Formation and reactivity of new Nicholas–Ferrier pyranosidic cations: novel access to oxepanes *via* a 1,6-hydride shift/cyclization sequence†

Ana M. Gómez,* Fernando Lobo, Daniel Pérez de las Vacas, Serafín Valverde and J. Cristóbal López*

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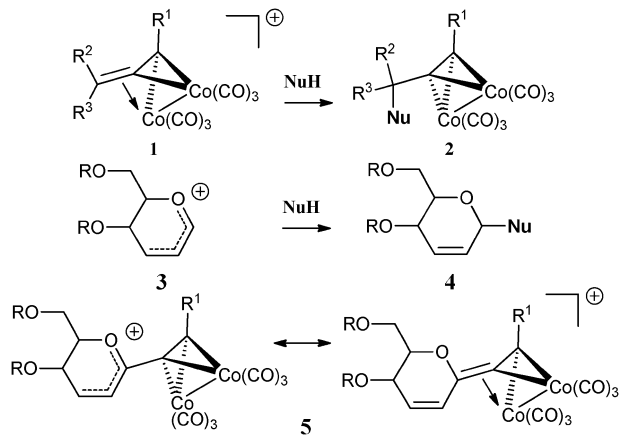
Pyranosidic allylic (Ferrier) cations that share dicobalt hexacarbonyl propargyl (Nicholas) stabilization at C-1 display a remarkable reactivity leading to either substituted oxepanes or 3-*C*-branched pyranosides, depending on the substituent at O-6.

The Nicholas reaction[1] and the Ferrier (I) rearrangement[2] are two well-known,[3] useful, synthetic transformations,[4,5] which have in common the intermediacy of cationic species such as **1** and **3**, respectively (Scheme 1). The reaction of these cations with nucleophiles (NuH) leads to propargylated derivatives (*e.g.* **2**) or allylic glycosides (*e.g.* **4**), respectively. Recently, some examples of novel Nicholas cations have appeared in the literature, such as a Nicholas dehydrotropylium ion,[6] or Nicholas dipoles derived from alkyne–cycloalkane dicobalt complexes.[7] In this context, we have studied the behavior of Nicholas pyranosidic oxocarbenium ions, which displayed an unexpected synthetic behavior.[8] Along this line, we became interested in the study of "Nicholas–Ferrier" cations, *e.g.* **5**, since they could display new reactivity regarding unsaturated carbohydrate derivatives and/or Nicholas cations.

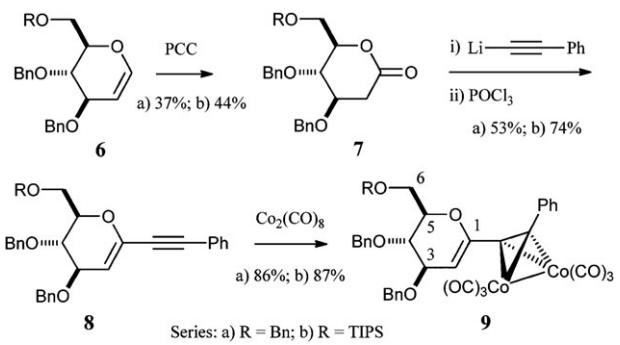
We now report that the reactivity of Nicholas–Ferrier cations, *e.g.* **5**, can be modulated by changes in the protecting group at O-6, thus leading to 3-*C*-branched pyranosides (by reaction with an external nucleophile), or to functionalized oxepanes through a reaction sequence that involves: (i) 1,6 hydride transfer; (ii) two-step electrophilic addition (Ad_E);[9] and (iii) pyranosidic ring opening.



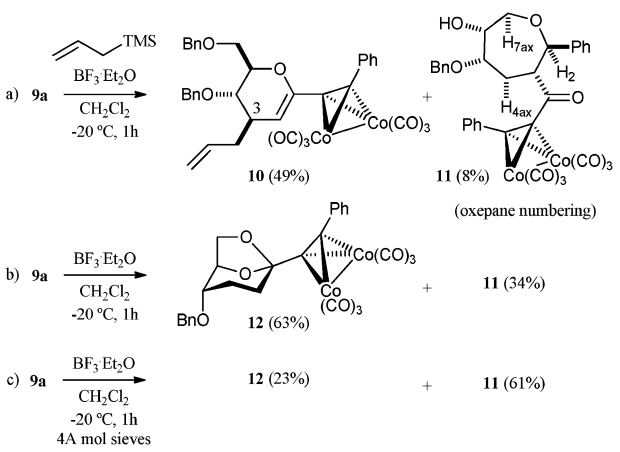
Scheme 1 Dicobalt hexacarbonyl coordinated propargyl cation (Nicholas cation) (**1**), Ferrier allylic cation (**3**), and Nicholas–Ferrier cation (**5**).

The precursors for the Nicholas–Ferrier cations **5** were derivatives **9**, prepared from enynes **8**.[10] The latter were readily obtained from D-glucals **6**,[11,12] *via* lactones **7**[13] (Scheme 2).

The reaction of tri-*O*-benzyl glucal **9a** with allyltrimethylsilane (3 equiv.) in CH_2Cl_2 at −20 °C, in the presence of $BF_3{\cdot}Et_2O$ (1.2 equiv.), yielded 3-*C*-allyl derivative **10** (49%) accompanied by oxepane **11** (which had not incorporated the allyl moiety, 8%) (Scheme 3a). When the reaction was carried out in the absence of allyltrimethylsilane, oxepane **11** was obtained in 34% yield, although the major reaction product was 1,6-anhydro derivative **12** (63%) (Scheme 3b). This (**11** : **12**) proportion could be reversed if molecular sieves were added to the reaction media, then oxepane **11** could be isolated in 61% yield (Scheme 3c).‡



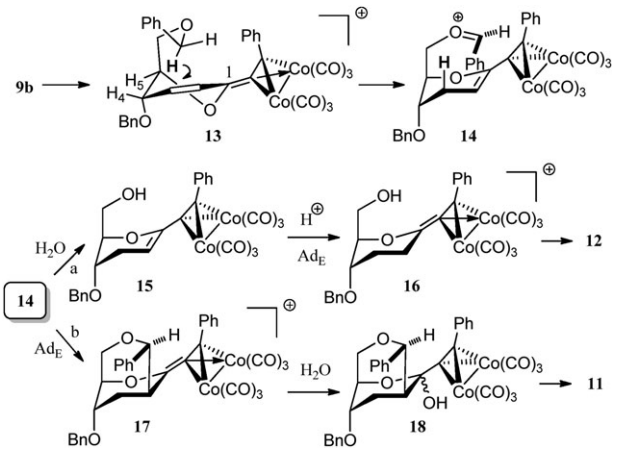
Scheme 2 Synthesis of "Nicholas–Ferrier" cation precursors, **9**.



Scheme 3 Reaction of **9a** with $BF_3{\cdot}Et_2O$, in the presence or absence of allyltrimethylsilane.

Instituto de Química Orgánica General (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain. E-mail: anagomez@iqog.csic.es, clopez@iqog.csic.es

† Electronic supplementary information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/c0cc00586j



Scheme 4 Proposed reaction pathways for the formation of **11** and **12**.

The structural assignment of compound **11** was based on the inspection of its NMR spectra (see Supplementary Information†). The stereochemistries at C-2 and C-3 (oxepane numbering) were assigned on the basis of a large $J_{2,3}$ = 10.2 Hz coupling constant, and observed NOEs between H-2, H-7_{ax} and H-4_{ax} (see Scheme 3).

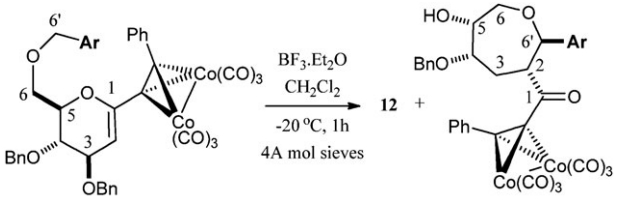
From these results, we were able to advance a mechanistic rationale that accounted for the formation of compounds **11** and **12** (Scheme 4). The first step would be a 1,6-hydride transfer[14,15] (**13** → **14**, Scheme 4) to generate a highly reactive oxocarbenium ion **14**. The latter could then follow two sets of transformations: (a) it could experience hydrolysis to a 6-OH derivative **15**, which upon protonation of the activated enyne moiety will form a pyranosidic Nicholas oxocarbenium ion[8] **16**, that will cyclize to **12**; or (b) it could experience a two-step Ad_E reaction[9,16] to give **17**, and thence **18**, whose ring opening would finally lead to oxepane **11**.

According to our proposed reaction pathway, the formation of oxepane **11**, over 1,6-anhydro derivative **12**, could be favored if hydrolysis of the oxocarbenium ion in intermediate **14** is decelerated, as was indeed observed when the reaction was carried out in the presence of freshly activated, crushed§ 4 Å molecular sieves (which excluded water needed for the hydrolysis of **14** from the reaction media, compare in Scheme 3, entries b and c).

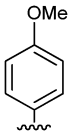
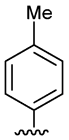
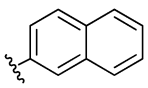
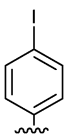
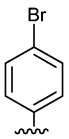
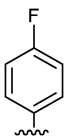
In order to evaluate the scope of this transformation, aiming at the preparation of functionalized oxepanes, we prepared compounds **19a–f**,¶ differing in the nature of the aromatic group at O-6, and submitted them to treatment with $BF_3{\cdot}Et_2O$ (CH_2Cl_2, −20 °C, 4 Å molecular sieves, Table 1). This study was also of interest from a mechanistic standpoint, since electron donating groups at the aromatic residue that will favor hydride transfer (**13** → **14**), will render the ensuing oxocarbenium ions less electrophilic, whereas electron withdrawing groups that would favor the electrophilic addition step (**14** → **17**) will make the hydride transfer step more difficult.

From the results in Table 1, it became apparent that substrates with electron donating substituents in the aromatic residue did not favor formation of oxepanes **20** (Table 1, entries (i, ii)). Conversely, *p*-fluoro derivative **19f** furnished a significant yield of oxepane **20f** (69%, Table 1, entry (vi)). *p*-Iodo and *p*-bromo derivatives, **19d** and **19e**, respectively, gave moderate yields of oxepanes **20d** and **20e** (Table 1, entries iv and v, respectively).

Table 1 Synthesis of oxepanes **20**, from differently substituted glycals, **19a–f**



19 **20** (carbohydrate numbering)[a]

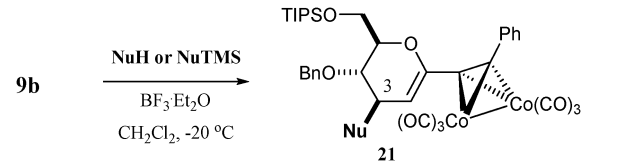
Entry	Starting material	Ar	Products (Isolated yields %)	
i	**19a**		**12** (79)	**20a** (traces)
ii	**19b**		**12** (27)	**20b** (38)[b]
iii	**19c**		**12** (30)	**20c** (62)
iv	**19d**		**12** (43)	**20d** (49)
v	**19e**		**12** (21)	**20e** (54)
vi	**19f**		**12** (15)	**20f** (69)

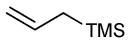
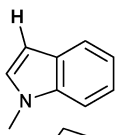
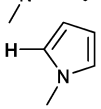
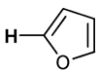
[a] Carbohydrate numbering is shown, to highlight the atom correlation between **19** and **20**. [b] Compound **15** was also isolated (19% yield).

A naphthyl derivative (**19c**) displayed a behavior similar to that of the parent phenyl derivative, **9b**, (compare Table 1, entry iii, with Scheme 3c). According to these results, electron withdrawing substituents in the aromatic ring, which render oxocarbenium intermediates, *e.g.* **14**, more electrophilic (therefore facilitating the Ad_E step) seem to favor oxepane formation.

Two new stereogenic centers are created in this process. The stereogenic center at C-2 (carbohydrate numbering, see Table 1) in oxepanes **11** and **20** is dictated by geometric restrictions in the approach of the C-6 substituent towards C-2 (Scheme 4). The stereogenic center at C-6′ (carbohydrate numbering, see Table 1) is the result of a preferred rotamer of the oxocarbenium ion (**14**), which locates the aryl residue away from the bulky dicobalt hexacarbonyl moiety in the transition state leading to cyclization (**14** → **17**, Scheme 4).

Table 2 Reaction of **9b** with carbon nucleophiles



Entry	Nucleophile	*t*/min	Product	Yield (%)
i		30	**21a**	70
ii		50	**21b**	59
iii		20	**21c**	57
iv		80	**21d**	93

Since the formation of oxepanes seemed to be triggered by the presence of benzyl-type substituents at O-6, it could be eliminated with the presence of a different substituent at O-6. Accordingly, the reaction of 6-*O*-triisopropylsilyl (TIPS) derivative **9b**, with carbon nucleophiles (3 equiv.) in CH_2Cl_2 at −20 °C, in the presence of $BF_3{\cdot}Et_2O$ (1.2 equiv.) led, in a stereocontrolled manner, to 3-deoxy-3-*C*-hex-1-enitol derivatives **21**, in moderate to good yields (Table 2).

The reaction of **9b** with allyltrimethylsilane furnished 3-*C*-branched derivative **21a** (Table 2, entry (i)). Likewise, the reaction of **9b** with *N*-methylindole, *N*-methylpyrrole, and furan yielded compounds **21b**, **21c**, and **21d**, respectively (Table 2, entries ii, iii and iv, respectively).

These transformations were completely regioselective, following a pattern commonly observed for allylic Nicholas cations, in which the nucleophile reacts at the terminus remote from the organometallic substituent,[17] rather than a Ferrier-type behavior, where the nucleophile normally enters at C-1.[2] The configuration at C-3 in compounds **21a–d** could be established based on the observed large $J_{3,4}$ coupling constants in ^{1}H NMR. The stereochemistry of the C-3 branch is the result of a preferred *anti* approach of the incoming nucleophile with respect to the substituent at C-4.[18]

In summary, novel Nicholas–Ferrier pyranosidic cations, with benzyl-type substituents at O-6, undergo a synthetically useful, stereocontrolled, transformation[19] to substituted oxepanes,[20] which involves 1,6 hydride shift/cyclization/ring opening. Work is currently underway with derivatives of type **9** to further explore its reactivity and potential synthetic applications.

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Notes and references

‡ The crucial role played by the dicobalt hexacarbonyl complex in these reactions (Scheme 3) was proved when compound **8a** (devoid of dicobalt hexacarbonyl) was treated with $BF_3{\cdot}Et_2O$ to yield a complex mixture of compounds.

§ When molecular sieves, 4 Å beads, were used, instead of powder activated 4 Å molecular sieves, the isolated yields of isolated **11** and **12** were 45% and 34%, respectively.

¶ Compounds **19a–f** were readily obtained from **8b**, by a reaction sequence that involved: desilylation, alkylation, and cobaltation.

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