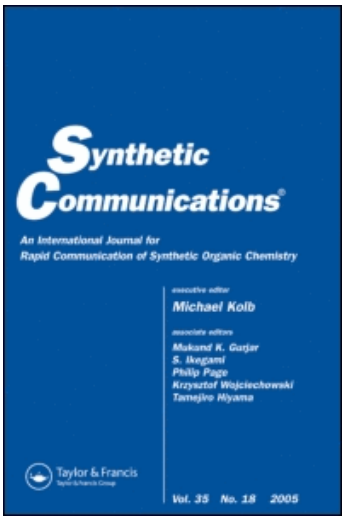

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One-Step Conversion of Ketones to Conjugated Acids Using Bromoform

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Abstract: Phase-transfer-catalyzed (PTC) reactions of ketones with bromoform and aqueous lithium hydroxide in alcoholic solvent result in the formation of α,β-unsaturated carboxylic acids. The reaction was performed at room temperature for 24 h. The corresponding conjugated acids were obtained from cyclic or aromatic ketones, whereas bromo acids were obtained from 4-oxo-piperidine-1-carboxylic acid ethyl ester (**13**) and 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (**14**).

Keywords: Bromoform, phase-transfer-catalyzed reaction, α,β-unsaturated carboxylic acids

INTRODUCTION

The synthesis of α,β-unsaturated carboxylic acids has gained considerable attention[1] because of the biologically important properties of these acids, their occurrence in natural products, and their use as precursors for the preparation of biologically active compounds.[2]

Many cyclic and acyclic conjugated acids were prepared from ketone or aldehyde cyanohydrines by sequential dehydration using phosphorous oxychloride/pyridine[3] or thionyl chloride[4] followed by acidic[5] or alkaline[6] hydrolysis of the resulting conjugated nitriles. Base-mediated

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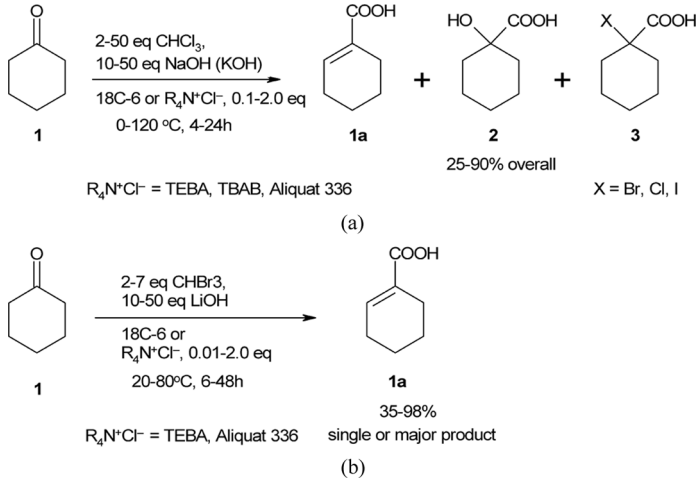
dehydrohalogenation of α-halocarboxylic esters produced conjugated systems in variable yields.[7] Both acyclic and cyclic β-keto esters were converted to (*E*) and (*Z*) conjugated acids via 4-halo-2-pyrazolin-5-on derivatives.[8] Vinyl triflates,[9] prepared from ketones, were reacted with CO in the presence of palladium catalysts to obtain conjugated acids. Variations of the Morita–Baylis–Hillman reaction were also used recently.[10] Cyclopentene carboxylates were obtained via novel catalytic asymmetric [3 + 2] cycloaddition.[11]

Conjugated esters and amides are versatile intermediates in organic synthesis. Of particular importance are their 1,4-additions of various carbon, oxygen, sulfur, and nitrogen nucleophiles. For example, enantioselective 1,4-addition of thiophenols to methyl cyclopentene carboxylate and methyl cyclohexenecarboxylate was achieved in the presence of chiral catalysts.[12] Thiols were added in the presence of a base.[13] Numerous enantioselective additions of chiral secondary amines were achieved, yielding the corresponding β-amino esters.[14] Enantioselective addition of achiral amines was achieved in the presence of chiral ligands.[15] Alkyl and aryl organocuprates react chemo- and stereoselectively to produce the corresponding 4-substituted saturated esters,[16] whereas enantioselective 1,4-addition of organolithium reagents was done in the presence of chiral ligands.[17] The addition of amide enolates was employed in alkaloid synthesis.[18]

Carbanions derived from fluoroform,[19] chloroform,[20] or bromoform,[21] readily react with aldehydes and ketones to form stable and isolable α-(trihalomethyl)carbinols. Those derived from fluoroform are significant precursors of diverse, pharmacologically active compounds possessing aliphatic CF_3 groups.[19] α-Trichloromethyl carbinols undergo a variety of transformations and are precursors to functionalized thiazolidinone,[22] α-amino acids via the Corey–Link reaction,[23] heterocycles,[24] chiral epoxides,[25] chiral 1-fluoro carboxylic acids,[26] chiral hydroxy acids,[27] and conjugated acids.[28]

RESULTS AND DISCUSSION

Initially, we attempted to prepare 1-chlorocyclohexane carboxylic acid from cyclohexanone and chloroform in the presence of 50% aqueous NaOH and quaternary ammonium chloride according to the published procedure.[29] However, it was found that under these conditions a considerable amount of cyclohexene carboxylic acid (**1a**) was obtained, too. Typically, the acid fraction of the product (Scheme 1a) contains cyclohexenecarboxylic acid (**1a**), 1-chlorocyclohexane carboxylic acid (**3a**), and 1-hydroxycyclohexane carboxylic acid (**2**) [according to gas chromatography (GC) and thin-layer chromatography (TLC)] in a variable ratio, depending on the reaction conditions.



Scheme 1. Reaction of cyclohexane with haloform under different conditions.

When bromoform was used instead of chloroform, cyclohexenecarboxylic acid (**1a**) was obtained as the main or sole acid product (Scheme 1b). To elucidate this effect, the reaction was systematically examined by varying the molar ratios of base, reactants, and phase-transfer catalyst (PTC). The effect of variation of temperature, reaction time, and cosolvent was studied, too. The obtained reaction mixtures (acid components) were examined by GC, TLC, and mass spectrometry (MS). Major variations included (a) alkaline hydroxyde [lithium hydroxide ($LiOH \times H_2O/H_2O$, 40–60% sodium hydroxide (NaOH), 40–60% potassium hydroxide (KOH)], 10–50 eq. to cyclohexanone; (b) haloform ($CHCl_3$, $CHBr_3$, CHI_3), 2–50 eq. to cyclohexanone; (c) phase catalyst [benzyltriethylammonium chloride (TEBA), tetrabutylammonium bromide TBAB), methyl trioctylammonium chloride (aliquat 336)] as well as 18-crown-6/KOH; (d) solvent [$PhMe/H_2O$, dimethyl sulfoxide (DMSO), CH_2Cl_2/H_2O, tetrahydrofuran (THF)/H_2O, *i*-PrOH/H_2O *t*-BuOH/H_2O, *t*-PentOH/H_2O and others]; (e) temperature (0–120°C) and reaction time (4–48 h).

The results are summarized in Table 1.

As can be seen from Table 1, when we used $CHBr_3$ instead $CHCl_3$ and LiOH instead KOH as the base in alcoholic solvent, the cyclohexenecarboxylic acid (**1a**) was obtained in the highest yield (entry 14). With chloroform, in the presence of 50% aqueous NaOH or KOH, cyclohexenecarboxylic acid and 1-hydroxycyclohexane carboxylic acid (**2**) were obtained (entries 1, 3, and 4, Table 1). When we used CHI_3 instead $CHCl_3$, 1-lodo-cyclohexanecarboxylic acid (**3c**) was also obtained (entry 6) as a product.

Table 1. Reaction of cyclohexanone with bromoform under different conditions

Entry	Products	Base/CHX_3	Temperature (°C)/time (h)	Solvent	Catalyst	Yield (%)[a]
1	**1a**+**2**	NaOH 50 eq	RT/12 h	Toluene/H_2O	Aliquat 336	60
		$CHCl_3$4 eq		1:1	0.1 eq	(6:4)[b]
2	**1a**+**2**	NaOH 20 eq	RFL/4 h	Toluene/H_2O	TBAB	70
		$CHBr_3$4 eq		4:1	0.25 eq	(7:3)
3	**1a**+**3a**[c]	KOH 15 eq	0°C/4 h	$CHCl_3/H_2O$	18C-6	25
		$CHCl_3$50 eq	RT/24 h	5:1	0.1 eq	(1:1)
4	**1a**+**2**	KOH 20 eq	RT/12 h	CH_2Cl_2/H_2O	18C-6	75
		$CHCl_3$4 eq		4:1	0.1 eq	(8:2)
5	**1a**+**2**+**3b**[c]	KOH 18 eq	RT/12 h	*t*-PentOH/H_2O	18C-6	90
		$CHBr_3$4 eq		5:1	0.1 eq	(85:10:5)
6	**1a**+**3c**[c]	KOH 10 eq	RT/24 h	*t*-BuOH/H_2O	18C-6	80
		$CHJ_3$2 eq		10:03	0.1 eq	(6:4)
7	**1a**+**2**	KOH 20 eq	RT/24 h	*i*-PrOH/H_2O	18C-6	70
		$CHBr_3$4 eq		1:1	0.1 eq	(8:2)
8	**1a**+**2**+**3b**[c]	KOH 18 eq	RT/24 h	*t*-PentOH/H_2O	18C-6	85
		$CHBr_3$4 eq		9:1	0.1 eq	(90:7:3)

9	**1a**	KOH 18 eq $CHBr_3$4 eq	RT/12 h	DMSO/H_2O 2:1	18C-6 0.1 eq	33
10	**3b**[c]	DBU 1 eq $CHBr_3$2 eq	RT/24 h	CH_2Cl_2	–	40
11	**1a**+**3**a[c]	LiOH 20 eq $CHBr_3$7 eq	0°C/4 h RT/24 h	*t*-BuOH/H_2O 10:03	TEBA 2eq	85 (1:1)
12	**1a**+**2**	LiOH 50 eq $CHBr_3$6 eq	RFL 6 h	*t*-BuOH/H_2O 5:1	TEBA 0,5 eq	35 (6:4)
13	**1a**+**2**	LiOH 10 eq $CHBr_3$2 eq	RT/12 h	*t*-PentOH/H_2O 5:02	TEBA 0,25 eq	40 (8:2)
14	**1a**	LiOH 20 eq $CHBr_3$4 eq	RT/24 h	*t*-BuOH/H_2O 5:1	TEBA 0,1 eq	95
15	**1a**	LiOH 20 eq $CHBr_3$4 eq	RT/48 h	CH_2Cl_2/H_2O 5.1	TEBA 0,2 eq	85
16	**1a**	LiOH 20 eq $CHBr_3$4 eq	RT/48 h	Toluene/H_2O 5:1	TEBA 0,2 eq	78

[a]Yields of isolated pure products.
[b]Ratio of isolated acids.
[c]**3a**, 1-chloro-cyclohexanecarboxylic acid; **3b**, 1-bromo-cyclohexanecarboxylic acid; and **3c**, 1-iodo-cyclohexanecarboxylic acid.

However, a 95% yield of 1a was obtained with lithium hydroxide as the base in t-Bu-OH/H_2O (entry 14). Use of KOH gives consistently higher yields than those obtained with sodium hydroxide (entries 4, 5, 6, and 8, Table 1) but lower than those obtained with LiOH. Using a larger excess of base (entries 1 and 12, Table 1) or haloform (entry 3, Table 1) resulted in lower yields of cyclohexenecarboxylic acid (**1a**) but increased yield of 1-hydroxycyclohexane carboxylic acid (**2**).

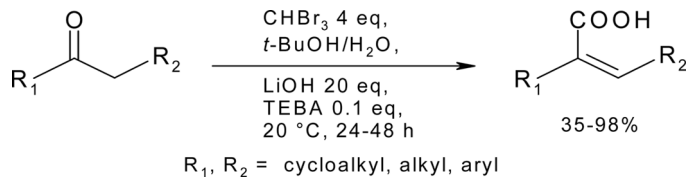
The reaction was carried out at room temperature for 24 h. Generally, higher temperatures, 80–120°C, favor higher yields of 1-hydroxycy clohexane carboxylic acid (**2**) (entries 2 and 12, Table 1).

The amount of catalyst is one of the critical factors affecting the reaction efficiency. The reduced amount of catalyst gave diminished yield of **1a**. The optimal amount of catalyst is 0.1 eq. (TEBA/LiOH) or (18C-6/KOH) in relation to ketone. For comparison, the reaction with 2 eq. TEBA gave 1-chloro-cyclohexanecarboxylic acid (**3a**) and cyclohexenecarboxylic acid (**1a**) in 1:1 ratio (entry 11, Table 1). In the absence of catalyst, either no reaction occured or the yields of conjugated acids were lower.

Higher yields are obtained in polar protic solvents. In polar aprotic solvents, 1-bromo-cyclohexane carboxylic acid (**3b**) was obtained as a minor or as a sole product using stoichiometric amounts of 1.8-diazabicyclo[5.4.0] undec-7-en (DBU) (entry 10). The use of less polar solvents resulted in lower yields of the desired conjugated acid (entries 1, 2, 9, 15, and 16, Table 1). In chloroform as a solvent, 1-chlorocyclohexane carboxylic acid (**3a**) was obtained in an amount equal to conjugated acids. Increased amount of co solvent H_2O resulted in lower yields of the desired conjugated acid but increased yield of the corresponding hydroxy acid (entry 7, Table 1).

Scheme 2 presents the optimized reaction of different ketones with bromoform. Table 2 lists all acids and their corresponding starting ketones used in this new one-pot reaction, shown in Scheme 2.

Corresponding bromo acids were obtained as main products from 4-oxo-piperidine-1-carboxylic acid ethyl ester (**13**) and 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (**14**), (entries 11 and 12, Table 2). In the crude reaction mixtures, corresponding conjugated acids were detected too (5–10%).



Scheme 2. Optimized reaction of different ketones with bromoform.

Table 2. All acids obtained in reactions of ketones with bromoform

Entry	Ketone	Acid	Yield[a] (%)
1	Cyclohexanone (**1**)	Cyclohex-1-enecarboxylic acid (**1a**)	95
2	4-*tert*-Butyl-cyclohexanone (**4**)	4-*tert*-Butyl-cyclohex-1-enecarboxylic acid (**4a**)	90
3	3-Methyl-cyclohexanone (**5**)	3-Methyl-cyclohex-1-enecarboxylic acid (**5a**)	95
4	4-Phenyl-cyclohexanone (**6**)	4-Phenyl-cyclohex-1enecarboxylic acid (**6a**)	95
5	4-Ethyl-cyclohexanone (**7**)	4-Ethyl-cyclohex-1-enecarboxylic acid (**7a**)	89.5
6	1-Phenyl-propan-1-one (**8**)	2-Phenyl-but-2-enoic acid (**8a**)	54
7	1-Phenyl-ethanone (**9**)	2-Phenyl-acrylic acid (**9a**)	50
8	Cyclopentanone (**10**)	Cyclopent-1-enecarboxylic acid (**10a**)	75
9	Cycloheptanone (**11**)	Cyclohept-1-enecarboxylic acid (**11a**)	43
10	Cyclododecanone (**12**)	Cyclododec-1-enecarboxylic acid (**12a**)	35[b]
11	4-Oxo-piperidine-1-carboxylic acid ethyl ester (**13**)	4-Bromo-piperidine-1,4 dicarboxylic acid monoethyl ester (**13a**)	77[b]
12	4-Oxo-piperidine-1-carboxylic acid *tert*-butyl ester (**14**)	4-Bromo-piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (**14a**)	65[b]
13	1,5-Diphenyl-pentan-3-one (**15**)	2-Hydroxy-2-phenethyl-4-phenyl-butyric acid (**15a**)	85

[a]Yields of isolated pure products.
[b]Reaction time was 48 h.

It is interesting to note that the reaction of 1,5-diphenyl-pentan-3-one (**15**), in all reaction conditions, gives 2-hydroxy-2-phenethyl-4-phenyl-butyric acid (**15a**) as the sole product (entry 13, Table 2).

ANTIPROLIFERATIVE ACTIVITY

The antiproliferative activity of obtained acids toward malignant cell lines was evaluated in this work, too. With the aim to determine the undesirable cytotoxic effect of investigated compounds on immune-competent cells, the normal peripheral blood mononuclear cells were used as target cells, too. The majority of synthesized conjugated acids exert antiproliferative activity in vitro toward HeLa, having IC_{50} values from 122.20 to 192 μM. The most active compound is cyclododec-1-enecarboxylic acid ($IC_{50} = 122$ μM toward HeLa cells). All examined compounds did not affect proliferation of healthy human blood peripheral mononuclear cells (PBMC and PBMC + PHA), $IC_{50} > 200$ μM, but all the studied compounds affected the survival of HeLa (cervical cancer cells line).

EXPERIMENTAL

General Procedure

All used chemicals were of analytical-reagent grade, purchased from Aldrich, Fluka, or Merck, and used without further purification. The NMR spectra were recorded on a Varian Gemini 2000 (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz) and on a Bruker Avance 500 spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) for samples in deuterated chloroform. Chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (TMS) as the internal standard. The infrared (IR) spectra were recorded on a Fourier-transform (FT) Perkin-Elmer 1725X spectrometer and Nicolet 6700 FT instrument and are expressed in centimeters^{-1}. The mass spectra were obtained on an Agilent Technologies 6210 TOF liquid chromatography/mass spectrometer (LC/MS) instrument (LC, series 1200). High-resolution mass spectra (HRMS) were obtained by the electron spray ionization (ESI) method. Melting points were determined on a Boetius PMHK apparatus and were not corrected. The elemental analyses were done on Elemetar-Vario EL III equipment.

Cyclohexene-1-carboxylic Acid (1a)

The flask was charged with LiOH solution (1.02 mol, 43.2 g, in 40 mL H_2O), *t*-BuOH (200 mL), cyclohexanone (0.05 mol, 5 g), and TEBA

(0.005 mol, 1.14 g). The mixture was stirred vigorously (large egg-shaped stirring bar) at 20–25°C, while bromoform (0.2 mol, 51.5 g) was added dropwise from the dropping funnel (~30 min). The reaction is exothermal, and the internal temperature was maintained at less than 50°C by external cooling (water bath). The stirring continued for 24 h, H_2O (300 mL) was added, and the organic layer was discarded. The aqueous layer was extracted with toluene (2×50 mL) and then acidified with HCl (20%) to pH ~1. The separated brown oil was extracted with toluene (3×50 mL), dried (anh. $MgSO_4$), concentrated, and fractionally distilled (short Vigreux column) under the reduced pressure. Cyclohexene-1-carboxylic acid was obtained as a colorless liquid, which solidified in the receiver. Yield: 6.33 g, 98%; bp: 145–146°C; mp: 36–38°C (lit. 38°C)[30]; ^{1}H NMR ($CDCl_3$, 200 MHz; δ ppm, J Hz): 11.65 (s, 1H), 7.14 (t, $J = 2$ Hz, 1H), 2.3 (m, 4H), 1.63 (m, 4H), 1.27 (m, 1H), 0.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz, δ ppm): 173.2 (CO), 142.4 (C), 129.6 (CH), 25.8 (CH_2), 23.5 (CH_2), 21.8 (CH_2), 21.1 (CH_2); IR (KBr): 3056, 2936, 2645, 1691, 1424, 1282, 1085 cm^{-1}; HRMS-ESI: calcd. for $C_7H_{10}O_2$ 126.0681; calcd. for $[M + H]^+$ 127.0753, found 127.0751.

tert-Butyl-cyclohex-1-enecarboxylic Acid (4a)

Mp: 182°C (lit. 182–183°C)[31]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.6 (s, 1H), 7.12 (t, $J = 3$ Hz, 1H), 2.5 (m, 1H), 2.28 (m, 1H), 2.13 (m, 1H), 1.94 (m, 2H), 1.3 (m, 1H), 1.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 172.1 (CO), 142.9 (C), 129.5 (CH), 43.1 (CH_2), 32.12 (CH_2), 27.7 (CH_2), 27.1 (CH_2), 25.2 (CH_2), 23.47 (CH_3); IR (KBr): 3297, 3415, 2958, 1681, 1644, 1276, 1177, 1085 cm^{-1}; HRMS-ESI: calcd. for $C_{11}H_{18}O_2$ 182.1306; calcd. for $[M + H]^+$ 183.1379, found 183.1385.

3-Methyl-cyclohex-1-enecarboxylic Acid (5a)

Mp: 26°C (lit. 26–27°C)[32]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11 (s, 1H), 7.16 (t, $J = 10$ Hz, 1H), 7.26 (t, $J = 10$ Hz, 1H), 7.12 (s, 1H), 6.98 (s, 1H), 2.5 (m, 1H), 2.4 (m, 1H), 2.3 (m, 1H), 1.8 (m, 4H), 1.2 (m, 1H), 1.17 (d, $J = 7$ Hz, 1H), 1.02 (d, $J = 7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 173.5 (CO), 173.3 (CO), 148.9 (CH), 142.5 (CH), 129.6 (C), 128.4 (C), 125.5 (C), 32.2 (CH_2), 31.3 (CH_2), 30.2 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 26.3 (CH_2), 24 (CH_2), 21.7 (CH_2), 21.1 (CH_3), 20.7 (CH_3); IR (KBr): 3409, 2927, 1709, 1459, 1236 cm^{-1}; HRMS-ESI: calcd. for $C_8H_{12}O_2$ 140.0837; calcd for $[M - H]^-$ 139.0764, found 139.0762.

4-Phenyl-cyclohex-1-enecarboxylic Acid (6a)

Mp: 196–199°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11 (s, 1H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.22 (m, 5H), 2.82 (m, 1H), 2.55 (m, 2H), 2.35 (m, 2H), 2.16 (m, 1H), 1.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.5 (CO), 146.03 (CH), 141.2 (C), 129.7 (C), 128.77 (CH), 127.01 (CH), 126.6 (CH), 39.24 (C), 34.12 (CH_2), 29.5 (CH_2), 24.73 (CH_2); IR (KBr): 3409, 2927, 1709, 1459, 1236 cm^{-1}; HRMS-ESI: calcd. for $C_{13}H_{14}O_2$ 202.0993; calcd for $[M + H]^+$ 203.1066, found 203.1057.

4-Ethyl-cyclohex-1-enecarboxylic Acid (7a)

Mp: 81–82°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11 (s, 1H), 7.1 (t, $J = 4$ Hz, 1H), 2.42 (m, 2H), 2.36 (m, 1H), 2.2 (m, 1H), 1.86 (m, 2H), 1.44 (m, 1H), 1.32 (m, 2H), 1.2 (m, 2H), 0.94 (t, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 172.23 (CO), 142.17 (CH), 129.53 (C), 34.22 (CH), 32.3 (CH); IR (KBr): 3411, 2961, 1708, 1446, 1298, 1227 cm^{-1}; HRMS-ESI: calcd. for $C_9H_{14}O_2 = 154.0993$; calcd. for $[M + H]^+$ 155.1067, found 155.1066.

2-Phenyl-but-2-enoic Acid (8a)

Mp: 138–139°C (lit. 132–137°C)[33]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.33 (m, 6H), 6.44 (q, $J = 7.5$ Hz, 1H), 2.16 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.18 (CO), 140.27 (CH), 138.2 (C), 134.13 (C), 128.34 (CH), 127.88 (CH), 127.63 (CH), 16.41 (CH_3); IR (KBr): 3520, 2977, 2940, 1694, 1602, 1113 cm^{-1}; HRMS-ESI: calcd. for $C_{10}H_{10}O_2$ 162.0681; calcd. for $[M + H]^+$ 163.0754, found 163.0748.

2-Phenyl-acrylic Acid (9a)

Mp: 101–102°C (lit. 139–140°C)[34]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.44 (m, 2H), 7.36 (m, 3H), 6.53 (s, 1H), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.18 (CO), 140.5 (CH_2), 136.11 (C), 129.36 (C), 128.43 (CH), 128.37 (CH), 128.15 (CH); IR (KBr) 3060, 1691, 1493, 1431, 1223, 1073 cm^{-1}; HRMS-ESI: calcd. for $C_9H_8O_2$ 148.0524; calcd. for $[M + H]^+$ 149.0597, found 149.0589.

Cyclopent-1-enecarboxylic Acid (10a)

Mp: 120–121°C (lit. 121°C)[30]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.92 (t, $J = 2$ Hz, 1H), 2.56 (m, 4H), 1.98 (m, 2H); ^{13}C NMR ($CDCl_3$,

125 MHz) δ: 169.16 (CO), 146.66 (CH), 135.77 (C), 33.61 (CH_2), 31.05 (CH_2), 23.14 (CH_2); IR (KBr) 2971, 2627, 1674, 1430, 1291 cm^{-1}; HRMS-ESI: calcd. for $C_6H_8O_2$ 112.0524; calcd. for $[M+H]^+$ 113.0597, found 113.0597.

Cyclohept-1-enecarboxylic Acid (11a)

Mp: 51°C (lit. 51°C)[30]; ^1H NMR ($CDCl_3$, 500 MHz) δ: 11 (s, 1H), 7.34 (t, $J = 7$ Hz, 1H), 2.7 (m, 2H), 2.5 (m, 2H), 1.55 (m, 2H), 1.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 173.33 (CO), 147.39 (CH), 135.78 (C), 31.97 (CH_2), 29 (CH_2), 26.95 (CH_2), 26.12 (CH_2), 25.6 (CH_2); IR (KBr): 2926, 2854, 1680, 1468, 1290 cm^{-1}; HRMS-ESI: calcd. for $C_8H_{12}O_2 = 140.0837$; calcd for $[M-H]^-$ 139.0764, found 139.0760.

Cyclododec-1-enecarboxylic Acid (12a)

Mp: 120–122°C (lit. 120–123°C)[8]; ^1H NMR ($CDCl_3$, 200 MHz) δ: 9.76 (s, 1H), 6.93 (t, $J = 8$ Hz, 1H), 6.28 (t, $J = 8$ Hz, 1H), 2.6 (m, 2H), 2.3 (m, 5H), 1.29 (m, 33H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 173.86 (CO), 148.64 (CH), 146.1 (CH), 131.4 (C), 129.4 (C), 42.62 (CH_2), 34 (CH_2), 33.65 (CH_2), 32.6 (CH_2), 29.74 (CH_2), 28.72 (CH_2), 27.2 (CH_2), 26.55 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26 (CH_2), 25.95 (CH_2), 25.894 (CH_2), 25.84 (CH_2), 25.78 (CH_2), 25.6 (CH_2), 25.1 (CH_2), 24.65 (CH_2), 24.56 (CH_2), 24.3 (CH_2), 24.1 (CH_2), 23.5 (CH_2), 23.38 (CH_2), 23.2 (CH_2), 22.89 (CH_2), 22.56 (CH_2), 22.14 (CH_2), 21.9 (CH_2), 19.2 (CH_2); IR (KBr): 2927, 2855, 1682, 1468,1289 cm^{-1}; HRMS-ESI: calcd. for $C_{13}H_{22}O_2$ 210.1620; calcd. for $[M+H]^+$ 211.1693, found 211.1683.

4-Bromo-piperidine-1,4-dicarboxylic Acid Monoethyl Ester (13a)

In a typical procedure, the flask was charged with $LiOH \times H_2O$ (0.23 mol, 9.8 g), *t*-BuOH (50 mL), H_2O (10 mL), 4-oxo-piperidine-1-carboxylic acid ethyl ester (commercially available from Aldrich, cat. no. 15,373-7) (0.011 mol, 2.0 g), TEBA (0.001 mol, 0.23 g), and bromoform (0.044 mol, 11.3 g). The mixture was stirred vigorously (egg-shaped stirring bar) at 20°C, for 48 h and then poured into H_2O (150 mL). It was extracted with ether (2×50 mL), and the organic extracts were discarded. The aqueous layer was acidified to pH ~1 at 0°C (20% HCl), the separated solid was extracted with ether (3×20 mL), and the combined extracts were washed with brine, dried (anh. $MgSO_4$), and concentrated

at 20°C. Recrystallization of the crude product from hexane gave white crystals of 4-bromo-piperidine-1,4-dicarboxylic acid monoethyl ester. Yield: 2.5 g, 77%; mp: 108°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.7 (s, 1H), 4.16 (q, $J = 7$ Hz, 2H), 3.83 (m, 2H), 3.44 (m, 2H), 2.22 (m, 2H), 2.12 (m, 2H), 1.27 (t, $J = 7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174.65 (CO), 155.76 (CO), 62.1 (CH_2), 59.88 (C), 41 (CH_2), 36.3 (CH_2), 14.8 (CH_3); IR (KBr): 2983, 1732, 1647, 1446, 1280, 1245, 1132 cm^{-1}; HRMS-ESI: calcd. for $C_9H_{14}BrNO_4$ 279.0106; calcd. for $[M-H]^-$ 280.0179, found 280.0169. Anal. calcd. for $C_9H_{14}BrNO_4$: C, 38.59%; H, 5.04%; N, 5.00%. Found: C, 38.57%; H, 4.99%; N, 5.03%.

4-Oxo-piperidine-1-carboxilic Acid–*tert*-butyl Ester (14)

A solution of 1-benzyl-piperidin-4-one (6 g, 0.032 mol) in MeOH (30 mL) was stirred at 5 atm. with Pd/C (10%, 1.5 g) in a Parr apparatus at 25°C. After 20 h, the reaction mixture was filtered through Celite, and the solvent was evaporated. The residual oil was dissolved in NH_3/H_2O (25 mL) and extracted with toluene. Evaporation of the dried organic extracts and purification of the oily residue by crystallization in hexane afforded the title compound **14** as white crystals. Yield: 4.9 g, 78%; mp: 72°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.72 (t, $J = 7$ Hz, 2H), 2.44 (t, $J = 7$ Hz, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 207.9 (CO), 80.44 (C), 42.93 (CH_2), 41.15 (CH_2), 28.33 (CH_3); IR (KBr): 3421, 2974, 1717, 1687, 1432, 1173 cm^{-1}.

4-Bromo-piperidine-1,4-dicarboxylic Acid Mono-*tert*-butyl Ester (14a)

The flask was charged with $LiOH \times H_2O$ (0.2 mol, 8.4 g), *t*-BuOH (50 mL), H_2O (10 mL), 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (0.010 mol, 2.0 g), TEBA (0.001 mol, 0.23 g), and bromoform (0.04 mol, 10.2 g). The mixture was stirred vigorously (egg-shaped stirring bar) at 20°C, for 48 h, poured into H_2O (150 mL), and extracted with ether (2×50 mL). The organic extracts were discarded. The aqueous layer was acidified to pH ~1 at 0°C, (20% HCl), the separated solid was extracted with ether (3×20 mL), and the combined extracts were washed with brine, dried (anh. $MgSO_4$), and concentrated at 20°C. The crude product, 4-bromo-1-(*tert*-butoxycarbonyl) piperidine-4-carboxylic acid, was recrystallized from hexane. Yield: 1.74 g, 65%; mp: 146°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.45 (*s*, 1H), 3.76 (*m*, 2H), 3.4 (*m*, 2H), 2.2 (*m*, 2H), 2.11 (*m*, 2H), 1.46 (*s*, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174.71 (CO), 154.9 (CO), 80.68 (C), 60.2 (C), 41 (CH_2), 36.4 (CH_2),

28.6 (CH_3); IR (KBr): 2978, 1737, 1648, 1441, 1243, 1166, 1076, 1050 cm^{-1}; HRMS-ESI: calcd. for $C_{11}H_{18}BrNO_4 = 307.0419$; calcd. for $[M-H]^-$ 306.0346, found 306.0280. Anal. calcd. for $C_{11}H_{18}BrNO_4$: C, 42.99%; H, 5.9%; N, 4.56%. Found: C, 43.25%; H, 5.70%; N, 4.59%.

2-Hydroxy-2-phenethyl-4-phenyl-butyric Acid (15a)

Mp: 161–162°C; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.35 (m, 6H), 2.84 (m, 1H), 2.52 (m, 1H), 2.1 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 181.5 (CO), 141.1 (C), 128.47 (CH), 128.43 (CH), 126.1 (CH), 77.63 (C), 40.95 (CH_2), 29.9 (CH_2); IR (KBr): 3445, 2959, 1723, 1455, 1273, 1112 cm^{-1}; HRMS-ESI: calcd for $C_{18}H_{20}O_3$ 284.1412; calcd. for $[M-H]^-$ 283.1340, found for $[M-H]^-$ 283.1338. Anal. calcd. for $C_{18}H_{20}O_3$: C, 76.01%; H, 7.09%. Found: C, 75.86%; H, 7.08%.

CONCLUSION

This method permits the one-pot preparation of a variety of conjugated acids in high yield by using the convenient LiOH base in alcohol/H_2O with PTC catalyst at room temperature.

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