

New Alkoxyzinc Salts Mediated Chemoselective Transesterification Reactions

Necdet COŞKUN, Mustafa ER

Uludağ University, Department of Chemistry, 16059, Bursa-TURKEY
coskun@uludag.edu.tr

Received 03.05.2005

A new chemoselective method for the transesterification of alkyl esters in the presence of in situ formed alkoxyzinc salts was developed. Electron-rich esters are less reactive than electron poor ones and this is the basis for the chemoselectivity of the reaction. Suggested mechanisms of the transesterification reactions are discussed.

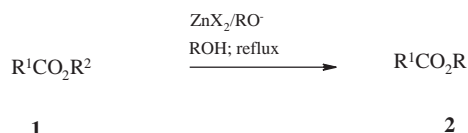
Key Words: Chemoselective transesterification, zinc bromide, zinc acetate, alkoxyzinc bromide, alkoxyzinc acetate.

Introduction

Although a number of transesterifications have been reported in the literature^{1–2}, investigations on the chemoselectivity of transesterifications have only appeared recently^{3–11}. We have reported results on the chemoselective transesterification reactions of alkyl esters with Reformatsky reagents under neutral conditions. We proved that electron-donating groups decrease the reactivity of aromatic esters while electron-withdrawing groups increase it. Aliphatic esters are much more reactive than the corresponding benzoic acid esters¹².

Here we report the potential of in situ formed alkoxyzinc bromides and acetates as chemoselective transesterification reagents. A comparison with zinc bromide, zinc acetate and alkoxyzinc acetate and base catalyzed transesterifications is also reported. Suggested mechanisms of the transesterification reactions are discussed.

To determine the scope and limitations of chemoselective transesterifications using alkoxyzinc compounds, a series of selected carboxylic acid esters were subjected to transesterification (see Table 1).

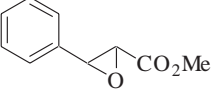
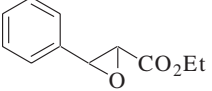


Scheme 1

Table 1. Transesterifications of esters with alkoxyzinc compounds.

Entry	Starting Ester	Product	Reagent eqv	React. Time h	Yield (%)
1	PhCO ₂ Me	PhCO ₂ Et	ZnBr ₂ /EtO ⁻ 5eqv	23 30	31 33
2	2-ClC ₆ H ₄ CO ₂ Me	2-ClC ₆ H ₄ CO ₂ Et	ZnBr ₂ /EtO ⁻ 5eqv	23 30	15 21
3	methyl 2-furoate	ethyl 2-furoate	ZnBr ₂ /EtO ⁻ 5eqv	24	60
4	ethyl 2-furoate	methyl 2-furoate	ZnBr ₂ /MeO ⁻ 5eqv	1 2 4	60 81 95
5	methyl 2-furoate	ethyl 2-furoate	EtO ⁻ 5eqv	0.45	8 ^a
6	PhCH=CHCO ₂ Me	PhCH=CHCO ₂ Et	ZnBr ₂ /EtOH 5eqv	1 2 22	3 5 18
7	PhCH=CHCO ₂ Me	PhCH=CHCO ₂ Et	ZnBr ₂ /EtO ⁻ 5eqv	2 4 19	7 13 37
8	PhCH=CHCO ₂ Et	PhCH=CHCO ₂ Me	ZnBr ₂ /MeO ⁻ 5eqv	1 2 4 6	47 59 82 95
9	PhCH ₂ CO ₂ Me	PhCH ₂ CO ₂ Et	ZnBr ₂ /EtO ⁻ 5eqv	1 3 23	11 23 40 ^b
10	PhCH ₂ CO ₂ Me	PhCH ₂ CO ₂ Et	ZnBr ₂ /EtO ⁻ 5eqv ^c	19 22 38	70 75 90
11	PhCH ₂ CO ₂ Me	PhCH ₂ CO ₂ i-Pr	ZnBr ₂ /i-PrO ⁻ 5eqv	25 52	24 32
12	PhCH ₂ CO ₂ Me	PhCH ₂ CO ₂ t-Bu	ZnBr ₂ /t-BuO ⁻ 5eqv	25	0
13	R=Me	R=Et	ZnBr ₂ /EtO ⁻ 5eqv	2	90
14	R=Me	R=Et	ZnBr ₂ /EtO ⁻ 5eqv	20	0
15	Ph CO ₂ Et	Ph CO ₂ Me	ZnBr ₂ /EtO ⁻ 5eqv	3	96
16	Ph CO ₂ Me	Ph CO ₂ Et	ZnBr ₂ /EtO ⁻ 5eqv	2	100
17	BHET ^d	DMT ^e	ZnBr ₂ /MeO ⁻ 10eqv ZnBr ₂ /MeOH 10eqv	1.5 6	100 100

Table 1. Continued

Entry	Starting Ester	Product	Reagent eqv	React. Time h	Yield (%)
18			ZnBr ₂ /EtO ⁻ 5eqv	3	62
19	PhCO ₂ Et	PhCO ₂ Me	Zn(AcO) ₂ /MeO ⁻ eqv	22	46
20	PhCO ₂ Et	PhCO ₂ Me	Zn(AcO) ₂ /MeOH eqv	22	53
21	PhCO ₂ Et	PhCO ₂ Me	ZnBr ₂ /MeOH eqv	22	41
22	PhCH=CHCO ₂ Et	PhCH=CHCO ₂ Me	Zn(AcO) ₂ /MeO ⁻ eqv	2 4 22	17 25 59
23	PhCH=CHCO ₂ Et	PhCH=CHCO ₂ Me	Zn(AcO) ₂ /MeOH eqv	1 3 22	8.5 20 69
24	PhCH=CHCO ₂ Et	PhCH=CHCO ₂ Me	ZnBr ₂ /MeOH eqv	22	56

^aFuroic acid sodium salt was the main product formed, yield 75%^b. The main product was the salt corresponding to the acid^c. The reaction was performed at room temperature. ^d Bishydroxyethylterephthalate; ^e Dimethylterephthalate.

Results and Discussion

Aromatic esters, unsubstituted or with electron-donating groups, undergo transesterification with poor yields (entry 1, Table 1 and entry 6, Table 2). However, the reaction of 3-nitrobenzoic acid ethyl ester proceeds in high yield (entry 4, Table 2). Alkyl furoates undergo transesterification with primary alcohols with much better yields than benzoic acid esters unsubstituted or having electron-donating groups (entries 3 and 4, Table 1). On the other hand, the transesterification of ethyl esters to methyl esters was shown to proceed more easily (entries 4 and 8, Table 1) than the reverse case (entries 3 and 7, Table 1). The transesterification of methyl 2-furoate to ethyl 2-furoate in the presence of an equimolar amount of sodium ethoxide produced only 8% transesterification product. The main product was the hydrolyzed ester (entry 5, Table 1). The conversion of methyl phenylacetate to the corresponding ethyl ester produced sodium phenylacetate as a byproduct, however, the reaction proceeded in high yield when it was performed at room temperature (entries 9 and 10, Table 1). It is clear that the sterical factor is important in the transesterification with alkoxyzinc salts. The yields were better when the selected alcohol was small (entries 9-12, Table 1). 5-(4-Methoxyphenyl)-3a,6-diphenyl-3a,4,5,6-tetrahydro-imidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid dimethyl ester¹³⁻¹⁴ was converted chemoselectively to the corresponding 5-(4-methoxyphenyl)-3a,6-diphenyl-3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazole-2,3-dicarboxylic acid methyl ethyl ester (entry 13, Table 1). The inertness of the compound in entry 14¹⁵ confirms the absolute selectivity of the transesterification in the cases of tetrahydro-imidazo[1,5-*b*]isoxazolecarboxylic acid esters. α,β -Unsaturated ethyl esters convert nearly quantitatively to the corresponding methyl esters in the presence of methoxyzinc bromide (entries 8 and 15, Table 1). The reaction is especially successful in the cases of α -ketoesters and terephthalic acid bis-(2-hydroxyethyl) ester (BHET) (entries 16 and 17, Table 1). Trans methyl glycidate was also successfully converted to the corresponding trans ethyl ester (entry 18). The comparison of the reaction times and the

yields of the reactions with the ZnBr_2 /alcohol system (entries 6 and 17, Table 1) and the alkoxide/ ZnBr_2 clearly shows that the latter is much more advantageous. The $\text{Zn}(\text{AcO})_2$ /alcohol system seems to be more effective than the ZnBr_2 /alcohol system (entries 20, 21, 23 and 24, Table 1). It was surprising that the $\text{Zn}(\text{AcO})_2$ /alcohol system was more efficient than the in situ formed alkoxide/ $\text{Zn}(\text{AcO})_2$ system (entries 19, 20, 22 and 23, Table 1).

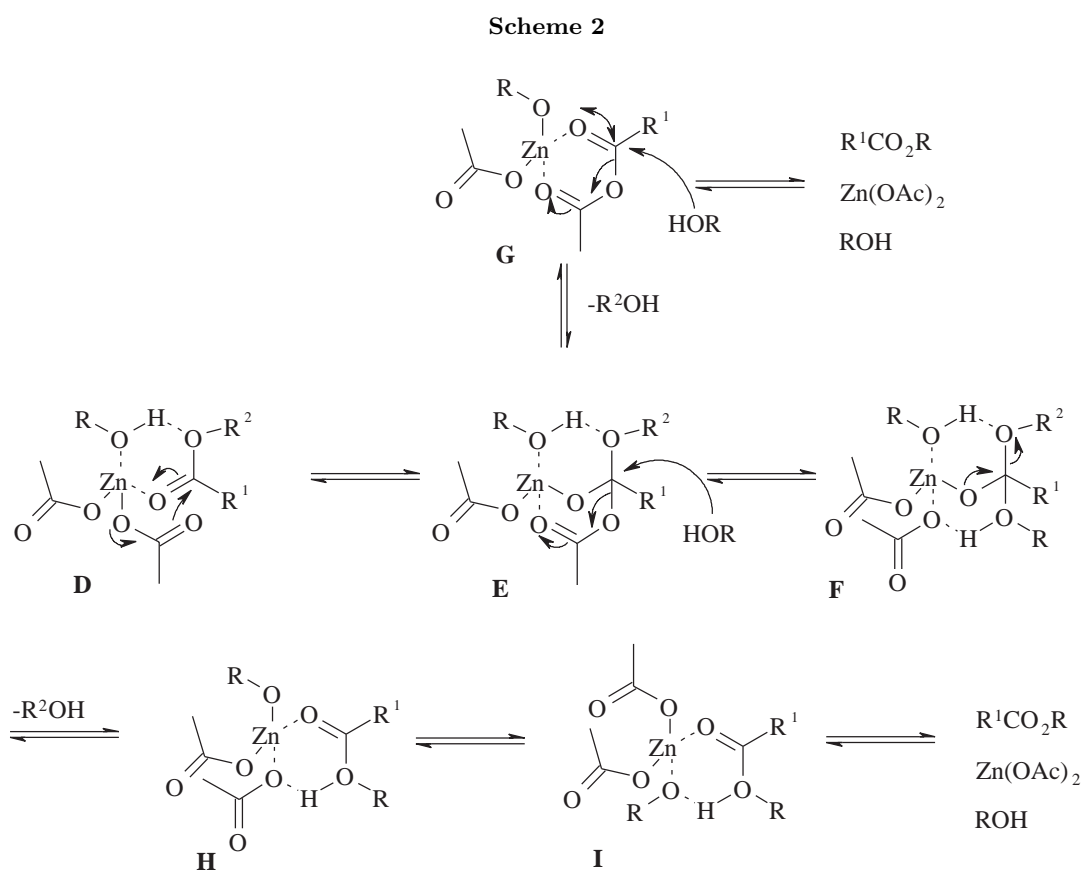
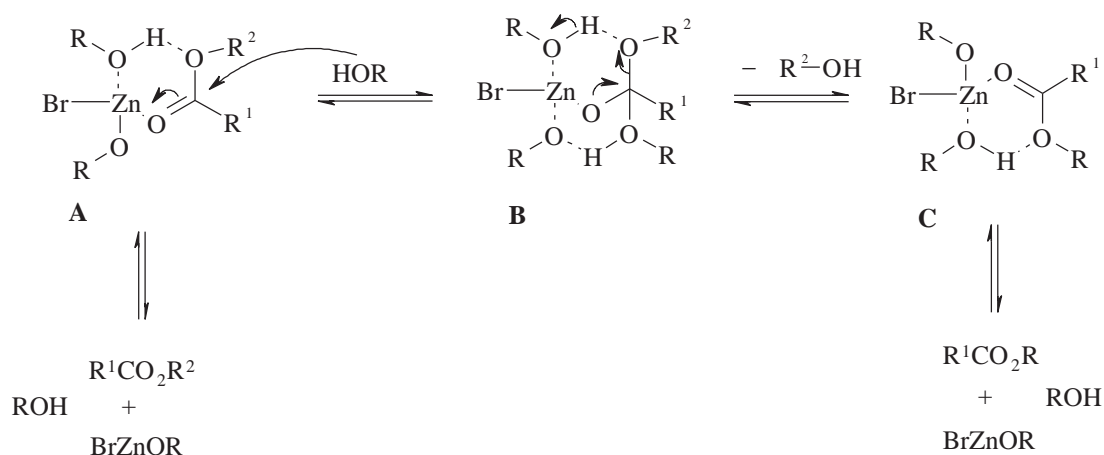
Table 2. Chemoselectivity in transesterifications of esters with alkoxyzinc salts.

Entry	Starting Esters	Product	Reagent eqv	React. Time h	Yield (%)
1	methyl 2-furoate	ethyl 2-furoate	$\text{ZnBr}_2/\text{EtO}^-$ 5eqv	24	55
	methyl benzoate	ethyl benzoate			21
2	methyl 2-furoate	ethyl 2-furoate	$\text{Zn}(\text{AcO})_2/\text{EtO}^-$ 5eqv	24	63
	methyl benzoate	ethyl benzoate			23
3	ethyl 2-furoate	methyl 2-furoate	$\text{Zn}(\text{Br})_2/\text{MeO}^-$ 5eqv	6	95
	ethyl benzoate	methyl benzoate			55
4	methyl MNB ^a	ethyl MNB	$\text{ZnBr}_2/\text{EtO}^-$ 5eqv	6	98
	methyl benzoate	ethyl benzoate			12
5	methyl 2-furoate	ethyl 2-furoate	EtO^- 1eqv	1	92
	methyl benzoate	ethyl benzoate			96
6	methyl PMB ^b	ethyl PMB	$\text{ZnBr}_2/\text{EtO}^-$ 5eqv	24	11
	methyl benzoate	ethyl benzoate			25

^a m-Nitrobenzoate; ^b p-Methoxybenzoate

To optimize the chemoselectivity of the reaction in the series of esters in Table 1 we subjected pairs of esters, as models for compounds having 2 ester groups, to transesterification with a 5-fold excess of the transesterification reagent and the yields of the product esters were determined by HPLC. It seems that the alkoxide/ $\text{Zn}(\text{AcO})_2$ system is slightly more chemoselective than alkoxide/ ZnBr_2 (entries 1 and 2, Table 2). Better selectivity is achieved when the alcohol part of the ester is smaller than the alkyl of the alkoxide (entries 1-3, Table 2). A combination of ester functions in aromatic rings having electron-withdrawing groups and unsubstituted aromatic esters gave a good selectivity (entry 4, Table 2). To assess the selectivity of the transesterification reaction under basic conditions we reacted a pair of esters with alkoxide and no difference in the yields of the product esters was found (entry 5, Table 2). An electron-withdrawing nitro group increases the reactivity of the corresponding aromatic ester, while the presence of an electron-donating group decreases its reactivity (entries 4 and 6, Table 2). In fact the data reported in Table 1 are a reliable basis for the assessment of the reactivity and chemoselectivity of the transesterification in the presence of alkoxyzinc salts.

We propose that the mechanism of the transesterification of esters **1** in the presence of alkoxyzinc salts involves the coordination of the ester through the acyl oxygen to give the intermediate complex **A** as shown in Scheme 2. The intermolecular nucleophilic attack of the alcohol could give intermediate **B**, which in turn undergoes elimination to give the corresponding alcohol and zinc coordinated transesterification product **C**. The latter is in equilibrium with the free ester and alkoxyzinc salt. The reason that alkoxyzinc bomides are more efficient reagents in the transesterification process than zinc bromide is probably their ability to give intermediates **B** stabilized by intramolecular hydrogen bonding. The steric and electronic effects observed agree with the proposed substitution mechanism.



It seems that $\text{Zn}(\text{OAc})_2$ is a more effective reagent than ZnBr_2 . The mechanism of transesterification by $\text{Zn}(\text{OAc})_2$ is probably a somewhat different from that of ZnBr_2 . The coordinated ester may undergo nucleophilic attack by the alcohol as in the case of transesterification mediated by alkoxyzinc bromide, or the ester carbonyl could be activated by the neighboring acetoxy group through forming intermediate **E** (Scheme 3), which could undergo substitution to give intermediate **F** and the elimination of R^2OH will give the new zinc coordinated ester **H**. The decomposition of complex **H** or maybe its isomer **I** gives the product ester. The elimination of R^2OH could precede the nucleophilic attack of ROH and the thus formed

mixed anhydride complex **G** could undergo substitution at sp^2 carbonyl carbon. The use of alkoxyzinc acetate instead of the zinc acetate itself does not enhance the yields, in contrast to the case with alkoxyzinc bromide. The decreased neighboring group effect of the acetoxy group in alkoxyzinc acetate coordinated ester is probably one of the reasons for the lower yields.

Thus a new high yield chemoselective transesterification method for alkyl esters in the presence of alkoxyzinc salts was developed. This reaction complements the reaction based on the Reformatsky reagent, which we have reported recently. The substituents' effects were shown to be the same in both reactions, namely electron-rich esters are less reactive than electron-poor ones, and this is the basis for the chemoselectivity of the reaction.

Experimental

Infrared spectra were recorded on a Mattson 1000 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer. Visualization was effected with UV light.

General procedure for transesterification of esters (1) with alkoxide/ ZnBr_2 . Sodium (0.115 g, 5 mmol) was placed in a flask with absolute ethanol (10 mL) and stirred until the reaction was completed. ZnBr_2 (1.125 g, 5 mmol) was added and the mixture stirred under reflux for 15 min. Compound **1** (1 mmol) was dissolved in ethanol (2 mL) added to the mixture and refluxed for a specified time. The reaction was monitored by HPLC. The excess alcohol was evaporated and the residue extracted with diethyl ether (2 X 10 mL) by heating. The combined extracts were washed with water (2 X 10 mL) and dried over anhydrous Na_2SO_4 . The compound was recrystallized from ethanol (entries 12-13, Table 1) or purified by flash column chromatography using silica gel as adsorbent and ethyl acetate and hexane as eluent in the other cases.

General procedure for transesterification of esters (1) with alkoxide/ $\text{Zn}(\text{AcO})_2$. Sodium (0.023 g, 1 mmol) was placed in a flask with absolute ethanol (10 mL) and stirred until the reaction was completed. $\text{Zn}(\text{AcO})_2 \cdot 2\text{H}_2\text{O}$ (0.2195 g, 1 mmol) was added and the mixture stirred under reflux for 15 min. Compound **1** (1 mmol) was added to the mixture and refluxed for a specified time. The reaction was monitored by HPLC. The excess alcohol was evaporated and the residue extracted with diethyl ether (2 X 10 mL) by heating. The combined extracts were washed with water (2 X 10 mL) and dried over anhydrous Na_2SO_4 . The compound was purified by flash column chromatography using silica gel as adsorbent and ethyl acetate-hexane as eluent in the other cases.

3-Phenyl-oxirane-2-carboxylic acid methyl ester. The compound was obtained in 86% yield from the reaction of trans phenyl glycidic acid with methanol in the presence of DCC and DMAP; oil; IR (neat) $\nu_{\text{C=O}}$ 1750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 3.52 (1H, d, $J = 2\text{Hz}$), 3.83 (3H, s), 4.10 (1H, d, $J = 2\text{Hz}$), 7.28-7.30 (2H, m), 7.34-7.37 (3H, m), ^{13}C NMR (100 MHz, CDCl_3): δ 52.8; 56.9; 58.2; 126.0; 128.9; 129.3; 135.1; 168.9;

3-Phenyl-oxirane-2-carboxylic acid ethyl ester. Yield 62%; oil; IR (neat) $\nu_{\text{C=O}}$ 1750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.33 (3H, t, $J = 7\text{Hz}$), 3.50 (1H, d, $J = 2\text{Hz}$), 4.09 (1H, d, $J = 2\text{Hz}$), 4.24-4.33 (2H, m), 7.28-7.31 (2H, m), 7.32-7.37 (3H, m), ^{13}C NMR (100 MHz, CDCl_3): δ 14.4; 57.0; 58.2; 62.0; 126.1; 129.0; 130.4; 134.2; 168.4;

General procedure for cotransesterification of esters (1). Sodium (0.115 g, 5 mmol) was placed in a flask with absolute ethanol (10 mL) and stirred until the reaction was completed. ZnBr_2 (1.125

g, 5 mmol) or $\text{Zn}(\text{AcO})_2 \cdot 2\text{H}_2\text{O}$ (1.098 g, 5 mmol) was added and the mixture stirred under reflux for 15 min. Two different esters (each 1 mmol) were added to the mixture, which was refluxed for a specified time. The reaction was monitored by HPLC. The excess alcohol was evaporated and the residue extracted with diethyl ether (2 X 10 mL) by heating. The combined extracts were washed with water (2 X 10 mL) and dried over anhydrous Na_2SO_4 . The yields of the products were determined by HPLC using column C_{18} and acetonitrile-water (40:60) system as an eluent.

Acknowledgement

The Uludağ University Research Fund is gratefully acknowledged for the financial support (Project No 2001-2).

References

1. K. Ramalinga, P. Vijayalakshmi and T.N.B. Kaimal, **Tetrahedron Lett.** **43**, 879-882 (2002). and references cited therein.
2. A. Rodríguez, M. Nomen, B.W. Spur and J.J. Godfroid, **Tetrahedron Lett.** **39**, 8563-8566 (1998).
3. V.S. Parmar, A.K. Prasad, H.N. Pati, R. Kumar, A. Azim, S. Roy and W. Errington, **Bioorg. Chem.** **27**, 119-134 (1999).
4. J.A. Carr and K.S. Bisht, **Tetrahedron** **59**, 7713-7724 (2003).
5. S.J. Roelens, **J. Org. Chem.** **61**, 5257-5263 (1996).
6. D.E. Ponde, V.H. Deshpande, V.J. Bulbule, A. Sudalai and A.S. Gajare, **J. Org. Chem.** **63**, 1058-1063 (1998).
7. B.C. Ranu and A. Hajra, **J. Chem. Soc. Perkin Trans. 1** **18**, 2262-2265 (2001).
8. B.P. Bandgar, L.S. Uppalla and V.S. Sadavarte, **Synlett.** **11**, 1715-1718 (2001).
9. A.G. Gonzalez, I. Brouard, F. Leon, J.I. Padron and J. Bermejo, **Tetrahedron Lett.** **42**, 3187-3188 (2001).
10. W. Bo, Y.L. Ming and S.J. Shuan, **Tetrahedron Lett.** **44**, 5037-5039 (2003).
11. S.P. Chavan, K. Shivasankar, R. Sivappa and R. Kale, **Tetrahedron Lett.** **43**, 8583-8586 (2002).
12. N. Coşkun and M. Er, **Tetrahedron**, **59**, 3481-3485 (2003).
13. N. Coşkun, F.T. Tat, Ö.Ö. Güven, D. Ülkü and C. Arıcı, **Tetrahedron Lett.** **41**, 5407-5409 (2000)
14. N. Coşkun, F.T. Tat and Ö.Ö. Güven, **Tetrahedron**, **57**, 3413-3417 (2001).
15. N. Coşkun and B. Yılmaz, **Synth. Commun.** **34**, 1617-1623 (2004).