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SHORT COMMUNICATION

UNPRECEDENTED ALKYLATION OF CARBOXYLIC ACIDS BY BORON TRIFLUORIDE ETHERATE

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ABSTRACT. The alkylation of carboxylic acids by an ethyl moiety of boron trifluoride etherate in the absence of ethyl alcohol from the reaction system is unexpected and novel. Both aromatic and aliphatic carboxylic acids were clearly alkylated affording good yields in short reaction times with the exception of nicotinic acid that necessitated an overnight reaction. It was noted that while *ortho*-substituted hydroxyl groups of carboxylic acids investigated were not affected by alkylation, those of *meta*- and *para*-substituted carboxylic acids were partially etherified. Furthermore, the alkylation reaction was found to be compatible with a range of functional groups such as halogens, amino and nitro groups except for the alkene function of undecylenic acid that underwent polymerisation with concomitant alkylation of its carboxylic acid function.

KEY WORDS: Carboxylic acids, Alkylation, Etherification, Functional groups, Boron trifluoride etherate

INTRODUCTION

The synthesis of *ortho*-acylphenols have aroused the interest of organic chemists not least ourselves because of their biological activities with many of the molecules present in an array of natural products [1]. Many of them have served as synthons for the synthesis of biologically active chalcones, flavanones, naphthoquinones and pesticides [2-3]. We got encouraged by reports of the synthesis of *ortho*-acylphenols catalysed by boron trifluoride [4] and that of deoxybenzoins from respective substituted phenols and phenyl acetic acids in the presence of boron trifluoride etherate (BTE) as Lewis acid catalyst and as solvent for the acylation reactions [5]. Given that we had substantial quantities of BTE in stock, we decided to test the reaction of carboxylic acids with differently substituted phenols. In place of the anticipated acylphenols, all carboxylic acids were alkylated forming carboxylic acid ethyl esters.

Carboxylic acid esters are basic compounds in organic synthesis. They find applications as pharmaceuticals, agrochemicals, cosmetics, flavours, electronic materials and also serve as synthons for synthetic intermediates. Their synthesis is widely achieved by the classical Fischer-Speier esterification by which carboxylic acids react with alcohols in the presence of acid catalysts [6]. This being a reversible condensation reaction, the desired esters can be obtained by using an excess of alcohol or by the azeotropic *in situ* removal of water. The formation of esters is not limited to the Fischer process alone but it can also be satisfactorily achieved by alkylation of carboxylic acids. A literature survey reveals different reaction conditions for the different alkylating agents such as orthoesters [7], N,N-dimethylformamide dialkyl acetals [8], triazene derivatives [9], *o*-dialkylisoureas [10], dimethylcarbonate [11], methylboronic acid [12], dimethylsulfoxide [13], methylsalicylate [14], terminal alkynes [15-17] and *in situ* generation of diazomethane, the latter reagent due to its explosive nature and cancer-causing properties has

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been largely replaced in recent years by trimethylsilyldiazomethane-hexane solution [18]. The alkylation process has gained popularity and is being applied in laboratories and in some cases in industry. While reports of the esterification of carboxylic acids catalysed by BTE are known and take place in the presence of an alcohol [19-21], the alkylation of carboxylic acids by an ethyl moiety of BTE in the absence of ethyl alcohol from the reaction system is unexpected and to the best of our knowledge has not been reported and therefore forms the basis of this communication.

EXPERIMENTAL

General. All chemicals were obtained from commercial sources and were used without further purification unless stated otherwise. Products were characterised by ^{1}H- and ^{13}C-NMR spectroscopy using a Varian spectrometer at 400 and 100 MHz for proton and carbon-13 respectively. Spectra were recorded in $CDCl_3$ solutions employing TMS as an internal reference. All spectra are reported as δ (ppm) values.

*Representative procedure (compound **1**)*. In a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser and a calcium chloride drying tube was placed nicotinic acid (1 g, 8.1 mmol) suspended in boron trifluoride etherate (10 mL). The reaction mixture was stirred and heated to 120 °C overnight during which the creamy reaction mixture changed into a brownish solution. Thin layer chromatography (hexane/ethyl acetate 3:1) revealed complete reaction. The cooled reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extract was washed to the end of effervescence with a saturated solution of $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo giving a crude yield of 1.11 g (92%). Column chromatography on silica gel (hexane/ethyl acetate 3:1) gave 0.99 g (82%) of a pleasant smelling oil. ^{1}H-NMR; $\delta_{(CDCl3)}$: 1.33 (t, 3H, J = 7.04), 4.33 (q, 2H, J = 7.04), 7.32 (dd, 1H, J = 7.82, 5.1), 8.22 (d, 1H, J = 7.83), 8.69 (d, 1H, J = 5.1), 9.14 (s, 1H). ^{13}C-NMR; $\delta_{(CDCl3)}$: 14.15, 61.32, 123.14, 126.20, 136.88, 150.79, 153.22, 165.16.

All the other products listed in Table 1 (**2–25**) were prepared analogous to the representative procedure.

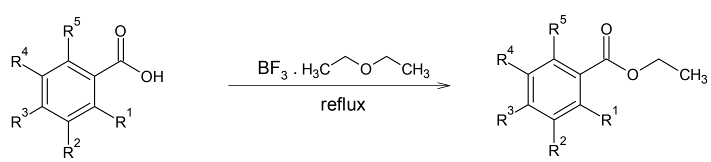


Table 1. Alkylation of carboxylic acids by boron trifluoride etherate.

Entry	Carboxylic acid	Ester product formed	Product number	% Yield	#Reference
1	Nicotinic	Ethyl nicotinate	**1**	82	[22]
2	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	**2**	73	[23-26]
3	$R_3 = Cl, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = Cl, R_1 = R_2 = R_4 = R_5 = H$	**3**	94	[26-27]
4	$R_3 = NH_2, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = NH_2, R_1 = R_2 = R_4 = R_5 = H$	**4**	99	[25, 28]
5	$R_2 = Br, R_1 = R_3 = R_4 = R_5 = H$	$R_2 = Br, R_1 = R_3 = R_4 = R_5 = H$	**5**	63	[29]
6	$R_2 = OH, R_1 = R_3 = R_4 = R_5 = H$	$R_2 = OH, R_1 = R_3 = R_4 = R_5 = H$	**6a**	56	[30]
		$R_2 = OEt, R_1 = R_3 = R_4 = R_5 = H$	**6b**	42	[31]
7	$R_1 = I, R_2 = R_3 = R_4 = R_5 = H$	$R_1 = I, R_2 = R_3 = R_4 = R_5 = H$	**7**	75	[32]
8	$R_3 = Br, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = Br, R_1 = R_2 = R_4 = R_5 = H$	**8**	80	[26, 33]
9	$R_3 = OH, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = OH, R_1 = R_2 = R_4 = R_5 = H$	**9a**	38	[24, 34]

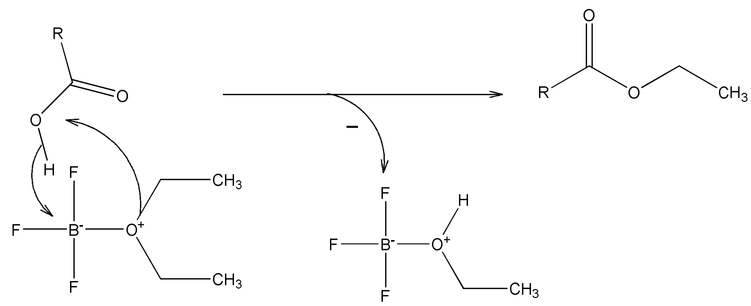
		$R_3 = EtO, R_1 = R_2 = R_4 = R_5 = H$	**9b**	35	[35]
10	$R_3 = O_2N, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = O_2N, R_1 = R_2 = R_4 = R_5 = H$	**10**	48	[26]
11	$R_3 = Me, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = Me, R_1 = R_2 = R_4 = R_5 = H$	**11**	80	[36]
12	$R_3 = MeO, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = MeO, R_1 = R_2 = R_4 = R_5 = H$	**12**	76	[37]
13	$R_1 = NH_2, R_2 = R_3 = R_4 = R_5 = H$	$R_1 = NH_2, R_2 = R_3 = R_4 = R_5 = H$	**13**	98	[25]
14	$R_1 = OH, R_2 = R_3 = R_4 = R_5 = H$	$R_1 = OH, R_2 = R_3 = R_4 = R_5 = H$	**14**	78	[38]
15	$R_3 = F, R_1 = R_2 = R_4 = R_5 = H$	$R_3 = F, R_1 = R_2 = R_4 = R_5 = H$	**16**	99	[39]
16	$R_2 = O_2N, R_1 = R_3 = R_4 = R_5 = H$	$R_2 = O_2N, R_1 = R_3 = R_4 = R_5 = H$	**16**	59	[26]
17	$R_3 = F, R_2 = O_2N, R_1 = R_4 = R_5 = H$	$R_3 = F, R_2 = O_2N, R_1 = R_4 = R_5 = H$	**17**	94	[40]
18	$R_1 = Cl, R_2 = R_3 = R_4 = R_5 = H$	$R_1 = Cl, R_2 = R_3 = R_4 = R_5 = H$	**18**	97	[26]
19	$R_1 = R_4 = OH, R_2 = R_3 = R_5 = H$	$R_1 = R_4 = OH, R_2 = R_3 = R_5 = H$	**19**	99	[34]
20	$R_2 = CO_2H, R_1 = R_3 = R_4 = R_5 = H$	$R_2 = CO_2Et, R_1 = R_3 = R_4 = R_5 = H$	**20**	69	[41]
21	$R_1 = CO_2H, R_2 = R_3 = R_4 = R_5 = H$	$R_1 = CO_2Et, R_2 = R_3 = R_4 = R_5 = H$	**21**	87	[42]
22	$C_6H_5(CH_2)_3CO_2H$	$C_6H_5(CH_2)_3CO_2Et$	**22**	86	[43]
23	$Cl(CH_2)_2CO_2H$	$Cl(CH_2)_2CO_2Et$	**23**	72	[44]
24	$CH_3[CH_2]_3CO_2H$	$CH_3[CH_2]_3CO_2Et$	**24**	86	[45]
25	$CH_2{=}CH(CH_2)_8CO_2H$	$[CH_2\text{-}CH]_n\text{-}(CH_2)_8CO_2Et$	**25**	Polymerized	

[#]indicates references for reactions investigated earlier under different conditions.

RESULTS AND DISCUSSION

The alkylation of carboxylic acids proceeded cleanly with good yields in the presence of boron trifluoride etherate as alkylating agent and solvent. The reactions were complete in 4 hours except for nicotinic acid which was refluxed overnight. Reported esterification of carboxylic acids catalysed by boron trifluoride or boron trifluoride etherate have all until now necessitated the presence of an alcohol [16]. On the other hand, the alkylation of carboxylic acids by an ethyl moiety of BTE alone is unexpected and to our knowledge unprecedented. The alkylation reaction was compatible with a range of functional groups such as halogens, amino and nitro groups. While the alkene function of undecylinic acid **25** polymerized in the reaction process, the acid moiety of the molecule was nevertheless alkylated as revealed by its NMR spectrum. The carboxylic acid groups of compounds **6** and **9** were alkylated, their hydroxyl groups were partly etherified forming compound **6b** and **9b**, respectively, while the hydroxyl groups in **6a** and **9a** remained untouched. It is noteworthy that as the acid in compound **14** was alkylated, its *ortho*-substituted hydroxyl group was not. Furthermore, both hydroxyl groups in compounds **19** were not etherified. No significant trend can be deduced from the reactions to explain why *ortho*-substituted hydroxyl groups in compounds **14** and **19** were not etherified at all, whereas *meta*- and *para*-substituted hydroxyl groups in compounds **6** and **9** were partly etherified to form compounds **6b** and **9b**, respectively. In all cases, the hydroxyl group of the carboxylic acid is etherified faster than the alcohol function due to its higher acidity. Phthalic and isophthalic acids were completely alkylated to afford esters **21** and **20**, respectively, without any trace of their mono ester formation. As we have established this alkylation reaction is not limited to aromatic compounds but can be extended to aliphatic carboxylic acid systems with good yields as demonstrated in compounds **22**, **23**, **24** and **25**.

The hitherto described alkylation of carboxylic acids in both aliphatic and aromatic systems is thought to proceed according to the following reaction mechanism:



CONCLUSION

Although the alkylation of carboxylic acids by boron trifluorde etherate is a clean reaction, it is unlikely that it would become the method of choice due to the prohibitive cost of boron trifluoride etherate compared to the classical Fischer esterification reagents. Nevertheless it is a transformation worthy of note and might find applications under special circumstances in organic syntheses.

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