Pyrazin-2(1*H*)-ones from 3,4-Disubstituted 4-Aminoisoxazol-5(4*H*)-ones

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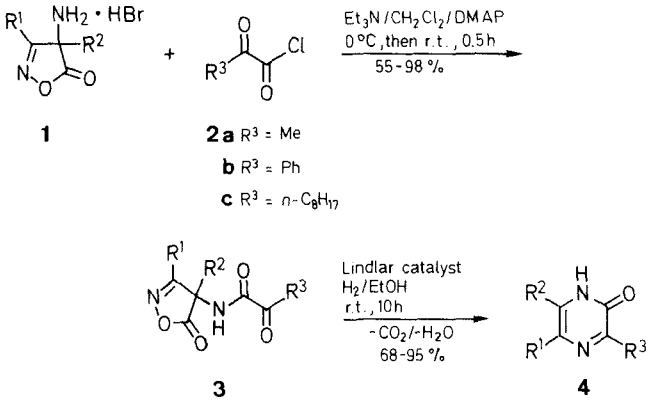
A new synthesis for 3,5,6-trisubstituted pyrazin-2(1*H*)-ones from 3,4-disubstituted 4-(phenyloxalylamino)- and 4-(alkyloxalylamino)-isoxazol-5(4*H*)-ones is reported.

We have previously reported on the synthesis of 3,4-disubstituted 4-aminoisoxazol-5(4*H*)-ones **1** from isoxazol-5(4*H*)-ones and on their use in a new synthesis, affording imidazoles in high yield.[1]

We report now a new and easy synthesis of trisubstituted pyrazin-2(1*H*)-ones **4** starting from 4-aminoisoxazol-5(4*H*)-ones **1** (Scheme). The amines **1** are first transformed into the corresponding α-oxo acid amides **3** by reaction with the corresponding oxo acid chlorides **2**.[2] The hitherto unknown 2-oxodecanoyl chloride (**2c**) was prepared according to a known method,[2] and used directly as raw material in the next step without purification due to its instability (Table 1). The amides **3** are reduced with hydrogen in the presence of Lindlar catalyst in ethanol at room temperature. Hydrogenolysis of the N–O bond, followed by decarboxylation and intramolecular cyclization gives pyrazinones **4** in good yield (Table 2). Hydrogenation with palladium on charcoal or with Raney-nickel is faster but always gives lower yields. Spectroscopic data of the new compounds are reported in Table 3.

This synthesis is a direct and convenient method for the preparation of trisubstituted pyrazin-2(1*H*)-ones **4**, as an alternative to the previously reported methods from α-amino acid amides and 1,2-dicarbonyl compounds.[3]



1 **2a** R^3 = Me; **b** R^3 = Ph; **c** R^3 = n-C_8H_{17}

3 **4**

1	R^1	R^2	3,4	R^1	R^2	R^3	3,4	R^1	R^2	R^3
a	Me	*i*-Pr	**aa**	Me	*i*-Pr	Me	**ca**	Ph	Bn	Me
b	Me	Bn	**ab**	Me	*i*-Pr	Ph	**cb**	Ph	Bn	Ph
c	Ph	Bn	**ac**	Me	*i*-Pr	n-C_8H_{17}	**cc**	Ph	Bn	n-C_8H_{17}
d	Ph	Et	**ba**	Me	Bn	Me	**da**	Ph	Et	Me
			bb	Me	Bn	Ph	**db**	Ph	Et	Ph
			bc	Me	Bn	n-C_8H_{17}				

Scheme

Melting points are determined on a Büchi apparatus and are uncorrected. IR spectra are recorded on a Perkin-Elmer 298 instrument, in Nujol mull for solids and liquid film for oils. ^{1}H-NMR are recorded on a Varian EM-390 or on a Bruker AC 300 spectrometer with TMS as internal standard in $CDCl_3$ if not stated otherwise. Lindlar catalyst (5% Pd–$CaCO_3$, poisoned with lead) obtained from Fluka. Column chromatography is performed on Merck Kieselgel 60, 0.063–0.2 mm. Evaporation is carried out under vacuum in a rotary evaporator.

Table 1. 3,4-Disubstituted 4-(Phenyloxalylamino)- and 4-(Alkyloxalylamino)isoxazol-5(4*H*)-ones **3** Prepared

Product	Yield (%)	mp (°C) (solvent)[a]	Molecular Formula[b]
3aa	87	117–118 (Et_2O)	$C_{10}H_{14}N_2O_4$ (226.2)
3ab	98	116–117 (*i*-Pr_2O)	$C_{15}H_{16}N_2O_4$ (288.3)
3ac	55	60–61 (Hx)	$C_{17}H_{28}N_2O_4$ (324.4)
3ba	80	139–140 (Et_2O)	$C_{14}H_{14}N_2O_4$ (274.3)
3bb	89	159–160[c] (CH_2Cl_2/Hx)	$C_{19}H_{16}N_2O_4$ (336.3)
3bc	77	103–104 (Et_2O/Hx)	$C_{21}H_{28}N_2O_4$ (372.4)
3ca	88	142–143 (CH_2Cl_2/Hx)	$C_{19}H_{16}N_2O_4$ (336.3)
3cb	88	156–157[c] (CH_2Cl_2/Hx)	$C_{24}H_{18}N_2O_4$ (398.4)
3cc	57	oil	$C_{26}H_{30}N_2O_4$ (434.5)
3da	82	96–97 (Et_2O/Hx)	$C_{14}H_{14}N_2O_4$ (274.3)
3db	93	153–154[c] (CH_2Cl_2/Hx)	$C_{19}H_{16}N_2O_4$ (336.3)

[a] Hx = hexane.
[b] Satisfactory microanalyses obtained: C ±0.12, H ±0.1, N ±0.12.
[c] With decomposition.

Table 2. Pyrazin-2(1*H*)-ones **4** Prepared

Product	Yield (%)	mp (°C) (solvent)[a]	Molecular Formula[b]
4aa	90	140–142 (Hx)	$C_9H_{14}N_2O$ (166.2)
4ab	81	187–188 (CH_2Cl_2/Hx)	$C_{14}H_{16}N_2O$ (228.3)
4ac	78	57–59 (Hx)	$C_{16}H_{28}N_2O$ (264.4)
4ba	77	156–157 (CH_2Cl_2/Hx)	$C_{13}H_{14}N_2O$ (214.3)
4bb	95	203–204 (CH_2Cl_2/Hx)	$C_{18}H_{16}N_2O$ (276.3)
4bc	68	114–115 (Et_2O/Hx)	$C_{20}H_{28}N_2O$ (312.4)
4ca	81	193–194 (CH_2Cl_2/Hx)	$C_{18}H_{16}N_2O$ (276.3)
4cb	92	258–260 (CH_2Cl_2/Hx)	$C_{23}H_{18}N_2O$ (338.4)
4cc	82	109–111 (Et_2O/Hx)	$C_{25}H_{30}N_2O$ (374.5)
4da	77	182–183 (CH_2Cl_2/Hx)	$C_{13}H_{14}N_2O$ (214.3)
4db	80	250–252 (CH_2Cl_2/Et_2O)	$C_{18}H_{16}N_2O$ (276.3)

[a] Hx = hexane.
[b] Satisfactory microanalyses obtained: C ±0.12, H ±0.1, N ±0.12.

2-Oxodecanoyl Chloride (2c):

A mixture of 2-oxodecanoic acid[4] (3.72 g, 20 mmol) and Cl_2CHOMe (2.7 mL, 30 mmol) is heated at an oil bath temperature of 50°C for 30 min. Evaporation at 5 Torr gives the chloride **2c** which is used directly in the next step without purification.

4-(Alkyloxalylamino)- or 4-(Phenyloxalylamino)isoxazol-5(4*H*)-ones 3; General Procedure:

The 4-aminoisoxazol-5(4*H*)-one hydrobromide **1** (4 mmol) is dissolved in CH_2Cl_2 (50 mL) and then Et_3N (1.4 mL, 10 mmol) and DMAP (50 mg, 0.41 mmol) are added. The solution is cooled to 0–5°C and the acid chloride **2** (5 mmol) in CH_2Cl_2 (10 mL) is added under stirring. After 30 min at r.t., the mixture is washed with H_2O (30 mL) and dil. aq HCl (4%, 30 mL). The organic layer is dried (Na_2SO_4), filtered and evaporated. The residue is purified by silica gel column chromatography, eluent hexane/CH_2Cl_2 (1:1).

Table 3. Spectral Data of Compounds **3, 4**

Product	IR (Nujol or film) (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
3aa	3380, 1798, 1724, 1685	1.05 (d, 3H, J = 7.5), 1.20 (d, 3H, J = 7.5), 2.02 (s, 3H), 2.26 (m, 1H), 2.50 (s, 3H), 7.45 (br s, 1H)[a]
3ab	3318, 1784, 1681, 1665	1.05 (d, 3H, J = 7), 1.22 (d, 3H, J = 7), 2.07 (s, 3H), 2.23 (m, 1H), 7.41 (m, 3H), 7.76 (br s, 1H),[a] 8.31 (m, 2H)
3ac	3365, 1793, 1722, 1680	0.86 (t, 3H, J = 7), 1.02 (d, 3H, J = 7.2), 1.15 (d, 3H, J = 7.2), 1.24 (m, 8H), 1.57 (m, 4H), 1.94 (s, 3H), 2.17 (m, 1H), 2.84 (t, 2H, J = 7), 7.32 (br s, 1H)[a]
3ba	3360, 1796, 1728, 1695	2.06 (s, 3H), 2.48 (s, 3H), 3.28 (m, 2H), 7.15 (m, 2H), 7.31 (m, 3H), 7.53 (br s, 1H)[a]
3bb	3318, 1798, 1681, 1664	2.12 (s, 3H), 3.33 (m, 2H), 7.10–7.60 (m, 8H), 7.75 (br s, 1H),[a] 8.33 (m, 2H)
3bc	3310, 1780, 1729, 1678	0.90 (m, 3H), 1.32 (m, 10H), 1.55 (m, 2H), 2.05 (s, 3H), 2.85 (t, 2H, J = 7), 3.26 (s, 2H), 7.25 (m, 5H), 7.66 (br s, 1H)[a]
3ca	3280, 1804, 1729, 1690	2.44 (s, 3H), 3.46 (m, 2H), 6.96 (m, 2H), 7.22 (m, 3H), 7.50 (m, 3H), 7.75 (m, 3H)[b]
3cb	3263, 1805, 1692, 1660	3.45 (d, 1H, J = 12), 3.52 (d, 1H, J = 12), 6.98 (m, 2H), 7.26 (m, 3H), 7.51 (m, 6H), 7.82 (m, 2H), 8.01 (br s, 1H),[a] 8.33 (m, 2H)
3cc	3300, 1800, 1725, 1680	0.86 (m, 3H), 1.31 (m, 10H), 1.51 (m, 2H), 2.82 (t, 2H, J = 7), 3.43 (d, 1H, J = 13), 3.56 (d, 1H, J = 13), 6.90 (m, 2H), 7.21 (m, 3H), 7.45 (m, 3H), 7.81 (m, 2H), 8.16 (br s, 1H)[a]
3da	3325, 1813, 1741, 1686	0.97 (t, 3H, J = 7.5), 2.26 (q, 2H, J = 7.5), 2.44 (s, 3H), 7.52 (m, 3H), 7.59 (br s, 1H)[a] 7.75 (m, 2H)
3db	3240, 1797, 1687, 1649	0.97 (t, 3H, J = 7.5), 2.25 (q, 2H, J = 7.5), 7.44 (m, 5H), 7.78 (m, 3H), 8.05 (br s, 1H)[a] 8.26 (m, 2H)
4aa	1647	1.35 (d, 6H, J = 7.5), 2.33 (s, 3H), 2.45 (s, 3H), 3.05 (m, 1H), 12.50 (br s, 1H)[a]
4ab	1642	1.39 (d, 6H, J = 7), 2.42 (s, 3H), 3.11 (m, 1H), 7.38 (m, 3H), 8.42 (m, 2H), 12.60 (br s, 1H)[a]
4ac	1653	0.86 (t, 3H, J = 7.5), 1.25 (m, 6H), 1.31 (m, 8H), 1.63 (m, 4H), 2.28 (s, 3H), 2.75 (m, 2H), 3.01 (m, 1H), 11.20 (br s, 1H)[a]
4ba	1647	2.37 (s, 3H), 2.46 (s, 3H), 3.95 (s, 2H), 7.28 (m, 5H), 13.05 (br s, 1H)[a]
4bb	1634	2.5 (s, 3H), 4.02 (s, 2H), 7.30 (m, 8H), 8.35 (m, 2H), 13.50 (br s, 1H)[a]
4bc	1649	0.86 (m, 3H), 1.30 (m, 10H), 1.65 (m, 2H), 2.38 (s, 3H), 2.75 (t, 2H, J = 7), 3.91 (s, 2H), 7.28 (m, 5H), 12.00 (br s, 1H)[a]
4ca	1667	2.49 (s, 3H), 4.01 (s, 2H), 7.20 (m, 5H), 7.42 (m, 5H), 12.02 (br s, 1H)[a]
4cb	1650	DMSO-d_6: 4.01 (s, 2H), 7.06 (m, 2H), 7.24 (m, 3H), 7.42 (m, 8H), 8.34 (m, 2H), 12.78 (br s, 1H)[a]
4cc	1661	0.86 (m, 3H), 1.25 (m, 10H), 1.69 (m, 2H), 2.75 (t, 2H, J = 7), 4.01 (s, 2H), 7.12 (m, 2H), 7.26 (m, 3H), 7.42 (m, 5H), 12.02 (br s, 1H)[a]
4da	1655	1.36 (t, 3H, J = 8), 2.55 (s, 3H), 2.73 (q, 2H, J = 8), 7.43 (m, 5H), 7.91 (br s, 1H)[a]
4db	1651	1.44 (t, 3H, J = 7.5), 2.82 (q, 2H, J = 7.5), 7.44 (m, 5H), 7.57 (m, 3H), 8.49 (m, 2H), 13.10 (br s, 1H)[a]

[a] Exchange with D_2O.
[b] 2H after D_2O.

3,5,6-Trisubstituted Pyrazin-2(1*H*)-ones 4; General Procedure:
The α-oxo acid amide **3** (2 mmol) is dissolved in EtOH (40 mL), Lindlar catalyst (120 mg) is added and the mixture is hydrogenated under atmospheric pressure at r.t. After 10 h the catalyst is filtered off, the solvent evaporated and the residue crystallized from the reported solvent (Table 2).

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