Pergamon

Tetrahedron Letters, Vol. 35, No. 23, pp. 4011-4014, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0687-S

Stereoselective Synthesis of Tetrahydrofurans and Tetrahydropyrans by Ni(0) Promoted Tandem Cyclization-Carbonylation

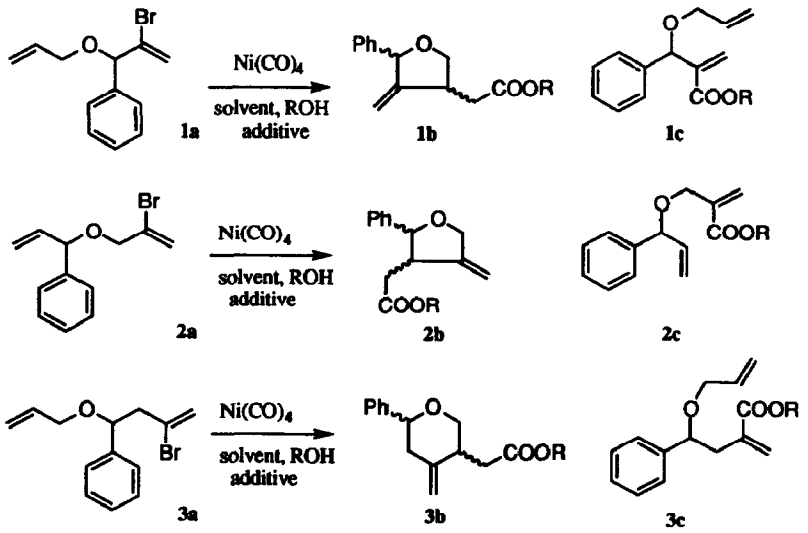
Antonio Delgado,* [1] Amadeu Llebaria, Francisco Camps, and Josep M. Moretó

Departament de Química Orgànica Biològica, C.I.D. (C.S.I.C.), Jordi Girona 18-26, 08034 Barcelona.

[1]Universitat de Barcelona, Facultat de Farmàcia, Laboratori de Química Farmacèutica, Avgda. Joan XXIII, s/n, 08028 Barcelona, Spain.

Abstract: Reaction of different vinyl bromides (**1a-3a**), bearing phenyl substituted alkenyloxyalkyl groups, with $Ni(CO)_4$ affords the corresponding substituted cyclic ethers **1b-3b** in moderate to good yields and high diastereoselectivity. In the cyclization of **1a**, the stereoselectivity of the process can be reversed by the use of additives, such as KOAc, TlOAc, Cs_2CO_3, and $KOCOCF_3$.

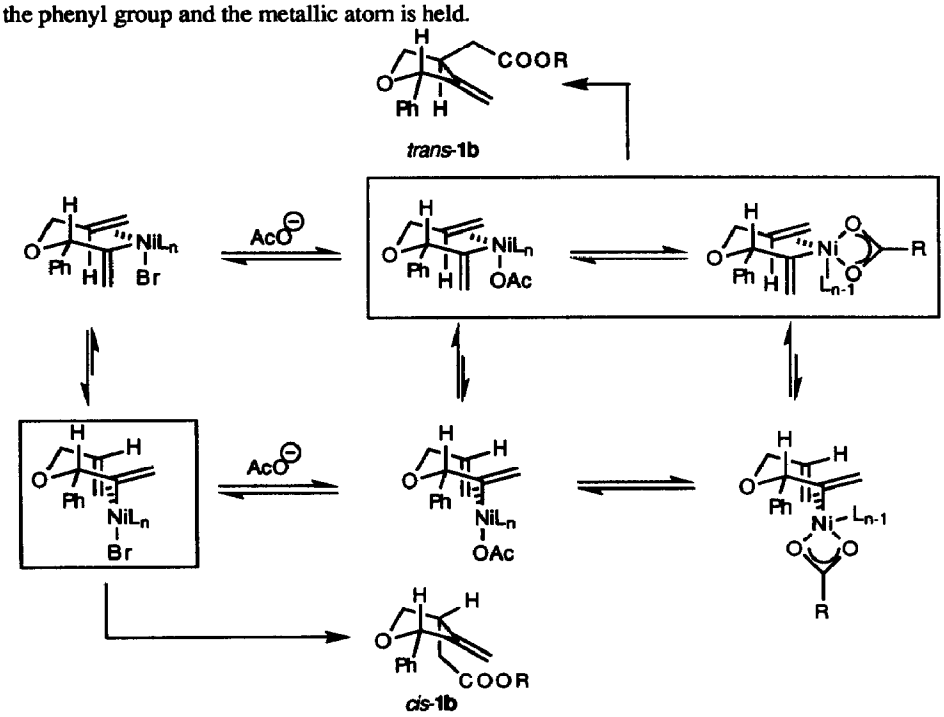
In our continuing effort to widen the scope of our recently developed nickel induced intramolecular cyclization and carbonylation of vinyl bromides with alkenes,[1,2] we wish to report in this communication our efforts addressed to the construction of oxygenated heterocyclic systems. In order to gain information about the stereochemical course of the metal induced cyclization step, substrates **1a-3a** bearing a phenyl substituent at different sites of the chain were used as suitable models.



Initial experiments were carried out under our previously developed standard conditions,[3] by treatment of halides **1a-3a** with tetracarbonylnickel[4] in acetonitrile in the presence of methanol (3 equiv.) and triethylamine. As expected, compounds **1b-3b**, arising from 5 or 6-Exo Trig cyclization processes were obtained as the only cycloadducts in modest to good yields (see Table).[5] As in the carbocyclic series,[1] open chain compounds **1c-3c** were also obtained as side products in variable yields. Replacement of methanol by bulkier alcohols such as isopropanol or *tert*-butanol reduced the formation of these compounds (entries 2, 8, 12, and 13).

Concerning the stereoselectivity of the cyclization step, whereas in the tetrahydrofuran series **2b**, *trans* isomers were predominant (entries 7-10), major *cis* isomers were obtained in the isomeric series **1b** (entries 1 and 2), and exclusive *cis* stereoselectivity between phenyl and ester groups was observed in the case of tetrahydropyran derivatives **3b** (entries 11-13). Interestingly, we found a reversal in the stereochemical outcome under the presence of certain additives in cyclizations leading to **1b** (entries 3-6). This effect was not observed for the isomeric tetrahydrofurans **2b** (entries 9 and 10). The use of additives in the related Heck reaction has been precedented in the literature,[6] and thallium salts, specially TlOAc, have been extensively used by Grigg *et al.* to effectively control the rate and the stereochemistry in palladium-catalyzed polyene cyclizations.[7]

Our results concerning the use of acetate as additive in related $Ni(CO)_4$ promoted intermolecular carbonylative cycloadditions,[8] although not fully understood, seem to indicate a ligand-like role for this ion within the coordination sphere of the metal. This behaviour could explain the stereochemical inversion observed in the presence of TlOAc, KOAc, and $KOCOCF_3$ under comparable conditions. Thus, as depicted below for **1a**, coordination of acetate at the vinyl-Ni intermediate would shift the conformational equilibrium, presumably to avoid 1,2 steric interactions with the vicinal phenyl group, towards an alternative chair-like conformer leading to *trans*-**1b**. This conformational bias would not be operative in the case of **2a**, where a relative 1,4 relationship between the phenyl group and the metallic atom is held.



Although the role of carbonate ions in this system remains also unclear, a similar effect to that of acetate should be considered (entry 5). Therefore, in using carboxylic acid salts as additives, it seems as though the stereochemical outcome of the process is mostly dependent on the nature of the substrate and, concerning the additive, on the ligand ability of the anion. The cation would be important for solubilization and, presumably, for removal of the halide ion from the coordination sphere of the metal, as shown in the case of Tl and Cs salts, which do not require the addition of Et_3N as a base.

Reaction of **3a** in MeOH, even in the presence of acetate afforded, in all cases, the open chain derivatives **3c** (compare entries 14 and 15 with entries 3, 4, 9, and 10), showing the less favourable nature of 6-Exo-Trig *vs* 5-Exo-Trig cyclizations. By using $KOCOCF_3$ as additive (entry 16), MeOH could be reduced to a stoichiometric amount without change in the stereochemistry of the resulting cycloadduct (compare entries 11 and 16). In agreement with the above assumption, a less sterically demanding 1,3 interaction between the phenyl group and the metal makes irrelevant the role of the additive on this process.

Further studies addressed to ascertain the role of additives and the influence of different substitution patterns in the chain on the stereoselectivity of this and related processes are currently underway in our laboratory.

TABLE. Intramolecular Cyclizations of Vinyl Halides [a]

entry	halide	solvent	ROH (equiv)	additive[b]	cycle[c] (%)	*cis:trans*[d]	open[c](%)
1	**1a**	acetonitrile	MeOH (3)	——	**1b** (76)	80:20	**1c** (13)
2	**1a**	acetonitrile	iPrOH (5)	——	**1b** (23)	70:30	——
3	**1a**	MeOH	——	KOAc	**1b** (47)	30:70	**1c** (24)
4	**1a**	MeOH	——	TlOAc[e]	**1b** (66)	30:70	——
5	**1a**	MeOH	——	Cs_2CO_3[e]	**1b** (10)	20:80	——
6	**1a**	MeOH	——	$KOCOCF_3$	**1b** (31)	30:70	——
7	**2a**	acetonitrile	MeOH (3)	——	**2b** (40)	40:60	**2c** (26)
8	**2a**	acetonitrile	iPrOH (5)	——	**2b** (23)	20:80	——
9	**2a**	MeOH	——	TlOAc[e]	**2b** (36)	20:80	**2c** (28)
10	**2a**	MeOH	——	KOAc	**2b** (50)	20:80	**2c** (26)
11	**3a**	acetonitrile	MeOH (1.2)	——	**3b** (28)	100:0	**3c** (38)
12	**3a**	acetonitrile	iPrOH (5)	——	**3b** (57)	100:0	**3c** (17)
13	**3a**	acetonitrile	tBuOH (5)	——	**3b** (51)	100:0	——
14	**3a**	MeOH	——	TlOAc[e]	**3b** (0)	——	**3c** (75)
15	**3a**	MeOH	——	KOAc	**3b** (0)	——	**3c** (98)
16	**3a**	acetonitrile	MeOH (1.2)	$KOCOCF_3$	**3b** (20)	100:0	**3c** (23)
17	**3a**	acetonitrile	MeOH (3)	Bu_4NOAc[f]	**3b** (0)	——	**3c** (92)[g]

a. For a general cyclization procedure, see ref.3; b. 3 equivalents; c. R=Me, iPr or t-Bu depending on the alcohol used (See Scheme 1); d. Inseparable mixture; e. No Et_3N was required for cyclization; f. Contains H_2O due to hygroscopicity; g. Carboxylic acid (R=H) was isolated instead of the methyl ester.

Acknowledgements: Financial support from DGICYT (Project PB 91-0612-C03-03) is gratefully acknowledged.

References and notes

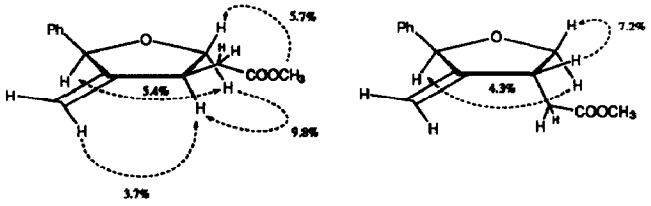
1. Llebaria, A.; Camps, F.; Moretó, J.M., *Tetrahedron Lett.*, **1992**, *33*, 3683-3686.

2. Llebaria, A.; Delgado, A.; Camps, F.; Moretó, J.M., *Organometallics*, **1993**, *12*, 2825-2831.

3. Typical experimental procedure: A solution of the starting bromide (1 mmol) in the appropriate solvent (20 mL, see Table) containing the additive (3 mmol) and Et_3N (6 mmol) under a stream of Ar was heated to 35°C and treated with $Ni(CO)_4$ (3 mmol) (CAUTION: see ref.4). When the starting bromide was completely consumed (TLC), a stream of Ar was passed thorough the reaction mixture and the volatiles were condensed in a cold trap containing iodine to destroy any unreacted nickel carbonyl. The residue was taken up in CH_2Cl_2, filtered through Celite, and evaporated to dryness. Flash chromatography (hexane-ethyl acetate 9:1 to 6:4) of the crude extract afforded the reaction products.

4. $Ni(CO)_4$ is an extremely toxic, volatile compound and precautions have to be taken during its use.

5. All new compounds have been characterized by spectroscopic techniques and elemental analysis or HRMS. Stereochemistry of compounds *cis*-**1b** and *trans*-**1b** (R=CH_3) has been assigned by NOE experiments, as indicated below.



cis-1b *trans-1b*

Sterochemistries of **2b** and **3b** were assigned on the basis of the magnitudes of J between C(2) and C(3) and C(5) and C(6) H protons, respectively, ($J_{H(2)-H(3)}$ *cis*-**2b** 5.2 Hz; *trans*-**2b**: 7.4 Hz, *cis*-**3b** $J_{H(6a)-H(5)}$= 2.7 Hz, $J_{H(6e)-H(5)}$= 0 Hz).

6. a) Overman, L.; Abelman, M.; Kucera, D.; Tran, V.; Ricca, D., *Pure Appl.Chem.*, **1992**, *64*, 1813-1819, and references therein; b) Meyer, F.; Brandenburg, J.; Parsons, P.; de Meijere, A., *J.Chem.Soc.Chem.Commun.*, **1992**, 390-392; c) Meyer, F.; Parsons, P.; de Meijere, A., *J. Org. Chem.*, **1991**, *56*, 6487-6488; d) Chida, N.; Ohtsuka, M.; Ogawa, S., *J. Org. Chem.*, **1993**, *58*, 4441-4447.

7. a) Grigg, R.; Sridharan, V., *Tetrahedron Lett.*, **1993**, *34*, 7471-7474; b) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T., *Tetrahedron*, **1992**, *48*, 7297-7320; c) Grigg, R.; Kennewell, P.; Teasdale, A.J., *Tetrahedron Lett.*, **1992**, *33*, 7789-7792; d) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A., *Tetrahedron Lett.*, **1991**, *32*, 687-690; e) Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Teasdale, A.; Thornton-Pett, M.; Worakun, T., *Tetrahedron*, **1991**, *47*, 9703-9720; f) Grigg, R.; Kennewell, P; Teasdale, A.; Sridharan, V., *Tetrahedron Lett.*, **1993**, *34*, 153-156.

8. a) Pagès, Ll.; Llebaria, A.; Camps, F.; Molins, E.; Miravitlles, C.; Moretó, J.M., *J. Am. Chem. Soc.*, **1992**, *114*, 10449-10461; b) Llebaria, A.; Moretó, J.M., *J. Organomet. Chem.*, **1993**, *451*, 1-13

(*Received in UK* 16 *February* 1994; *revised* 7 *April* 1994; *accepted* 8 *April* 1994)