ORGANIC LETTERS

2006
Vol. 8, No. 15
3187−3190

Formation and Reactivity of Novel Pyranosidic Nicholas Oxocarbenium Ions: Access to *C*-Ketosides and Branched-Chain *C*-Ketosides

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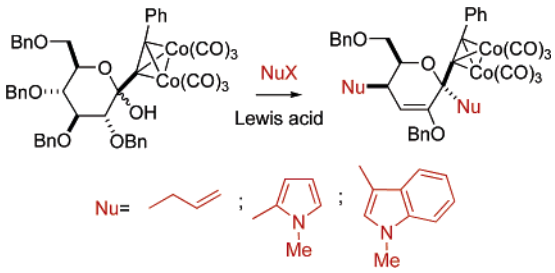
Received April 17, 2006

ABSTRACT



Dicobalt hexacarbonyl propargyl complexes, prepared from alkynyl ketoses, display an unexpected reactivity when treated with Lewis acids in the presence of nucleophiles and furnish *C*-ketosides, branched-chain *C*-ketosides, or branched-chain *C*-glycals depending on the nucleophile and the carbohydrate starting material.

Much of the rich chemistry of carbohydrates emanates from synthetic transformations on carbenium ions, e.g., **1**, generated at the anomeric position,[1] with *O*- and *C*- glycosylation being particularly important reactions.[2,3] On the other hand, propargyl cation dicobalt hexacarbonyl complexes, e.g., **2**,[4] are one of the most widely employed transition-metal-stabilized reactive intermediates in organic synthesis (Figure 1).[5,6] Their chemistry, normally referred to as the Nicholas reaction,[7] is a well-established protocol for the incorporation of nucleophiles at propargylic cationic centers.

In this paper, we discuss the remarkable reactivity of "Nicholas pyranosidic oxocarbenium ions" (**3**),[8] in which the anomeric cation enjoys additional stabilization from a dicobalt hexacarbonyl (DCHC) propargyl group. Indeed, we show their usefulness for the preparation of *C*- and *N*-ketosides and branched pyranoses. These studies emanated from our recent efforts on the preparation of *C*-ketosides by Lewis acid catalyzed *C*-glycosidation of ketoses.[9−11]

(1) (a) *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, 2001. (b) *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, 2000.

(2) For reviews on *O*-glycosylation: (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235. (c) Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 294−308. (d) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531. (e) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095−1121. (f) Davies, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137−2160. (g) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576−1624.

(3) For reviews on *C*-glycosylation: (a) Postema, M. H. D. *Tetrahedron* **1992**, *40*, 8545−8599. (b) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20. (c) Levy, D. E.; Tang, C. *The Chemistry of* C*-Glycosides*; Pergamon: Oxford, 1995. (d) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913−9959.

(4) "Nicholas' cations" should be regarded as cobalt-cluster-stabilized carbenium ions rather than propagyl cations. See refs 5 and 6.

(5) (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982−1994, 14 Volume Set*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, Chapter 7.1, pp 685−702.

(6) Reviews: (a) Went, M. J. *Adv. Organomet. Chem.* **1997**, *41*, 69−125. (b) Müller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021−2033. (c) Greeen, J. R. *Current. Org. Chem.* **2001**, *5*, 809−826. (d) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133−4170.

(7) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *48*, 4163−4166.

10.1021/ol060929+ CCC: $33.50
Published on Web 06/23/2006

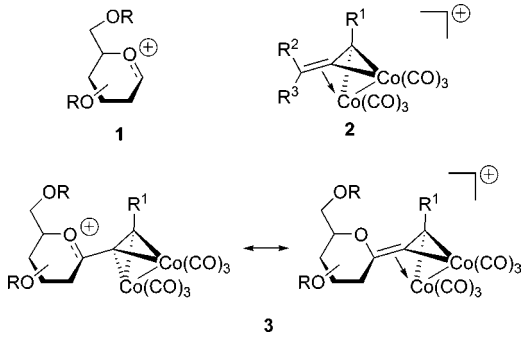


Figure 1. Oxocarbenium ion **1**, dicobalt hexacarbonyl coordinated propargyl cation (Nicholas cation) **2**, and Nicholas oxocarbenium ion **3**.

As starting materials to our study we used D-glucose- and D-galactose-derived DCHC propargyl complexes **4**−**6**, readily prepared from the corresponding alkynyl ketoses[11] by treatment with $Co_2(CO)_8$ in CH_2Cl_2 at room temperature (Figure 2). Their coupling reactions with nucleophiles were carried

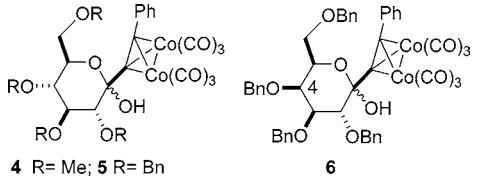
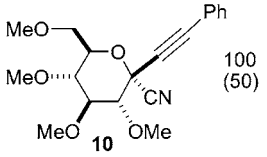
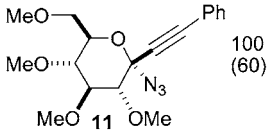
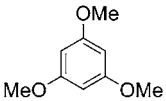
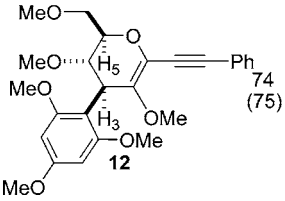


Figure 2. Dicobalthexacarbonyl complexes **4**−**6**.

out in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$, and product demetalation was effected by treatment with I_2[12] or *N*-methylmorpholine *N*-oxide monohydrate (NMO).[13]

In our first set of experiments, we reacted DCHC propargyl ketose **4** with trimethylsilyl cyanide (**7**), trimethylsilyazide (**8**), and 1,3,5-trimethoxybenzene **9**, and the results are displayed in Table 1. Reaction of **4** with trimethylsilyl

Table 1. $BF_3{\cdot}OEt_2$-Catalyzed Reaction of Dicobalthexacarbonyl Propargyl Ketose **4** with Nucleophiles **7**−**9** Followed by Demetalation with I_2 in THF

entry	nucleophile	temp °C (time)	product	yields (%) addition (demetalation)
i	Me_3SiCN **7**	-20 (3h)	 **10**	100 (50)
ii	Me_3SiN_3 **8**	-30 (0.5h)	 **11**	100 (60)
iii	 **9**	-30 (3h)	 **12**	74 (75)

cyanide and azide (entries *i* and *ii*) led, after deprotection, to compounds **10** and **11**.[11b] However, the reaction of **4** with aryl derivative **9** led to the branched chain *C*-glycal **12**. The structural assignment of **12** was based on its ^1H and ^{13}C NMR spectra as well as HSQC correlations and decoupling experiments. Location of the aryl substituent at C-3 was inferred by the HSQC correlation ($CDCl_3$) between H-3 (4.43 ppm) and C-3 (39.08 ppm), and the stereochemistry at C-3 was established by the existence of an NOE (C_6D_6) between H-5 (3.93 ppm) and H-3 (4.80 ppm) as shown in Table 1.

An equally unexpected compound **16** containing two allyl residues was obtained by reaction of **4** with allyltrimethylsilane **13** and subsequent demetalation (Table 2, entry *i*). The structure of **16** was assigned on the basis of its mass, ^1H and ^{13}C NMR, HMQC, and HMBC spectra. The stereochemistry of the allyl residues was unambiguously assigned on the basis of observed NOEs of H-4′ with H-6 and H-1′ with H-5 (Table 2, entry *i*). The reaction of **5** with allyltrimethylsilane also produced unsaturated bis-allyl ketoside **17** (Table 2, entry *ii*). Likewise, the reaction of **5** with *N*-methylpyrrole (**14**) and *N*-methylindole (**15**) resulted in the formation of unsaturated carbohydrate derivatives **18** and **19** (Table 2, entries *iii* and *iv*), also incorporating two nucleophilic residues at C-1 and C-4. However, attempts at deprotecting the alkyne moiety in these compounds have so far proven elusive.

Next, a conflicting result was observed when the "galacto" DCHC propargyl ketose **6** was reacted with nucleophiles **13**-

(8) Several applications of the Nicholas reaction in the carbohydrate field have been described: (a) Tanaka, S.; Tsukiyama, T.; Isobe, M. *Tetrahedron Lett.* **1993**, *34*, 5757−5760. (b) Tanaka, S.; Isobe, M. *Tetrahedron* **1994**, *50*, 5633−5644. (c) Isobe, M.; Jiang, Y. *Tetrahedron Lett.* **1995**, *36*, 567−570. (d) Jiang, Y.; Isobe, M. *Tetrahedron* **1996**, *52*, 2877−2892. (e) Jiang, Y.; Ichikawa, Y.; Isobe, M. *Synlett* **1995**, 285−288. (f) Jiang, Y.; Ichikawa, Y.; Isobe, M. *Tetrahedron* **1997**, *53*, 5103−5122. (g) Tanaka, S.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7801−7804. (h) Tanaka, S.; Tatsuta, N.; Yamashita, O.; Isobe, M. *Tetrahedron* **1994**, *50*, 12883−12894. (i) Isobe, M.; Yenjai, C.; Tanaka, S. *Synlett* **1994**, 916−918. (j) Tanaka, S.; Isobe, M. *Synthesis* **1995**, 859−862. (k) Désiré, J.; Veyrières, A. *Carbohydr. Res.* **1995**, *268*, 177−186. (l) Streicher, H.; Geyer, A.; Schmidt, R. R. *Chem. Eur. J.* **1996**, *2*, 502−510. (m) Mukai, C.; Itoh, T.; Hanaoka, M. *Tetrahedron Lett.* **1997**, *38*, 4595−4598. (n) Yenjay, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509−2520. (o) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665−2676.

(9) These compounds are the *C*-glycosides of keto sugars: Tam, T. F.; Fraser-Reid, B. *J. Org. Chem.* **1980**, *45*, 1344−1346.

(10) They have also been referred to as bis-*C*,*C*-glycosides: Paquette, L. A.; Kinney, M. J.; Dullweber, U. *J. Org. Chem.* **1997**, *62*, 1713-1722.

(11) (a) Gómez, A. M.; Uriel, C.; Jarosz, S.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2002**, *43*, 8935−8940. (b) Gómez, A. M.; Uriel, C.; Jarosz, S.; Valverde, S.; López, J. C. *Eur. J. Org. Chem.* **2003**, 4830−4837.

(12) Magnus, P.; Davies, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1522−1524.

(13) Krafft, M. E.; Cheung, Y. Y.; Wright, C.; Cali, R. *J. Org. Chem.* **1996**, *61*, 3912−3915.

Table 2. $BF_3{\cdot}OEt_2$-Catalyzed Reaction of "Gluco" Dicobalthexacarbonyl Ketoses **4** and **5** with Nucleophiles **13**−**15**

entry	substrate + nucleophile	temp °C (time)	product	yields (%) addition (demetalation)[a,b]
i	**4** + **13**	-30 (3h)	**16**	64 (100)[b]
ii	**5** + **13**	-30 (2h)	**17**	66 (85)[a]
iii	**5** + **14**	-20 (12h)	**18**	18 (42)[c] ---[a,b]
iv	**5** + **15**	-20 (12h)	**19**	45 (61)[c] ---[a,b]

[a] *N*-Methylmorpholine *N*-oxide (NMO). [b] I_2, THF. [c] Based on recovered starting material.

15; this process furnished the *expected C*-ketosides **20**−**22** (Table 3, entries *i*−*iii*). Reaction of **6** with 1,3,5-trimethoxy-

Table 3. $BF_3{\cdot}OEt_2$-Catalyzed Reaction of "Galacto" Dicobalthexacarbonyl Ketose **6** with Nucleophiles **13**−**15** Followed by Demetalation with NMO or I_2

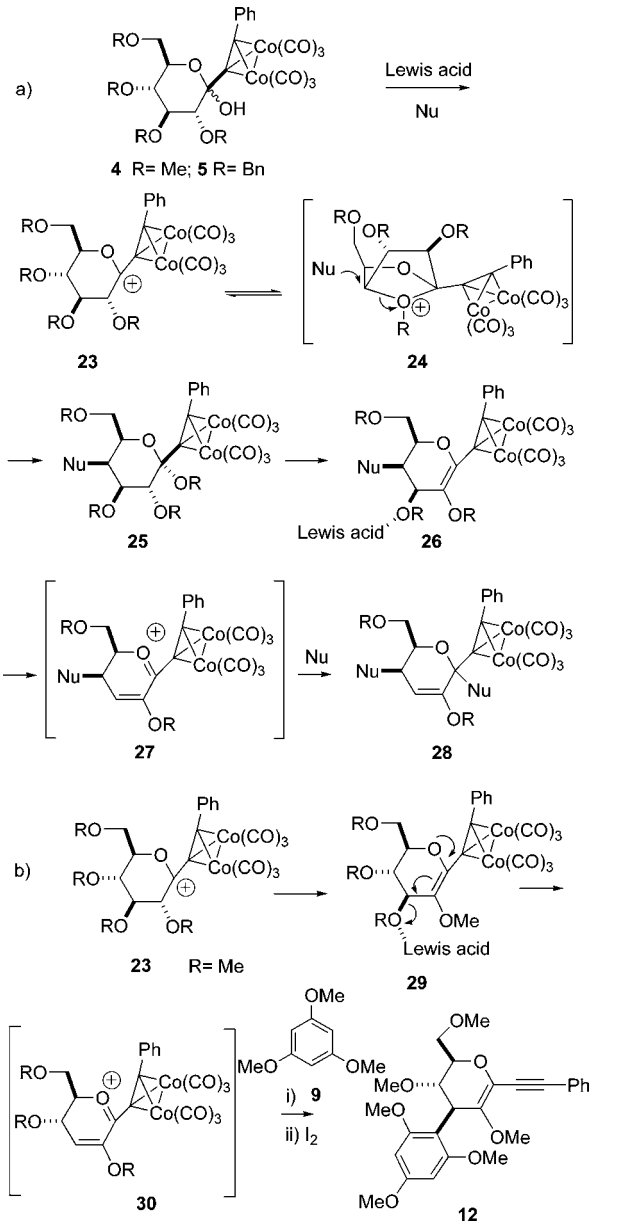
entry	nucleophile	temp °C (time)	product	yields (%) addition (demetalation)[a,b]
i	**13**	-30 (0.5h)	**20**	90 (67)[b]
ii	**14**	-30 (3h)	**21**	82(90)[c] (66)[b]
iii	**15**	-30 (1h)	**22**	97 (66)[b]

[a] *N*-Methylmorpholine *N*-oxide (NMO). [b] I_2, THF. [c] Based on recovered starting material.

benzene (**9**) did not yield any coupled product, at −30 °C, and resulted in the decomposition of **6** at room temperature.

A reaction pathway which accommodates these results is outlined in Scheme 1. Treatment of the gluco-DCHC

Scheme 1. Possible Reaction Pathway for the Formation of Branched *C*-Ketosides from **4** and **5**



propargylketoses (**4**, **5**) with $BF_3{\cdot}Et_2O$ provokes the formation of an anomeric cation **23**, which might be in equilibrium with a bicyclic dioxolanyl ion **24**[14] (Scheme 1a). This equilibrium allows the entry of a given nucleophile at C-1 (Table 1, entries *i* and *ii*) or its stereoselective incorporation

(14) Structurally related 1,4-anhydroaldoses (2,7-dioxabicyclo[2.2.1]-heptane derivatives) with the D-gluco-configuration have been prepared: (a) Sato, T. Nakamura, H.; Ohno, Y.; Endo, T. *Carbohydr. Res.* **1990**, *199*, 31−35. (b) Cerny, M. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 121−198.

at C-4 by an anti approach to the existing C(4)−O bond to yield ketoside intermediate **25**. The latter might experience elimination[15] leading to *C*-glycal **26** which, might behave as a Ferrier-type substrate[16] (or a vinylogous Nicholas system) leading to a "Ferrier−Nicholas" allylic cation **27**, which could trap the nucleophile at the anomeric position, thus leading to **28**.

On the other hand, oxocarbenium ion **23** in the presence of "unreactive"[17] **9** (Scheme 1b) could undergo deprotonation[15] leading to **29** which, as above, could lead to DCHC-propargyl-stabilized allylic oxocarbenium ion **30**. The latter would then experience the attack of the bulky nucleophile (**9**) at the less substituted C-3 position rather than at C-1, with an anti orientation with respect to the substituent at C-4 and hence give products such as **12**. The stereochemistry at C-1 was expected to be the one shown in Tables 1−3 (arising from an axial approach of the nucleophile to the anomeric carbenium ion) in keeping with literature precedents.[18]

The contrasting behavior of "gluco" and "galacto" derivatives (**4** and **6**) toward 1,3,5-trimethoxybenzene (compound **4** afforded **12**, whereas **6** failed to give any coupled product) can be rationalized according to the proposed reaction pathway (Scheme 1a,b), since it is well-documented that the configuration at C-4 affects appreciably the Ferrier rearrangement and the "galacto" isomer is noticeably more problematic.[19] The different behavior between "gluco" and "galacto" isomers toward nucleophiles (compare Table 2, entries *ii*−*iv* with the results in Table 3) can be rationalized on the basis of the difficulty in the forming bicyclic dioxolanyl ions in the "galacto" compounds in these type of systems.[20]

The results obtained in this study clearly illustrate the influence of the DCHC group in the Lewis acid-catalyzed reactions of propargyl ketoses.[11] The participation of "Ferrier−Nicholas" cations (e.g., **27** and **30**) in these processes also provides a rationale for the presence of the 2,3-unsaturation in compounds **12** and **16**−**19** (Scheme 1a,b). The DCHC-propargyl hemiacetal, upon treatment with $BF_3 \cdot Et_2O$, undergoes a completely chemoselective cleavage of the exocyclic C−O bond.[21] We have not observed any endocyclic C−O bond cleavage as previously found by Isobe and co-workers[8a,c,j,22] and more recently by Désiré and Veyrières[8k] on DCHC-propargyl *C*-glycosides.

In summary, the presence of a DCHC propargyl complex at the anomeric position in a ketose has a profound influence on the reactivity, inducing a completely new set of transformations in some alkynyl ketoses.[11] These transformations are relevant from a synthetic standpoint, since they allow the incorporation of two nucleophile units in a carbohydrate derivative, and from a biological perspective, since hybrid natural products[23] have emerged as a promising approach to diversity oriented synthesis.[24,25] Furthermore, incorporation of a metallic fragment into organic compounds can be of interest in the emerging field of bio-organometallic chemistry.[26]

Acknowledgment. This research was supported with funds from the Dirección General de Enseñanza Superior (Grant No. PPQ2003-00396). C.U. thanks the CSIC for financial support.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H, ^{13}C, and two-dimension NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060929+

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(16) (a) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, 199−266. (b) Ferrier, R. J. *Topics in Current Chemistry*; Springer-Verlag: Berlin, 2001; Vol. 215, pp 153−175. (c) Ferrier, R. J.; Zubkov, O. A. *Org. React.* **2003**, *62*, 569−736. (d) Ferrier, R. J.; Hoberg, H. O. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 55−119.

(17) The lack of reactivity of **9** toward ketosydic anomeric cations has to be ascribed to its steric bulk, since **9** is known to react with pyranosidic cations from aldoses to give *C*-glycosides: Schmidt, R. R.; Hoffman, M. *Tetrahedron Lett.* **1982**, *23*, 409−412.

(18) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.

(19) See pag 583 in ref 16c.

(20) Since 1,4-anhydro sugars have been also prepared from D-galacto isomers (Cerny, M. *Adv. Carbohydr. Chem. Biochem.* **2003**, *58*, 121−198. Also: Bullock, C.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1990**, *197*, 131−138), we believe that the presence of the DCHC-propargyl group at C-1 plays a role in determining the formation of the corresponding furanilium ion from **6**.

(21) Alkoxy-DCHC-propargylium cations have been reported: see ref 5a. Also: (a) Montaña, A. M.; Cano, M. *Tetrahedron* **2002**, *58*, 933−951. (b) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353−4363.

(22) (a) Tanaka, S.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7801−7804. (b) Tanaka, S.; Tatsuta, N.; Yamashita, O.; Isobe, M. *Tetrahedron* **1994**, *50*, 12883−12894.

(23) See, for example: (a) Hopen, S.; Emde, U.; Friedrich, T.; Grubert, L.; Koert, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 2099−2102. (b) Tietze, L. F.; Schneider, G.; Wölfling, J.; Nöbel, T.; Wulff, C.; Schubert, I.; Rübeling, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2469−2470.

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(26) For an overview in this field, see: Dagani, R. *Chem. Eng. News* **2002**, *80*, 23.