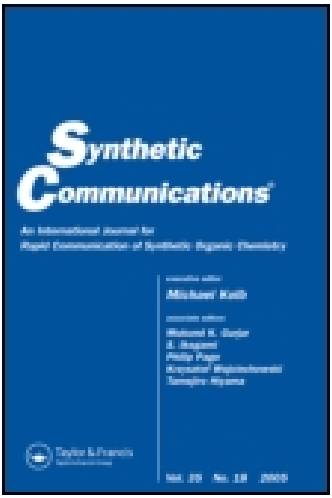


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Enantioselective Synthesis of (R)-2-Methylalkanoic Acids: A Convenient Approach to α-Substituted Chiral Carboxylic Acid Derivatives

Shyam Shirali [a] & Aijun Zhang [a]
[a] Chemicals Affecting Insect Behavior Laboratory , Beltsville Agricultural Research Center-West USDA , ARS, Beltsville, Maryland, 20705, USA
Published online: 10 Jan 2011.

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 18, pp. 3435–3441, 2004



# Enantioselective Synthesis of (*R*)-2-Methylalkanoic Acids: A Convenient Approach to α-Substituted Chiral Carboxylic Acid Derivatives

**Shyam Shirali and Aijun Zhang***

Chemicals Affecting Insect Behavior Laboratory, Beltsville Agricultural Research Center-West USDA, Beltsville, Maryland, USA

## ABSTRACT

Racemization-free deacylation of *N*-acylimidazolidine-2-ones using lithium hydroperoxide affords the corresponding α-substituted chiral carboxylic acids in high yield while permitting recovery of the chiral auxiliary.

*Key Words:* Alkylation; Chiral; Enantioselctive; Lithium hydroperoxide.

α-Substituted carboxylic acids are useful chiral synthons for many natural products,[1] and auxiliary-mediated asymmetric alkylation reactions for the

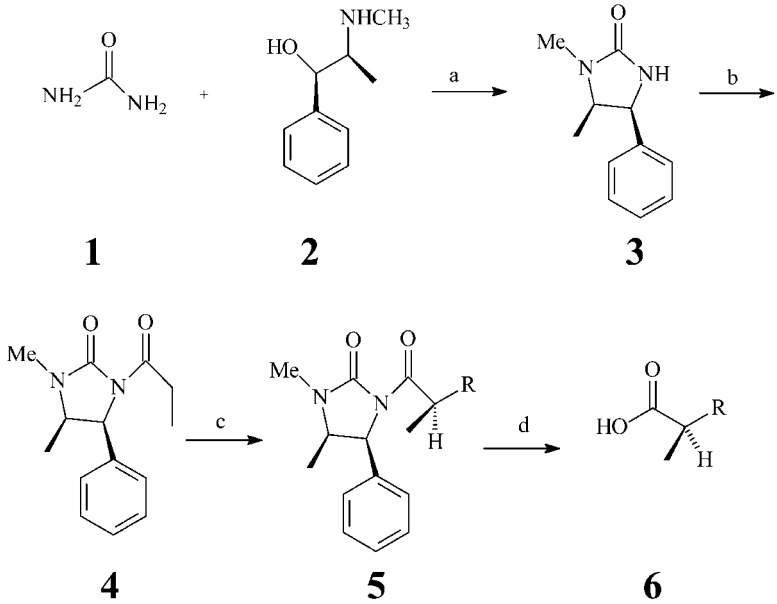
*Correspondence: Aijun Zhang, Chemicals Affecting Insect Behavior Laboratory, Beltsville Agricultural Research Center-West USDA, ARS, Beltsville, MD 20705, USA; E-mail: zhanga@ba.ars.usda.gov.



DOI: 10.1081/SCC-200030650 0039-7911 (Print); 1532-2432 (Online)

production of enantiomerically pure $\alpha$-substituted acid derivatives have recently received a great deal of attention.[2] In this regard, base-assisted alkylation[6a,b] of *N*-acylimidazolidine-2-one has created a lot of interest in this field. Lithium hydroperoxide has been used in chiral auxiliary removal of *N*-acylated-oxazolidin-2-one derivatives,[3] D-xylose-derived *N*-acylated-oxazolidin-2-one derivatives,[4] *N*-acylated-dihydropyprimidin-4-one derivatives,[5a] and *N*-acyl-imidazolidine-2-ones leading to amino acids[5b–f] with variable ee of newly created chiral centers. In our hands, a number of reagents were tried for hydrolysis, and here we report the details of our investigation on the alkylation of *N*-acylated-imidazolidine-2-one derivatives[6] and the use of lithium hydroperoxide at 50°C for racemization-free deacylation to provide $\alpha$-alkylcarboxylic acids. This approach afforded the desired $\alpha$-substituted carboxylic acids in high chemical yield and high enantiomeric purity with concomitant recovery of the chiral auxiliary. The synthetic route is outlined in Sch. 1.

At the outset, we chose to prepare (4*S*,5*R*)-1,5-dimethyl-4-phenyl imidazolidine-2-one, **3** according to the procedure of Close.[7] Treatment of **3**




***Scheme 1.*** (a) 170°C–175°C, 1.5 hr, 200°C–210°C, 1 hr. (b) *n*-Butyllithium, 0°C, 1 hr, propanoyl chloride, 0°C, 2.5 hr. (c) LDA, −78°C, 1 hr alkyl halide, 0°C, 12 hr. (d) $LiOH/H_2O_2$, $H_2O$/THF, 50°C, 24 hr.

with an equimolar quantity of *n*-butyllithium in tetrahydrofuran at 0°C, followed by propanoyl chloride gave **4** in quantitative yield. Further alkylation of **4** with lithium diisopropylamide, alkyl iodide, and hexamethylphosphoramine (HMPA) gave the alkylated acylimidazolidinone **5**. Compounds **5a–5d** were very easily hydrolyzed with lithium hydroxide monohydrate/hydrogen peroxide at 50°C for 24 hr to give the corresponding chiral acids in high yields and enantiomeric purity along with 70%–80% recovery of the chiral auxiliary (Table 1).

The distereomeric excesses and absolute configurations were determined by $^{1}H$ nuclear magnetic resonance (NMR) and $^{13}C$ NMR spectroscopy by observing the doublet of the CHPh proton of the auxiliary moiety **5**, which shows a different chemical shift in the two diastereomers. The enantiomeric excesses of (*R*)-2-methylalkanoic acids were obtained by gas chromatographic analyses using a $\beta$-cyclodextrin-derived chiral column. Having established a practical pathway to $\alpha$-substituted carboxylic acids, we studied the generality of the method, as shown in the scheme, by making analogs **6a–d**.

In summary, *N*-acylation of chiral imidazolidine-2-one **3**, stereoselective alkylation, and racemization-free deacylation of the alkylated *N*-acylated-imidazolidine-2-ones **5a–d** using lithium hydroperoxide was accomplished to provide $\alpha$-substituted chiral carboxylic acids in high yield and high enantiomeric purity (97%–99%) while permitting recovery of the chiral auxiliary.

## EXPERIMENTAL

NMR-spectra were recorded in $C_6D_6$ $CDC_{13}$ (Aldrich) solution on a Bruker QE Plus spectrometer at 300 MHz for $^{1}H$ and 75 MHz for $^{13}C$, respectively. The chemical shifts are expressed in ppm relative to the residual solvent for $^{1}H$ ($CDCl_3$ at $\delta$ 7.25 ppm) or to the central peak of $CDCl_3$ $^{13}C$ signal (at

***Table 1.*** Alkylation of *N*-acylated-imidazolidine-2-one derivatives.

| Entry | Substrate | Yield (%)[a] | ee (%) | $[\alpha]_D$[b] | Recovery (%)[c] |
|---|---|---|---|---|---|
| **a** | R = $CH_2CH_3$ | 76 | 97 | −10.0 | 75 |
| **b** | R = $(CH_2)_4CH_3$ | 83 | 99 | −4.1 | 79 |
| **c** | R = $(CH_2)_3Ph$ | 81 | 99 | −6.6 | 72 |
| **d** | R = $CH_2CH = C(CH_3)_2$ | 80 | 97 | −8.3 | 78 |

[a]Isolated yield of **6**.
[b](c 0.1, MeOH).
[c]Isolated yield of chiral auxiliary **3**.

77.0 ppm). Chiral gas chromotography (GC) analyses were carried on a HP 6890 GC equipped with a 30-m × 0.25-mm ID, 0.25-μm film-thickness β-DEX 120 [20% permethylated alpha-cyclodextrin in SPB-35 poly (35% phenyl/65% dimethylsiloxane)] capillary column (Supelco, Inc., Bellefonte, PA) in the split mode (100 : 1) with hydrogen as carrier (55 cm/sec, 100°C isothermal). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25°C. Melting points were determined on a hot stage and are uncorrected. Flash column chromatography was carried out on silica gel (70–230 mesh, Aldrich Chemical Company, Milwaukee, WI) unless otherwise stated.

**(4*S*,5*R*)-1,5-Dimethyl-3-propionyl-4-phenylimidazolidine-2-one, 4.** A solution of (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidine-2-one **3** [7]1.0 g (5.2 mmol) in dry tetrahydrofuran (20 mL) was treated with an equimolar amount of *n*-butyllithium (1*M*) at 0°C. After the solid had dissolved, the clear solution was stirred an additional 0.5 hr at 0°C, then propanoyl chloride 0.5 mL (5.5 mmol) dissolved in tetrahydrofuran (10 mL) was added drop-wise and the mixture was stirred for 1 hr at 0°C. Work-up with saturated ammonium chloride and extraction with dichloromethane (100 mL × 2) followed by flash chromatography (ethyl acetate : hexanes 1 : 1) afforded pure **4** 1.1 g in 86% yield. m.p.: 90°C–91°C (lit.[6a] 90°C); GC/MS: 246 (11), 189 (15), 175 (4), 132 (100), 105 (4), 77 (21), 58 (76); optical rotation: $[\alpha]_D + 65$ (c 1, MeOH).

**General procedure for alkylation of 3-propanoylimidazolidine-2-one, 5a–d.** To a cooled solution of 3-acylimidazolidine-2-one **4**, 4.1 g (24.4 mmol) lithium diisopropylamide (LDA) (24.4 mmol) in THF was added drop-wise at −78°C. After 1 hr a solution of the appropriate alkyl halide (29.28 mmol) and HMPA (29.28 mmol) in THF (15 mL) was slowly added and the mixture was allowed to warm to 0°C in 12 hr. Work-up with HCl (2*M*) and extraction with $CH_2Cl_2$ (100 mL × 2) followed by flash chromatography (hexanes : ethyl acetate, 2 : 1) yielded the products **5a–d** as distereomeric mixtures, the ratios of which were determined on the basis of spectral data. (**5a**) m.p., 105°C–107°C; $^1$H NMR: δ 0.78 (t, 3H, J = 7 Hz), 0.79 (d, 3H, J = 7Hz), 1.1 (d, 3H, J = 6 Hz), 2.8 (s, 3H), 1.3 (m, 1H), 1.7 (m, 1H), 2.8 (s, 3H), 3.9 (m, 2H), 5.29 (d, 1H, J = 6.0 Hz), 7.1–7.35 (m, 5H, Ar); $^{13}$C NMR: δ 152.2, 136.9, 128.4, 127.9, 127.0, 126.9, 77.4, 77.0, 76.7, 59.4, 53.7, 39.0, 38.9, 28.2, 27.0, 16.2, 15.0, 11.4; MS *m/z*: 274 (100), 259 (66), 246 (9), 217 (4), 189 (66), 175 (17), 132 (69), 118 (15), 105 (6), 91 (8), 77 (10), 58 (31); $[\alpha]_D + 71.8$ (c 1, MeOH). (**5b**) m.p., 70°C–72°C; $^1$H NMR: δ 0.8 (d, 3H, J = 6.0 Hz), 0.81 (t, 3H, J = 6.0 Hz), 1.1 (d, 3H, J = 6.0 Hz), 1.15–1.3 (m, 5H), 1.65 (m, 2H), 2.82 (s, 3H), 3.9 (dq, 1H, J = 6.0 Hz), 5.3 (d, 1H, J = 7.0 Hz), 7.3 (m, 5H, Ar); $^{13}$C NMR: δ 177.6, 155.4, 137.0, 126.5, 125.9, 59.2, 53.7, 37.2, 35.4, 31.2, 28.4, 27.9, 22.6, 16.0, 14.6, 14.0; MS *m/z*: 316 (11), 259 (100), 246 (73), 189 (74), 175 (12), 132 (10), 113 (15), 77 (2), 58 (43); $[\alpha]_D + 41.66$ (c 1, MeOH). (**5c**) m.p., 80°C–82°C; $^1$H NMR: δ 0.84 (d, 3H, J = 6.5 Hz), 1.15 (d, 3H, J = 6.8 Hz), 1.4–1.8 (m, 2H),

2.55 (m, 2H, $CH_2Ph$), 2.86 (s, 3H), 3.9 (m, 1H), 5.3 (d, 1H, J = 7.0 Hz), 7.3 (m, 10H, 2Ar); $^{13}C$ NMR: $\delta$ 176.9, 155.4, 148.3, 137.0, 128.8, 128.5, 126.5, 125.9, 59.2, 53.7, 38.2, 36.2, 34.6, 28.5, 16.6, 14.6; MS *m/z*: 364 (11), 321 (2), 273 (2), 259 (17), 246 (9), 189 (100), 175 (6), 132 (26), 117 (8), 91 (90), 77 (10), 58 (25); $[\alpha]_D + 30.0$ (c 1, MeOH). (**5d**) m.p., 150°C–153°C; $^1H$ NMR: $\delta$ 1.16 (d, 3H, J = 6.8 Hz), 1.6 (s, 3H), 2.1–2.5 (m, 1H), 3.85 (m, 1H), 5.0 (m, 1H), 5.3 (d, 1H, J = 9 Hz), 7.3 (m, 5H, Ar); $^{13}C$ NMR: $\delta$ 169.8, 156.3, 134.5, 137.0, 126.5, 125.9, 124.4, 54.1, 53.7, 40.0, 28.4, 28.1, 25.6, 17.6, 15.8, 14.6; MS *m/z*: 314 (2), 246 (5), 189 (61), 175 (7), 132 (39), 113 (53), 104 (11), 91 (17), 81 (24), 69 (32), 58 (100), 41 (29); $[\alpha]_D + 65.0$ (c 1, MeOH).

**General procedure for the preparation of (*R*)-2-methylalkanoic acids, 6a–6d.** To a solution of (4*S*,5*R*,2′*R*)-1,5-dimethyl-4-phenyl-3-[(2′alkyl)] imidazolidine-2-one, **5**, 2.2 g (8.33 mmol) in THF : $H_2O$ (20 mL, 3 : 1) was added 30% $H_2O_2$ 11.33 g (12 eq, 99.9 mmol) and LiOH, 1.05 g (3 eq, 24.99 mmol) at ice-bath temperature. The reaction mixture was heated to 50°C in an oil bath for 24 hr. After the reaction was complete, it was quenched with 10% $Na_2S_2O_3$ at 0°C and the pH was adjusted to 9–10. THF was removed with a rotary evaporator and the residual oil was extracted with petroleum ether (50 mL × 3) to obtain (*R*)-2-methyl alkanoic acids **6a–d**. The chiral auxiliary was recovered in quantitative yield by filtering the colorless solid. (**6a**) b.p. 70°C–72°C/12 mm (lit.[9a] 74°C–75°C/12 mm). $^1H$ NMR: $\delta$ 0.9 (t, 3H, J = 7.0 Hz), 1.17 (3H, J = 7 Hz), 1.7 (m, 2H), 2.39 (m, 1H), 10.3 (bs, 1H); $^{13}C$ NMR: $\delta$ 183.4, 41.0, 26.6, 16.4, 11.4; MS *m/z*: 102 (12), 87 (33), 74 (100), 57 (51), 50 (1), 41 (36). (**6b**) b.p. 124°C–126°C/12 mm (lit.[9b] 128°C/12 mm); $^1H$ NMR: $\delta$ 0.87 (t, 3H, J = 7 Hz), 1.18 (d, 3H, J = 6.0 Hz), 1.3–1.7 (m, 8H), 2.45 (m, 1H); $^{13}C$ NMR: $\delta$ 182.8, 34.0, 32.1, 27.3, 22.5, 16.2, 14.0; MS *m/z*: 144, 101 (12), 87 (29), 74 (100), 69 (6), 57 (18), 45 (18), 41 (32). (**6c**) b.p. 140°C–143°C/12 mm (lit.[9c] 141°C–143°C/12 mm); $^1H$ NMR: $\delta$ 1.2 (d, 3H, J = 7.0 Hz), 1.5–1.7 (m, 4H), 2.5 (m, 1H), 2.65 (t, 2H, $CH_2Ph$, J = 7.0 Hz), 7.1–7.4 (m, 5H); $^{13}C$ NMR: $\delta$ 182.1, 140.7, 129.4, 128.5, 125.8, 39.1, 35.1, 33.1, 28.2, 16.8; MS *m/z*: 192 (15), 174 (21), 146 (3), 131 (9), 117 (15), 104 (38), 91 (100), 74 (32), 65 (17), 45 (16). (**6d**) b.p. 120°C–122°C/15 mm (lit.[9d] 124–125°C/15 mm); $^1H$ NMR: $\delta$ 1.15 (d, 3H, J = 7.0 Hz), 1.6 (s, 3H), 1.69 (s, 3H), 2.16 (m, 1H), 2.36 (m, 1H), 2.5 (m, 1H), 5.1 (m, 1H, HC═C); $^{13}C$ NMR: $\delta$ 182.9, 131.9, 121.2, 40.5, 28.9, 25.6, 17.8, 16.0; MS *m/z*: 142 (11), 96 (3), 87 (4), 81 (7), 74 (17), 69 (100), 55 (17), 45 (11), 41 (71).

## ACKNOWLEDGMENTS

We thank Ms. Junying Nie of the Chemicals Affecting Insect Behavior Laboratory for assistance with syntheses. Mention of tradenames or

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Received in the USA May 27, 2004