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PRINS REACTION USING TRIOXANE FOR TRISUBSTITUTED, *cis*-FUSED HEXAHYDRO-2*H*-FURO[3,2-*b*]PYRAN DERIVATIVE

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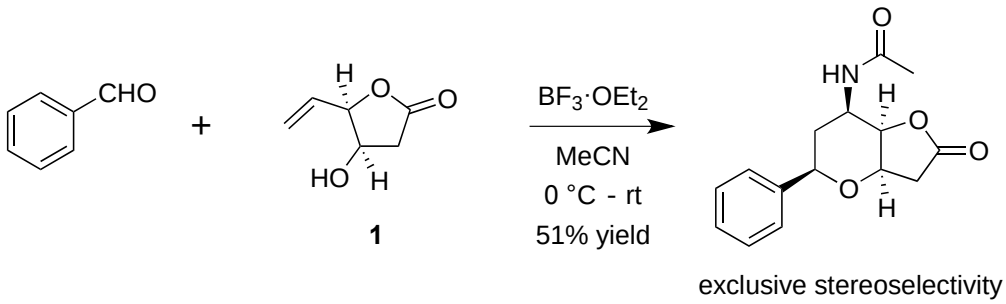
Abstract – The construction of *cis*-fused heterobicyclic system involved in neuroactive natural products such as dysiherbaine has been accomplished by employing Prins strategy using 1,3,5–trioxane as an equivalent for formaldehyde. The reactions allowed stereoselective construction of the trisubstituted *cis*-fused hexahydro-2*H*-furo[3,2-*b*]pyran with maximum yield of 60%.

The tetrahydropyrans are crucial class of ring system that exist as constituents in many bioactive natural products.[1] They play significant role as critical parts of structures in drug discovery and research.[1,2] In our laboratory we have been specially paying attention to the *cis*-fused heterobicyclic system that can be found in neuronally active agents such as dysiherbaine.[3]

It has been noted that the reaction of homoallylic alcohols with aldehyde in the presence of acid catalyst produces a lots of tetrahydropyran derivatives.[2] This reaction is known as Prins cyclization.[4] It has also been recognized that the rate of Prins cyclization relies on the type of aldehyde used; the reaction proceeds smoothly with cinnamaldehyde in comparison with benzaldehyde or acrolein.[2,3] It has been predicted, however, that Prins cyclization would be challenging using formaldehyde or the equivalents to assemble tetrahydropyran structure.[5]

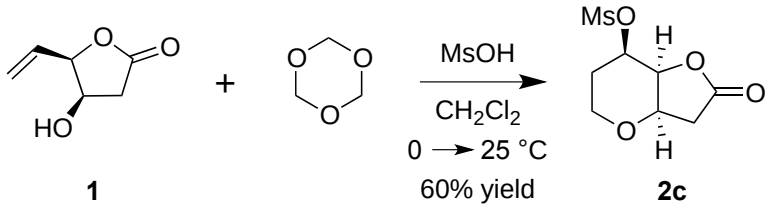
Stereoselectivity in Prins cyclization has been also of interest. Although Prins cyclization leading to trisubstituted *cis*-fused hexahydro-2*H*-furo[3,2-*b*]pyran derivatives (*cis*-fused THP derivatives) had not been well explored and the stereochemical course could not be predicted until recently, in 2002, Alder et al. had described the theoretical examination for this type of transformation,[6] and stereoselective Prins cyclization of homoallylic alcohol for trisubstituted *cis*-fused THP derivatives was thereafter disclosed in

2010.[7] Cheered by that work, in 2016, our group examined Prins-Ritter reaction for *cis*-fused cyclic ethers and found that the stereochemistry can be controlled efficiently (Scheme 1).[3]



Scheme 1. Our previous Prins-Ritter reaction of homoallylic alcohol **1** leading to *cis*-fused tetrahydropyran[3]

Emboldened by the results, in this work, we decided to study the more challenging synthesis of trisubstituted *cis*-fused THP derivatives by Prins strategy using some equivalents for formaldehyde. Here, we report our efforts along this line toward discovery of the combination of 1,3,5-trioxane and methanesulfonic acid (MsOH), that stereoselectively gives functionalized tetrahydropyran **2c** (Scheme 2).



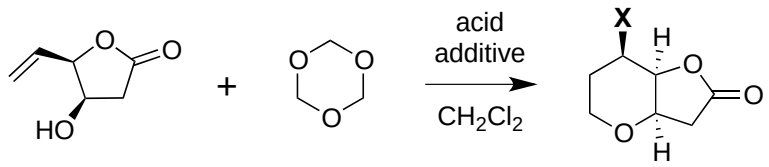
Scheme 2. Prins cyclization of 1,3,5-trioxane with homoallylic alcohol **1** (this work)

Homoallylic alcohol **1** was synthesized in 2 steps from D-gluconolactone, according to the reported procedure (results not shown).[8] In this study, we utilized various Brønsted and Lewis acids such as trifluoroacetic acid (TFA),[9] $AlCl_3$,[10] *p*-toluenesulfonic acid (TsOH),[11] and MsOH[12] for Prins cyclization (Table 1). In general, the reaction was conducted by addition of acid (3 equiv) and additive (3 equiv) to the mixture of the substrate **1** (1 equiv) and 1,3,5-trioxane (2 equiv) in CH_2Cl_2 (procedure **A**).

Initially, using TFA (entries 1 and 2)[9] and $AlCl_3$ (entry 3),[10] we observed no reaction but some decompositions. We also observed no reaction under conditions employing iodine reported by Yadav (entry 4).[7] Gratifyingly, however, Prins reaction product was detected by procedure **B**, where acid alone was first mixed with 1,3,5-trioxane before the addition of substrate **1** (entry 5). When TsOH was used (entry 6, procedure **A**),[11] Prins product was obtained in low yield (20%) comparable to that in entry 5. In entries 5 and 6, the products were obtained as the mixture with other unidentified products, and hence, the

structures were not well characterized. Inspired by the outcome, we tested MsOH which allowed more encouraging yield (entry 7). Here, the Prins product was cleanly isolated by silica-gel column chromatography as colorless crystals. The *cis*-fused tetrahydropyran structure was characterized using NMR spectroscopy and X-ray crystallographic analysis (Figure 1). Absolute configuration of **2c** has been determined based on the Flack parameter (0.08(4)) obtained from the single crystal X-ray diffraction measurement at 183 K.[13]

Table 1. Prins reaction of homoallylic alcohol **1** with 1,3,5-trioxane mediated by various acids and additives



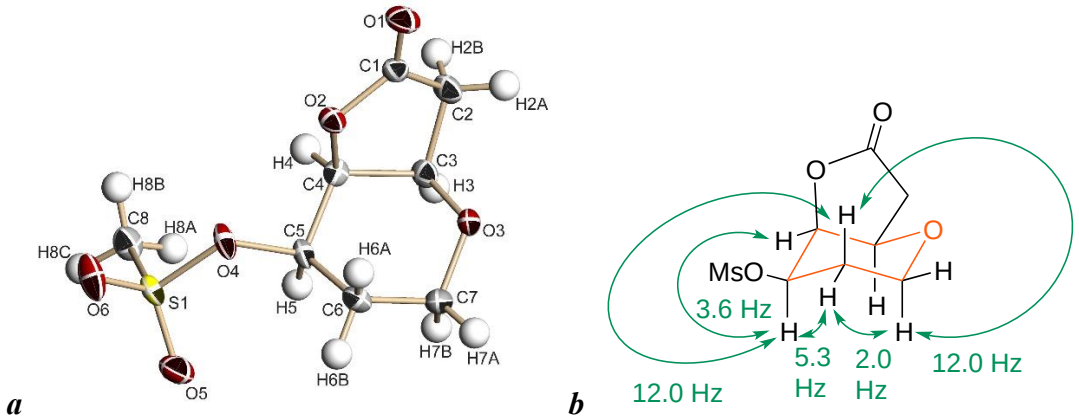
1

2a (**X** = Cl)
2b (**X** = OTs)
2c (**X** = OMs)

entry[a]	acid	additive	procedure[b]	temp. (˚C)	time (h)	**X**	yield (%)[c]
1	TFA	-	**A**	25	7	OTFA	0
2	TFA	NaI[14]	**A**	40	24	OTFA	0
3	$AlCl_3$	TMSCl[10]	**A**	25	24	Cl	0
4	-	I_2[7]	**A**	25	19	I	0
5	$AlCl_3$[12]	-	**B**	25	4	Cl	16[d]
6[e]	TsOH[11]	-	**A**	60	4	OTs	20[d]
7	MsOH[12]	-	**A**	25	8	OMs	39
8	MsOH	I_2	**A**	25	2	OMs	41
9	MsOH	I_2	**A**	25	19	OMs	43
10	MsOH	I_2	**A**	0	23	OMs	45
11	MsOH	NaI[14]	**A**	40	22	OMs	20
12	MsOH	-	**B**	25	12	OMs	51
13	MsOH	-	**B**	0	45	OMs	54
14[f]	MsOH	-	**B**	0 ⟶ 25	15	OMs	60

[a]Unless otherwise noted, 0.2 mmol of **1** was used. [b]Procedure **A**: Acid, 1,3,5-trioxane, and substrate **1** mixed all at once; Procedure **B**: Acid mixed with 1,3,5-trioxane for 30 min at rt before addition of substrate **1**. [c]Yield determined after column chromatography. [d]Yield determined by ^{1}H NMR analysis of the crude product. [e]Chlorobenzene was used for a solvent. [f]Large-scale synthesis with 1 g of **1**.

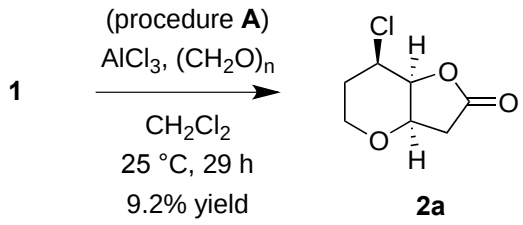
As a pursuit to enhance the yield, iodine was added and the yield augmented only marginally (entries 8-10). It should be noted that the reaction well proceeds at 0 °C (entry 10). Addition of NaI declined the yield to 20% even at elevated temperature (entry 11).[14] To further improve the yield, we have applied inverse mode of addition (procedure **B**), and the positive effect was obviously observed (entry 12). Finally, the procedure **B** at lower temperature gave the outstanding yield of 54% (entry 13). Gram-scale reaction was also found to proceed in 60% yield with exclusive stereoselectivity (entry 14), showing the possible value of the product **2c** for a building block or a precursor for more complex *cis*-fused THP derivatives such as dysiherbaine,[15] the potent agonist for ionotropic glutamate receptor. Further struggles (for instance, longer reaction time or the use of large excess of reagents) to enhance the yield were fruitless.



a ORTEP representation drawn at 50% probability level for the ellipsoid obtained from single crystal X-ray diffraction measurement at 183 K. ***b*** *J* coupling analysis (400 MHz, $CDCl_3$)

Figure 1. Structural analysis of the Prins product **2c**

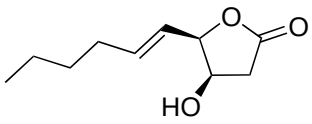
In all entries, neither starting material **1** nor other products with definitive structure were isolated, and our continuing efforts are currently directed towards higher yield of Prins product **2**. Nevertheless, however, the reactions solely allowed construction of the trisubstituted *cis*-fused THP derivatives which is not readily accessible by other means.[2]



Scheme 3. Prins cyclization of paraformaldehyde[5] with homoallylic alcohol **1**

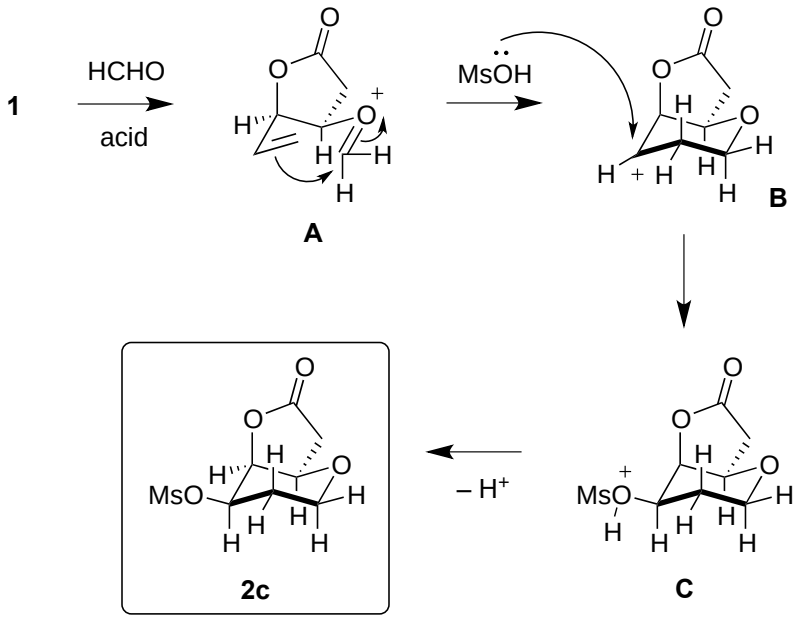
It should be also noted that replacing 1,3,5-trioxane with paraformaldehyde afforded only a trace amount of tetrahydropyran **2a** as shown in Scheme 3, indicating poor reactivity of paraformaldehyde under these reaction conditions.[5]

We also studied disubstituted alkene **3** for the Prins reaction (Figure 2). To our disappointment, however, messy products mixture was only obtained under the optimized conditions shown in Table 1 (entry 14).



3

Figure 2



Scheme 4. A probable reaction mechanism[2,3,6]

Mechanistically (Scheme 4), the reaction is obviously mediated by formaldehyde, generated by 1,3,5-trioxane and MsOH, from the observation that the yield was improved in the procedure **B** where homoallylic alcohol **1** was added to the premixed solution of 1,3,5-trioxane and MsOH. Then, MsOH-mediated condensation of homoallylic alcohol **1** and formaldehyde would generate oxocarbenium ion **A**,[2] which automatically reacts via chair-like six-membered fashion of cyclization to form carbocation **B**. Cation **B** then endures intermolecular nucleophilic attack by MsOH from the equatorial face of the pseudochair tetrahydropyran ring to furnish **2** after deprotonation of cation **C**.[3,16]

In conclusion, we have studied Prins reaction leading to *cis*-fused THP derivatives, with homoallylic

alcohol **1** and unreactive formaldehyde equivalents mediated by various acids. As a result, we achieved the construction of *cis*-fused THP derivative motif in 60% yield characteristically found in neuroactive natural products such as dysiherbaine. The reaction was found to proceed with exclusive *cis*-diastereoselectivity. Thus, Prins reaction using 1,3,5-trioxane for trisubstituted *cis*-fused THP derivatives is anticipated to serve as a general methodology using other homoallylic alcohols for synthesis of tetrahydropyran motifs which are otherwise not readily accessible.[3]

EXPERIMENTAL

General methods

All reagents were purchased at the highest commercial grade and used directly. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 plate (0.25-mm thickness). Flash column chromatography was carried out using Merck silica gel 60N (100-210 mesh) or Fuji Silicia silica gel BW-300 (200-400 mesh), unless otherwise stated. Specific rotation $[\alpha]_D$ were recorded on a JASCO P-1030 polarimeter. IR spectra were recorded on a JASCO FT/IR-400 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE 400 spectrometer. Chemical shift values are reported in δ (ppm) with reference to internal residual solvent [^{1}H NMR, $CDCl_3$ (7.24); ^{13}C NMR, $CDCl_3$ (77.0)]. Coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations were used to designate the multiplicities; s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, dddd = double double double doublet, m = multiplet, br = broad. ESI-TOF mass spectra were measured with a Sciex TripleTOF5600 spectrometer.

Procedure for the synthesis of 2c. To a stirred solution of 1,3,5-trioxane (1.40 g, 15.6 mmol) and MsOH (1.49 mL, 23.4 mmol) in CH_2Cl_2 (111 mL) at rt for 1 h was added homoallylic alcohol **1** (1.00 g, 7.80 mmol) at 0 °C. After stirring at rt for 13 h, the mixture was diluted with EtOAc (20 mL) and poured into water (10 mL). Organic layer was separated and aqueous layer was extracted with EtOAc (3 × 20 mL). Combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (BW-300, EtOAc/Et_2O = 1:9) to give **2c** (1.11 g, 60.2%) as colorless crystals: Mp 143–145 °C; $[\alpha]_D^{19.5}$ -31.86 (*c* 0.14, MeOH); IR (neat) 3024, 2933, 2869, 1786, 1355, 1171, 960 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (ddd, *J* = 12.1, 5.3, 3.6 Hz, 1H), 4.62 (m, 1H), 4.31 (m, 1H), 3.98 (ddd, *J* = 12.2, 4.4, 2.3 Hz, 1H), 3.48 (ddd, *J* = 12.0, 12.0, 2.0 Hz, 1H), 3.09 (s, 3H), 2.67 (dd, *J* = 18.0, 4.8 Hz, 1H), 2.55 (d, *J* = 18.0 Hz, 1H), 2.16 (dddd, *J* = 12.5, 12.5, 12.5, 4.2 Hz, 1H), 1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 76.8, 74.0, 73.7, 64.1, 39.2, 38.1, 26.4; HRMS (ESI) Calcd for $C_8H_{12}O_6SNa$ $[M+Na]^+$ 259.0248. Found 259.0242.

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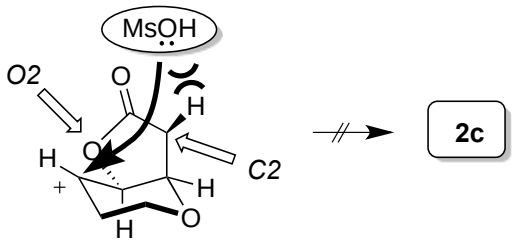
REFERENCES AND NOTES

1. U. Biermann, A. Lützen, and J. O. Metzger, *Eur. J. Org. Chem.*, 2006, 2631.
2. B. V. S. Reddy, D. N. Chaya, J. S. Yadav, D. Chatterjee, and A. C. Kunwar, *Tetrahedron Lett.*, 2011, **52**, 2961.
3. M. Chiba, Y. Ishikawa, R. Sakai, and M. Oikawa, *ACS Comb. Sci.*, 2016, **18**, 399.
4. H. J. Prins, *Chem. Weekblad*, 1919, **16**, 1072.
5. For successful example, see; J. O. Metzger and U. Biermann, *Bull. Soc. Chim. Belg.*, 1994, **103**, 393.
6. R. W. Alder, J. N. Harvey, and M. T. Oakley, *J. Am. Chem. Soc.*, 2002, **124**, 4960.
7. J. S. Yadav, B. V. S. Reddy, A. P. Singh, D. N. Chaya, D. Chatterjee, and A. C. Kunwar, *Tetrahedron Lett.*, 2010, **51**, 1475.
8. R. A. Fernandes and P. Kattanguru, *Asian J. Org. Chem.*, 2013, **2**, 74.
9. J. de Vicente, P. Tivitmahaisoon, P. Berry, D. R. Bolin, D. Carvajal, W. He, K.-S. Huang, C. Janson, L. Liang, C. Lukacs, A. Petersen, H. Qian, L. Yi, Y. Zhuang, and J. C. Hermann, *ACS Med. Chem. Lett.*, 2015, **6**, 1019.
10. G.-Q. Liu, B. Cui, R. Xu, and Y.-M. Li, *J. Org. Chem.*, 2016, **81**, 5144.
11. K. Harada, S. Nishino, H. Shima, M. Nishimura, and K. Hirotsu, 2001, WO2001042232A1.
12. J. Jaśkowska, K. Chorabik, and Z. Majka, *Technical Transactions*, 2015, **1**, 29.
13. Crystal data of **2c** at 183 K: Monoclinic, $P2_1$, a = 5.4916(9) Å, b = 8.1129(13) Å, c = 11.8188(19) Å, α = 90°, β = 98.559(2)°, γ = 90°, V = 520.70(15) Å^3, Z = 2, D_{calc} = 1.500 Mg m^{-3}, R_1 = 0.0618 (0.0622), wR_2 = 0.1529 (0.1557) for 1981 reflections with $I > 2\sigma(I)$ (for 2018 reflections (2687 total measured)), goodness-of-fit on F^2 = 0.759, largest diff. peak (hole) = 0.950 (-1.276) e Å^{-3}, absolute structure parameter = 0.08(4). Deposition number CCDC-1821749 for compound **2c**. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
14. S. Nishino, K. Hirotsu, and H. Shima, 2007, JP2007161628A.
15. R. Sakai, H. Kamiya, M. Murata, and K. Shimamoto, *J. Am. Chem. Soc.*, 1997, **119**, 4112.
16. Another carbocation intermediate **D** shown below, wherein O2 and C2 groups take pseudoequatorial and pseudoaxial orientations, respectively, may be possible. In our case, however, the pathway is not

operative probably due to a steric interaction with the proton at C2.



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