Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A New Synthesis of Isochromans and Phtalans

M. Ahmar [a] & R. Bloch [a]
[a] Laboratoire des Carbocycles (Associé au CNRS) , Institut de Chimie Moléculaire d'Orsay, B[acaron]t. 420 Université de Paris-Sud , 91405, ORSAY, France
Published online: 23 Sep 2006.

To cite this article: M. Ahmar & R. Bloch (1992) A New Synthesis of Isochromans and Phtalans, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:10, 1417-1420

To link to this article: http://dx.doi.org/10.1080/00397919208021607

SYNTHETIC COMMUNICATIONS, 22(10), 1417-1420 (1992)

A NEW SYNTHESIS OF ISOCHROMANS AND PHTALANS.

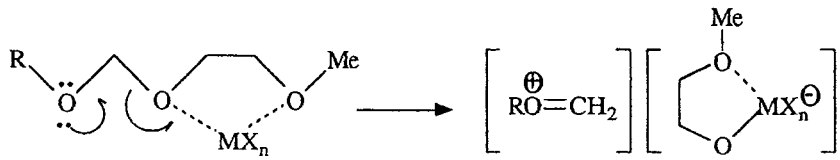
M. Ahmar and R. Bloch*

Laboratoire des Carbocycles (Associé au CNRS),
Institut de Chimie Moléculaire d'Orsay, Bât. 420
Université de Paris-Sud, 91405 ORSAY (France)

Abstract : A short and efficient synthesis of isochromans and phtalans has been devised. This synthesis involves the intramolecular Friedel-Crafts cyclialkylation of oxonium species generated by reaction of MEM ethers with Lewis acids.

Methoxymethyl (MOM), methylthiomethyl (MTM) and methoxyethoxymethyl (MEM) ethers are very useful hydroxyl protective groups [1] which can be easily cleaved by various Lewis acids such as boron halides derivatives [2], titanium tetrachloride [3,4] or zinc bromide [3].

The overall mechanism of the cleavage of MEM and MOM ethers with Lewis acids has been recently investigated [2b,4] and it has been shown that the favored pathway gave rise to an intermediate oxonium species **2**.

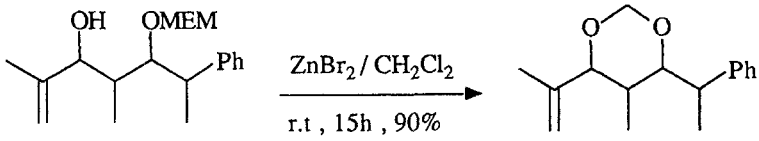


1 **2**

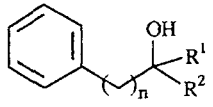
This electrophilic intermediate has been trapped by alcohols [2b] or reacted with allylsilanes [4]. We have also observed that this reactive intermediate can be

* To whom correspondence shoud be addressed

trapped intramolecularly by a proximate hydroxyl group to give a cyclic methylene ketal [5] :



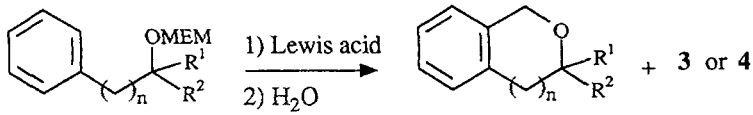
We wish to report here that oxonium species **2**, generated from MEM ethers **5** and **6** of benzylic or homobenzylic alcohols , undergo very easily intramolecular Friedel-Crafts cyclialkylation leading to an efficient synthesis of heterocyclic compounds such as 3,4-dihydro-(1H)-2-benzopyrans **8** (isochromans)[6,7] or 1,3-dihydroisobenzofurans **7** (phtalans) [6].



3 n = 0
4 n = 1

a : $R^1 = R^2 = H$
b : $R^1 = H$, $R^2 = C_6H_{13}$
c : $R^1 = CH_3$, $R^2 = C_4H_9$

ref.3



5 n = 0
6 n = 1

7 n = 0
8 n = 1

Table 1 summarizes the results of a series of experiments conducted with two Lewis acids : Zinc bromide and Titanium tetrachloride.

As can be seen from the table, titanium chloride appears to be an excellent reagent for the intramolecular cyclization reaction. The nature of the starting alcohol plays an important role during the reaction since the yields are increasing with the substitution (entries 3, 5, 7). It must also be noticed that, although it has been reported to be a difficult process [8], cyclizations leading to five membered rings (entries 1 and 2) takes place in the same conditions than the ones used for the formation of six membered rings.

Table 1 : **Synthesis of isochromans and phtalans by intramolecular Friedel-Crafts cyclialkylations.**

Entry	*Substrate*	*Lewis acid*	*Reaction time (h)* a)	*Products (yield)* b)
1	**5**	$ZnBr_2$	24	**7** (50%) + **3** (15%)
2	**5**	$TiCl_4$	10 c)	**7** (60%) + **3** (10%)
3	**6a**	$ZnBr_2$	24	**8a** (42%) + **4a** (15%)
4	**6a**	$TiCl_4$	2	**8a** (85%) + **4a** (5%)
5	**6b**	$ZnBr_2$	16	**8b** (79%) + **4b** (10%)
6	**6b**	$TiCl_4$	2	**8b** (98%)
7	**6c**	$ZnBr_2$	15	**8c** (91%) + **4c** (< 5%)
8	**6c**	$TiCl_4$	2	**8c** (99%)

a) All the reactions were conducted in methylene chloride at room temperature with $ZnBr_2$ and at -30°C with $TiCl_4$.
b) Yields for pure isolated compounds.
c) 4 hours at -30°C followed by 6 h at room temperature.

Experimental - Typical procedure

To a stirred solution of MEM ether **6c** (400 mg, 1.42 mmol) in methylene chloride (15 mL), cooled to -30°C under argon, was added 1.7 mL (1.7 mmol) of a 1M solution of titanium tetrachloride in methylene chloride. After two hours at -30°C, the mixture was allowed to warm to 0°C and quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (70 : 30 pentane-ether) to give 290 mg (99%) of **8c** as an oil. IR (film) : 3040, 3020, 1590, 1500, 1080 cm^{-1}. ^1H NMR (200 MHz, acetone d_6) : δ 7.2 - 6.95 (m, 4H) ; 4.68 (s, 2H) ; 2.65 (AB system, $\Delta\upsilon_{AB}$ = 25.68 Hz, J_{AB} =17.12 Hz, 2H) ; 1.67 - 1.12 (m, 6H) ; 1.15 (s, 3H) ; 0.89 (t, J = 7 Hz, 3H). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30 ; H, 9.87. Found : C, 82.30 ; H, 10.03.

References and Notes

(1) Greene, T.W. and Wuts, P.G.M., "*Protective Groups in Organic Synthesis*", Second edition, John Wiley and sons, New York, **1991**, p. 17.

(2) a) Williams, D.R.; Sakdarat, S. *Tetrahedron Lett.* **1983**, *24* , 3965.
b) Guindon, Y.; Yoakim, C.; Morton, H.E. *J. Org. Chem.* **1984**, *49* , 3912.
c) Corey, E.J.; Hua, D.H.; Seitz, S.P. *Tetrahedron Lett.* **1984**, *25* , 3.
d) Boeckman, R.K.Jr.; Potenza, J.C. *Tetrahedron Lett.* **1985**, *26* , 1411.

(3) Corey, E.J.; Gras, J.L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(4) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496.

(5) Ahmar, M.; Bloch, R. unpublished results.

(6) For previous syntheses of isochromans and phtalans see a) Hepworth, J.P., "*Comprehensive Heterocyclic Chemistry*", Vol. *3*, Pergamon Press, London, **1984**, pp. 787-789; b)Kirmse,W.; Kund,K. *J.Org.Chem.* **1990**, *55*, 2325 and references therein.

(7) While this work was in progress, the formation of isochroman (50%) and deprotected alcohol (20%) has been observed during the reaction of phenethyl MOM ether with $MgBr_2$ in ether : Kim, S.; Kee, I.S.; Park, Y.H.; Park, J.H. *Synlett,* **1991**, 183.

(8) Taylor, S.K.; Hockerman, G.H.; Karrick, G.L.; Lyle, S.B.; Schramm, S.B. *J. Org. Chem.* **1983**, *48* , 2449 and references there in.

(Accepted in The Netherlands 20 December, 1991)