A Simple, Powerful, and Efficient Method for Transesterification

Otto Meth-Cohn

National Chemical Research Laboratory, Council for Scientific and Industrial Research, P.O. Box 395, Pretoria 0001, South Africa

Aromatic and α,β-unsaturated methyl esters undergo efficient transesterification at ambient temperature or below with primary, secondary, or (particularly) tertiary alcohols in the presence of butyl-lithium in tetrahydrofuran solution.

Transesterification is in general an unsatisfactory synthetic method but of enormous potential in synthesis. Severe conditions are usually required and the reaction is especially ineffective with tertiary or sterically hindered alcohols.[1] This synthetic approach is nevertheless desirable since simple esters are frequently isolated or produced and require further transposition to higher analogues, usually by way of the corresponding acid. I herein describe a very mild and simple method for converting methyl esters into their homologues which is especially suited to tertiary and sterically congested systems.

Underlying the dramatic developments in organolithium chemistry in recent years is the phenomenal affinity lithium has for oxygen lone-pair electrons, thereby facilitating contiguous metallation. However, the focus of attention has been upon *C*-lithio reagents or non-nucleophilic *N*-lithio species (*e.g.* lithium di-isopropylamide). The role of nucleophilic lithium alkoxides has largely been overlooked. This note concerns the use of lithium alkoxides in tetrahydrofuran (THF) solution for effecting transesterification of methyl esters particularly of aromatic and α,β-unsaturated acids (Scheme 1 and Table 1). Aliphatic esters appear to be decidedly less reactive in this reaction.

Several fascinating features emerge from this study.†

(i) All the reactions proceed at or below ambient temperature. Electron deficient esters (expts. 4—10, 14—19, 24—26) generally react within minutes. The longest reaction times involve overnight treatment.

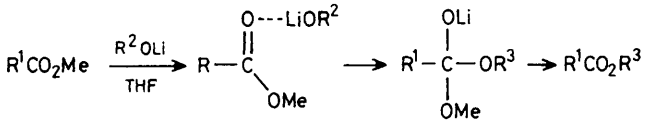
(ii) For secondary and tertiary alcohol equimolar amounts of the ester and alcohol suffice for good yields. Although roughly one molar equivalent of butyl-lithium per mole of alcohol was generally employed, use of less (expts. 7, 9, 25, 26) suffices but lengthens reaction times. Alcohols insoluble in THF [*e.g.* (**1**)] frequently dissolve on addition of butyl-lithium. With primary alcohols (*e.g.* expts. 8—10) an excess of the alcohol is

† A typical reaction is as follows. To (−)-menthol (0.01 mol) in dry stirred THF (20 ml) in an ice-bath under nitrogen was added n-butyl-lithium in hexane (1.6 M; ~0.01 mol) and methyl *p*-methoxybenzoate (0.01 mol). The reaction was monitored by t.l.c. (20% diethyl ether–light petroleum; ~50% in 1 h; 70% in 6 h). After 18 h water and ether were added and the organic layer was dried, evaporated, and flash chromatographed (20% diethyl ether–light petroleum). The product was further distilled in a Kugelrohr apparatus (215 °C at ~0.5 mmHg) to give *p*-methoxybenzoyl menthoate (92%) as a colourless liquid.

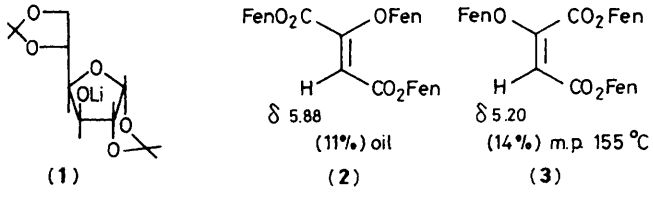
Table 1. Transesterifications using LiOR in THF.

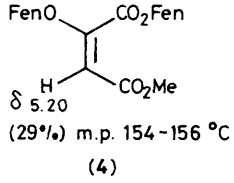
Expt.	Reactants (mol)[a] Ester	Alcohol	BuLi (mol)	Time /h	Temp.[b] /°C	Yield[c] (%)	M.p. (b.p.)[d] (°C)	Lit. m.p. (b.p.)[ref.] (°C)
1	$PhCO_2Me$	Bu^tOH (2)	2	18	RT	100	(60, 3 mmHg)	(94, 10 mmHg)[2]
2	$PhCO_2Et$	Bu^tOH (2)	2	18	RT	61		
3	$PhCO_2Ph$	Bu^tOH	1	18	RT	27		
4	$2\text{-}O_2NC_6H_4CO_2Me$	Bu^tOH	1	3	RT	74		[3]
5	$3\text{-}O_2NC_6H_4CO_2Me$	Bu^tOH	1	1	<5	89	29—30	31[4]
6	$4\text{-}O_2NC_6H_4CO_2Me$	Bu^tOH	1	1	<5	8	114—115	115.5[5]
7	$4\text{-}O_2NC_6H_4CO_2Me$	Bu^tOH	0.17	6	<5	40		
8	$4\text{-}O_2NC_6H_4CO_2Me$	$CH_2=CHCH_2OH$	1	1	<5	50(3a)[e]		
9	$4\text{-}O_2NC_6H_4CO_2Me$	$CH_2=CHCH_2OH$ (3)	1	1	<5	70(30)[e]		
10	$4\text{-}O_2NC_6H_4CO_2Me$	$CH_2=CHCH_2OH$ (18)[f]	1	1	<5	64(18)[e]		
11	$4\text{-}MeOC_6H_4CO_2Me$	(−)-Menthol	1	18	RT	92	(215)	
12	$1,4\text{-}C_6H_4(CO_2Me)_2$	Bu^tOH	1	18	RT	mono 19(2a)[e] di 34	(150) 69 (175) 118—119	68.5—69[6] 119.5—120[6]
13	$1,4\text{-}C_6H_4(CO_2Me)_2$	Bu^tOH (3)	3	3	<5	mono 15 di 74		
14	$2\text{-}PyCO_2Me$	Bu^tOH	1	1	<5	77	(105)	
15	$3\text{-}PyCO_2Me$	Bu^tOH	1	1	<5	84	(90)	(108, 8 mmHg)[7]
16	$3\text{-}PyCO_2Me$	Me_2EtCOH	1	2	<5	76	(120)	
17	$3\text{-}PyCO_2Me$	(+)-Fenchol	1	0.2	<5	98	(190)	
18	$3\text{-}PyCO_2Me$ (2)	Cholesterol	1	18	RT	94	150—152	152—154[8]
19	$4\text{-}PyCO_2Me$ (2)	Lanosterol	1	2	<5	73		
20	$CH_2=CHCO_2Me$ (3)	(−)-Menthol	1	18	RT	93	(75)	(128, 18 mmHg)[9]
21	$CH_2=CHCO_2Me$ (3)	(−)-Borneol	1	1	<5	82	(75)	(55—56, 0.1 mmHg)[10]
22	$PhCHCHCO_2Me$	Bu^tOH	1	18	RT	78	(100)	(144, 8 mmHg)[11]
23	$PhCHCHCO_2Me$	Bu^tOH (2)	2	1	RT	80		
24	Me_2fumarate	Bu^tOH (1.5)	1.5	0.5	−10	mono 27 di 50	46	46[12]
25	Me_2fumarate	(−)-Menthol (2)	1	0.25	−10	mono 16 di 50	(120) (145)[g]	-[13]
26	Me_2fumarate	(−)-Menthol(3)	1	0.25	−10	mono 41 di 54		

[a] Unless otherwise specified one equivalent of reactant is used; Py = pyridyl. [b] RT = room temperature. [c] Yields are of isolated material after flash chromatography and (with liquids and low-melting solids) distillation. [d] b.p. refers to Kugelrohr distillation at *ca.* 0.5 mmHg, unless noted otherwise. [e] % Recovery of starting ester in parentheses. [f] The alcohol was used as solvent. [g] $[\alpha]_D^{23}$ 92.9° (*c* 0.7, chloroform); lit.[13] $[\alpha]_D^{23}$ −102.0 ± 2° (*c* 1.6, chloroform).



Scheme 1





Scheme 2. Fen = (+)-Fenchyl.

necessary for good yields (~3 equiv.). Ethyl esters undergo alcoholysis but with poorer equilibration in the desired direction and lower reaction rates (expt. 2). Phenyl esters appear to offer no advantage being slower and less effective in the transesterification (expt. 3). Commercial alcohols were used directly *without* drying.

(iii) Of the solvents studied the reaction is significantly faster in THF than in benzene and reactions in both are faster than in hexane. Furthermore, in benzene and hexane solutions, it appeared that methyl cinnamate underwent some isomerisation as well as transesterification. Dry THF (sodium and benzophenone) was employed. Use of the alcohol as solvent (expt. 10) did not prove worthwhile.

(iv) Aromatic esters react without problems. α,β-Unsaturated esters behave normally without isomerisation, though yields from methyl fumarate were only moderate, suggesting that some Michael addition and subsequent degradation (retro-aldol?) occurred. Asymmetric alcohols reacted without loss of chiral integrity (expt. 25). Methyl esters are not only ubiquitous and readily prepared but in most cases small amounts of unchanged material, being more polar, are easily removed from the product by flash chromatography or occasionally by distillation. A major limitation of the method involves alcohols that strongly complex the lithium intramolecularly such as sugar derivatives [*e.g.* (**1**) which is unchanged on treatment with methyl nicotinate for 18 h]. Polymerisable compounds such as methyl acrylate are best used in excess

(expts. 20, 21). Also, when the alcohol is precious or difficult to separate from the product ester (*e.g.* expts. 18, 19) an excess of the methyl esters obviates the problem. Dimethyl acetylenedicarboxylate rapidly undergoes competitive Michael addition and ester exchange even at −78 °C, the products (**2**)—(**4**) being isolated amongst others, when three equivalents of (+)-fenchol were employed (Scheme 2).

(v) The success of this transesterification would appear derived from (a) the strong complexation of the lithium alcoholate to the ester carbonyl group *via* 'lithium bonding', (b) the lower pK_a of methanol compared to higher homologous alcohols, encouraging efficient equilibration to produce esters. The lack of success with aliphatic esters is at present unclear.

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