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# A New Route to Amino-2-propanol Structures with Adrenergic β-blocker Activity Using Low Valent Titanium

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**Abstract**: Amino-2-propanol structures can be obtained by addition to dibenzyl acetals of *in situ* generated dihalocarbenes using **LVT** (Low Valent Titanium). This methodology can be used to obtain adrenergic β-blockers with amino-2-propanol structure. Tetrahalomethanes are the best dihalocarbene precursors. The yields obtained using halofluoromethanes can be increased by addition of carbontetrachloride. A process that can imply halogen transfer may be proposed.


The β-blocker adrenergic activity is found in molecules which contain 1-aryloxy-3-alkylamino-2-propanol structures. Various synthetic approaches have been developed to these interesting drugs[1] which imply chemical and/or enzymatic functionalization processes of synthons with three carbon atoms and their subsequent connection to the corresponding aromatic groups.

In our work we outline a new simple method of building the chain of amino-2-propanol based on the reaction of dihalocarbene with dibenzyl acetals, through the employment of low valent titanium (**LVT**)[2], and the subsequent reaction with an amine (Scheme 1). The yields obtained using LVT with some target aldehydes are shown in Table 1.

We have previously used this method to prepare (R,S)-2-arylpropionic acids by addition of dihalocarbenes to C=O, with excellent yields[3].

We observe in Table 1 that only tetrahalomethanes can be used in the reaction ($CHCl_3$ gives olefin by coupling or no reaction is observed). This result agrees with the previously reported data in the preparation of (R,S)-2-arylpropionic acids with **LVT**[3]. This finding suggests that the formation of $X_2C$: in the reaction medium, is critical in the synthesis of the dihaloepoxide (Scheme 1).

SCHEME 1

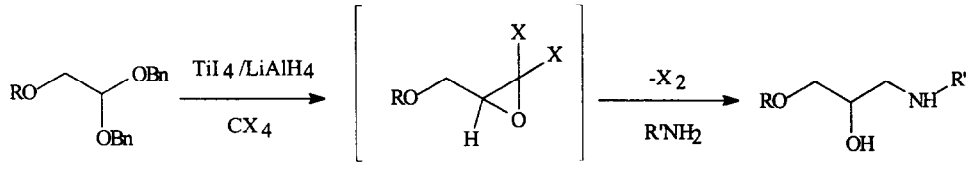
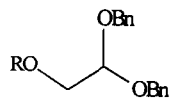
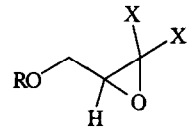


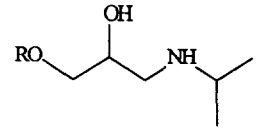
Table 1. Reaction Yields Obtained in the Addition of $X_2C$: to some Dibenzyl acetals.



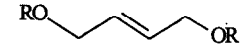

DBA




DHE




AP




OL

| DBA | Halomethane | Amine | DHE[c] | %AP[a] | %OL[a] | E/Z ratio |
|---|---|---|---|---|---|---|
| R=phenyl | $CCl_4$ | i-propyl | X=X=Cl | 45 | 15 | 73/27 |
| | $CHCl_3$ | | | -- | 45 | 70/30 |
| | $CF_2Br_2$ | | | 40[b] | 20 | 74/25 |
| | $CCl_4$ | n-butyl | X=X=Cl | 53 | 29 | 70/30 |
| | $CF_2Br_2$ | | | 42[b] | 22 | 77/23 |
| | $CCl_4$ | t-butyl | | 32 | 26 | 79/21 |
| | $CFCl_3$ | | X=F X=Cl | 28[b] | 20 | 75/25 |
| | $CCl_4$ | benzyl | X=X=Cl | 26 | 18 | 78/22 |
| R=α-naphthyl | $CCl_4$ | i-propyl | X=X=Cl | 35 | 20 | 90/10 |
| | $CHCl_3$ | | | -- | 50 | 90/10 |
| | $CF_2Br_2$ | | | 45[b] | 25 | 90/10 |
| | $CCl_4$ | n-butyl | X=X=Cl | 45 | 30 | 90/10 |
| | $CF_2Br_2$ | | | 42[b] | 26 | 85/15 |
| | $CCl_4$ | t-butyl | X=X=Cl | 35 | 30 | 80/20 |
| | $CFCl_3$ | | X=F X=Cl | 28[b] | 23 | 90/10 |
| | $CCl_4$ | benzyl | X=X=Cl | 33 | 19 | 90/10 |
| R=methyl | $CCl_4$ | i-propyl | X=X=Cl | 30 | 15 | 62/38 |
| | $CHCl_3$ | | | -- | -- | -- |
| | $CF_2Br_2$ | | | 20[b] | 20 | 60/40 |
| | $CCl_4$ | n-butyl | X=X=Cl | 35 | 29 | 60/40 |
| | $CF_2Br_2$ | | | 27[b] | 20 | 65/35 |
| | $CCl_4$ | t-butyl | X=X=Cl | 25 | 20 | 60/40 |
| | $CFCl_3$ | | X=F X=Cl | 20[b] | 25 | 60/40 |
| | $CCl_4$ | benzyl | X=X=Cl | 20 | 20 | 60/40 |

a) Yield in isolated product: DBA= dibenzyl acetals; DHE= dihaloepoxide; AP = amino propanol; OL = olephin. b) The yield increases by 20-25 % when $CCl_4$ is added. c) see literature[4].

The regioselectivity - directed towards C-2 -in the nucleophile ring opening of the epoxide intermediate by the amine is not influenced by it. A SN2 mechanism is observed in all reactions. The steric hindrance due to the presence of the aromatic ring does not reduce the yield of the amino-alcohol .

The main problem of this methodology, is the control and minimization of the carbonylic coupling that gives an alkene which is promoted by transition metals in low valence states[5]. This drawback may be reduced using solvents with slight coordination efficiency towards Ti(0) - probably the active species - such as THF. Solvents

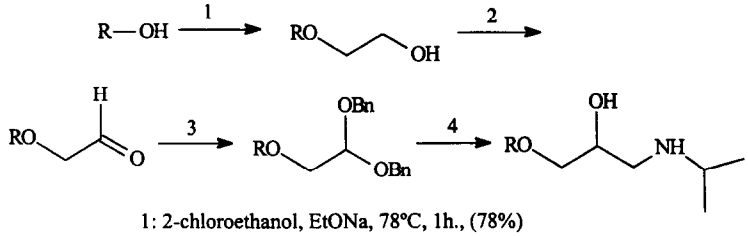
with nule (alkanes) or high (pyridine) coordination efficiency give poor results[6]. The stereoselectivity of the olefin formation (E/Z-ratio), depends on the steric bulk of the alkyl-aryl groups. Thus, the observed E/Z ratios shows the preference for formation of E-isomers as coupled products.

The presence of fluorine in the halogenomethane reduces the yield of amino-2-propanol (Table 1). Probably the atom of fluorine[7] in the dihaloepoxide intermediate hinders the nucleophile opening processes by the amine, due to the stability of C-F bond. Morover, fluorine reduces the reactivity of the carbene center necessitating more drastic conditions than in the standard ones, to achieve the product. Secondary products of condensation between the aldehyde and the primary amine, used as nucleophile, appear.

Recently, halogen exchange reactions using tetrachloro and tetrabromomethane have been described[8]. Taking advantage of this fact in our process, to avoid the drawback involved with the use of fluoromethanes in the generation of carbenes, we have used these exchange reactions to increase the yields to 20-25% greater than the ones found using fluoromethanes in absence of tetrachloro or tetrabromomethane.

The observed yields decrease when this process is applied to alkyl-oxy-aldehydes as substrates (Table 1). This can be related to difficulties in the isolation of the final product and not to a lack of reactivity.
The synthesis of the amino-2-propanols is summarised in Scheme 2.

SCHEME 2




1: 2-chloroethanol, EtONa, 78°C, 1h., (78%)
2: Potassium ferrate, dichloromethane, RT, 24h., (70%)
3: Benzylic alcohol, $H^+$, RT, 24 h., (80%)
4: $TiI_4/LiAlH_4$, halomethane, 0°C, THF, isopropylamine.

## Experimental

**Procedure to obtain propranolol using $CF_2Br_2(Cl_4C)$:**

In a flask under nitrogen, dry THF (250 ml), was cooled to -5°C and $TiI_4$(27.8g, 0.05 mol) was added . A suspension of $LiAlH_4$ (4.74g, 0.125 mol) in THF(50ml), was then added to the mixture over 30 ml. Then α-naphthyloxy-acetaldehyde dibenzyl acetal[10] (0.05 mol) in $CF_2Br_2$ (12.8 ml, 0.14 mol) was added to the mixture, which was stirred for 15 min, after $CCl_4$ (6.8 ml, 0.07 mol) was added to the solution, then the mixture was refluxed

for 6 h.(TLC). Finally an excess of isopropylamine (8.5 ml, 0.1 mol) was added and the mixture was stirred at room temperature for 2 h. The crude product was purified by chromatography on silicagel using $CH_2Cl_2$ as the eluent[11]. E/Z ratio was measured by $^1$H-NMR. The structure of the organic compounds was determined by NMR.

**Acknowledgements**

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11. m.p.: 94 °C (lit[1] 93 °C). IR: 3270-3054 (- OH, - NH) cm$^{-1}$.$^1$H- RMN($CDCl_3$, 250 MHz) δ: 8,26-6,80 (m,7H, aromat.); 4,18 (m, 3H, CH, $CH_2$); 2,94 (m, 3H, CH - N, $CH_2$- N); 1,16 (d,6H, $CH_3$) ppm. $^{13}$C-RMN($Cl_3CD$, 62,89 MHz) δ: 154,4 ($C_1$); 134,6 ($C_{10}$); 127,6 ($C_5$); 126,5 ($C_6$); 125,9 ($C_3$); 125,6 ($C_9$); 125,4 ($C_7$); 121,9 ($C_8$); 120,7 ($C_4$); 105,0 ($C_2$); 70,8 ($CH_2$ -OR); 68,6(CH -OH); 49,5 ($CH_2$ - N); 49,0 (CH - N); 23,3 and 23,2 (2 $CH_3$) ppm.

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