Mild hydrolysis or alcoholysis of amides. Ti(IV) catalyzed conversion of primary carboxamides to carboxylic acids or esters[1,2]

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This paper is dedicated to Professor David B. MacLean

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Reaction of primary amides (e.g., **1***a* or **6–13**) or *O*-methylhydroxamates (**1***b* and **1***c*) with a catalytic amount of $TiCl_4$ and one equivalent of aqueous HCl converts these compounds in good yields to carboxylic esters (when an alcohol is used as solvent) or to carboxylic acids (when 9 : 1 dioxane : H_2O is used as solvent). These conversions are chemoselective for primary amides: mono- and dialkyl amides are not affected by the reaction conditions. The hydrolysis conditions described do not compromise the stereochemical integrity of an adjacent chiral center. This is exemplified by the hydrolysis of naproxen amide (**34**) to naproxen (**33**) without detectable racemization as determined by chiral HPLC.

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La réaction des amides primaires (par exemple **1***a* ou **6–13**) ou des *O*-méthylhydroxamates (**1***b* ou **1***c*) avec une quantité catalytique de $TiCl_4$ et un équivalent de HCl aqueux permet de transformer ces composés, avec d'excellents rendements, en esters carboxyliques (lorsqu'on utilise un alcool comme solvant) ou en acides carboxyliques (lorsqu'on utilise un mélange 9 : 1 dioxane : eau comme solvant). Ces transformations sont chémosélectives pour les amides primaires; les mono- et dialkyl amides ne sont pas affectés par les conditions des réactions. Les conditions d'hydrolyse décrites ne compromettent pas l'intégrité stéréochimique d'un centre chiral adjacent. Pour démontrer cette assertion, on présente comme exemple l'hydrolyse de la naproxenamide (**34**) en naproxen (**33**) qui, d'après une CLHP chirale, se fait sans racémisation détectable.

[Traduit par la rédaction]

We have shown that the *O*-methyl hydroxamic acid moiety is an efficient, easy to prepare *ortho*lithiation directing group for aryl and toluyl systems (1).[4] In addition, we demonstrated that reduction of the *O*-methyl hydroxamic acids to carboxamides could be efficiently accomplished with two equivalents of titanium(III) chloride in alcoholic solution (2). With aqueous (but not anhydrous) titanium(III) chloride it was noted that after prolonged reaction times some of the carboxamide was converted into the carboxylic ester corresponding to the alcohol used. Since Ti(III) chloride had no effect on the primary amide it was assumed that Ti(IV), formed as a consequence of the reduction of the hydroxamate, was the agent responsible for promoting the alcoholysis of the amide. Not only was this supposition found to be correct, it was also shown that the alcoholysis was catalytic in Ti(IV).[5] This paper describes optimized conditions for effecting the Ti(IV) catalyzed conversion of primary amides (**1***a*, **6–13**) to the corresponding carboxylic acids or esters. Also described herein are conditions for the Ti(IV) catalyzed alcoholysis and hydrolysis of *O*methylphenylacetohydroxamate (**1***b*) and *O*-methylbenzylhydroxamate (**1***c*).

Depending on whether an aqueous or alcoholic solvent is used, treatment of N-unsubstituted carboxamides with a catalytic amount of titanium(IV) chloride and one equivalent of aqueous hydrochloric acid converts this class of compounds into the corresponding carboxylic acids or esters. Thus, heating the carboxamide in a solution of the appropriate alcohol containing 10 mol% aqueous $TiCl_4$ and one molar equivalent of hydrochloric acid gave the corresponding esters in good yields (Table 1; refs. 2–15). The carboxylic acids were obtained when 10% aqueous dioxane was used as the solvent (Table 2; refs. 2–20). Not surprisingly, ester-amides **11** and **12** were both hydrolyzed completely to diacids when subjected to the aqueous hydrolysis conditions. Treatment of *O*-methylhydroxamates **1***b* and **1***c* with $TiCl_4$ also resulted in alcoholysis (in alcohol with one molar equivalent of hydrochloric acid, Table 1) or hydrolysis (in 10%aqueous dioxane, Table 2). Although these reactions did proceed in the absence of added aqueous hydrochloric acid, addition of one molar equivalent of aqueous HCl increased the rate considerably. Neither of these reactions proceeded appreciably, however, in the absence of Ti(IV).

Titanium(IV) alkoxides also catalyze the transformation of primary carboxamides to esters. For example, $Ti(OMe)_4$, $Ti(OEt)_4$, and $Ti(OiPr)_4$, in the appropriate alcohol as solvent, catalyze the conversion of **1***a* to the methyl, ethyl, and isopropyl esters **2**, **3**, and **4**, respectively. These results would suggest that the Ti(IV) species involved in the alcoholysis reaction probably is not $TiCl_4$, but rather some intermediate $Ti(Cl)_x(OR)_y$ complex. The Lewis acids boron trifluoride etherate, tin(IV) chloride, and silicon(IV) chloride (12) also catalyze these transformations, although with less efficiency than titanium(IV) chloride (Table 1).

N-Alkyl and *N,N*-dialkyl carboxamides are not affected under the conditions that transform unsubstituted carboxamides to esters or acids. For example, when monoethyl amide **35***a* or diethyl amide **35***b* are subjected to the reaction conditions that successfully converted **1** to **2** or **3**, they were recovered quanti-

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[2]Contribution No. 879 from the Syntex Institute of Organic Chemistry.

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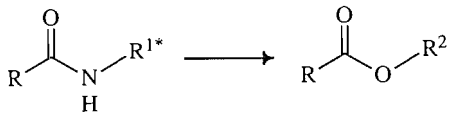
[4]Titanium trichloride has also been shown to reduce *N*-oxides and oximes (2*b*) and nitro groups (2*c*).

[5]A 1 M solution of $TiCl_4$ in either toluene or CH_2Cl_2 was used (Aldrich).

TABLE 1. Ti(IV), Si(IV), Sn(IV) and BF_3-OEt_2 catalyzed amide alcoholysis

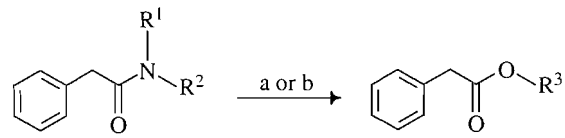


*R^1 = OCH_3 for entries

1*a*, **1***b* and H for all others

Reactant	R	Ref.[a]	Reagent	Solvent[b]	Time (h)	Product	R^2	Yield (%)	MP (°C)(Sol)	Lit MP (°C)	Ref.[c]
1*a*	$CH_2C_6H_5$	2, 3	$TiCl_4$	MeOH	3	**2**	CH_3	86	218–220 (MeOH)	220	3, 10
1*a*	$CH_2C_6H_5$	2, 3	$TiCl_4$	EtOH	17	**3**	C_2H_5	92	224–226 (EtOH)	226	3
1*a*	$CH_2C_6H_5$	2, 3	$TiCl_4$	i-PrOH	22	**4**	i-C_3H_7	87	BP 62 (0.3 Torr)	BP 65 (0.3 Torr)	3, 10
1*b*	$CH_2C_6H_5$	2, 3	$TiCl_4$	MeOH	16	**2**	CH_3	91	218–220 (MeOH)	220	3
1*b*	$CH_2C_6H_5$	2, 3	$TiCl_4$	EtOH	3	**3**	C_2H_5	85	224–226 (EtOH)	226	11
1*c*	C_6H_5	2, 3	$TiCl_4$	EtOH	48	**14**	C_2H_5	81	BP 210	BP 212	4
6	C_6H_5	4	$TiCl_4$	EtOH	36	**14**	C_2H_5	78	BP 210	BP 212	4
7	C-C_6H_{11}	5	$TiCl_4$	MeOH	26	**15**	CH_3	<10[d]	—	—	—
8	C_4H_9	—	$TiCl_4$	EtOH	25	**16**	C_2H_5	<10[d]	—	—	—
9	$CH(C_6H_5)_2$	6	$TiCl_4$	EtOH	40	**17**	C_2H_5	52	56 (hex–Et_2O)	58	12
10	$C_{15}H_{31}$	7	$TiCl_4$	EtOH	12	**18**	C_2H_5	74	28–30 (pentane)	26–28	7
11	4-$CH_3O_2CC_6H_4$	8	$TiCl_4$	EtOH	14	**19**	C_2H_5	76	BP 139–140	BP 140–142	13
12	$C_2H_5O_2C(CH_2)_3$	9	$TiCl_4$	EtOH	10	**20**	C_2H_5	90	BP 214	BP 230	14
13	4-$CH_3OC_6H_4$	8	$TiCl_4$	EtOH	11	**21**	C_2H_5	69	BP 262	BP 269	15
1*a*	$CH_2C_6H_5$		$TiCl_4$	EtOH	12	**3**	C_2H_5	93			
1*a*	$CH_2C_6H_5$		$SiCl_4$	MeOH	16	**2**	CH_3	49			
1*a*	$CH_2C_6H_5$		$SnCl_4$	MeOH	14	**2**	CH_3	41			
1*a*	$CH_2C_6H_5$		BF_3–OEt_2	EtOH	10	**2**	C_2H_5	38			
1*a*	$CH_2C_6H_5$		$Ti(OCH_3)_4$	MeOH	15	**3**	CH_3	73			
1*a*	$CH_2C_6H_5$		$Ti(OEt)_4$	EtOH	17	**2**	C_2H_5	81			
1*a*	$CH_2C_6H_5$		$Ti(Oi\text{-}Pr)_4$	i-PrOH	19	**4**	i-C_3H_7	79			

[a]Preparation of reactant.
[b]Reactions were performed under refluxing conditions.
[c]Physical properties citation.
[d]Products are quite volatile.



1*a*, $R^1 = R^2 = H$
1*b*, **1***c*,† $R^1 = OCH_3$, $R^2 = H$
35*a*, R^1 = Et, $R^2 = H$
35*b*, $R^1 = R^2$ = Et

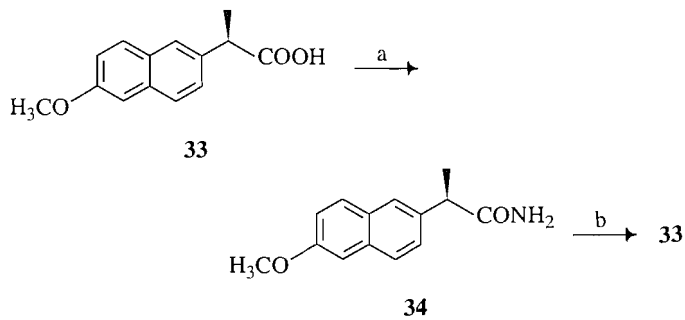
2, R^3 = Me
3, R^3 = Et
4, R^3 = iPr
5, $R^3 = H$

†See entry **1***c*, Table 1.

a. $TiCl_4$ (10 mol%), molar equiv. HCl, 1 molar equiv. H_2O, solvent, reflux
b. $Ti(OR)_4$ (10 mol%), 1 molar equiv. HCl, 1 molar equiv. H_2O, solvent, reflux

For entries **35***a* and *b*, only starting amide was recovered after prolonged treatment using reaction conditions "a"

SCHEME 1



a. 1. $(ClCO)_2$, EtOAc, $NaHCO_3$, 2. NH_4OH
b. $TiCl_4$ (10 mol%), 1 molar equiv. HCl, 9:1 dioxane: H_2O, reflux

SCHEME 2

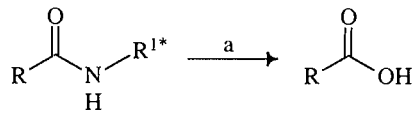
tatively, even after prolonged (>48 h) reaction times (Scheme 1).[6]

Traditional methods to hydrolyze primary carboxamides usually require strongly basic or acidic conditions (21*b*, *c*). Under these conditions, a chiral center adjacent to the carbonyl group can be racemized. $TiCl_4$ catalyzed hydrolysis of naproxen amide (**34**) (synthesized from naproxen (**33**) via the acid chloride (22) to naproxen (**33**) (Scheme 2) occurred without detectable racemization, as determined by HPLC. This implies that the mechanism of hydrolysis does not involve enolization of the carbonyl group.

In conclusion, this study has shown that catalytic $TiCl_4$ and $Ti(OR)_4$ in the presence of aqueous HCl efficiently converts unsubstituted carboxamides to esters or acids. Two *O*-methyl hydroxamic acids are also shown to be converted to esters or acids by these conditions. Further, the hydrolysis reaction is

[6]A mild three-step method for tertiary amide hydrolysis has been reported (21*a*).

TABLE 2. $TiCl_4$ catalyzed amide hydrolysis



*R^1 = OCH_3 for entries

1*b*, **1***c* and H for all others

Reactant	R	Ref.[b]	Reagent	Solvent	Time (h)	Product	Yield[c] (%)	MP (°C)(Sol)	Lit. MP (°C)	Ref.[d]
1*a*	$CH_2C_6H_5$	2, 3	$TiCl_4$	9:1 Diox.:H_2O	20	**25**	87	74–76 (Tol)	76	16
1*b*	$CH_2C_6H_5$	2, 3	$TiCl_4$	9:1 Diox.:H_2O	17	**25**	91	74–76 (Tol)	76	16
1*c*	C_6H_5	2, 3	$TiCl_4$	9:1 Diox.:H_2O	24	**26**	79	28–31 (EtOAc)	30–32	5
6	C_6H_5	4	$TiCl_4$	9:1 Diox.:H_2O	15	**27**	85	119–120 (H_2O)	121–122	17
7	C_6H_{11}	5	$TiCl_4$	9:1 Diox.:H_2O	19	**26**	86	29–32 (EtOAc)	30–32	5
9	$CH(C_6H_5)_2$	6	$TiCl_4$	9:1 Diox.:H_2O	24	**28**	92	143–146 (EtOAc)	147–149	12
10	$C_{15}H_{31}$	7	$TiCl_4$	9:1 Diox.:H_2O	22	**29**	87	63–63 (Hex)	63–64	7
11	4-$CH_3O_2CC_6H_4$	8	$TiCl_4$	9:1 Diox.:H_2O	21	**30**[e]	78	>285	>300	18
12	$C_2H_5O_2C(CH_2)_3$	9	$TiCl_4$	9:1 Diox.:H_2O	20	**31**[f]	90	88–89 (acetone)	95–96	19
13	4-$CH_3OC_6H_4$	10	$TiCl_4$	9:1 Diox.:H_2O	19	**32**	93	180–184 (EtOAc)	183	20

[a]All reactions carried out in the following manner: approximately 1 molar in substrate in a mixture of 9:1 dioxane: H_2O, approximately 0.1 molar equiv. $TiCL_4$, approximately 1 molar equiv. aqueous HCl. This mixture was heated under reflux for the time specified in Table 2.
[b]Preparation of reactant.
[c]Isolated yields.
[d]Physcial properties citation.
[e]Terephthalic acid.
[f]Glutaric acid.

mild enough to leave adjacent chirality uncompromised, presenting an advantage over traditional, more vigorous, hydrolysis methods.

Experimental section

Melting points are uncorrected. All compounds reported are known and referenced where they appear in the tables. Determinations of enantiomeric purity were performed by analysis by direct HPLC using a Spectra-Physics 8800 ternary pump, Spectra-Physics SP8780 autosampler, and a Spectra Physics Spectra 100 variable wavelength detector connected to a Chiral-AGP column. The following conditions were used: column: Chiral AGP, 100 × 4.0 mm, 5 μm; mobile phase: 99.5% 4 mM NaH_2PO_4 + Na_2HPO_4 pH 7.0, 0.5% 2-PrOH;low rate: 0.8 mL/min; temperature: ambient; detection: 262 nm (22).

Optical rotations were measured on a JASCO DIP-360 instrument.

*General method for the syntheses of primary carboxamides or O-methylphenylacetohydroxamate (**1**b) or methylbenzylhydroxamate (**1**c)*

To a stirred solution of carboxylic acid in methylene chloride (CH_2Cl_2) at 0°C was added oxalyl chloride (2 molar equiv.) and *N,N*-dimethylformamide (DMF, 1 drop). The mixture was allowed to warm to room temperature and subsequently the CH_2Cl_2 was removed in vacuo. The residue was dissolved in CH_2Cl_2, cooled to 0°C, and treated with either NH_4OH (excess, to give the primary amide) or methoxylamine hydrochloride (1 equiv., and Et_3N, 2 equiv., to give the *O*-methyl hydroxamic acid). The reaction mixture was allowed to warm to room temperature and was shaken with 1 M HCl. The organic layer was separated and dried with Na_2SO_4, filtered, and the solvent was removed in vacuo to give the product.

*General method for the titanium(IV) chloride mediated alcoholysis of primary carboxamides or Omethylphenylacethydroxamate (**1**b) or methylbenzylhydroxamate (**1**c)*

To a solution of carboxamide or *O*-methyl hydroxamic acid (1 equiv.) in the appropriate alcohol (approximately 1 M in substrate) was added aqueous $TiCl_4$ (0.1 molar equiv.) and aqueous HCl (1 molar equiv.). The reaction mixture was then brought to reflux for the specified amount of time (Table 1). After being allowed to cool to room temperature, the reaction mixture was poured onto ice–H_2O and brought to neutrality with 1 M NaOH. Extraction with ethyl acetate (EtOAc), removal of water with Na_2SO_4, filtration again, and finally removal of solvent in vacuo gave the ester. If necessary, the product was recrystallized from the appropriate solvent.

*General method for the titanium(IV) chloride mediated conversion of primary carboxamides or Omethylphenylacethydroxamate (**1**b) or methylbenzylhydroxamate (**1**c) to carboxylic acids*

To a solution of carboxamide or *O*-methyl hydroxamic acid (1 equiv.) in 9:1 dioxane:H_2O(approximately 1 M in substrate) was added aqueous $TiCl_4$ (0.1 molar equiv.) and aqueous HCl (1 molar equiv.). The reaction mixture was then brought to reflux for the specified amount of time (Table 2). After being cooled to room temperature, the reaction mixture was poured onto ice–H_2O. Extraction with EtOAc, removal of water with Na_2SO_4, filtration again, and finally removal of solvent in vacuo gave the acid. If necessary, the product was recrystallized from the appropriate solvent.

General method for the Lewis acid mediated alcoholysis of primary carboxamides

To a solution of carboxamide (1 equiv.) in EtOH (approximately 1 M in amide) was added $SiCl_4$, $SnCl_4$, or BF_3_Et_2O (0.1 molar equiv.). To this mixture was added aqueous HCl (1 molar equiv.). The reaction mixture was then brought to reflux for the specified amount of time (Table 1). After being allowed to cool to room temperature, the reaction mixture was poured onto ice–H_2O and brought to neutrality with 1 M NaOH. Extraction with EtOAc, removal of water with Na_2SO_4, filtration again, and finally removal of solvent in vacuo gave the ester. If necessary, the product was recrystallized from the appropriate solvent.

General method for the $Ti(OR)_4$ mediated alcoholysis of primary carboxamides

To a solution of carboxamide (1 equiv.) in EtOH (approximately 1

M in amide) was added $Ti(OMe)_4$, $Ti(OEt)_4$, or $Ti(OiPr)_4$ (0.1 molar equiv.). To this mixture was added aqueous HCl (1 molar equiv.). The reaction mixture was then brought to the temperature specified for each entry in Table 1 for the specified amount of time. After being allowed to cool to room temperature, the reaction mixture was poured onto ice–H_2O and brought to neutrality with 1 M NaOH. Extraction with EtOAc, removal of water with Na_2SO_4, filtration, and finally removal of solvent in vacuo gave the ester. If necessary, the product was recrystallized from the appropriate solvent.

*6-Methoxy-α-methyl-2-naphthaleneacetamide (**34**)*

To a stirred solution of 6-methoxy-α-methyl-2-naphthaleneacetic acid (**33**) (27.4 g, 0.12 mol) in EtOAc (400 mL) and aqueous $NaHCO_3$ (400 mL of a 1 M solution) at 0°C was added oxalyl chloride (20.7 mL, 0.24 mol). The reaction mixture was allowed to warm to room temperature. The layers were allowed to separate and the organic layer was dried with Na_2SO_4, filtered, and evaporated in vacuo. The residue was redissolved in CH_2Cl_2 (450 mL), cooled to 0°C, and treated dropwise with NH_4OH (50 mL of a 37% aqueous solution). The reaction mixture was allowed to warm to room temperature and was carefully acidified with HCl (1 M) to pH 4. The organic layer was separated and dried with Na_2SO_4, filtered, and the solvent was removed in vacuo to give crude **34**. Recrystallization (acetone–hexane) gave crystalline **34** (26.1 g, 95%); mp 173–176°C (acetone–hexane) (lit. (22) mp 172–175°C); $[\alpha]^{25}_D$ + 20 (*c* 1, $CHCl_3$) (lit. (22) $[\alpha]^{25}_D$ + 20.2 (*c* 1, $CHCl_3$).

*6-Methoxy-α-methyl-2-naphthaleneacetic acid (naproxen) (**33**)*

To a solution of **34** (2.3 g, 0.01 mol) in 9:1 dioxane:H_2O (10 mL) was added aqueous $TiCl_4$ (1 mL, 1 M in $TiCl_4$, in CH_2Cl_2 or toluene) and aqueous HCl (1 mL of a 1 M solution). The reaction mixture was then brought to reflux for 15 h. After cooling to room temperature, the reaction mixture was poured onto ice–H_2O. Extraction with EtOAc, removal of water with Na_2SO_4, filtration again, and finally removal of solvent in vacuo gave the acid **33** as a solid that was crystallized from acetone–hexane (2.21 g, 96%; mp 153–155°C (acetone–hexane) (lit. (22) mp 154–155°C); $[\alpha]^{32}_D$ +66 (*c* 1, $CHCl_3$) (lit. (22) $[\alpha]^{25}_D$ + 66 (*c* 1, $CHCl_3$). Serially increasing injections of **33** (0.2–0.5 mg) dissolved in the mobile phase (1–5 μL) showed that **33** was 99.0% (*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid (22). This is compared to a USP batch that was shown to be 99.2% (*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid.

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