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A New Synthesis of Isochromans and Phtalans

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A NEW SYNTHESIS OF ISOCHROMANS AND PHTALANS.

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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.

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

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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.

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.

<u>Table 1</u>: 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	TiCl4	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	6 b	TiCl4	2	8b (98%)
7	6 c	$ZnBr_2$	15	8c (91%) + 4c (< 5%)
8	6c	TiCl4	2	8c (99%)

a) All the reactions were conducted in methylene chloride at room temperature with ZnBr₂ and at -30°C with TiCl₄.

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 NaHCO₃ (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 d₆) : δ 7.2 - 6.95 (m, 4H); 4.68 (s, 2H); 2.65 (AB system, $\Delta v_{AB} = 25.68$ 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 C₁₄H₂₀O: C, 82.30; H, 9.87. Found: C, 82.30; H, 10.03.

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b) Yields for pure isolated compounds.

c) 4 hours at -30°C followed by 6 h at room temperature.

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