Oxime Esters as Acylating Agents in the Aminolysis Reaction. A Simple and Chemoselective Method for the Preparation of Amides from Amino Alcohols

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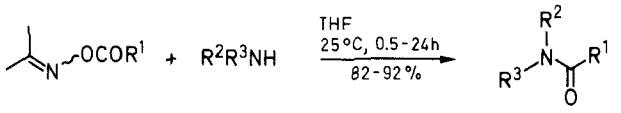
Oxime esters, such as acetone *O*-alkanoyl-, *O*-alkenoyl- or *O*-benzyloxycarbonyloximes, react with amines under extremely mild conditions to give the corresponding amides in very good yield. When amino alcohols are used a total chemoselectivity is observed.

Acid halides or anhydrides are the most commonly used acid derivatives for the preparation of amides.[1] However, in some cases these substrates may not prove adequate due to their instability or the reaction conditions employed in these processes. On the other hand, amides are interesting compounds, mainly owing to their biological activities and the natural occurrence of their derivatives, e.g., peptides and proteins. For this reason, the development of new and simple methods for the synthesis of the peptide bond always constitute an important addition to the field of natural products synthesis.

The aminolysis of unactivated esters is known to be a difficult reaction.[2] However, there is considerable interest in the formation of amides from carboxylic acid derivatives and amines, because this reaction is important in the synthesis of peptides and lactams. Acylation of amines with esters has been carried out under a wide variety of conditions. Recently, some methods of direct aminolysis of unactivated esters,[3] carboxylic acids,[4] and β-oxo esters[5] have been reported.

Oxime esters **1** have been used for the enzymatic transesterification reaction.[6] We have shown a useful synthesis of compounds **1** through an enzymatic oximolysis reaction.[7] Moreover, oxime derivatives **1** can be prepared by reaction of oximes and acyl halides.[8] These imino compounds are stable and can be handled without the need for special precautions. We have prepared various acetone oxime esters through our enzymatic method or via the reaction of an oxime with acyl chlorides, and have studied their utility in the preparation of different amides from amines. In addition, we have examined the possibilities of this reaction in the selective synthesis of amides from amino alcohols.



1 **2** **3a-r**

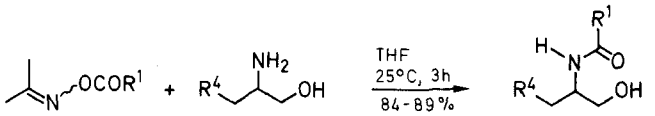
3	R^1	R^2	R^3	3	R^1	R^2	R^3
a	Me	$-(CH_2)_5-$		**j**	Me	H	$HO(CH_2)_5$
b	Me	H	Ph	**k**	Me	H	$HO(CH_2)_6$
c	Me	H	4-MeC_6H_4	**l**	Pr	H	$HO(CH_2)_3$
d	MeCH=CH	H	PhC(Me)H	**m**	Pr	H	$HO(CH_2)_5$
e	MeCH=CH	H	c-C_6H_{11}	**n**	Pr	H	$HO(CH_2)_6$
f	MeCH=CH	H	CH_2=$CHCH_2$	**o**	BnO	H	$HO(CH_2)_3$
g	MeCH=CH	H	Bn	**p**	BnO	H	$HO(CH_2)_4$
h	MeCH=CH	H	Bu	**q**	BnO	H	$HO(CH_2)_5$
i	Me	H	$HO(CH_2)_3$	**r**	BnO	H	$HO(CH_2)_6$

Amines **2** react with different oxime esters **1** in the absence of a catalyst and extremely mild conditions. Aliphatic amines react immediately with saturated oxime esters in an organic solvent in practical quantitative yields. When unsaturated oxime esters are used longer reaction times are necessary.

We have felt it to be of interest to check the chemoselectivity of the process with bifunctional compounds and we have extended this reaction to include amino alcohols. At first, we studied the reaction of **1** with α,ω-amino alcohols **2** where the amino and hydroxy groups are on a primary carbon. In every case the corresponding amide is formed and the products of *O*-acylation or diacetylation are not detected.

In an attempt to corroborate the chemoselectivity of this process with amino alcohols, we studied the reaction of 2-amino-1-butanol and 2-amino-1-pentanol with different oxime esters **1**. In every case, the formation of the corresponding amide was observed, and the primary hydroxy group was not acylated.

It is of note that acetone *O*-(benzyloxy)carbonyloxime **1** (R^1 = OBn) is easily prepared through the reaction of benzyl chloroformate and the oxime, and is a stable compound which has a similar reactivity to the other aliphatic oxime esters. For this reason, we believe that this method may prove to be of great use in the protection of



1 **4** **5a-e**

5	R^1	R^4	5	R^1	R^4
a	Me	Me	**d**	Me	Et
b	Pr	Me	**e**	Pr	Et
c	BnO	Me			

amino groups under mild conditions in compounds of interest such as amino acids, peptides or aminolactams.

In conclusion, we have described a general, new and simple procedure for the preparation of amides. In addition, the versatility of oxime esters in amide bond formation is shown, and this method could be useful for the selective formation of amides in nitrogen bifunctional compounds.

Amines, amino alcohols, benzyl chloroformate are purchased from Aldrich Chemical Co. Reagents quality solvents are used without further purification.

Acetone *O*-(Benzyloxy)carbonyloxime, Typical Procedure:
In a round-bottomed flask fitted with magnetic stirrer and addition funnel, benzyl chloroformate (1.7 mL, 12 mmol) is added dropwise to a solution of acetone oxime (0.7 g, 10 mmol) in pyridine (1.8 mL, 20 mmol). When the addition is finished, the mixture is poured into 3 N HCl (6 mL). CH_2Cl_2 (3 × 20 mL) is then added and the organic phase is separated, washed with H_2O (10 mL), and dried (Na_2SO_4). The solvent is evaporated and the crude product is crytallized from hexane as a white solid; yield: 1.4 g (70%); mp 46°C.

$C_{11}H_{13}NO_3$	calc.	C 63.67	H 6.28	N 6.76
(207.2)	found	63.51	6.34	6.80

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.99 (s, 3 H, Me), 2.02 (s, 3 H, Me), 5.25 (s, 2 H, CH_2), 7.32–7.48 (m, 5 H, Ph).

^{13}C-NMR ($CDCl_3$/TMS): δ = 16.2 (Me), 21.1 (Me), 69.3 (CH_2), 128.1 (5C_{arom}), 134.5 (C_{arom}), 153.4 (C=N) and 163.1 (C=O).

Amides 3a–h; General Procedure:
To a solution of amine **2** (10 mmol) in THF (20 mL) is added the oxime ester **1** (10 mmol). After being stirred at r.t. the solvent is evaporated to give the amides **3a–h** and acetone oxime. Compounds **3a–h** are purified by recrystallization in hexane/$CHCl_3$.

Amides 3i–r; General Procedure:
To a solution of amino alcohol **2** (10 mmol) in THF (20 mL) is added the oxime ester **1** (10 mmol). After being stirred at r.t. during 3 h the solvent is evaporated to give the amides **3i–r** and acetone oxime. Compounds **3i–r** are purified by crystallization in hexane (solids) or by a short silica gel column (oils).

Amides 5a–e; General Procedure:
To a solution of 2-amino-1-alkanol **4** (10 mmol) in THF (15 mL) is added the oxime ester **1** (10 mmol). After being stirred at r.t. during 3 h the solvent is evaporated to give the amides **5** and acetone oxime. Compounds **5** are purified: by crystallization in hexane, **5e**, or by a flash silica gel column with Et_2O/hexane (3:1), **5a–d**.

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Table. Amides **3** and **5** Prepared from Amines **2** and Amino Alcohols **2, 4**

Product	Reaction Time[a] (h)	Yield (%)	mp[b] (°C)	Molecular Formula	IR[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d], δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d], δ	MS (70 eV)[e] m/z (%)
3a	0.5	89	102–103	$C_7H_{13}NO$	1674, 1592	1.64 (m, 2H), 1.80 (m, 4H), 1.98 (s, 3H), 3.04 (t, 4H)	22.6 (t), 22.7 (t), 24.2 (q), 43.9 (t), 178.7 (s)	127 (M^+, 1), 42 (100)
3b	24	84	114–115	C_8H_9NO	1666, 1600	2.18 (s, 3H), 7.10 (t, 1H), 7.32 (t, 2H), 7.45 (d, 2H), 8.78 (brs, 1H)	24.3 (q), 120.0 (d), 124.2 (d), 128.8 (d), 137.9 (s), 169.0 (s)	135 (M^+, 23), 93 (100)
3c	24	83	145–146	$C_9H_{11}NO$	1662, 1600	2.13 (s, 3H), 2.31 (s, 3H), 7.11 (d, 2H), 7.26 (brs, 1H), 7.37 (d, 2H)	20.8 (q), 24.2 (q), 120.1 (d), 129.3 (d), 133.8 (s), 135.3 (s), 168.6 (s)	149 (M^+, 35), 107 (89), 106 (100)
3d	2	90	95–96	$C_{12}H_{15}NO$	1661, 1558	1.51 (d, 3H), 1.71 (d, 3H), 4.19 (q, 1H), 5.54 (d, 1H), 6.45 (m, 1H), 7.28 (m, 5H), 7.67 (brs, 1H)	17.2 (q), 21.6 (q), 50.5 (d), 126.2 (d), 127.7 (d), 128.5 (d), 128.7 (d), 138.5 (d), 139.9 (s), 173.6 (s)	189 (M^+, 1), 106 (100)
3e	0.5	90	96–97	$C_8H_{15}NO$	1654, 1559	1.15 (m, 2H), 1.35 (m, 4H), 1.64 (m, 4H), 1.95 (s, 3H), 3.76 (m, 1H), 5.58 (brs, 1H)	23.2 (t), 24.7 (t), 25.3 (t), 32.9 (t), 48.1 (d), 169.1 (s)	141 (M^+, 7), 56 (99), 43 (100)
3f	3	86	32–33	$C_7H_{11}NO$	1660, 1558	1.87 (d, 3H), 3.94 (t, 2H), 5.13 (d, 2H), 5.21 (d, 1H), 5.79 (brs, 1H), 5.84 (m, 1H), 6.86 (m, 1H)	17.1 (q), 41.3 (t), 115.3 (t), 124.8 (d), 133.8 (d), 138.8 (d), 165.9 (s)	125 (M^+, 33), 69 (100)
3g	0.5	85	108–109	$C_{11}H_{13}NO$	1670, 1625	1.79 (d, 3H), 3.92 (s, 2H), 5.71 (d, 1H), 5.80 (brs, 1H), 6.71 (m, 1H), 7.39 (m, 5H)	17.9 (q), 43.7 (t), 127.7 (d), 127.9 (d), 128.3 (d), 128.7 (d), 135.9 (s), 140.1 (d), 173.2 (s)	175 (M^+, 21), 160 (87), 39 (100)
3h	5	89	30–31	$C_8H_{15}NO$	1662, 1558	1.35 (m, 2H), 1.50 (m, 2H), 1.85 (d, 3H), 1.93 (t, 3H), 3.30 (q, 2H), 5.43 (brs, 1H), 5.80 (d, 1H), 6.83 (m, 1H)	13.7 (q), 17.6 (q), 20.0 (t), 31.6 (t), 39.1 (t), 125.2 (d), 139.3 (d), 166.4 (s)	141 (M^+, 3), 84 (10), 69 (100)
3i	3	85	oil	$C_5H_{11}NO_2$	1651, 1559	1.69 (dt, 2H, J = 5.6, 5.8), 2.00 (s, 3H), 3.39 (q, 2H), 3.64 (t, 2H), 4.20 (brs, 1H), 6.39 (brs, 1H)	22.2 (q), 31.3 (t), 35.9 (t), 58.6 (t), 171.1 (s)	117 (M^+, 6), 99 (36), 43 (100)
3j	3	87	oil	$C_7H_{15}NO_2$	1651, 1559	1.42 (m, 2H), 1.60 (m, 4H), 1.97 (s, 3H), 2.45 (brs, 1H), 3.24 (q, 2H), 3.63 (t, 2H), 6.00 (brs, 1H)	21.6 (q), 22.2 (t), 28.0 (t), 31.1 (t), 38.5 (t), 60.6 (t), 170.2 (s)	145 (M^+, 2), 43 (100)
3k	3	84	36–37	$C_8H_{17}NO_2$	1651, 1563	1.41 (m, 4H), 1.54 (m, 4H), 1.97 (s, 3H), 3.24 (q, 2H), 3.63 (t, 2H), 5.82 (brs, 1H)	22.1 (q), 24.8 (t), 26.0 (t), 28.6 (t), 31.8 (t), 38.8 (t), 61.2 (t), 170.5 (s)	159 (M^+, 1), 43 (100)
3l	3	89	oil	$C_7H_{15}NO_2$	1648, 1567	0.94 (t, 3H), 1.66 (m, 4H), 2.18 (t, 2H), 3.37 (q, 2H), 3.62 (t, 2H), 6.16 (brs, 1H)	13.1 (q), 18.7 (t), 31.4 (t), 35.7 (t), 37.7 (t), 58.5 (t), 174.0 (s)	145 (M^+, 15), 127 (44), 43 (100)
3m	3	85	oil	$C_9H_{19}NO_2$	1646, 1559	0.94 (t, 3H), 1.41 (m, 2H), 1.62 (m, 6H), 2.15 (t, 2H), 3.26 (q, 2H), 3.63 (t, 2H), 5.67 (brs, 1H)	13.0 (q), 18.6 (t), 22.5 (t), 28.5 (t), 31.4 (t), 37.6 (t), 38.7 (t), 61.1 (t), 173.4 (s)	173 (M^+, 3), 43 (100)
3n	3	83	44–45	$C_{10}H_{21}NO_2$	1636, 1541	0.94 (t, 3H), 1.39 (m, 4H), 1.55 (m, 4H), 1.66 (m, 2H), 2.09 (brs, 1H), 2.14 (t, 2H), 3.25 (q, 2H), 3.63 (t, 2H), 5.67 (brs, 1H)	13.6 (q), 19.1 (t), 25.2 (t), 26.4 (t), 29.3 (t), 32.3 (t), 38.4 (t), 39.1 (t), 62.0 (t), 173.4 (s)	187 (M^+, 1), 43 (99), 41 (100)

Table. (continued)

Product	Reaction Time[a] (h)	Yield (%)	mp[b] (°C)	Molecular Formula	IR[c] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[d], δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d], δ	MS (70 eV)[e] m/z (%)
3o	3	82	48–49	$C_{11}H_{15}NO_3$	1685, 1536	1.70 (dt, 2H, J = 5.8, 6.0), 2.19 (brs, 1H), 3.36 (q, 2H), 3.68 (t, 2H), 5.07 (brs, 1H), 5.11 (s, 2H), 7.35 (m, 5H)	32.4 (t), 37.8 (t), 59.5 (t), 66.7 (t), 128.0 (d), 128.1 (d), 128.5 (d), 136.5 (s), 157.3 (s)	209 (M^+, 2), 108 (34), 91 (100)
3p	3	90	78–79	$C_{12}H_{17}NO_3$	1686, 1535	1.58 (m, 4H), 1.95 (brs, 1H), 3.24 (q, 2H), 3.67 (t, 2H), 4.95 (brs, 1H), 5.10 (s, 2H), 7.34 (m, 5H)	26.4 (t), 29.5 (t), 40.8 (t), 62.1 (t), 66.5 (t), 127.9 (d), 127.9 (d), 128.4 (d), 136.5 (s), 156.6 (s)	223 (M^+, 2), 108 (33), 91 (100)
3q	3	91	43–44	$C_{13}H_{19}NO_3$	1686, 1536	1.42 (m, 2H), 1.57 (m, 4H), 3.21 (q, 2H), 3.64 (t, 2H), 4.79 (brs, 1H), 5.09 (s, 2H), 7.34 (m, 5H)	22.7 (t), 29.4 (t), 31.9 (t), 40.7 (t), 62.1 (t), 66.3 (t), 127.8 (d), 128.3 (d), 136.4 (s), 156.5 (s)	237 (M^+, 1), 108 (39), 91 (100)
3r	3	92	79–80	$C_{14}H_{21}NO_3$	1686, 1531	1.37 (m, 4H), 1.54 (m, 4H), 3.20 (q, 2H), 3.63 (t, 2H), 4.75 (brs, 1H), 5.10 (s, 2H), 7.34 (m, 5H)	25.1 (t), 26.2 (t), 29.7 (t), 32.3 (t), 40.7 (t), 62.3 (t), 66.4 (t), 127.8 (d), 128.3 (d), 136.4 (s), 156.3 (s)	251 (M^+, 1), 108 (32), 91 (100)
5a	3	89	oil	$C_6H_{13}NO_2$	1651, 1558	0.94 (t, 3H), 1.54 (m, 2H), 2.01 (s, 3H), 3.61 (m, 2H), 3.83 (m, 1H), 4.11 (brs, 1H), 6.36 (brs, 1H)	10.1 (q), 22.6 (q), 23.6 (t), 52.7 (d), 63.5 (t), 171.0 (s)	131 (M^+, 1), 58 (66), 43 (100)
5b	3	86	oil	$C_8H_{17}NO_2$	1643, 1549	0.94 (t, 3H), 0.95 (t, 3H), 1.57 (m, 4H), 2.19 (t, 2H), 3.62 (m, 2H), 3.85 (m, 1H), 3.85 (brs, 1H), 6.02 (brs, 1H)	10.1 (q), 13.2 (q), 18.9 (t), 23.6 (t), 38.1 (t), 52.6 (d), 63.7 (t), 173.8 (s)	159 (M^+, 1), 141 (1), 58 (100)
5c	3	84	37–38	$C_{12}H_{17}NO_3$	1694, 1536	0.94 (t, 3H), 1.52 (m, 2H), 2.47 (brs, 1H), 3.63 (m, 3H), 4.94 (brs, 1H), 5.10 (s, 2H), 7.34 (m, 5H)	10.2 (q), 24.1 (t), 54.5 (d), 64.3 (t), 66.5 (t), 127.8 (d), 127.9 (d), 128.3 (d), 136.3 (s), 156.8 (s)	223 (M^+, 1), 108 (3), 91 (100)
5d	3	88	oil	$C_7H_{15}NO_2$	1651, 1558	0.93 (t, 3H), 1.43 (m, 4H), 2.01 (s, 3H), 3.46 (brs, 1H), 3.63 (m, 2H), 3.93 (m, 1H), 6.12 (brs, 1H)	13.4 (q), 18.7 (t), 22.5 (q), 32.7 (t), 50.9 (d), 63.8 (t), 170.7 (s)	145 (M^+, 2), 72 (84), 43 (100)
5e	3	87	40–41	$C_9H_{19}NO_2$	1634, 1557	0.93 (t, 3H), 0.96 (t, 3H), 1.44 (m, 4H), 1.67 (m, 2H), 2.19 (t, 2H), 2.88 (brs, 1H), 3.62 (m, 2H), 3.97 (m, 1H), 5.62 (brs, 1H)	13.6 (q), 13.8 (q), 19.1 (t), 19.2 (t), 33.2 (t), 38.6 (t), 51.3 (d), 65.2 (t), 174.0 (s)	172 (M^+, 2), 142 (29), 72 (100)

[a] Reactions are carried out at 25°C

[b] Uncorrected, measured with Gallenkamp Melting Point Apparatus.

[c] Compounds **3k, 3n, 3o, 3p, 3q, 3r, 5c, 5e** in KBr disc, **3i, 3j, 3l, 3m, 5a, 5b, 5d** in NaCl cell and **3a–h** are measured in $CHCl_3$ on a Perkin-Elmer 1720-X FT Spectrophotometer.

[d] Recorded on a Bruker AC-300 Spectrometer.

[e] Recorded on a Hewlett Packard 5897A Spectrometer.

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