A 4-Dimethylaminopyridine-Catalyzed Aminolysis of β-Ketoesters. Formation of β-Ketoamides

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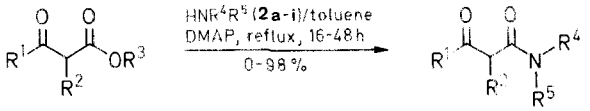
Alkyl 3-oxoalkanoates (β-ketoesters) react with amines in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) under mild conditions to form 3-oxoalkanamides (β-ketoamides) in good yields.

With the aim of building alkaloid and lactam skeletons, we needed a series of 2-substituted 3-oxoalkanamides (β-ketoamides) as starting materials. These amides can be prepared by autocondensation of *N,N*-diethylacetamide,[1] by cyclization of *N*-alkyladipamic esters,[2] by treatment of carboxamides with phosgene or phosphorylchloride,[3-5] by addition of enamines to isocyanates,[6] from phenyl isocyanate in the presence of α-acylphosphonium ylides,[7] and from α-acylketenes.[8] Aminolysis of β-ketoesters is a very useful reaction, but high temperatures[9] and long reaction times are required and often only low yields of



1a-c **3aa-3cb**

1	R^1	R^2	R^3
a	$-(CH_2)_3-$		Me
b	$-(CH_2)_4-$		Et
c	CH_3	H	Me

2	R^4	R^5
a	$CHCH_2=CH_2$	$CH_2CH=CH_2$
b	$-(CH_2)_2O(CH_2)_2-$	
c	$-(CH_2)_4-$	
d	$CH_2C\equiv CH$	Me
e	H	*i*-Pr
f	Pr	Pr
g	H	4-$CH_3C_6H_4$
h	$CH_2CH=CH_2$	Ac
i	$CH_2CH=CH_2$	Ts

Table. 3-Oxoalkanamides **3** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c] or Lit. mp (°C)	IR[d] ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ
3aa	20	94	oil	$C_{12}H_{17}NO_2$ (207.2)	1730, 1625, 1460, 1430, 1405, 1320, 1290, 1200, 990, 920	1.80–2.60 (m, 6H); 3.35–3.45 (t, 1H, J = 7.5); 3.65–3.90 (m, 2H); 4.25–4.40 (m, 2H); 5.10–5.25 (m, 4H); 5.65–5.90 (m, 2H)	21.16, 27.66, 38.72, 49.41, 52.16, 116.57, 132.86, 169.11, 214.80
3ab	48	89	44	$C_{10}H_{15}NO_3$ (197.2)	1725, 1625, 1460, 1435, 1350, 1310, 1290, 1275, 1255, 1220, 1140, 1115, 1065, 1025	1.60–1.95 (m, 1H); 2.10–2.35 (m, 4H); 2.45–2.60 (m, 1H); 3.30–3.50 (m, 3H); 3.55–3.65 (m, 1H); 3.65–3.80 (m, 4H); 3.80–3.95 (m, 1H)	20.65, 26.78, 38.24, 42.26, 51.15, 66.42, 166.47, 213.73
3ac	48	87	51	$C_{10}H_{15}NO_2$ (131.2)	1740, 1625, 1430, 1340, 1215, 1135, 1100	1.65–1.90 (m, 5H); 2.00–2.20 (m, 4H); 2.30–2.45 (m, 1H); 3.15–3.40 (m, 4H); 3.65–3.75 (m, 1H)	20.95, 24.30, 26.84, 38.43, 45.68, 53.74, 167.17, 214.77
3ah	48	0					
3ai	48	0					
3ba	16	98	oil	$C_{13}H_{19}NO_2$ (221.3)	1695, 1625, 1440–1405, 1280, 1175, 1120, 990, 915	1.50–1.80 (m, 2H); 1.85–2.05 (m, 3H); 2.05–2.35 (m, 2H); 2.40–2.55 (m, 1H); 3.40–3.50 (m, 1H); 3.60–3.80 (m, 3H); 4.15–4.25 (m, 1H); 5.00–5.20 (m, 4H); 5.60–5.80 (m, 2H)	23.42, 26.60, 30.27, 41.76, 47.86, 54.24, 116.74, 133.27, 169.54, 207.24
3bd	48	70	oil	$C_{11}H_{15}NO_2$ (193.2)	330, 2395, 1700, 1640, 1450, 1400, 1220–1190, 1125, 925	1.60–2.60 (m, 9H); 3.00 (s, 3H); 3.55–3.70 (m, 1H); 4.05–4.20 (m, 1H); 4.45–4.50 (m, 1H)	23.59, 27.19, 30.25, 34.47, 36.53, 39.44, 42.01, 54.57, 71.96, 169.42, 207.08
3be	16	74	110	$C_{10}H_{17}NO_2$ (183.2)	3340, 1690, 1665, 1635, 1535–1510, 1460, 1450, 1380, 1355, 1225–1190, 1125, 1065	1.15–1.22 (m, 6H); 1.60–2.50 (m, 8H); 3.10–3.20 (m, 1H); 4.00–4.20 (m, 1H); 6.80–6.85 (br s, 1H)	22.67, 24.02, 27.23, 31.29, 41.24, 42.08, 56.03, 168.04, 210.33
3bf	48	95	47	$C_{13}H_{23}NO_2$ (225.3)	1710, 1630, 1470, 1455, 1440, 1420, 1375, 1345, 1315, 1290, 1230–1200, 1135, 1115, 1085, 1055	0.85–0.95 (m, 6H); 1.15–2.65 (m, 12H); 3.00–3.60 (m, 5H)	10.77, 20.32, 21.86, 22.85, 26.42, 41.26, 47.08, 53.58, 168.76, 207.03
3bg	20	70[e]	106	$C_{14}H_{17}NO_2$		[Keto Form]: 1.60–2.60 (m, 8H); 2.25 (s, 3H); 3.20–3.35 (m, 1H); 7.00–7.50 (m, 4H); 8.20 (br s, 1H) [Enol Form]: 1.60–2.60 (m, 8H); 2.27 (s, 3H); 7.00–7.50 (m, 4H); 9.15 (br s, 2H)	[Keto Form]: 20.79, 23.30, 27.64, 30.94, 42.36, 58.73, 120.21, 129.84, 133.45, 137.51, 168.56, 207.97 [Enol Form]: 20.79, 22.55, 24.28, 30.08, 42.36, 98.42, 134.12, 136.55, 172.08, 172.25
3ca	48	83[e]	oil	$C_{10}H_{15}NO_2$ (181.2)	3610, 3400, 1700, 1650, 1615, 1400, 1350, 1230–1170, 1150, 985, 920, 900	[Keto Form]: 2.20 (s, 3H); 3.50 (s, 2H); 3.80–3.90 (m, 4H); 5.10–5.25 (m, 4H); 5.70–5.85 (m, 2H) [Enol Form]: 1.80 (br s, 1H); 1.90 (s, 3H); 3.80–4.05 (m, 4H); 5.10–5.30 (m, 4H); 5.30 (s, 1H); 5.70–5.85 (m, 2H)	[Keto Form]: 30.39, 47.67, 49.92, 116.98, 132.68, 166.84, 202.56 [Enol Form]: 21.94, 49.92, 87.11, 116.83, 132.59, 172.00, 175.09
3cb	20	92[e]	70	71[9]	3610, 3420, 1720, 1630, 1590, 1440, 1360, 1300, 1270, 1110	[Keto Form]: 2.20 (s, 3H); 3.40–3.50 (m, 2H); 3.50–3.70 (m, 8H) [Enol Form]: 1.90 (s, 3H); 2.85 (br s, 1H); 3.50–3.70 (m, 8H); 5.40 (s, 1H)	[Keto Form]: 29.80, 42.59, 49.64, 67.21, 166.29, 206.08 [Enol Form]: 21.81, 47.27, 67.21, 87.00, 174.12, 176.29

[a] Yield of isolated product based on **1**.
[b] Uncorrected, measured with a Büchi 510 apparatus.
[c] Satisfactory microanalyses: C ±0.19, H ±0.16, N ±0.07.
[d] Recorded on a Philips SP 300 IR spectrophotometer.
[e] Keto/Enol ratios according to ^{1}H-NMR: **3bg**, 3.0 : 1.0; **3ca**, 3.3 : 1.0; **3cb**, 3.9 : 1.0.

β-ketoamides are obtained due to the competitive formation of 3-amino-2- or -3-alkenoic esters.[10] The aminolysis of *S-tert*-butyl 3-oxoalkanethioates in the presence of silver(I) trifluoroacetate[11] has also been proposed as a mild method for the preparation of β-ketoamides but this reaction requires the previous formation of the 3-oxoalkanethioic *S*-esters from the β-ketoesters.[12]

We report here a one-pot procedure for the high-yield conversion of β-ketoesters **1** into β-ketoamides **3** (3-oxoalkanamides). This procedure is based on the observation that 4-dimethylaminopyridine (DMAP) is an effective catalyst for the transesterification of β-ketoesters[13] and the aminolysis of methyl phosphonoacetate.[14]

The reaction of β-ketoesters **1** with various primary and secondary amines **2** in refluxing toluene gives β-ketoamides **3** in good yields (Table, products **3aa–3ac** and **3ba–3cb**). The IR, ^{1}H-NMR, ^{13}C-NMR spectra indicate that compounds **3** are present in the keto form only, with the exception of **3bg, 3ca**, and **3cb** for which the enol form can also be detected (Table). When the nucleophilicity of the amine is decreased by an *N*-acyl or *N*-tosyl group, the formation of β-ketoamides is not observed (Table, products **3ah, 3ai**). This difference in reactivity between secondary amines and amides towards β-ketoesters in our method is useful as it can be employed to differenciate between amino groups in natural product synthesis.

***N,N*-Diallyl-2-oxocyclopentanecarboxamide (3aa); Typical Procedure:**
A mixture of diallylamine (**2a**; 2.7 g, 28 mmol, 2 equiv), methyl 2-oxocyclopentanecarboxylate (**1a**; 2.0 g, 14 mmol, 1 equiv), and DMAP (0.5 g, 42 mmol, 0.3 equiv) in toluene (20 mL) is heated to reflux for 20 h under argon. The solvent is then removed under reduced pressure and the residue is purified by flash chromatography on a silica gel column (15 cm × 4 cm; 230–400 mesh) using EtOAc/pentane (20:80) as eluent; yield: 2.72 g (94%); oil.

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(1) Montagne, M. *C.R. Acad. Sci.* **1931**, *192*, 111.
Utzinger, G.E. *Helv. Chim. Acta* **1952**, *35*, 1359.
(2) Johnson, D.H. *J. Chem. Soc.* **1958**, 1624.
(3) Seefelder, M. *German Patent* 1089760 (1958), BASF; *C.A.* **1962**, *56*, 1326.
(4) Bredereck, H., Gompper, R., Klemm, K. *Chem. Ber.* **1959**, *92*, 1456.
(5) Eilingsfeld, H., Seefelder, M., Weidinger, H. *Angew. Chem.* **1960**, *72*, 836.
(6) Hünig, S., Hübner, K., Benzing, E. *Chem. Ber.* **1962**, *95*, 926.
(7) Bestmann, H.J., Kumar, K. *Chem. Ber.* **1983**, *116*, 2708.
(8) Cossy, J., Belotti, D., Thellend, A., Pete, J.P. *Synthesis* **1988**, 720.
(9) Couturier, M., Blanc, P. *Bull. Soc. Chim. Fr.* **1958**, 151.
(10) Fierz-David, H.E., Ziegler, E. *Helv. Chim. Acta* **1928**, *11*, 776.
Hauser, C.R., Reynolds, G.A. *J. Am. Chem. Soc.* **1948**, *70*, 2402.
Limpach, L. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 970.
Misani, F., Bogert, M.T. *J. Org. Chem.* **1945**, *10*, 347.
Coffey, S., Thomson, J.K., Wilson, F.J. *J. Chem. Soc.* **1936**, 856.
Matsuo, K., Kimura, K., Kinuta, T., Takai, N., Tanaka, K. *Chem. Pharm. Bull.* **1984**, *32*, 4197.
Labelle, M., Gravel, D. *J. Chem. Soc. Chem. Commun.* **1985**, 105.
(11) Ley, S.V., Woodward, P.R. *Tetrahedron Lett.* **1987**, *28*, 3019.
(12) Booth, P.M., Fox, C.M.J., Ley, S.V. *Tetrahedron Lett.* **1983**, *24*, 5143; *J. Chem. Soc. Perkin Trans. 1* **1987**, 121.
Clarke, T., Ley, S.V. *J. Chem. Soc. Perkin Trans. 1* **1987**, 131.
Ley, S.V., Woodward, P.R. *Tetrahedron Lett.* **1987**, *28*, 345.
(13) Taber, D.F., Amedio, J.C., Jr., Patel, Y.K. *J. Org. Chem.* **1985**, *50*, 3618.
(14) Hatakeyama, S., Satoh, K., Sakurai, K., Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713.