catalytic hydrogenation of nitrile group in compounds **6a**–**e** in the presence of Raney nickel and ammonia in methanol[18] led to the corresponding amino derivatives **7a**–**e** in quantitative yields.

In summary, novel tetrahydropyran derivatives of 8-oxabicyclo[5.4.0]undecane family were synthesized in good yields using simple procedures. The key Prins cyclization diastereoselectively occurred in the presence of heteropoly metallophosphoric acids under the microwave irradiation.

Table 1 Conditions of Prins–Ritter and Prins cyclizations of compound **4**.

Reactants (1.5 equiv.)	Conditions/catalytic system	*T*/°C	*t*/h	Product	Overall yield (%)
5a,**b**	1.1 equiv. $ClSO_3H$/THF	0–20	3–4	**6a** **6b**	– –
5a–**c**	1.1 equiv. $ClSO_3H$/THF	–40	3–4	**6a** **6b** **6e**	72 65 60
	6.0 equiv. TFA/DCM	20–40	6–7	**6c** **6d** **6f**	25 12 –
	$H_3PMo_{12}O_{40}$ (5.0 mol%)/ H_2O–dioxane (5:2)	~100	36–48	**6c** **6d** **6f**	42 40 –
	$H_3PW_{12}O_{40}$ (5.0 mol%)/ H_2O–dioxane (5:2)	~100	36–48	**6c** **6d** **6f**	37 35 –
	$H_3PMo_{12}O_{40}$ (3.0 mol%)/ H_2O–dioxane (5:2)/ microwave irradiation	120	2	**6c** **6d** **6f**	75 68 –
	$H_3PW_{12}O_{40}$ (3.0 mol%)/ H_2O–dioxane (5:2)/ microwave irradiation	140	3	**6c** **6d** **6f**	70 63 traces

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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.2015.09.022.

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[§] *Compounds* **6c**,**d** *(general procedure)*. A suspension of compound **4** (4.8 g, 20 mmol), carbonyl compound **5a**,**b** (22 mmol) and heteropoly molybdophosphoric acid $H_3PMo_{12}O_{40}$ (1.1 g, 0.6 mmol) in water–dioxane mixture (5 : 2, 20 ml) was heated under microwave irradiation at 130 °C over 3 h. Then, the reaction mixture was diluted with DCM (250 ml) and washed with brine (150 ml). The organic layer was filtered through the pad of celite and dried over Na_2SO_4. The solvents were removed under reduced pressure. A residue was purified by flash chromatography on silica gel (eluent, ethyl acetate) to give compounds **6c**,**d**, respectively.

11-Hydroxy-4,9-diphenyl-8-oxabicyclo[5.4.0]undecane-4-carbonitrile **6c**: yield 5.2 g (75%), white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: –1.25 (m, 1H), 1.37 (m, 2H), 2.00 (m, 2H), 2.05 (m, 2H), 2.25 (m, 2H), 2.30 (m, 1H), 2.45 (m, 1H), 3.50 (m, 2H), 4.50 (dd, 1H, *J* 12.0 and 4.0 Hz), 4.75 (d, 1H, *J* 5.0 Hz), 7.25 (m, 1H), 7.32 (m, 5H), 7.40 (t, 2H, *J* 8.5 Hz), 7.52 (d, 2H, *J* 8.5 Hz). MS, m/z: 348.1 $[M+H]^+$. Found (%): C, 79.53; H, 7.23; N, 4.17. Calc. for $C_{23}H_{25}NO_2$ (%): C, 79.51; H, 7.25; N, 4.03.

For characteristics of compound **6d**, and for synthesis and characteristics of compounds **7a**–**e**, see Online Supplementary Materials.