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Protected propargylic acetals. Nicholas–Prins cyclization leading to functionalized 2-alkynyl-tetrahydropyrans. Intramolecular trapping by allenes

Clarisse Olier,[a] Stéphane Gastaldi,[a] Gérard Gil[b] and Michèle P. Bertrand[a,*]

[a]*LCMO, UMR 6517, Boite 562, Université Paul Cézanne, Faculté des Sciences et Techniques, St Jérôme, 13397 Marseille Cedex 20, France*

[b]*Laboratoire de Stéréochimie Dynamique et Chiralité, UMR 6180, Université Paul Cézanne, Faculté des Sciences et Techniques, St Jérôme, 13397 Marseille Cedex 20, France*

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Abstract—Dicobalt hexacarbonyl complexes derived from propargylic acetals undergo Lewis acid-mediated Nicholas–Prins cyclization in the presence of homoallylic alcohols. The trapping of the resulting cyclic carbocation enables the synthesis of a series of functionalized tetrahydropyrans. The complexation of the triple bond contributes to the suppression of the side reactions and very significantly increases both the yield and the diastereoselectivity of the reaction. Homoallenic alcohols lead to dienic compounds through proton elimination.

1. Introduction

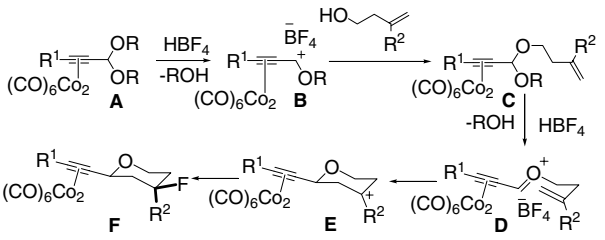
The reactivity of alkyne dicobalt hexacarbonyl-stabilized carbocations, commonly called Nicholas cations, has been extensively studied. Nicholas reaction has emerged as a powerful tool for the formation of C–C and C-heteroatom bonds. Both inter- and intramolecular trapping by nucleophiles have led to brilliant synthetic applications.[1]

We have recently reported, that functionalized alkynyl cyclohexanes could be prepared via intramolecular trapping of Nicholas cation by terminal double bonds.[2] This reaction was unexpected in view of previous reports on the trapping of complexed propargylic cations by non-activated alkenes.[3] Following on this study, we have investigated the formal synthesis of 2-alkynyl tetrahydropyrans[4] through Nicholas–Prins cyclization. The sequence occurs upon the treatment of cobalt complexed propargylic acetals with homoallylic or homoallenic alcohols in the presence of different Lewis acids.[5] The protection of the triple bond was shown to strongly improve both the yield and the diastereoselectivity of the reaction.

2. Results and discussion

As exemplified in Scheme 1, for the synthesis of fluorinated derivatives, Prins cyclization is preceded by the intermolecular trapping of the 'doubly stabilized' cation **B** by the homoallylic alcohol, immediately followed by the formation of a new oxocarbenium ion **D**, which is itself captured intramolecularly by the double bond. The resulting carbocation **E** is then trapped by the external nucleophile.

The results obtained with homoallylic alcohols and *o*-vinyl phenols are given in Table 1. The different propargylic acetals and the unsaturated alcohols used in this study are given in Figures 1 and 2. The products' structures are given in Figure 3. For comparison sake, the re-



Scheme 1. Reaction mechanism.

Keywords: Alkyne complexes; Nicholas reaction; Prins cyclization; Carbocations; Tetrahydropyrans.
* Corresponding author. E-mail: michele.bertrand@univ-cezanne.fr

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Table 1. Reactions with homoallylic alcohols, *o*-vinyl phenols, and homoallenic alcohols

Entry	Alcohol (substrate)	Lewis acid	Products isolated yield (%)	Cis/trans ratio
1	**4a** (**1**)[a]	$TiCl_4$	**7a** (58)	64/36
2	**4a** (**1**)[a]	$BF_3{\cdot}OEt_2$	**8a** (52)	83/17
3	**4a** (**1′**)	$BF_3{\cdot}OEt_2$	**8a**[b] (20)[d]	41/59
4	**4a** (**1**)[a]	TMSOTf	**9a** (66)	>99/1
5	**4a** (**1′**)	TMSOTf	**9a**[b] (40)[d]	63/37
6	**4a** (**1**)[a]	HBF_4	**8a** (63)	93/7
7	**4a** (**1′**)	HBF_4	**8a**[b] (51)[d]	57/43
8	**4a** (**2**)[a]	HBF_4	**10a** (85)	42/58
9	**4a** (**3**)[a]	HBF_4	**11a** (80)	41/59
10	**4b** (**1**)[a]	$TiCl_4$	**7b** (66)	7/93
11	**4b** (**1′**)	$TiCl_4$	**7b** (27)	nd
12	**4b** (**1**)[a]	$BF_3{\cdot}OEt_2$	**8b/12b** 85/15 (64)	64/36
13	**4b** (**1**)[a]	$BF_3{\cdot}OEt_2$[c]	**13b/12b** 70/30 (53)	70/30
14	**4b** (**1**)[a]	HBF_4	**8b/12b** 96/4 (65)	6/94
15	**5b** (**1**)[a]	TMSOTf	**14b** (29)	
16	**4a** (**1**)	HBF_4[e]	**15a** (43)	>99/1
17	**4a** (**2**)	HBF_4[e]	**16a** (32)	>99/1

[a] The reactions were carried out at room temperature in dichloromethane, on 0.3–0.4 mmol of complex in the presence of 1.1 equiv of alcohol and 2.0 equiv of Lewis acid, unless otherwise stated.
[b] The products are intended non-complexed.
[c] The reaction was performed in nitromethane.
[d] ^1H NMR yield using pentamethylbenzene as internal standard.
[e] The reaction was performed in freshly distilled dry acetonitrile.

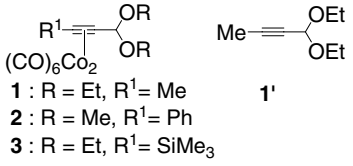

Figure 1. Propargylic acetals.

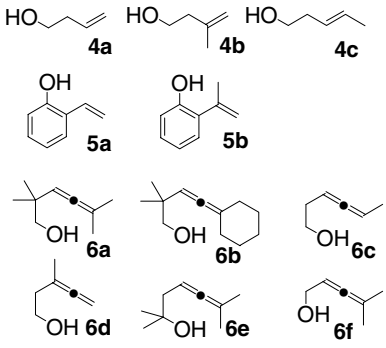

Figure 2. Unsaturated alcohols.

sults of Prins cyclizations performed on non-complexed acetal **1′** in the presence of alcohol **4a** are given in entries 3, 5, and 7, and in entry 11 for alcohol **4b**.

When conducted in dichloromethane in the presence of $TiCl_4$, HBF_4 or $BF_3{\cdot}OEt_2$, the reactions carried out on complexes **1**–**3** and alcohol **4a** led to 4-halogenated tetrahydropyrans isolated as a mixture of stereoisomers

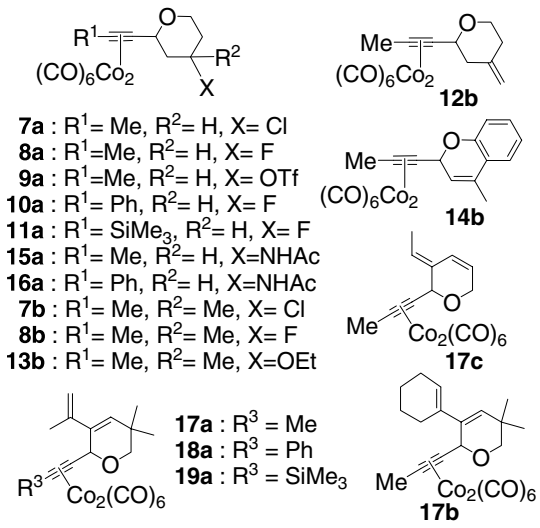

Figure 3. Products' structures.

in yields ranging from 52% to 85% (entries 1, 2, 6, 8, and 9). High diastereoselectivity was observed for the formation of fluoride **8a** (entries 2 and 6). The cis/trans ratio was far lower for the reaction leading to chloride **7a** (entry 1). The cyclization carried out in the presence of TMSOTf (entry 4) led cleanly to triflate **9a** isolated as a single cis stereoisomer. The structures of cis and trans isomers were assigned from the characteristic coupling patterns of the protons α to the polar substituents.[6] When 3-hexen-1-ol (**4c**) bearing a non-terminal double bond was used, the reaction led to a complex mixture of products that could not be isolated as pure samples and thereby were not identified.

Comparatively, the reactions performed on the non-complexed acetal **1′** led to the expected tetrahydropyrans but in far lower yields and selectivity (entries 3, 5, 7, and 11).[7] As an example, 3-ethoxybut-2-enal and 4-ethoxybut-3-en-2-one resulting from the degradation of **1′** were detected in the crude mixture (20% overall NMR yield) in the presence of HBF_4 (entry 7).[8]

Prins cyclization is reputedly stereoselective.[9] According to DFT calculations, the secondary 4-tetrahydropyranyl cation **E** adopts a chair conformation, where stabilization occurs through the overlap of both the oxygen equatorial lone pair and the empty p orbital at the cationic center with the C2–C3 and C5–C6 bonds orbitals.[10] Optimal delocalization places the hydrogen atom at C4 in a pseudoaxial position. Thereby, preferential equatorial attack of the nucleophile leading to cis isomers should be expected. This is the case for the fluorinated product **8a** in entries 2 and 6, and for triflate **9a** in entry 4. In this respect, the bulky complexed triple bond is likely to lock the conformation of the cyclic intermediate **E** and thus it contributes to increase the diastereomeric ratio compared to non-complexed substrate (entries 2/3; 4/5; and 6/7).

The formation of a large amount of trans isomer, as observed in entries, 1, 8, and 9, might result from thermodynamic control. Epimerization at C1 is possible via

reversible Nicholas reaction.[4a] When a pure isolated sample of *cis*-**7a** was allowed to react with $TiCl_4$ for 30 min, a 60/40 ratio of cis and trans isomers was formed.

Another rationale, in agreement with Rychnovsky proposal for trans selective Prins reactions, involves the concept of 'least motion pathway' from a tight ion-pair (**D**).[9a,11] As stated in our previous note,[2] the latter are likely to be involved in a non-dissociative solvent like CH_2Cl_2.

When the reaction led to a tertiary 4-tetrahydropyranyl cation, the formation of the tertiary chloride **7b** was highly trans selective (entry 10). The overall yield in tertiary fluoride **8b** was lowered by the regioselective formation of alkene **12b** through competitive elimination (entries 12–14). The amount of elimination was slightly higher when using $BF_3{\cdot}OEt_2$ (entries 12/14). Concomitantly, the cis/trans ratio increased as if the olefin was mainly formed at the expense of the trans fluoride.[12] The amount of **12b** increased even more when dichloromethane was replaced by nitromethane (entry 13), a solvent which has a medium dielectric constant and favors the formation of loose ion pairs. However, there was no more trapping of the cation by the fluoride anion. Only the trapping by ethanol released in the reaction medium during the reaction was detected. This argues in favor of the model of tight ion pairs in the low polarity solvent.

The diastereomeric ratios of the halogenated products in entries 10 and 14 are also in agreement with previous reports on Prins reaction.[13] In contrast to the secondary cation, the tertiary one is more stable in a planar geometry[10] and the reaction would lead to the thermodynamic product with the halogen atom in the axial position.

It can be noted that the substituent at the terminus of the 'formal' triple bond has also a significant influence upon the diastereoselectivity (entries 6, 8, and 9). Due to the change in the hybridization state of the triple bond carbons upon complexation, the bulk of the remote substituent influences the diastereoselectivity significantly. The diastereoselectivity should be influenced by the preferred conformation around the equatorial C–C bond adjacent to the complex. Bulky substituents (R^1) may hinder one face and destabilize the cis isomer.

The reactions where *o*-vinylphenols **5a**–**b** were used as partners for complexed acetal **1** led to rather disappointing results (Table 1, entry 15). This is probably due to stereoelectronic factors. In the absence of the methyl group geminated to the aromatic ring, there is no impediment to the conjugation of the double bond with the aromatic system. The double bond is pushed outward, therefore, the preferred conformation of the π system does not enable overlapping with the empty orbital at the cationic carbon center in the oxocarbenium ion. No cyclization was observed. However, due to the steric effect of the methyl group that prevents conjugation and makes the overlap possible, phenol **5b** led to **14b** but in rather low yield. In addition, the increased nucleophilicity of the double bond due to the electron-donating effect of the methyl group cannot be neglected.[14]

Table 2. Intramolecular trapping with allenic alcohols[15]

Entry	Alcohol (substrate)	Lewis acid	Products isolated yield (%)
1	**6a** (**1**)[a]	HBF_4	**17a** (87)
2	**6a** (**2**)[a]	HBF_4	**18a** (76)
3	**6a** (**3**)[a]	HBF_4	**19a** (50)
4	**6b** (**1**)[a]	HBF_4	**17b** (55)
5	**6c** (**1**)[a]	HBF_4	**17c** (55)

[a] The reactions were carried out at room temperature in dichloromethane, on 0.3–0.4 mmol of complex in the presence of 1.1 equiv of alcohol and 1.0 equiv of Lewis acid.

Much to our disappointment, the reactions performed in acetonitrile led to amides **15a** and **16a** in rather moderate yields, but with a high selectivity (entries 16–17).

Regarding the use of allenes as internal traps (Table 2), only homoallenic alcohol led to reactions having some synthetic value. In this case, the final cation would lose regioselectively a proton to give conjugated dienes (**17**–**19**). In the case of allene **6c**, with no gem dimethyl group at C5, the proton would be abstracted from C5. To the best of our knowledge, there are rather few examples of Prins cyclization involving allenes as internal trap. Prins cyclizations through TMSOTf-mediated cyclization onto an activated silylated allene was shown to give conjugated dienes.[16] Aza-Prins cyclization onto allenes has also been reported by Hanessian.[17] No cyclization product was isolated from alcohols **6d** and **6e**.[18] No 5-*endo* ring closure was observed using allenic alcohol **6f**.

In conclusion, protection of the triple bond as dicobalt hexacarbonyl complex enabled the synthesis of 2-alkynyl tetrahydropyrans functionalized at C4 via Lewis acid mediated-Prins cyclization in the presence of homoallylic alcohols. Both the yield and the diastereoselectivity were improved compared to the use of non-complexed acid-sensitive substrates. The outcome of the reaction depended on the nature of both the Lewis acid and the solvent. When acetonitrile was used as the solvent, a Prins–Ritter sequence led to amides in moderate yields. The use of homoallenic alcohols led to dienic products.

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6. As examples, the axial pseudo-propargylic protons give a ddd ($J = 11.3$, 1.7 Hz, $^4J_{HF} = 1.7$ Hz) in *cis*-**8a**, a dd ($J = 11.1$, 1.9 Hz) in *cis*-**7a**, and a dd ($J = 11.3$, 1.9 Hz) in *cis*-**9a**. The axial protons at C4 are characterized by dtt ($^2J_{HF} = 49.1$ Hz, $J_{HH} = 11.0$, 4.9 Hz) in **8a**, tt patterns ($J = 11.4$–11.9, 4.3–5.1 Hz) in **7a** and **9a**. The equatorial proton at C4 in *trans*-**8a** exhibits a t ($J = 3.0$ Hz).
7. Only ^{1}H NMR yields, based on the characteristic signals of protons at the stereocenters, were determined using pentamethylbenzene as internal standard. The isolation of the pure products was made difficult due to the low polarities of all products.
8. The characteristic signals of 4-ethoxybut-3-en-2-one are: ^{1}H NMR, δ 5.60 (d, $J = 12.8$ Hz, 1H), 7.55 (d, $J = 12.8$ Hz, 1H); ^{13}C NMR, δ 107.6 (CH), 176.7 (CH), 197.8 (C=O). The characteristic signals of 3-ethoxybut-2-enal are: ^{1}H NMR, δ 5.39 (d, $J = 7.6$ Hz, 1H), 9.75 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR, δ 105.2 (CH), 162.8 (C), 190.9 (C=O). Their identification was further confirmed by performing a blank experiment by reacting **1′** with HBF_4 in dichloromethane.
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15. Typical experimental procedure: *Hexacarbonyl[*μ-η^4-{*5,6-dihydro-5,5-dimethyl-2-(2-phenylethynyl)-3-(prop-1-en-2-yl)-2H-pyran*}*] dicobalt* (**18b**). 2,2,5-Trimethylhexa-3,4-dien-1-ol (43 mg, 0.31 mmol) and HBF_4 (38 μL, 0.28 mmol) were successively added, under inert atmosphere, to a solution of **2** (131 mg, 0.28 mmol) in freshly distilled dichloromethane (0.9 mL). The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched by the addition of water (5 mL) and the aqueous layer was extracted twice with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Liquid chromatography on silica gel (pentane) afforded **18b** (99 mg, 0.21 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.10 (s, 3H), 1.89 (s, 3H), 3.36 (d, $J = 11.1$ Hz, 1H), 3.63 (d, $J = 11.3$ Hz, 1H), 4.86 (s, 1H), 4.97 (s, 1H), 5.76 (s, 1H), 5.86 (s, 1H), 7.33 (m, 3H), 7.45 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7 (CH_3), 24.9 (CH_3), 27.3 (CH_3), 32.5 (C), 71.5 (CH_2), 73.7 (CH), 93.9 (C), 98.0 (C), 114.9 (CH_2), 127.8 (CH), 128.9 (CH), 129.9 (CH), 133.9 (CH), 137.2 (C), 138.9 (C), 140.6 (C), 199.8 (CO). HRMS (TOF MS ES+); MH+, Calcd [M+1] for $C_{24}H_{20}O_7Co_2$: 538.9945; found: 538.9939.
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