

NEW OXIDATIVE ESTERIFICATION OF ALCOHOLS WITH ALDEHYDES BY THE Br_2 -HMPT- NaHCO_3 .

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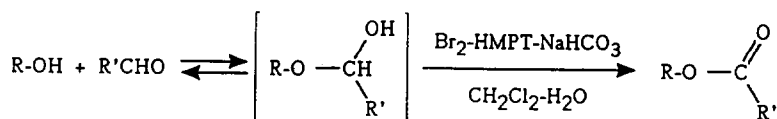
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Summary: *A new aldehyde-mediated oxidative esterification using a bromine/HMPT complex in the presence of sodium hydrogen carbonate is described.*

The conversion of aldehydes into esters in the presence of alcohols has been reported by many investigators (1-3). The use of bromine with sodium hydrogen carbonate (3) and sodium hypochlorite in acetic acid solution (2) was described to be very efficient in this oxidation. The transformation of primary alcohols to duplicate esters was also observed with the bromine (or chlorine)- hexamethylphosphoramide (HMPT) complex (4) and hypochlorite reagents (5).

The key-step in these oxidations is the formation of an hemiacetal intermediate between the aldehyde used, or formed in the reaction medium, and the alcohol.

Until now, the use of this reaction in synthesis was limited to the oxidation of aldehydes and primary alcohols to esters. We thought it interesting to investigate the application of the reaction in the esterification of an alcohol function using an aldehyde in the oxidative medium.



We studied some of the best halogenated reagents reported for the oxidation to esters via hemiacetal intermediates. It was found that the bromine-HMPT complex with sodium hydrogen carbonate in a two-phase system (4) gives the best results. The use of HMPT (6) accelerates considerably the oxidation by bromine and lowers the rate of halogenation which is the main secondary reaction in the oxidations with halogens and halogen derivatives. It contributes to the transfer of hydrobromic acid to the buffer phase and

consumes the excess of bromine at the end of the reaction. The carboxylic acid possibly formed by oxidation of the aldehyde is readily eliminated from the organic phase by sodium hydrogen carbonate.

A variety of alcohols were esterified by this system in the presence of an aldehyde. The results are summarized in table I for a two-fold molecular excess of alcohol.

The yields were dramatically increased when aliphatic aldehydes were used (entries 1-5). The yields in the esterification of aliphatic and benzylic primary alcohols were excellent. With secondary alcohols the reaction competes with the oxidation to ketones ⁽⁴⁾ (entry 14), but good yields could be obtained when a large excess of aldehyde and oxidant was used (entry 15). The tertiary alcohols gave lower yields because of the difficult formation of the hemiacetal intermediate (entry 16). The reaction could be extended to diols (entries 18 and 19).

In the case of unsaturated alcohols, the bromination of the double bond preceded the esterification. Nevertheless, the unsaturation could be recovered by debromination with sodium iodide in acetone after decantation and evaporation of dichloromethane (entry 17).

In summary, the application of this oxidative system to a variety of alcohols and aldehydes affords a convenient method for the transformation of primary and secondary alcohols and diols to esters and diesters, respectively.

TABLE I

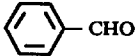

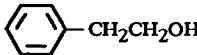
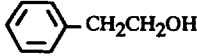
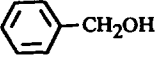
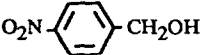
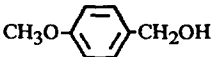
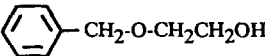
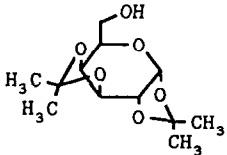
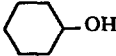
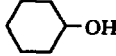
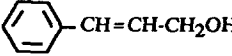
Entry	Alcohol	Aldehyde	Br ₂ equiv.	Yields ^(a) %
1	CH ₃ (CH ₂) ₈ CH ₂ OH	CH ₃ (CH ₂) ₂ CHO	1.5	94
2	CH ₃ (CH ₂) ₈ CH ₂ OH	CH ₃ -CHO	1.7	88
3	CH ₃ (CH ₂) ₈ CH ₂ OH	 CHO	2.5	11 (b)
4	CH ₃ (CH ₂) ₈ CH ₂ OH	 CHO	2.5	32 (c)
5	CH ₃ (CH ₂) ₈ CH ₂ OH	CH ₃ (CH ₂) ₆ CHO	1.5	94
6	 CH ₂ CH ₂ OH	CH ₃ (CH ₂)CHO	2.5	89
7	 CH ₂ CH ₂ OH	CH ₃ -CHO	2	95

TABLE I
 (continuation)

8	$\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	1.5	95
9		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	2.5	92 (d)
10		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	2.5	85
11		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	3	50 (e)
12		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	1.5	95
13		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	8	70
14		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	1.5	40
15		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	4	71
16	$\text{CH}_3\text{-CH}_2\text{-}\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}\text{-OH}$	$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	4	34
17		$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	4	59
18	$\text{HOCH}_2(\text{CH}_2)_4\text{-CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	4	94 (f)
19	$\text{CH}_3\text{-CHOH-CH}_2\text{-CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	5	73 (f)

(a) Isolated yield

(b) 72% of $\text{CH}_3\text{-(CH}_2)_8\text{-COO-CH}_2\text{-(CH}_2)_8\text{-CH}_3$ are also obtained in this entry.(c) 58% of $\text{CH}_3\text{-(CH}_2)_8\text{-COO-(CH}_2)_8\text{-CH}_3$ are also obtained in this entry.

(d) 3% of benzaldehyde are also obtained

(e) 16% of p-methoxybenzaldehyde and 27% of p-methoxybenzylbromide are also obtained in this experiment.

(f) Yield of the diester.

General Procedure: A mixture of alcohol (10 mM, unless otherwise indicated), aldehyde (5 equiv.), HMPT (0.5 - 1 equiv.) and sodium hydrogen carbonate (more than 2 equiv. relative to bromine) in 20 ml dichloromethane and 20 ml water is stirred in a water-ice bath and the bromine solution (3-5 M in chloroform) is added dropwise. The stirring is continued until decoloration of the solution (generally 30-60 minutes). The organic phase is separated and the aqueous phase is extracted with dichloromethane. The combined organic layers are dried ($MgSO_4$) and evaporated under reduced pressure. The ester is purified by column chromatography on silica gel (7).

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- 6 *In some cases, it was possible to substitute the HMPT by some other co-reagents like N-methylpyrrolidone and tetramethylurea in excess. But the results in general was better with HMPT.*
- 7 *Physical and analytical data of these compounds were analogous to those previously described.*

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