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A New Method for the Synthesis of Amides from Amines: Ruthenium Tetroxide Oxidation of *N*-Protected Alkylamines

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A simple synthetic method for the preparation of amides from the corresponding primary alkylamines was elaborated using ruthenium tetroxide (RuO_4) oxidation as a key step.

Keywords——oxidation; ruthenium tetroxide oxidation; alkylamine; alkylamide; amide synthesis; ruthenium tetroxide; two-phase method

Although a large variety of methods are available for the synthesis of primary amides, there are only a few methods[1] for oxidation of primary alkylamines to the corresponding amides, *i.e.*, constructing a carbonyl moiety at the methylene next to the amine nitrogen. In our previous paper,[2] we reported a convenient method for the synthesis of acyclic imides from *N*-acyl alkylamines by ruthenium tetroxide (RuO_4) oxidation.[3] As a continuation of our work on the application of RuO_4 oxidation to nitrogen-containing compounds, we now report a general synthetic method for the preparation of primary amides from alkylamines using this oxidation, as outlined below (Chart 1).

$$\underset{\textbf{1a—o}}{RCH_2NH_2} \longrightarrow \underset{\textbf{2a—o}}{RCH_2NH\text{–}Boc} \xrightarrow{RuO_4} \underset{\textbf{3a—o}}{RCONH\text{–}Boc} \longrightarrow \underset{\textbf{4a—o}}{RCONH_2}$$

R = alkyl, aryl (see Table I)
Boc = *tert*-butoxycarbonyl

Chart 1

For the protection of amines, we chose the *tert*-butoxycarbonyl (Boc) group, which had been established by us[4] to be very stable against RuO_4 oxidation and also easily removable from the resulting amides after the oxidation. *N*-Boc alkylamines were readily prepared from a variety of alkylamines (**1a—o**) with *tert*-butyl *S*-4,6-dimethylpyrimid-2-ylthiocarbonate (Boc-S reagent).[5]

The RuO_4 oxidation of *N*-Boc alkylamines (**2a—o**) was carried out at room temperature according to our improved procedure[6] using catalytic amounts of ruthenium dioxide ($RuO_2 \cdot xH_2O$) and an excess of 10% aqueous sodium metaperiodate ($NaIO_4$) in a two-phase system of ethyl acetate (AcOEt)–H_2O. The oxidation proceeded smoothly with a consistent yellow color which indicated the existence of active RuO_4 generated *in situ* under above conditions. A number of *N*-Boc alkylamines were transformed into the corresponding *N*-Boc amides (**3a—o**). The results are summarized in Table I. The *N*-Boc amides (**3a—o**) were

TABLE I. Synthesis of Amides (**4a—o**) from Alkylamines (**1a—o**)

	1	2	3		4		
	(RCH_2NH_2) R	Yield (%)	Reaction time (h)	Yield (%)	Yield (%)	mp (°C)	Reported mp (°C)
a	CH_3	92	1	80	95	80—82	82[8]
b	C_2H_5	93	1	90	95	78—80	81[8]
c	C_3H_7	90	1	89	95	115—116	115[8]
d	$C_{17}H_{35}$	95	3	98	97	108.5—109	108.5—109[8]
e	$NH_2CH_2CH_2$	96[a]	1.5	94[b]	98	153—154[c]	148[c,9]
f	$ClCH_2$	91	15	89	94	115—117	121[8]
g	$ClCH_2CH_2$	90	10	92	92	96—98	98—101[10]
h	4-Me–C_6H_4	90	0.25	68	95	160—161	160[8]
i	4-MeO–C_6H_4	92	0.25	65	95	161—162	163[8]
j	C_6H_5	94	0.5	70	96	129—130	130[8]
k	4-Cl–C_6H_4	92	0.5	85	94	170—171	170[8]
l	4-MeOOC–C_6H_4	94	2	92	95	210—211	204—206[11]
m	4-NO_2–C_6H_4	91	5.5	86	92	198—200	200[8]
n	$C_6H_5CH_2$	90	1.5	23	93	153—155	156[8]
o	4-Br–$C_6H_4CH_2$	92	6	76	94	197—198	192—194[8]

a) The structure of **2e** is Boc–$NHCH_2CH_2CH_2NH$–Boc. *b*) The structure of **3e** is Boc–$NHCH_2CH_2CONH$–Boc. *c*) Listed as the HCl salt (**4e**·HCl).

characterized on the basis of their analytical and spectral properties (Table III). Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were most effective for detection of the amide carbonyl functions produced by the oxidation. In the oxidation of *N*-Boc arylalkylamines (**2h—o**) having an aromatic ring, which is well known to be susceptible to RuO_4 oxidant,[7] it was found that the substituent on the ring can affect the stability of the ring, the oxidation rate, or both. Selective mono-oxidation occurred in the oxidation of the trimethylenediamine derivative (**2e**) having two methylenes to be oxidized. One of them was readily oxidized within 1.5 h to produce an amide carbonyl group, which slowed down the oxidation of the other methylene in the molecule.

Deprotection of the *N*-Boc amides (**3a—o**) was accomplished at room temperature with trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2) for 1 h to give the desired amides (**4a—o**) in high yields. The results are included in Table I.

Mild reaction conditions, simple work-up, and high yields of the expected products at each step make this method a useful contribution to amide synthesis. Our recent success[1c] in the first chemical conversion of L-α,ω-diamino acids to L-ω-carbamoyl-α-amino acids has exemplified its general synthetic utility.

Experimental

All melting points are uncorrected. See ref. 1*c* for details of instrumentation and measurements. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet.

***N*-Boc Amines (2a—o): General Procedure**——A solution of *tert*-butyl *S*-4,6-dimethylpyrimid-2-ylthiocarbonate (60 mmol) in dioxane (30 ml) was slowly added to a solution of an alkylamine (**1**, 50 mmol, but 25 mmol for **1e**) and triethylamine (55 mmol) in water (30 ml) with stirring. The mixture was stirred at room temperature for 6 h. The solution was made acidic with 6 N HCl, while being cooled in an ice bath, and then was extracted with AcOEt (3 × 20 ml). The combined extracts were washed with water (2 × 10 ml), dried over magnesium sulfate, and evaporated *in vacuo* to produce the crude product, which was purified either by recrystallization or by vacuum distillation. The

TABLE II. Physical Properties and Spectral Data for *N*-Boc Amines (**2a—o**)

Compound	mp (°C) or bp (°C/mmHg)	Molecular formula[a]	IR[b] ν_{max} cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
2a	58/7	$C_7H_{15}NO_2$ (145.2)	3350, 1690, 1510	1.11 (3H, t, J=7 Hz), 1.44 (9H, s), 2.98—3.28 (2H, m), 4.84 (1H, br)
2b	68/8	$C_8H_{17}NO_2$ (159.2)	3350, 1690, 1510	0.90 (3H, t, J=7 Hz), 1.44 (9H, s), 1.37—1.73 (2H, m), 4.73 (1H, br)
2c	75/7	$C_9H_{19}NO_2$ (173.2)	3350, 1690, 1510	0.92 (3H, t, J=7 Hz), 1.45 (9H, s), 1.21—1.73 (4H, m), 2.94—3.17 (2H, m), 4.65 (1H, br)
2d	55—56	$C_{23}H_{47}NO_2$ (369.6)	3396, 1694, 1520	0.88 (3H, t, J=6 Hz), 1.44 (9H, s), 1.0—2.0 (32H, m), 2.88—3.20 (2H, m), 4.61 (1H, br)
2e[c]	110—111	$C_{13}H_{26}N_2O_4$ (274.4)	3340, 1702, 1538	1.44 (18H, s), 1.0—1.90 (2H, m), 3.04—3.32 (4H, m), 5.02 (2H, br)
2f	75/8	$C_7H_{14}ClNO_2$ (179.6)	3360, 1704, 1522	1.45 (9H, s), 3.31—3.69 (4H, m), 5.11 (1H, br)
2g	105/8	$C_8H_{16}ClNO_2$ (193.7)	3350, 1698, 1522	1.42 (9H, s), 1.97 (2H, m), 3.17—3.42 (2H, m), 3.59 (2H, t, J=7 Hz), 4.90 (1H, br)
2h	72.5—73	$C_{13}H_{19}NO_2$ (221.3)	3450, 1710, 1600, 1500	1.49 (9H, s), 2.43 (3H, s), 4.30 (2H, d, J=7 Hz), 4.96 (1H, br), 7.24 (4H, s)
2i	—[d]	$C_{13}H_{19}NO_3$ (237.3)	3350, 1690, 1614, 1500	1.48 (9H, s), 3.82 (3H, s), 4.28 (2H, d, J=7 Hz), 5.00 (1H, br), 6.94 and 7.31 (2H×2, each d, J=8 Hz)
2j	—[d]	$C_{12}H_{17}NO_2$ (207.3)	3350, 1680, 1500	1.48 (9H, s), 4.32 (2H, d, J=7 Hz), 5.04 (1H, br), 7.36 (5H, s)
2k	75—76	$C_{12}H_{16}ClNO_2$ (241.7)	3370, 1690, 1600, 1510	1.47 (9H, s), 4.29 (2H, d, J=7 Hz), 5.05 (1H, br), 7.05 and 7.30 (2H×2, each d, J=8 Hz)
2l	73.5—74	$C_{14}H_{17}NO_5$ (279.3)	3355, 1730, 1686, 1610, 1520	1.45 (9H, s), 3.90 (3H, s), 4.35 (2H, d, J=7 Hz), 5.12 (1H, br), 7.34 and 7.98 (2H×2, each d, J=8 Hz)
2m	109—110	$C_{12}H_{16}N_2O_4$ (252.3)	3340, 1690, 1610, 1524	1.47 (9H, s), 4.45 (2H, d, J=7 Hz), 5.38 (1H, br), 7.53 and 8.27 (2H×2, each d, J=8 Hz)
2n	54	$C_{13}H_{19}NO_2$ (221.3)	3380, 1688, 1600, 1525	1.45 (9H, s), 2.80 (2H, t, J=7 Hz), 3.26—3.52 (2H, m), 4.69 (1H, br), 7.12—7.49 (5H, m)
2o	61—62	$C_{13}H_{18}BrNO_2$ (300.2)	3370, 1675, 1595, 1525	1.44 (9H, s), 2.74 (2H, t, J=7 Hz), 3.22—3.48 (2H, m), 4.54 (1H, br), 7.04 and 7.44 (2H×2, each d, J=8 Hz)

a) All compounds were analyzed for C, H, and N; the analytical results were within ±0.3% of the calculated values. *b*) IR spectra were measured in KBr tablet or $CHCl_3$ solution. *c*) The structure of **2e** is Boc–$NHCH_2CH_2CH_2NH$–Boc. *d*) This sample was not distilled, but was purified by column chromatography.

physical and spectral data of the *N*-Boc amines (**2a—o**) are listed in Table II.

RuO_4 Oxidation of *N*-Boc Amines (2a—o): General Procedure——A solution of an *N*-Boc amine (**2**, 10 mmol) in AcOEt (30 ml) was added to a mixture of ruthenium dioxide hydrate [$RuO_2 \cdot xH_2O$, Aldrich Chemical Co.] (150 mg) and 10% aqueous $NaIO_4$ (80 ml). The mixture was vigorously stirred in a sealed flask at room temperature. After the starting material had disappeared as determined by thin layer chromatography (TLC), the layers were separated. The aqueous layer was extracted with AcOEt (3×20 ml). The combined organic solution was treated with isopropyl alcohol (2 ml) for 2—3 h to decompose the oxidant (RuO_4) and then the black precipitates (RuO_2) were filtered off. The filtrate was washed with H_2O (2×10 ml), dried over magnesium sulfate, and concentrated under reduced pressure to yield the crude product, which was purified by recrystallization. The results are given in Table I and the physical and spectral data of the *N*-Boc amides (**3a—o**) are listed in Table III.

Deprotection of *N*-Boc Amides (3a—o) to Amides (4a—o): General Procedure——An *N*-Boc amide (**3**, 20 mmol) was dissolved in a mixture of CH_2Cl_2 (15 ml) and TFA (15 ml). The mixture was stirred at room temperature for 1 h and then evaporated *in vacuo*. The resulting residue was purified by recrystallization to afford the pure amide (**4**). The product **4e** was converted to the HCl salt by addition of ethanolic HCl to the crude **4e**. The results are summarized in Table I. Identification of the amides (**4a—o**) was done by comparison of their physical and spectral data with those of authentic samples or with reported data.

TABLE III. Physical Properties and Spectral Data for *N*-Boc Amides (**3a**—**o**)

Compound	mp (°C)	Molecular formula[a]	IR[b] ν_{max} cm^{-1}	^{1}H-NMR ($CDCl_3$) δ	^{13}C-NMR (C=O)[c] ($CDCl_3$) δ
3a	79—80	$C_7H_{13}NO_3$ (159.2)	3420, 1790, 1755, 1715, 1482	1.54 (9H, s), 2.40 (3H, s), 8.20 (1H, br)	172.9
3b	120—121	$C_8H_{15}NO_3$ (173.2)	3420, 1788, 1755, 1710, 1480	1.15 (3H, t, J=7 Hz), 1.50 (9H, s), 2.73 (2H, q, J=7 Hz), 7.80 (1H, br)	176.02
3c	97.5—98	$C_9H_{17}NO_3$ (187.2)	3420, 1785, 1755, 1700, 1480	0.97 (3H, t, J=7 Hz), 1.50 (9H, s), 1.41—1.89 (2H, m), 2.68 (2H, t, J=7 Hz), 7.75 (1H, br)	175.14
3d	53—54	$C_{23}H_{45}NO_3$ (383.6)	3220, 1756, 1694	0.88 (3H, t, J=6 Hz), 1.48 (9H, s), 1.0—1.96 (30H, m), 2.68 (2H, t, J=7 Hz), 7.72 (1H, br)	175.19
3e[d]	92—93	$C_{13}H_{24}N_2O_5$ (288.3)	3476, 3260, 1756, 1706	1.41 and 1.46 (9H×2, each s), 2.88 (2H, t, J=6 Hz), 3.24—3.52 (2H, m), 5.12 (1H, br), 7.78 (1H, br)	174.12
3f	88—89	$C_7H_{12}ClNO_3$ (193.6)	3220, 1754, 1706, 1500	1.52 (9H, s), 4.89 (2H, s), 8.80 (1H, br)	167.43
3g	96.5—97	$C_8H_{14}ClNO_3$ (207.7)	3220, 1758, 1700, 1500	1.52 (9H, s), 3.26 (2H, t, J=7 Hz), 3.81 (2H, t, J=7 Hz), 7.77 (1H, br)	172.11
3h	131—132	$C_{13}H_{17}NO_3$ (235.3)	3440, 1778, 1710, 1612, 1475	1.53 (9H, s), 2.40 (3H, s), 7.30 and 7.83 (2H×2, each d, J=8 Hz), 8.45 (1H, br)	165.43
3i	119—120	$C_{13}H_{17}NO_4$ (251.3)	3440, 1778, 1690, 1606, 1470	1.53 (9H, s), 3.87 (3H, s), 6.98 and 7.91 (2H×2, each d, J=8 Hz), 8.45 (1H, br)	165.04
3j	136—137	$C_{12}H_{15}NO_3$ (221.3)	3440, 1780, 1712, 1602, 1470	1.54 (9H, s), 7.43—7.69 (3H, m), 7.83—8.03 (2H, m), 8.44 (1H, br)	165.62
3k	147—148	$C_{12}H_{14}ClNO_3$ (255.7)	3430, 1780, 1692, 1595 1470	1.57 (9H, s), 7.59 and 8.00 (2H×2, each d, J=8 Hz), 8.66 (1H, br)	164.89
3l	132—133.5	$C_{14}H_{17}NO_5$ (279.3)	3260, 1768, 1750, 1734, 1684, 1522	1.51 (9H, s), 3.94 (3H, s), 7.92 and 8.10 (2H×2, each d, J=8 Hz), 8.48 (1H, br)	165.20
3m	142—143.5	$C_{12}H_{14}N_2O_5$ (266.3)	3425, 1782, 1720, 1692, 1605, 1525	1.54 (9H, s), 8.16 and 8.40 (2H×2, each d, J=8 Hz), 8.92 (1H, br)	164.69
3n	80—81	$C_{13}H_{17}NO_3$ (235.3)	3400, 1783, 1750, 1700, 1600, 1480	1.52 (9H, s), 4.08 (2H, s), 7.45 (5H, s), 8.06 (1H, br)	163.62
3o	130.5—131	$C_{13}H_{16}BrNO_3$ (314.2)	3280, 1780, 1752, 1530	1.48 (9H, s), 4.00 (2H, s), 7.12 and 7.41 (2H×2, each d, J=8 Hz), 7.60 (1H, br)	172.31

a) All compounds were analyzed for C, H, and N; the analytical results were within ±0.3% of the calculated values. *b*) IR spectra were measured in KBr tablet or in $CHCl_3$ solution. *c*) Amide carbonyl carbon produced by the oxidation. *d*) The structure of **3e** is Boc–$NHCH_2CH_2CONH$–Boc.

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