Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2023, **33**, 648–649

Mendeleev Communications

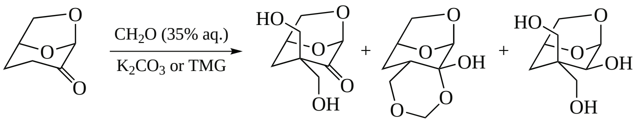
Reactions of cyrene with formaldehyde

Yuliya A. Khalilova, Liliya Kh. Faizullina, Shamil M. Salikhov and Farid A. Valeev*

*Ufa Institute of Chemistry, Ufa Federal Research Centre of the Russian Academy of Sciences,
450054 Ufa, Russian Federation. E-mail: sinvmet@anrb.ru*

DOI: 10.1016/j.mencom.2023.09.019

Cyrene reacts with 35% aqueous formaldehyde in the presence of K_2CO_3, tetramethylguanidine and Et_3N to give three products, *viz.*, major α,α-bis(hydroxymethyl) derivative, a product of its keto group reduction, and 3,5,11,12-tetraoxatricyclo[7.2.1.0^{2,7}]dodecan-2-ol. The options for the derivatization of the hydroxy groups with benzyl, tosyl, isopropylidene, and methylene acetal protecting groups were studied.



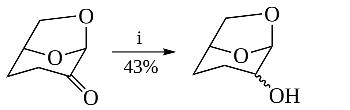
Keywords: cyrene, levoglucosenone, formaldehyde, enolization, chiral dioxane, diol.

Cyrene **1**, a dihydro derivative of levoglucosenone, undergoes nucleophilic substitution reactions with benzyl and allyl bromides[1,2] as well as aldol condensation with various aldehydes[1,3] to afford α-derivatized products. Aldol condensation with conjugated aldehydes is followed by dehydration to give the corresponding enones.[1,3] Depending on the conditions, these reactions are complicated by the self-condensation of cyrene.[4] The use of aldehydes more reactive than cyrene should probably allow this side effect to be diminished somewhat.

To check this assumption, we studied herein the possibility of aldol condensation of cyrene **1** with extremely reactive formaldehyde in more detail. Previously, the reactions between these compounds in the presence of LDA[1,2,5] resulted in the stereoselective reduction of the keto group to yield diastereomeric alcohols **2**,[6] most likely through the Cannizzaro mechanism (Scheme 1).

In this work, with the use of 35% aqueous formaldehyde in the presence of weak base such as AcONa, cyrene **1** remained inert. On moving to K_2CO_3, the reaction led to three compounds: keto diol **3**, a product of addition of two formaldehyde molecules; dioxane **4**, and triol **5** (Scheme 2, conditions i). It should be noted that reduction of the keto group yielding triol **5** occurred stereospecifically. Previously, the formation of the same three products **3**–**5** was observed when the reaction was carried out in MeCN in the presence of tetramethylguanidine (TMG, conditions iii).[1,7] The reaction in propan-2-ol (conditions ii) in the presence of Et_3N[8] resulted in keto diol **3** and dioxane **4** while triol **5** was not detected. Performing the reactions for a longer time resulted in significant drop in the yield due to lability of keto diol **3**.

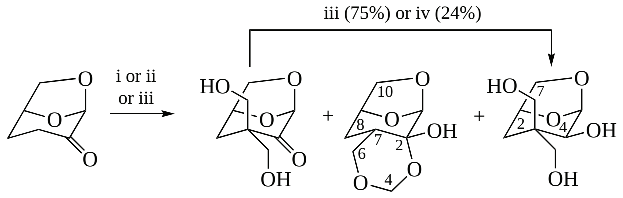
Since the rigidly bound asymmetric centers of the bicyclic system of enone **1** are not affected by the reaction, it is obvious that the products **3**–**5** have the corresponding absolute configuration. Their HMBC spectra manifest the interaction of protons of the 1,6-anhydro bridge with the carbon of the acetal center, which proves that the 1,3-dioxolane ring is preserved. The presence of a NOE effect between the H^4/H^{2B} and H^{2A}/H^{7A} protons in the NOESY spectrum suggests the *S*-configuration of the C^4 center in triol **5**.



1 **2** *S*/*R* = 15 : 1

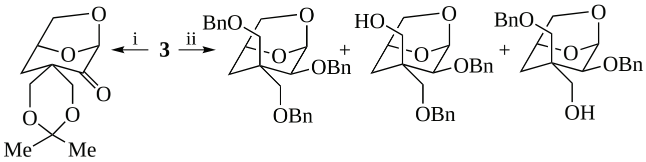
Scheme 1 *Reagents and conditions*: i, CH_2O, LDA, THF, –10 → → –40 → –78 °C, 2–3 min.

The structure of dioxane **4** is indicated by the signal for the nodal quaternary carbon atom C^2 at *δ* 91.76 and that for the dioxymethylene moiety at *δ* 87.42. The H^{4A}/C^2, H^{4A}/C^6 and H^{6A}/C^8 correlation peaks observed in the HMBC spectrum indicate that a 1,3-dioxane moiety is annulated with the pyran ring. The presence of a NOE effect between the H^{10A}/H^7 protons in the NOESY spectrum is the evidence for the *S*-configuration of the C^7 center. Dioxane **4** can be formed both from the initial cyrene **1** or *via* aldol **3** through the retro-aldol decomposition releasing formaldehyde molecule. To identify the pathways of the formation of dioxane **4**, keto diol **3** was dissolved in acetonitrile and treated with TMG,[7] with or without formaldehyde (see Scheme 2). In both cases, triol **5** was obtained in 75 and 24% yields, respectively, while dioxane **4** was not formed. These results suggest that keto diol **3** and dioxane **4** can be formed through parallel pathways according to conventional concepts (see Online Supplementary Materials, Scheme S1). Interestingly, competing self-condensation of cyrene **1** was never observed in all reactions studied, apparently, due to high activity of



1	**3**	**4**	**5**
	44% (i)	25% (i)	23% (i)
	36% (ii)	23% (ii)	15% (iii)
	45% (iii)	12% (iii)	

Scheme 2 *Reagents and conditions*: i, CH_2O (35% aq.), K_2CO_3, 25 °C, 1 h; ii, CH_2O (35% aq.), Et_3N, Pr^iOH, 25 °C, 15 min; iii, CH_2O (35% aq.), TMG, MeCN, 25 °C, 20–30 min; iv, TMG, MeCN, 25 °C, 30 min.



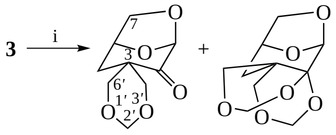
6, 13% **7**, 8% **8a**, 5% **8b**, 5%

Scheme 3 *Reagents and conditions*: i, Me$_2$C(OMe)$_2$, *p*-TsOH, CH$_2$Cl$_2$, 25 °C, 6 h; ii, BnCl, NaH, DMSO, 25 °C, 1 h.

formaldehyde when the reactions begin immediately and end within 15–60 min depending on the base used.

To check the utility of keto diol **3** as a new stable compound in subsequent syntheses, we studied the possibility of protecting its hydroxy groups (Scheme 3). Acetonide **6** was obtained in a low (13%) yield on treatment with 2,2-dimethoxypropane in the presence of *p*-TsOH in CH$_2$Cl$_2$. Benzylation of keto diol **3** with MeS(O)CH$_2$Na–BnCl resulted in three products, tribenzylate **7** and dibenzylates **8a**,**b**, also in small yields (see Scheme 3). Treatment of compound **3** with *p*-TsCl–Py in the presence of DMAP resulted in hardly identifiable products. The low yields of these anticipated derivatives are believed to be primarily caused by its lability, namely, due to its tendency to undergo a retro-aldol decay. The shielding effect of 1,6-anhydro bridge also plays a noticeable role. Moreover, derivatization of the first hydroxy group with a bulky substituent would affect the conformation of the molecule so that this substituent becomes oriented to an equatorial position, which should hinder the second derivatization.

The formation of spirocyclic derivatives with *gem*-dimethyl groups at C^2 is also hindered under these conditions. Indeed, when keto diol **3** was treated with SOCl$_2$ in DMSO,[9] keto dioxane **9** and ketal **10** were isolated in moderate yields (Scheme 4). The formation of the spiro-1,3-dioxane structure **9** is indicated by the signals of the nodal quaternary carbon atom C^3 at δ 44.99, two –CH$_2$–O moieties at δ 73.84 and 74.74, and the methylenedioxy moiety at δ 94.00. The H$^{6'A}$/C^3, H$^{4'A}$/C^3, H$^{2'A}$/C$^{6'}$ and H$^{2'A}$/C$^{4'}$ correlation peaks observed in the HMBC spectrum indicate the formation of a spiro-1,3-dioxane moiety at the C^3 position.



9, 24% **10**, 34%

Scheme 4 *Reagents and conditions*: i, SOCl$_2$, DMSO, 65 °C, 1 h.

In conclusion, triol **5** is the most stable cyrene derivative obtained by its reaction with aqueous formaldehyde. Its yields can be improved upon isolation of keto diol **3** and repeated processing under the same conditions. The possibilities of its further employment will be the topic of our next studies.

The authors are grateful to Circa Group for providing industrial grade cyrene. This work was carried out within the Subjects of the Government Assignment (nos. 122031400259-1 and 122031400282-9). NMR spectra were recorded using the equipment of the Center for Collective Use of Scientific Equipment ‘Chemistry’ and the Regional Center for Collective Use ‘Agidel’ of the Ufa Institute of Chemistry of the Russian Academy of Sciences. The structures of compounds were determined by means of ^{1}H and ^{13}C NMR spectroscopy using standard HHCosy, HSQC, HMBC, and NOESY two-dimensional correlation techniques and mass spectrometry (for details, see Online Supplementary Materials).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.019.

References

1 E. T. Ledingham, K. P. Stockton and B. W. Greatrex, *Aust. J. Chem.*, 2017, **70**, 1146.
2 L. Kh. Faizullina, Yu. A. Khalilova, L. Sh. Karamysheva, Sh. M. Salikhov and F. A. Valeev, *Mendeleev Commun*., 2022, **32**, 546.
3 L. Kh. Faizullina, Yu. A. Khalilova, L. Sh. Karamysheva, A. D. Badikova, S. M. Salikhov and F. A. Valeev, *Bashkir. Khim. Zh*., 2022, **29**, 25 (in Russian).
4 K. L. Wilson, A. R. Kennedy, J. Murray, B. Greatrex, C. Jamieson and A. J. B. Watson, *Beilstein J. Org. Chem.*, 2016, **12**, 2005.
5 (*a*) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1972, 1317; (*b*) G. Stork and J. D’Angelo, *J. Am. Chem. Soc.*, 1974, **96**, 7114; (*c*) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, 1975, **97**, 6260; (*d*) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, 1975, **97**, 4745.
6 B. T. Sharipov, A. N. Davydova, L. Kh. Faizullina and F. A. Valeev, *Mendeleev Commun.*, 2019, **29**, 200.
7 N. Hossain, H. van Halbeek, E. De Clercq and P. Herdewijn, *Tetrahedron*, 1998, **54**, 2209.
8 D. H. R. Barton, W. B. Motherwell and S. Zard, *J. Chem. Soc., Chem. Commun.*, 1982, 551.
9 (*a*) S. J. Benkovic and J. M. Fedor, *J. Am. Chem. Soc.*, 1972, **94**, 8928; (*b*) Guiso, C. Procaccio, M. R. Fizzano and F. Piccioni, *Tetrahedron Lett.*, 1997, **38**, 4291.

Received: 3rd May 2023; Com. 23/7163