Transesterification of α-Substituted Esters Mediated by Potassium Carbonate

Dominik Jańczewski, Ludwik Synoradzki,* Marek Włostowski

Laboratory of Technological Processes, Faculty of Chemistry, Warsaw University of Technology, ul. Noakowskiego 3, 00-664 Warszawa, Poland
Fax +48(22)6255317; E-mail: Ludwik.Synoradzki@chemix.ch.pw.edu.pl
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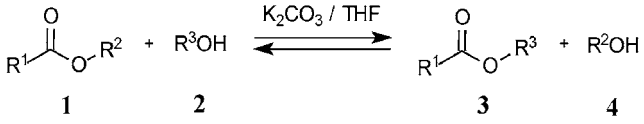
Abstract: α-Substituted esters were efficiently and easily transesterificated at room temperature in the presence of potassium carbonate. α-Halo esters can be transesterificated without substitution of the halogen atom.

Key words: transesterification, catalysis, α-substituted esters, potassium carbonate, haloesters

Transesterification is a well known reaction catalyzed both by acids or bases.[1] α-Hydroxy[2,3] and α-benzyl esters[4–6] were reported to undergo transesterification in the presence of K_2CO_3. Unsubstituted esters were also found to react under these conditions however in this case high temperature, pressure and a phase transfer catalyst (PTC) were necessary.[7]

We now would like to report that also some α-halo and α-alkoxy methyl and ethyl esters enter readily the transesterification reaction catalyzed by K_2CO_3 (Table 1). The alcohol of our interest was *N*-(2-hydroxy-ethyl)-phthalimide (**2a**), however, other alcohols such as benzyl alcohol (**2h**) and ethoxyethanol (**2i**) also reacted with α-chloroesters in good yields (Scheme 1).



Scheme 1

The substitution reaction proceeds selectively at the carbon atom of the alkoxycarbonyl group and, surprisingly, an exchange of the halogen atom in haloesters was not observed under the reaction conditions.[8]

The reaction is carried out at room temperature and after about 48 hours reaches the state of equilibrium.[9a] The yield of product **3** can be easily increased when ethanol or methanol, formed during the reaction, are removed by distillation[9b] (Table 2).

We compared the rate of the transesterification reaction of ethyl (**1a**) and methyl (**1a′**) chloroacetates with **2a** and found that although the reaction of **1a′** was faster than the reaction of **1a**, the state of equilibrium was achieved at approximately the same level (Figure 1).

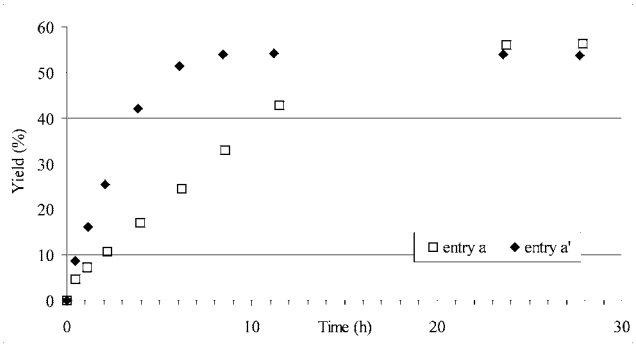


Figure 1 Transesterification of alkyl chloroacetates (**1a**, **1a′**) with **2a** (yield determined by HPLC)

We examined the influence of the PTC catalyst on the reaction rate and yield. We found that the yield of the reaction **1a** with **2a** did not depend on the presence of crown ether or tetrabutylammonium bromide; the state of equilibrium was reached at the same time with and without the catalyst.

We also tried to extend the reaction range to unsubstituted esters. We found that at room temperature ethyl acetate (**1g**) did not react with **2a** at all. When the reaction mixture was refluxed for 200 hours, product **3g** was obtained in low (12%) yield. On the basis of this experiment we assume that the presence of a substituent such as a halogen atom or an alkoxy group at the α-position to the ester is necessary and activates the transesterification reaction.

References

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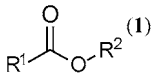
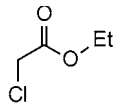
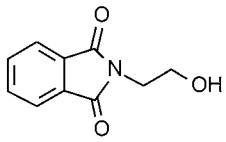
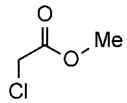
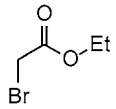
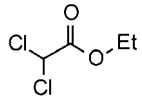
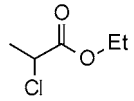
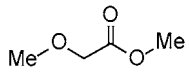
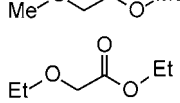
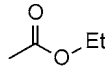
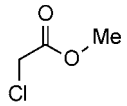
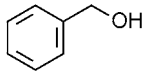
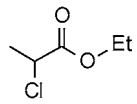
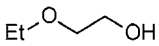
Table 1 Transesterification – Conditions and Yields

Entry	Reactants		Molar ratio **1/2**	Time (h)[a]	Yield of **3** (%),[b] (%)[c]
	 (**1**)	R_3OH (**2**)			
a			10	48	56, (88)
a′		as above	10	24	53, (96)
b		as above	5	24	52, (64)
c		as above	10	24	60, (74)
d		as above	10	48	45, (60)
e		as above	10	48	26, (51)
f		as above	10	48	30, (46)
g		as above	25	200	12[d]
h			5	72	46
i			5	48	38

[a] Reaction time (procedure I[9a]).
[b] Yield obtained according to procedure I[9a] (determined by GC or HPLC).
[c] Yield obtained according to procedure II[9b] (isolated product).
[d] Reaction was carried out under reflux conditions.

Table 2 Increase of Yield by Periodic Removal of Ethanol (Entry **a**)[9b]

	Step I 48 h	Step II Distillation + 48 h	Step III Distillation + 48 h
Observed yield (%)[a]	56.2	79.8	88.4

[a] Yield determined by HPLC.

(8) The product of halogen substitution was obtained in case **a** by application of a stronger base (sodium hydride). Similar examples were reported: (a) Troostwijk, J. E.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1977**, 932. (b) Asthana, P.; Prasad, M.; Rastogi, S. N. *Indian J. Chem., Sect. B* **1987**, *26*, 330.

(9) (a) **Procedure I** (for **3a–i**)**:** The amount of 0.02 mol of alcohol **2**, 13.8 g (0.1 mol) of K_2CO_3, corresponding amount of ester **1** (see Table 1) and 40 mL of THF were placed in a round-bottomed flask. The reaction mixture was vigorously

stirred at r.t. (**g** – at boiling point) with a glass stirrer (blade dimension 4 cm) at 1200 rpm. (b) **Procedure II** (for **3a–f):** Procedure II as in procedure I. After reaching the final reaction time of procedure I, THF and alcohol **4** were evaporated with a rotary evaporator (30 °C, 120 hPa, 1 h). Fresh THF, 40 mL, was added to the solid residue, and the reaction mixture was vigorously stirred again for the same time. Evaporation and stirring were repeated once more. (c) **Isolation and Purification:** The crude reaction mixture was filtrated through a layer of celite and silica gel in order to separate the potassium carbonate. Solvent, excess of ester **1**, unreacted alcohol **2h**, **2i** and alcohol **4** were evaporated with a rotary evaporator (40 °C, 3 hPa). In the case of **3a**, **3h**, **3i** the products were pure enough for spectral analysis. In the case of **3b–g** unreacted **1** was recrystallized from dichloromethane, the filtrate was evaporated under reduced pressure to give the product. Compounds **3a–3f** were additionally crystallized from ethanol at –10 °C for mp, spectral and CHN analysis. (d) **Spectroscopic and Analytical Data:** ^{1}H NMR: (200 MHz, $CDCl_3$), IR: (KBr). **Chloroacetic Acid 2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl Ester (3a):** ^{1}H NMR: δ = 7.77 (m, 4 H, Ar), 4.41 (t, 2 H, *J* = 5.2 Hz, NCH_2CH_2O), 4.03 (s, 2 H, $COCH_2Cl$), 3.96 (t, 2 H, *J* = 5.2 Hz, NCH_2CH_2O). IR: $\nu_{C=O}$ 1770, 1752, 1708 cm^{-1}; $\nu_{Ph\text{-}H}$ 722 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClNO_4$: C, 53.85; H, 3.77; Cl, 13.25;, N, 5.23. Found: C, 53.82; H, 3.97; Cl, 13.23; N, 5.01. Mp: 129.8–130.5 °C. **Bromoacetic Acid 2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl Ester (3b):** ^{1}H NMR: δ = 7.80 (m, 4 H, Ar), 4.42 (t, 2 H, *J* = 5.3 Hz, NCH_2CH_2O), 4.00 (t, 2 H, *J* = 5.3 Hz, NCH_2CH_2O), 3.82 (s, 2 H, CH_2Br). IR**:** $\nu_{C=O}$ 1772, 1748, 1708 cm^{-1}; $\nu_{Ph\text{-}H}$ 724 cm^{-1}. Anal. Calcd for $C_{12}H_{10}BrNO_4$: C, 46.18; H, 3.23; N, 4.49. Found: C, 46.17; H, 3.29; N, 4.28. Mp: 124 °C. **Dichloroacetic Acid 2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl Ester (3c):** ^{1}H NMR: δ = 7.79 (m, 4 H, Ar), 5.92 (s, 1 H, $COCHCl_2$), 4.51 (t, 2 H, *J* = 5.3 Hz, NCH_2CH_2O), 4.03 (t, 2 H, *J* = 5.3 Hz, NCH_2CH_2O). IR: $\nu_{C=O}$ 1776, 1760, 1720, 1708 cm^{-1}; $\nu_{Ph\text{-}H}$ 724 cm^{-1}. Anal. Calcd for $C_{12}H_9Cl_2NO_4$: C, 47.71; H, 3.00; N, 4.64. Found: C, 47.31; H, 2.93; N, 4.63. Mp: 100.3–101.5 °C. **2-Chloropropionic Acid 2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl Ester (3d):** ^{1}H NMR: δ = 7.79 (m, 4 H, Ar), 4.45 (m, 2 H, NCH_2CH_2O), 4.35 (q, 1 H, *J* = 7 Hz, $CHClCH_3$), 4.00 (m, 2 H, NCH_2CH_2O), 1.65 (d, 3 H, *J* = 7 Hz, $CHClCH_3$). IR: $\nu_{C=O}$ 1780, 1752, 1716 cm^{-1}; $\nu_{Ph\text{-}H}$ 728 cm^{-1}. Anal. Calcd for $C_{13}H_{12}ClNO_4$: C, 55.43; H, 4.29; N, 4.97. Found: C, 55.54; H, 3.99; N, 5.14. Mp: 49.1–49.7 °C. **Methoxyacetic Acid 2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl Ester (3e):** ^{1}H NMR: δ = 7.77 (m, 4 H, Ar), 4.39 (t, 2 H, *J* = 5.3 Hz, NCH_2CH_2O), 3.98 (s, 2 H, $COCH_2O$), 3.95 (t, 2 H, *J* = 5.3 Hz, NCH_2CH_2O), 3.39 (d, 3 H, OCH_3). IR: $\nu_{C=O}$ 1772, 1752, 1712 cm^{-1}; $\nu_{Ph\text{-}H}$ 728 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32,.Found: C, 59.65; H, 5.18; N, 5.18. Mp: 67.6–67.9 °C. **Ethoxyacetic Acid 2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl Ester (3f):**[10] ^{1}H NMR: δ = 7.79 (m, 4 H, Ar), 4.40 (t, 2 H, *J* = 5.2 Hz, NCH_2CH_2O), 4.04 (s, 2 H, $COCH_2O$), 3.97 (t, 2 H, *J* = 5.2 Hz, NCH_2CH_2O), 3.56 (q, 2 H, *J* = 7 Hz, OCH_2CH_3), 1.20 (t, 3 H, *J* = 7 Hz, OCH_2CH_3). IR: $\nu_{C=O}$ 1776, 1760, 1712 cm^{-1}; $\nu_{Ph\text{-}H}$ 720 cm^{-1}. Mp: 54.5–54.8 °C. **Acetic Acid 2-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)ethyl Ester (3g):**[11] ^{1}H NMR: δ = 7.79 (m, 4 H, Ar), 4.31 (t, 2 H, *J* = 5.4 Hz, NCH_2CH_2O), 3.95 (t, 2 H, *J* = 5.4 Hz, NCH_2CH_2O), 2.01 (s, 3 H, CH_3). IR: $\nu_{C=O}$ 1776, 1740, 1712 cm^{-1}. $\nu_{Ph\text{-}H}$ 720 cm^{-1}. Mp: 88.1–88.4 °C. **Chloroacetic Acid Phenylmethyl Ester (3h):**[12] ^{1}H NMR: δ = 7.38 (m, 5 H, Ar), 5.22 (s, 2 H, $PhCH_2O$), 4.10 (s, 2 H, $COCH_2Cl$). IR: $\nu_{C=O}$ 1756 cm^{-1}; $\nu_{Ph\text{-}H}$ 792, 752, 704 cm^{-1}. **2-Chloropiopionic Acid-2-ethoxyethyl Ester (3i):** ^{1}H NMR: δ = 4.42 (q, 1 H, *J* = 7 Hz, $CHClCH_3$), 4.30 (m, 2 H, CH_2CO), 3.65 (m, 2 H, OCH_2CH_2), 3.52 (q, 2 H, *J* = 7 Hz, CH_3CH_2O), 1.68 (d, 3 H, *J* = 7 Hz, $CHClCH_3$), 1.90 (t, 3 H, *J* = 7 Hz, CH_3CH_2O). IR: $\nu_{C=O}$ 1752 cm^{-1}.

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