Pergamon

Tetrahedron Letters, Vol. 37, No. 39, pp. 7023-7026, 1996

0040-4039/96 \$15.00 + 0.00

PII: S0040-4039(96)01539-0

Asymmetric Diels-Alder : Monobenzylated Isosorbide and Isomannide as Highly Effective Chiral Auxiliaries

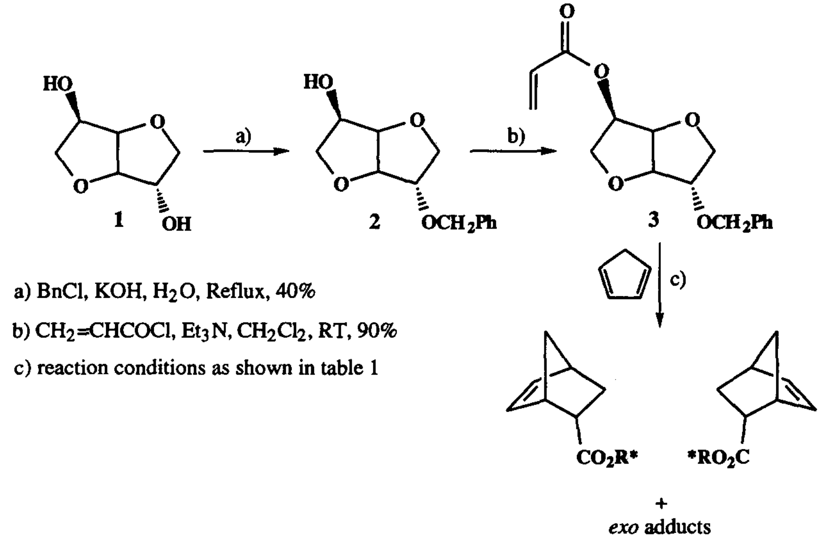
André Loupy *, Daphné Monteux

Laboratoire des Réactions Sélectives Sur Supports, Associé au CNRS, Bâtiment 410,
Université de Paris-Sud, 91405, Orsay France.

Abstract : Lewis acid promoted Diels-Alder reactions of acrylate esters from monobenzylated isosorbide or isomannide and cyclopentadiene provided exclusively *endo*-adducts with good yields and high diastereoselectivities. The R/S selectivities are quasi total and opposed using either isosorbide or isomannide derivatives. Copyright © 1996 Published by Elsevier Science Ltd

1,4:3,6 dianhydro-D-glucitol (isosorbide) **1** is an important well-documented by-product of the starch industry obtained by dehydration of D-glucitol[1]. It is thermally stable, of low cost, and available in large quantities. Since a few years, our laboratory bears interest on this compound and their monobenzylated derivatives in position 2 or 5[2,3]. These chiral monoalcohols are consequently serious candidates in asymmetric synthesis[4].

In this paper, we report the results obtained for the Diels-Alder reaction of acrylate **3** derived from *exo*-monobenzylated isosorbide **2** with cyclopentadiene (Scheme 1).



a) BnCl, KOH, H_2O, Reflux, 40%
b) CH_2=CHCOCl, Et_3N, CH_2Cl_2, RT, 90%
c) reaction conditions as shown in table 1

Scheme 1

Different Lewis acids were tested as well as montmorillonites which were previously shown to be efficient in this procedure[5,6]. The Diels-Alder reaction of chiral dienophile **3** and cyclopentadiene was carried out in different solvents. The analysis of the cycloadducts was performed using ^{1}H NMR. The diastereomeric ratio was determined by ^1H NMR and confirmed by visualization, after reduction with $LiAlD_4$, of enantiomers in a polybenzyl L-glutamate liquid-crystal through deuterium NMR[7] spectroscopy which also allows the determination of absolute configurations[8].

Table 1 Diels-Alder Reactions of Acrylate Ester from Isosorbide **3** with Cyclopentadiene [9]

Entry	Catalyst (equiv.)	Solvent	Temp.°C (time)	Yield a) (%)	Endo/Exo b)	R endo/S endo b) c)
1	-	CH_2Cl_2	20 (24h)	68	60:40	54:46
2	$SnCl_4$ (1)	"	20(45mn)	71	89:11	12:88
3	$SnCl_4$ (2)	"	-78 (15mn)	80	>99:1	9:91
4	"	"	**20 (10mn)**	**77**	**>99:1**	**4:96**
5	"	Et_2O	20(1h)	74	>99:1	28:72
6	"	PhMe	-78 (30mn)	92	>99:1	12:88
7	$TiCl_4$(2)	CH_2Cl_2	-78 (15mn)	80	>99:1	14:86
8	$EtAlCl_2$ (2)	"	-78 (15mn)	80	>99:1	74:26
9	"	"	20 (15mn)	71	89:11	65:35
10	"	Et_2O	20(1h)	60	93:7	87:13
11	$ZnCl_2$ (2)	CH_2Cl_2	20(2h)	96	82:18	67:33
12	$AlEt_3$ (2)	"	20(15h)	36 f)	70:30	54:46
13	BF_3-OEt_2(2)	"	20(5h)	29 f)	85:15	72:28
14	KSF d)	"	20(48h)	99	66:34	58:42
15	K10 d)	"	20(48h)	40 f)	69:31	69:31
16	$ZnCl_2$/ K10 d) e)	"	20(16h)	91	83:17	66:34
17	$ZnCl_2$/ K10 d)e) (2)	"	20 (several days)	50	>99:1	64:36

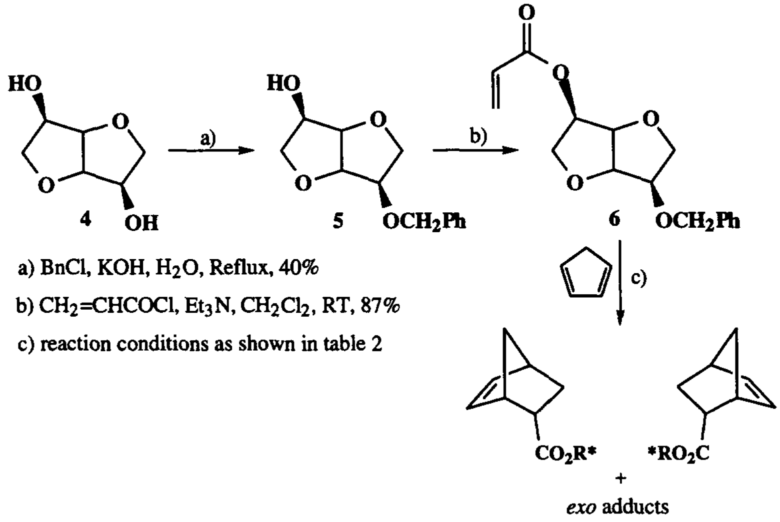
a) isolated yields b) determined by ^1H NMR c) confirmed by deuterium NMR spectroscopy
d) 1g of microwave dried solid for 1 mmole of substrat e) $ZnCl_2$/K10 is a Fluka product (0.35 mmol Zn /g)
f) incomplete reaction

The present Diels-Alder reaction showed the following selectivity:

1) Lewis acid with only a single coordination site ($EtAlCl_2$ and BF_3,OEt_2) showed R-*endo* selectivity (entries 8-10, 13).
2) chelating Lewis acids ($SnCl_4$ and $TiCl_4$) showed S-*endo* selectivity (entries 2-7).
3) solid Brönsted acids (K10 and KSF clays) gave lower yields or/and selectivities (entries 14-17).
4) the CH_2Cl_2 is a better solvent than Et_2O or PhMe (entries 4-6).

When compared to litterature[10], the results we obtained show the interest of isosorbide derivatives as chiral auxiliary. Results are at least as good or even better than those using classical camphor, menthol or 8-phenyl menthol derivatives[11] or more recently L-quebrachitol (a cyclitol)[12], sulfonamido indanols[13] and 9-anthrylcarbinols[14].

Furthermore, we evaluated the behaviour of monobenzylated isomannide **5** as a very close parent molecule, isomannide **4** being the isomer of isosorbide where both hydroxyl groups in position 2 and 5 are endo (scheme 2).



a) BnCl, KOH, H_2O, Reflux, 40%

b) CH_2=CHCOCl, Et_3N, CH_2Cl_2, RT, 87%

c) reaction conditions as shown in table 2

Scheme 2

Table 2 Diels-Alder Reactions of Acrylate Ester from Isosorbide **6** with Cyclopentadiene in CH_2Cl_2

Entry	Catalyst (equiv.)	Temp.°C (time)	Yield (%)	Endo / Exo	R endo/S endo
18	$SnCl_4$ (2)	-78 (30mn)	20	>99:1	60:40
19	**$EtAlCl_2$ (2)**	**-70 (1h)**	**79**	**>99:1**	**95:5**
20	$ZnCl2$ / K10	20 (16h)	93	80:20	66:34 a)

a) absolute configuration was confirmed by optical rotation of alcohol resulting from $LiAlH_4$ reduction of cycloadducts ($[\alpha]^{22}_D$ + 28 (c 1.065, EtOH 95%) lit. $[\alpha]^{22}_D$ + 87 (c 1.0, EtOH 95%))[15].

When compared to isosorbide derivative (Table 1, entry 8), using $EtAlCl_2$ as a catalyst, a significant improvement in R-*endo* selectivity is obtained (entry 19).

This result thus constitutes a noticeable complement to the $SnCl_4$-promoted reaction with isosorbide derivative (Table 1, entry 4) where almost complete S-*endo* selectivity is observed.

The exaltation of R-*endo* selectivity with the isomannide auxiliary can be due to a π-stacking interaction between acrylate double bond and phenyl moiety from benzylic protection. Further studies are in development to check this point.

Acknowledgments: we are grateful to the Université de Paris-sud and CNRS for financial supports and to MERS for a grant (D.M) and Roquette-Frères for a kind gift of isosorbide and isomannide. We are also indebted to Dr. Arnaud Haudrechy for stimulating discussions.

REFERENCES AND NOTES

1. Flèche, G.; Huchette, H. *Starch / Stärke* **1986**, *38*, 26-30.
2. Abenhaïm, D.; Loupy, A.; Munnier, L.; Tamion, R.; Marsais, F.; Quéguiner, G. *Carbohydr.Res.* **1994**, 261, 255-266.
3. Tamion, R.; Marsais, F.; Ribéreau, P.; Quéguiner, G.; Abenhaïm, D.; Loupy, A.; Munnier, L. *Tetrahedron: Asymmetry* **1993**, 4, 1879-1890.
4. Tamion, R.; Marsais, F.; Ribéreau, P.; Quéguiner, G. *Tetrahedron: Asymmetry* **1993**, 4, 2415-2418.
5. Cativiela, C.; Figueras, F.; Fraile, J.M.; Garcia , J.I.; Mayoral, J.A. *Tetrahedron: Asymmetry* **1991**, 2, 953-956.
6. Cativiela, C.; Figueras, F.; Fraile, J.M.; Garcia , J.I.; Mayoral, J.A. *Tetrahedron: Asymmetry* **1993**, 4, 223-228.
7. a) Bayle, J.P.; Courtieu, J.; Gabetty, E.; Loewenstein, A.; Péchiné, J.M. *New J.Chem.* **1992**, 16, 837-838.
   b) Meddour, A.; Canet, I.; Loewenstein, A.; Péchiné, J.M.; Courtieu, J. *J.Am.Chem.Soc.* **1994**, 116, 9652-9656.
   c) Canet, I.; Meddour, A.; Loewenstein, A.; Péchiné, J.M.; Courtieu, J. *J.Am.Chem.Soc.* **1995**, 117, 6520-6526.
8. Meddour, A.; Haudrechy, A.; Berdagué, P.; Picoul, W.; Courtieu, J. *Tetrahedron: Asymmetry* (submitted for publication).
9. Typical procedure: 200 mg of chiral acrylate was dissolved under argon in the adequate solvent before addition of cyclopentadiene (2-5 equivalents). After cooling at the desired temperature, the catalyst is introduced. Reactions were hydrolyzed with $NaHCO_3$ or NH_4Cl solutions. They are monitored by tlc and analyzed by ^1H and ^{13}C NMR and GC-MS. The order of reactants addition is not important.
10. Narasaka, K. *Synthesis* **1991**, 1-11.
11. Oppolzer, W.; *Angew.Chem.Int.Ed.Engl.* **1984**, 23, 876-889.
12. Akiyama, T.; Horiguchi,N.; Ida, T.; Ozaki, S.; *Chem. Lett.* **1995**, 975-976.
13. Carrière, A.; Virgili, A. *Tetrahedron: Asymmetry* **1996**, 7, 227-230.
14. Ghosh, A.K.; Mathivanan, P. *Tetrahedron: Asymmetry* **1996**, 7, 375-378.
15. Berson, J.A.; Walia, J.S.; Remanick, A.; Suzuki, S.; Reynolds-Warnhoff, P.; Willner, D. *J.Am.Chem.Soc.* **1961**, 83, 3986-3997.

(Received in France 2 *July* 1996; *accepted* 6 *August* 1996)