An Efficient Synthesis of *N,N*-Disubstituted 5-Aminooxazoles

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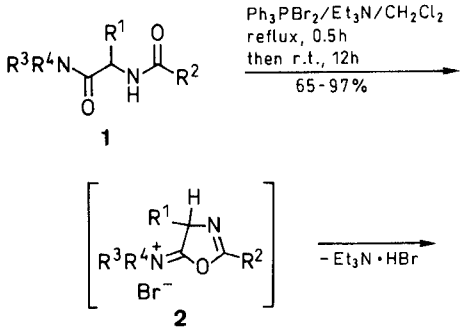
N,N-Disubstituted 5-aminooxazoles including 4-unsubstituted derivatives, were prepared from the corresponding α-acylamino amides by treatment with dibromotriphenylphosphorane and triethylamine in refluxing dichloromethane in a novel, convenient and efficient one-pot procedure.

N,N-Disubstituted 5-aminooxazoles, which are the only stable type of 5-aminooxazoles,[1] have been shown to be useful synthons for heterocyclic ring formation. The ability of oxazoles to behave as azadienes in Diels–Alder reactions with olefinic or acetylenic dienophiles is utilized for the preparation of pyridine and furan derivatives.[2] For instance, Kondrat'eva et al.[3] reported the condensation of *N,N*-disubstituted 5-aminooxazoles with maleimide into 3-hydroxy- or 3-aminopyridine derivatives. Although the yields of 3-hydroxypyridines were only modest, this result is of considerable interest, indicating the possibility of synthesizing pyridoxines in such a way. The condensation of *N,N*-disubstituted 5-aminooxazoles with diazonium salts to 1,2,4-triazole derivatives, as well as the conversion of 4-trifluoroacetyl-5-aminooxazoles by hydroxylamine into isoxazoles were described by Clerin and Fleury.[4]

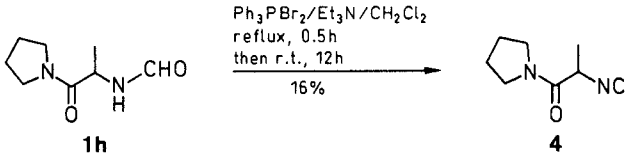
Relatively few literature reports of the preparation of *N,N*-disubstituted 5-aminooxazoles have been made. Clerin et al.[5] have prepared these compounds by cyclization of the corresponding α-acylamino amides in the presence of trifluoroacetic anhydride. If, however, the 4-position of synthesized oxazole was not substituted, the primary reaction product was converted further, by electrophilic attack, into the 4-trifluoroacetyl derivative. The trifluoroacetyl group can be removed by hydrolysis and subsequent decarboxylation. Kondrat'eva et al.[6] have described the synthesis of *N,N*-disubstituted 5-aminooxazoles by a direct condensation of α-acylamino acids with secondary amines in the presence of phosphorus oxychloride, but the yields were disappointing, especially in the case of 4-unsubstituted oxazoles. *N,N*-Disubstituted 5-aminooxazoles have also been synthesized by means of the multistep method from *N*-(1,2,2,2-tetrachloroethyl)amides via [2,2-dichloro-1-(acylamino)vinyl]triphenylphosphonium chlorides and (5-aminooxazol-3-yl)triphenylphosphonium chlorides, the yield of the last step amounting only to 32–41 %.[7] Push–pull stabilized *N*-unsubstituted, *N*-monosubstituted and *N,N*-disubstituted 5-amino-4-cyanooxazoles have been synthesized from *N*-acylderivatives of 2-amino-3,3-dichloroacrylonitrile by treatment with amines.[8] There are also several other reports on the synthesis of *N*-unsubstituted and *N*-monosubstituted 5-aminooxazoles.[9]

We have now developed a facile and efficient synthesis of *N,N*-disubstituted 5-aminooxazoles. We found that treatment of tertiary α-acylamino amides with dibromotriphenylphosphorane and triethylamine in refluxing dichloromethane gave good to excellent yields of the corresponding 5-aminooxazoles.



1-3	R^1	R^2	R^3	R^4	1-3	R^1	R^2	R^3	R^4
a	H	Me	Me	Me	**e**	H	Ph	Me	Me
b	H	Me	Me	Ph	**f**	Me	Ph	$-(CH_2)_2O(CH_2)_2-$	
c	H	Me	$-(CH_2)_4-$		**g**	Bn	Me	$-(CH_2)_5-$	
d	H	Me	$-(CH_2)_5-$						

The α-acylamino amides **1** are readily available by condensation of α-acylamino acids with secondary amines in the presence of dicyclohexylcarbodiimide (DCC). In contrast to the previously described syntheses[5,6] our method makes it possible to obtain directly also 4-unsubstituted 5-aminooxazoles, which are of special interest because of the high reactivity of the 4-position towards electrophilic agents. However, the procedure described here is not applicable to the synthesis of 2-unsubstituted 5-aminooxazoles from α-formylamino amides. As it might be expected basing on our previous results,[10] attempts to convert α-formylamino amide **1h** into the corresponding 5-aminooxazole were unsuccessful due to the dehydration of amide to α-isocyano amide **4**.



In summary, the present method offers a very convenient way to *N,N*-disubstituted 5-aminooxazoles, including 4-unsubstituted compounds. The advantages of this method are reasonable yields, the short reaction time, and the ease with which the reaction can be performed in a one-pot procedure with readily available starting materials.

Purification of Br_2, Et_3N, Ph_3P and CH_2Cl_2 has been described in previous papers.[11] The amide **1f** was prepared from *N*-benzoyl-DL-alanine ethyl ester according to the procedure given by Clerin and Fleury.[5] *N*-Formyl-DL-alanine was prepared by the reported procedure.[12] The other reagents were of commercial quality. Melting points, determined in capillary tubes, are uncorrected. Microanalyses were obtained using a Perkin-Elmer 240 MC-1 element analyser. Mass spectra were recorded on a Gas-Chromatograph Mass Spectrometer LKB 2091 with DEI ionization. IR

Table. α-Acylamino Amides **1** and *N,N*-Disubstituted 5-Aminooxazoles **3** Prepared

Product	Yield[a] (%)	mp (°C) (solvent) or bp (°C)/mbar	Molecular Formula[b] or Lit. mp (°C) or bp (°C)/mbar	IR (CH_2Cl_2) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
1a	61	52–54 (benzene/hexane)	$C_6H_{12}N_2O_2$ (144.2)	3403, 1650	2.03 (s, 3H, CH_3CO), 2.98 [s, 6H, $(CH_3)_2N$], 4.02 (d, 2H, J = 4.3, CH_2NH), 6.98 (br, 1H, NH)	
1b	55	129–130 (MeOH)	138[6]	3452, 1657	1.98 (s, 3H, CH_3CO), 3.27 (s, 3H, CH_3N), 3.71 (d, 2H, J = 4.1, CH_2NH), 6.55 (br, 1H, NH), 7.08–7.50 (m, $5H_{arom}$)	
1c	80	113–114 (benzene/hexane)	$C_8H_{14}N_2O_2$ (170.2)	3411, 1673, 1646	1.80–2.17 (m, 7H, $CH_3CO + CH_2CH_2CH_2CH_2$), 3.26–3.64 (m, 4H, $CH_2CH_2CH_2CH_2$), 3.95 (d, 2H, J = 4.0, CH_2NH), 6.73 (br, 1H, NH)	
1d	72	90.5–92 (benzene/hexane)	$C_9H_{16}N_2O_2$ (184.2)	3409, 1671, 1642	1.38–1.76 [m, 6H, $CH_2(CH_2)_3CH_2$], 2.03 (s, 3H, CH_3CO), 3.22–3.70 [m, 4H, $CH_2(CH_2)_3CH_2$], 4.00 (d, 2H, J = 4.1, CH_2NH), 6.83 (br, 1H, NH)	
1e	52	112–113 (MeOH)	112–113[5]	3403, 1648	3.00 [s, 6H, $(CH_3)_2N$], 4.19 (d, 2H, J = 3.9, CH_2NH), 7.23–7.49 (m, 4H, $3H_{arom}$ + NH), 7.72–7.85 (m, $2H_{arom}$)	
1g	83	118–119 (MeOH)	$C_{16}H_{22}N_2O_2$ (274.3)	3420, 3310, 1671, 1632	1.30–1.66 [m, 6H, $CH_2(CH_2)_3CH_2$], 1.96 (s, 3H, CH_3CO), 2.96 (d, 2H, J = 6.8, CH_2CH), 3.03–3.58 [m, 4H, $CH_2(CH_2)_3CH_2$], 4.99–5.27 (m, 1H, CH_2CHNH), 6.52 (br, 1H, NH), 7.12–7.38 (m, $5H_{arom}$)	
1h	85	158–160/0.7	$C_8H_{14}N_2O_2$ (170.2)	3408, 1712, 1685, 1639	1.36 (d, 3H, J = 6.8, CH_3CH), 1.80–2.09 (m, 4H, $CH_2CH_2CH_2CH_2$), 3.21–3.72 (m, 4H, $CH_2CH_2CH_2CH_2$), 4.52–4.95 (m, 1H, CH_3CHNH), 7.00 (br, 1H, NH), 8.09 (s, 1H, HCO)	
3a	65	93–96/60	74–76/20[7]	1621, 1599	2.31 (s, 3H, CH_3C), 2.73 (s, 6H, $(CH_3)_2N$, 5.74 (s, 1H, CH)	126 (M^+, 100)
3b	94	104–106/0.8	114–116/1.3[6]	1598	2.36 (s, 3H, CH_3C), 3.20 (s, 3H, CH_3N), 6.45 (s, 1H, CH), 6.71–6.94 (m, $3H_{arom}$), 7.07–7.33 (m, $2H_{arom}$)	188 (M^+, 98), 118 (100)
3c	83	132–136/40	$C_8H_{12}N_2O$ (152.2)	1621, 1598	1.84–2.02 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.31 (s, 3H, CH_3), 3.08–3.24 (m, 4H, $CH_2CH_2CH_2CH_2$), 5.66 (s, 1H, CH)	152 (M^+, 100)
3d	79	144–148/43	$C_9H_{14}N_2O$ (166.2)	1611	1.45–1.82 [m, 6H, $CH_2(CH_2)_3CH_2$], 2.31 (s, 3H, CH_3), 2.86–3.12 [m, 4H, $CH_2(CH_2)_3CH_2$], 5.82 (s, 1H, CH)	166 (M^+, 100)
3e	66	100–104/ 0.13–0.27	92–96/0.13[7]	1617, 1601	2.86 [s, 6H, $(CH_3)_2N$], 6.00 (s, 1H, CH), 7.30–7.42 (m, $3H_{arom}$), 7.77–7.90 (m, $2H_{arom}$)	188 (M^+, 96), 116 (100)
3f	80	148–150/ 0.27–0.4	55.5–56.5[5]	1659, 1633, 1604	2.16 (s, 3H, CH_3), 2.95–3.14 (m, 4H, OCH_2CH_2N), 3.72–3.84 (m, 4H, OCH_2CH_2N), 7.26–7.50 (m, $3H_{arom}$), 7.77–7.95 (m, $2H_{arom}$)	244 (M^+, 100)
3g	97	112–117/0.07	$C_{16}H_{20}N_2O$ (256.3)	1666, 1640	1.39–1.82 [m, 6H, $CH_2(CH_2)_3CH_2$], 2.29 (s, 3H, CH_3), 2.79–3.10 (m, 4H, $CH_2(CH_2)_3CH_2$), 3.72 (s, 2H, CH_2), 7.11–7.31 (m, $5H_{arom}$)	256 (M^+, 31), 43 (100)

[a] Yield of isolated product **1** or **3** based on α-acylamino acid or α-acylamino amide **1**, respectively.
[b] Satisfactory microanalyses obtained: C ±0.20, H ±0.19, N ±0.23.

spectra were obtained using a Zeiss Specord 71 IR spectrophotometer. ^1H NMR spectra were obtained at 80 MHz on a Tesla BS 587 spectrometer.

α-Acylamino Amides 1a–e and 1g–h; General Procedure:
To a solution of DCC (8.24 g, 40 mmol) in CH_2Cl_2 (80 mL) α-acylamino acid (40 mmol) was added. The mixture was vigorously stirred at r.t. for 1 h, then amine (40 mmol) was added all at once, the mixture was further stirred for 3 h and kept overnight at r.t. The precipitated 1,3-dicyclohexylurea was filtered off, the filtrate was evaporated to dryness at reduced pressure. The crude amide **1e** was purified by recystallization from MeOH, whereas the amides **1a–d** and **1g** were sublimed (90–125°C/0.07–0.13 mbar) and then recrystallized using the solvents given in Table. Only in the case of the amide **1h** the oily residue was distilled under vacuum.

***N,N*-Disubstituted 5-Aminooxazoles 3; General Procedure:**
In a dried, Ar filled flask fitted with a dropping funnel and a condenser protected by a $CaCl_2$ guard-tube Ph_3P (6.29 g, 24 mmol) was dissolved in CH_2Cl_2 (50 mL) and a solution of Br_2 (1.23 mL, 24 mmol) in CH_2Cl_2 (10 mL) was added. After 0.5 h a solution of Et_3N (8.3 mL, 60 mmol) and α-acylamino amide (20 mmol) in CH_2Cl_2 (20 mL) was added all at once, the mixture was refluxed under Ar for 0.5 h and kept overnight (12 h) at r.t. The mixture was

diluted with hexane (80 mL), the precipitated $Et_3N \cdot HBr$ was filtered off, the filtrate was evaporated to dryness at reduced pressure. The residue was extracted with boiling hexane (3 × 100 mL), the combined extracts were cooled to r.t., the precipitated Ph_3PO was filtered off and the filtrate was evaporated at reduced pressure. The oily residue was distilled under vacuum to give 5-aminooxazole **3**.

1-(2-Isocyanopropionyl)pyrrolidine (4):
Compound **4** was obtained following the same procedure as described above for the preparation of 5-aminooxazoles, but with amide **1h** as starting material. The crystalline residue obtained after the extraction with boiling hexane and evaporation of the solvent was sublimed (80–85 °C/0.07 mbar) and the sublimate was recrystallized from hexane; yield: 0.469 g (16%); mp 73–74 °C.

$C_8H_{12}N_2O$ (152.2) calc. C 63.13 H 7.95 N 18.41
found 63.32 7.96 18.23

MS: *m/z* (%) = 152 (M^+, 2), 55 (100).

IR (CH_2Cl_2): ν = 1664 (C=O), 2148 cm^{-1} (N=C).

^1H NMR ($CDCl_3$/TMS): δ = 1.58 (d, 3H, J = 6.6, $C\underline{H}_3CH$), 1.81–2.16 (m, 4H, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 3.35–3.74 (m, 4H, $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 4.42 (q, 1H, J = 6.6, $CH_3C\underline{H}$).

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