

Efficient and chemoselective alkyl bromoacetate–Zn mediated transesterification method

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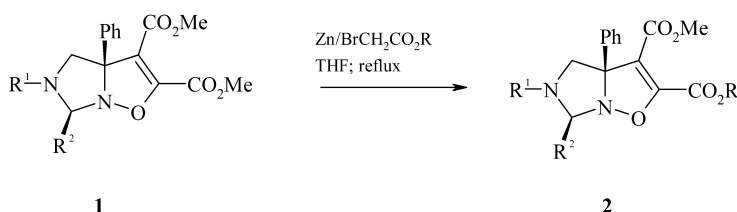
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Abstract—Alkyl bromoacetates were shown to be versatile transesterification reagents. Isoxazoles underwent chemoselective transesterification when treated with alkyl bromoacetate–Zn in THF at reflux. A suggested mechanism of the new reaction was discussed. © 2003 Elsevier Science Ltd. All rights reserved.

Transesterification of esters is a widely used process in academia and industry. A number of transesterifications have been reported in the literature^{1,2} and investigations on the chemoselectivity of transesterifications have appeared recently.³ The chemoselective capabilities of porcine pancreatic lipase and *Candida rugosalipase* have been reported for selective acetylation and deacetylation of hydroxymethylated phenols and hydroxyaryl alkyl ketones and their peracetylated derivatives.^{3a} Organotin-mediated monoacylation of diols,^{3b} transesterification and trans-thioesterification of β -keto esters with a variety of alcohols and thiols catalyzed by natural kaolinitic clay are described.^{3c} An efficient method for the chemoselective one-step conversion of tetrahydropyranyl ethers of primary alcohols into the corresponding acetates through an indium triiodide catalyzed transesterification process in ethyl

the benzoyl (benzoate and *p*-bromobenzoate) groups present in the molecule.^{3f}

Recently, we have reported results on the 1,3-dipolar cycloaddition reaction of imidazoline 3-oxides with DMAD and the reactions of the obtained adducts **1**.^{4a} Selective Michael addition of methoxide ion^{4b} prompted us to investigate the reaction of organozinc compounds obtained from α -bromoacetic acid esters and Zn with isoxazoles **1**. This would be an important step in the synthesis of tricarboxylic acids such as citric and isocitric acids. However, the conjugate addition of the ethoxycarbonylmethyl anion to C-2 of compounds **1** attempted under Reformatsky reaction conditions led to the formation of compounds **2** instead of any conjugate addition reaction (Scheme 1 and Table 1).



Scheme 1.

acetate has been reported.^{3d} Facile and selective transesterification of β -keto esters using *N*-bromosuccinimide as an efficient and neutral catalyst is also described.^{3e} The acetyl group was chemoselectively cleaved in the presence of *p*-toluenesulfonic acid in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ without affecting

Table 1. Chemoselective transesterification of 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles

Entry	R	R ¹	R ²	Yield ^a of 2 (%)
a	Et	4-MeC ₆ H ₄	H	90
b	Et	4-MeOC ₆ H ₄	H	89
c	Et	4-ClC ₆ H ₄	H	91
d	Et	4-MeC ₆ H ₄	Ph	94
e	Et	4-MeOC ₆ H ₄	Ph	95

^a Yields of isolated pure compounds.

Keywords: chemoselective transesterification; Reformatsky reagent.

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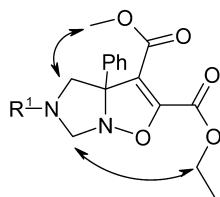
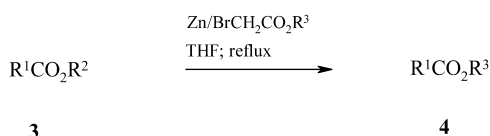


Figure 1. Selected NOESY correlations for **2a,c**.



Scheme 2.

Here we report a new high yield transesterification reaction of alkyl esters with Reformatsky reagents at neutral conditions. The chemoselectivity of this transesterification is also discussed.

The structure of **2** was unequivocally proved to be the corresponding isoxazole-2,3-dicarboxylic acid 3-methyl ester 2-ethyl ester. The IR spectra of the products are nearly indistinguishable from those of the starting isoxazoles, they have the same carbonyl patterns in their IR spectra as the starting isoxazoles. The ¹H NMR spectra are different from those of the starting compounds only with the triplet and quartet instead of the singlet at 3.85 ppm corresponding to the methoxy group at C-2 linked carbonyl.

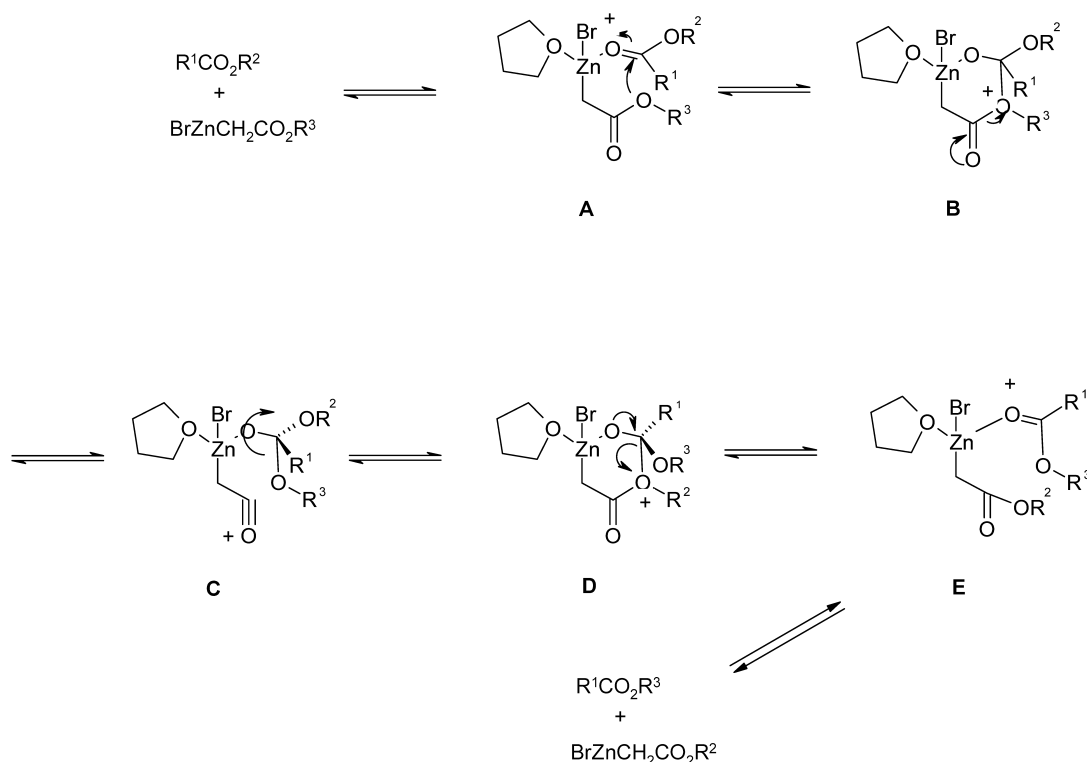
The NOESY spectra of the compounds **2a,c** show a clear

Table 2. Transesterifications of esters with Reformatsky reagents

Entry	Starting ester	Product	Reagent (equiv.)	Reaction time (h)	Yield (%)
1	PhCO ₂ Me	PhCO ₂ Et	BrCH ₂ CO ₂ Et/Zn (5)	2	13
				3	19
				10	31
				16	31
				4	15
2	2-ClC ₆ H ₄ CO ₂ Me	2-ClC ₆ H ₄ CO ₂ Et	BrCH ₂ CO ₂ Et/Zn (20) BrCH ₂ CO ₂ Et/Zn (5)	2	80
				2.5	28
				4	38
				5	43
				4	55
3	4-MeOC ₆ H ₄ CO ₂ Me	4-MeOC ₆ H ₄ CO ₂ Et	BrCH ₂ CO ₂ Et/Zn (20) BrCH ₂ CO ₂ Et/Zn (5)	20	86
				2.5	8
				4	13
				4	20
				4	20
4			BrCH ₂ CO ₂ Et/Zn (20) BrCH ₂ CO ₂ Et/Zn (5)	20	70
				2	75
5	PhCH ₂ CO ₂ Me	PhCH ₂ CO ₂ Et	BrCH ₂ CO ₂ Et/Zn (5)	4	80
				8	95
				2.5	44
6	PhCH ₂ CH ₂ CO ₂ Et	PhCH ₂ CH ₂ CO ₂ <i>i</i> -Pr	BrCH ₂ CO ₂ <i>i</i> -Pr/Zn (5)	4	62
				8	91
				2	46
7	PhCH=CHCO ₂ Me	PhCH=CHCO ₂ Et	BrCH ₂ CO ₂ Et/Zn (1)	2	93
				4	29
				10	32
				2	50
				4	56
				10	62
				2	60
				8	69
				12	90
				25	0
8 ^b	R=Me	R=Et	BrCH ₂ CO ₂ Et/Zn (5)	16	No reaction
				16	No reaction
				16	No reaction
				16	No reaction
				16	No reaction

^a The amounts of iodine as in Ref. 1.

^b The starting adduct was obtained from the 1,3-dipolar cycloaddition of corresponding imidazoline 3-oxide and methylphenylpropionate and characterized by spectral means.



Scheme 3.

correlation between the ethyl group's methylene signal at 4.25 ppm and the part of the methylene AB system at 4.36 ppm. On the other hand, the methyl protons of the ester group give cross peaks with the methylene protons at C-4 (Fig. 1). 2-Phenyl-5-*p*-tolyl-3a,4,5,6-tetrahydro-imidazo-[1,5-*b*]isoxazole-3-carboxylic acid methyl ester remains unchanged in the same reaction conditions thus confirming the position of the transesterification (Scheme 2 and Table 2).

To our knowledge these are the first examples of chemoselective transesterifications using organozinc compounds. To determine the scope and limitations of the reaction a series of selected carboxylic acid esters were subjected to transesterification (Table 2) in the presence of the Reformatsky reagents. The transesterification of methyl cinnamate with ethanol in the presence of catalytic amounts of I_2 or conc. H_2SO_4 proceeds with low yields when a five fold excess of ethanol was used. The yields are low even when it was used as a solvent (Table 2 entry 7).

The low reactivity of the aromatic esters **1–3**, (the reactions requires large excess of the organozinc species to get a good yield) encouraged us to explore the chemoselectivity limits of the reaction in the series of esters **1–8**. Thus we have subjected pairs of esters, with different reactivities, as models for compounds having two ester groups to transesterification with a five fold excess of ethyl bromoacetate/Zn and the yields of the product esters were determined by HPLC. In the case of methyl benzoate and methyl furoate the ratio of the ethyl esters was 1:9 after 2.5 h reflux. In the case of methyl phenylacetate and methyl *p*-methoxybenzoate the ratio of the ethyl esters was 1:10 under the same reaction conditions. These and the results

presented in Table 2 clearly confirm 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 esters. 2-Furoate is much more reactive than the corresponding benzoates, entry 4. On the other hand, the presence of an electron-donating group β to the conjugated ester carboxyl decreases its reactivity (entry 8 Table 2). All these are a reliable basis for the assessment of the reactivity and chemoselectivity of the developed transesterification method.

We propose that the mechanism of the transesterification of adducts **1a–e** and esters **3** in the conditions of the Reformatsky reaction involves the coordination of the ester through the acyl oxygen⁵ as shown in transition state **A** in Scheme 3. For aliphatic, conjugated and aromatic esters, the transition state may involve the solvent molecule, while the presence of an α oxygen in the ester may serve as a readily coordinating atom instead of the solvent molecule. Intramolecular cyclization of intermediate **A** could give **B** which in turn undergo ring opening to give acylium species **C**. Rotation around the Zn coordinated oxygen–carbon bond and recyclization of **C** will give **D** the ring opening and decomposition of which afford the transesterified ester and the new Reformatsky reagent. To prove the formation of the proposed new Reformatsky reagent in the reaction conditions we have treated the mixture of methyl 2-chlorobenzoate and ethyl 2-furoate with ethyl bromoacetate/Zn and the reaction was monitored by HPLC. The formation of methyl 2-furoate was evidence in support of the assumed mechanism. The observed substituent effects on the reactivity of esters are in good agreement with the cyclization recyclization mechanism discussed.

Thus a new high yield chemoselective transesterification reaction of alkyl esters with Reformatsky reagent at neutral conditions was developed. Electron-rich esters were shown to be less reactive than electron poor ones and this was the basis for the chemoselectivity of the reaction.

1. Experimental

Melting points were taken on a Electrothermal Digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. Proton magnetic resonance spectra were recorded on a Bruker Dpx 400 MHz spectrometer. All spectra were taken in CDCl₃. Mass spectra were routinely recorded at 70 eV by electron impact. Visualization was effected with UV light. Freshly prepared imidazoline 3-oxide adducts with DMAD were used after recrystallization from ethanol. Commercially available esters or prepared by routine methods were used as starting materials as well as for comparison.

1.1. General procedure for transesterification of isoxazoles (1) and esters (3)

Zinc powder (0.328 g, 5 mmol) was placed in a flask with THF (2 mL) and refluxed for 15 min. Ethyl bromoacetate (0.835 g, 5 mmol) dissolved in THF (10 mL) was added and the mixture stirred at 50–55°C for 20 min. After the green colored solution is formed compound **1** or **3** (1 mmol) dissolved in THF (2 mL) was added and the mixture was refluxed for the specified time. The reaction was monitored by TLC or by HPLC for the reactions of esters **3**. The solvent was evaporated and the residue dissolved in diethyl ether (30 mL) at heating. The compound was recrystallised from ethanol in the cases of **2a–c,e** or purified by flash column chromatography using silica gel as adsorbent and ethyl acetate and hexane as eluent in the cases of **2d** and esters **4**.

1.1.1. 3a-Phenyl-5-p-tolyl-3a,4,5,6-tetrahydro-imidazo[1,5-b]isoxazole-2,3-dicarboxylic acid 2-ethyl ester 3-methyl ester (2a). The compound was obtained according to the general procedure. Yield 0.367 g, 90%. The melting point of the colorless crystals after recrystallization from ethanol is 126.7–127.2°C. IR (KBr) $\nu_{\text{C=O}}$ 1750, 1716; $\nu_{\text{C=C}}$ 1665 cm⁻¹; ¹H NMR CDCl₃ δ 1.36 (3H, t, $J=7.1$ Hz), 2.30 (3H, s), 3.46 (1H, d, $J=9.8$ Hz), 3.68 (3H, s), 4.26 (1H, d, $J=10.9$ Hz), 4.37 (2H, q, 7.1), 4.65 (1H, d, $J=9.8$ Hz), 5.07 (1H, d, $J=10.9$ Hz), 6.73 (2H, d, $J=8.0$ Hz), 7.08 (2H, d, $J=8.0$ Hz), 7.28–7.39 (3H, m), 7.63 (2H, d, $J=8.0$ Hz); ¹³C NMR CDCl₃ δ 14.4; 20.9; 52.1; 57.6; 63.2; 76.5; 83.4; 110.9; 115.8; 127.3; 128.5; 128.8; 129.6; 130.3; 141.2; 144.2; 152.2; 159.4; 162.9. Anal. calcd for C₂₃H₂₄N₂O₅ (408.46) C, 67.63; H, 5.92; N, 6.86. Found C, 67.29; H, 6.04; N, 6.81. MS m/z 408 (M⁺).

1.1.2. 5-(4-Methoxy-phenyl)-3a-phenyl-3a,4,5,6-tetrahydro-imidazo[1,5-b]isoxazole-2,3-dicarboxylic acid 2-ethyl ester 3-methyl ester (2b). Yield, 0.382 g, 89%. The melting point of the colorless crystals after recrystallization from ether–petroleum ether is 98–99.7°C. IR (KBr) $\nu_{\text{C=O}}$ 1750, 1716; $\nu_{\text{C=C}}$ 1665 cm⁻¹; ¹H NMR CDCl₃ δ 1.36 (3H, t, $J=7.1$ Hz), 3.42 (1H, d, $J=9.7$ Hz), 3.66 (3H, s), 3.79

(3H, s), 3.88 (3H, s) 4.18 (1H, d, $J=10.8$ Hz), 4.36 (2H, q, 7.1), 4.62 (1H, d, $J=9.7$ Hz), 5.09 (1H, d, $J=10.8$ Hz), 6.72 (2H, d, $J=8.9$ Hz), 6.85 (2H, d, $J=8.9$ Hz), 7.28–7.39 (3H, m), 7.60 (2H, d, $J=7.3$ Hz); ¹³C NMR CDCl₃ δ 14.4; 52.1; 56.1; 58.2; 63.2; 76.5; 83.1; 110.9; 115.2; 117.1; 127.4; 128.4; 128.7; 140.7; 141.4; 152.6; 154.0; 159.1; 163.0. Anal. calcd for C₂₃H₂₄N₂O₆ (424.46) C, 65.08; H, 5.70; N, 6.60. Found C, 65.05; H, 5.71; N, 6.65. MS m/z 424 (M⁺).

1.1.3. 5-(4-Chloro-phenyl)-3a-phenyl-3a,4,5,6-tetrahydro-imidazo[1,5-b]isoxazole-2,3-dicarboxylic acid 2-ethyl ester 3-methyl ester (2c). Yield, 0.390 g, 91%. The melting point of the colorless crystals after recrystallization from ether–petroleum ether is 130.1–131.2°C. IR (KBr) $\nu_{\text{C=O}}$ 1750, 1716; $\nu_{\text{C=C}}$ 1665 cm⁻¹; ¹H NMR CDCl₃ δ 1.36 (3H, t, $J=7.1$ Hz), 3.50 (1H, d, $J=9.7$ Hz), 3.68 (3H, s), 4.29 (1H, d, $J=10.8$ Hz), 4.36 (2H, q, 7.1), 4.7 (1H, d, $J=9.7$ Hz), 5.03 (1H, d, $J=10.8$ Hz), 6.70 (2H, d, $J=8.9$ Hz), 7.24 (2H, d, $J=8.9$ Hz), 7.28–7.42 (3H, m), 7.63 (2H, d, $J=7.3$ Hz); ¹³C NMR CDCl₃ δ 14.4; 52.3; 57.4; 63.2; 76.0; 83.0; 111.4; 116.7; 125.1; 127.3; 128.6; 128.8; 129.6; 141.0; 145.1; 152.4; 158.9; 162.9. Anal. calcd for C₂₂H₂₁ClN₂O₅ (428.88) C, 61.61; H, 4.94; N, 6.53. Found C, 61.76; H, 5.13; N, 6.54.

1.1.4. 3a,6-Diphenyl-5-p-tolyl-3a,4,5,6-tetrahydro-imidazo[1,5-b]isoxazole-2,3-dicarboxylic acid 2-ethyl ester 3-methyl ester (2d). Yield, 0.455 g, 94%. Oily product IR (neat) $\nu_{\text{C=O}}$ 1750, 1716; $\nu_{\text{C=C}}$ 1665 cm⁻¹; ¹H NMR CDCl₃ δ 1.36 (3H, t, $J=7.1$ Hz), 2.23 (3H, s), 3.62 (3H, s), 4.13 (1H, d, $J=10.5$ Hz), 4.36 (2H, q, 7.1), 4.76 (1H, d, $J=10.5$ Hz), 5.97 (1H, s), 6.64 (2H, d, $J=8.9$ Hz), 7.01 (2H, d, $J=8.9$ Hz), 7.21–7.39 (8H, m), 7.57 (2H, d, $J=7.3$ Hz). Anal. calcd for C₂₉H₂₈N₂O₅ (484.56) C, 71.88; H, 5.82; N, 5.78. Found: C, 72.00; H, 5.75; N, 5.90.

1.1.5. 5-(4-Methoxy-phenyl)-3a,6-diphenyl-3a,4,5,6-tetrahydro-imidazo[1,5-b]isoxazole-2,3-dicarboxylic acid 2-ethyl ester 3-methyl ester (2e). Yield, 95%. The melting point of the colorless crystals after recrystallization from ether–petroleum ether is 104–105.3°C. IR (KBr) $\nu_{\text{C=O}}$ 1750, 1716; $\nu_{\text{C=C}}$ 1665 cm⁻¹; ¹H NMR CDCl₃ δ 1.36 (3H, t, $J=7.1$ Hz), 3.70 (3H, s), 3.75 (3H, s), 4.18 (1H, d, $J=10.5$ Hz), 4.36 (2H, q, 7.1), 4.68 (1H, d, $J=10.5$ Hz), 5.87 (1H, s), 6.73–6.77 (4H, m), 7.29–7.40 (8H, m), 7.59 (2H, d, $J=7.4$ Hz); ¹³C NMR CDCl₃ δ 14.4; 52.3; 56.00; 59.2; 63.2; 80.5; 88.8; 111.6; 115.0; 117.3; 127.0; 127.3; 128.1; 128.2; 128.7; 128.9; 137.8; 140.5; 141.8; 152.1; 153.7; 159.2; 163.2. Anal. calcd for C₂₉H₂₈N₂O₆ (500.56) C, 69.59; H, 5.64; N, 5.60. Found C, 69.65; H, 5.69; N, 5.62. MS m/z 500 (M⁺).

Acknowledgements

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