COMMUNICATIONS

An Improved Synthesis of 2-Amino-1,3-oxazoles under Basic Catalysis

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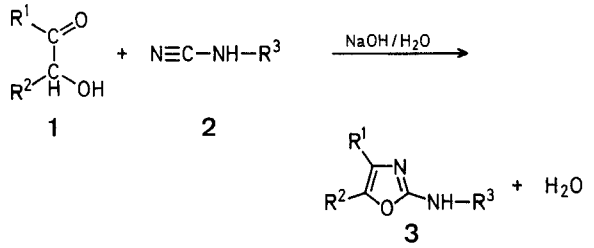
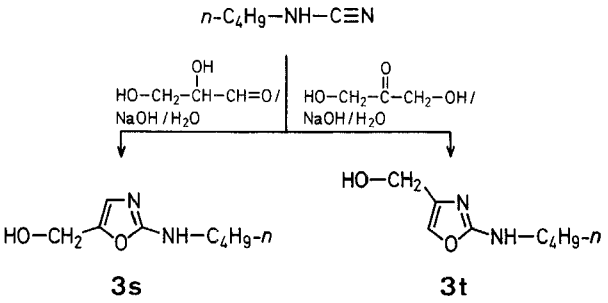
Two methods are generally used to prepare 2-amino-1,3-oxazoles (**3**). The first involves the reaction of α-halocarbonyl compounds with urea in dimethylformamide at high temperature for several hours[1]. As several 2-amino-1,3-oxazoles are thermally unstable, this route has distinct limitations, e.g. this reaction has been shown to be inapplicable to the synthesis of 2-amino-4-methyl-1,3-oxazole[2]. Also temperature control of the reaction is critical as substantial amounts of imidazole or imidazolone products may be formed[1]. An alternative approach is the reaction of an α-hydroxyketone with cyanamide[2] or a substituted cyanamide[3]. This reaction has been conducted at 40–50° in aqueous solution[2] or in the presence of a mineral-acid catalyst[3]. In our hands, application of either of these approaches often gave 2-amino-1,3-oxazoles (**3**) in low yield and contaminated with involatile (presumably polymeric) impurities. In the present study, we demonstrated that the reaction is enhanced by basic catalysis.

The method described involves mixing a cyanamide (**2**) and a suitable hydroxyketone (**1**) in aqueous sodium hydroxide. No heat is required and the product, if crystalline, separates cleanly from the reaction mixture or is partitioned into a suitable organic solvent. If the hydroxyketone or cyanamide are not water soluble an organic cosolvent (e.g. tetrahydrofuran, dioxan) may be used in the reaction. The yields are particularly good (see Table) for the preparation of 2-alkylamino-1,3-oxazoles under a variety of basic conditions, but in the case of *N*-unsubstituted amino derivatives, careful attention to pH and reaction time is required (see Figures 1 and 2).



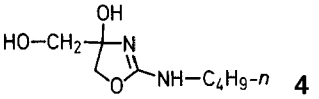
1 **2** **3**

Mechanistically, this reaction may be interpreted in two ways: (a) as nucleophilic attack of cyanamide salt at the carbonyl of the substrate; (b) as the reaction of the sodium enolate of the carbonyl compound with the cyanamide. The latter possibility seemed less likely and further evidence against it was obtained by studying the condensation of an alkylcyanamide with glyceraldehyde and also with dihydroxyacetone. If the enolate of the carbonyl compound played a significant part in this reaction, both would yield the same 1,3-oxazole. Thus, when butylcyanamide[4] reacted with dihydroxyacetone in aqueous solution, a crystalline product was isolated, m.p. 57–59°, and identified as 2-butylamino-4-hydroxymethyl-1,3-oxazole (**3t**) by its spectral characteristics. However, when the reaction was repeated with glyceraldehyde the product isolated had m.p. 87–88° and proved to be 2-butylamino-5-hydroxymethyl-1,3-oxazole (**3s**).



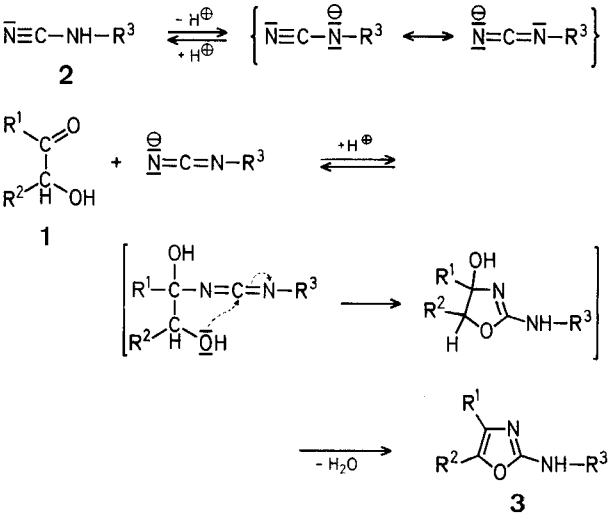
3s **3t**

Thus, the condensation in these cases does not occur via the carbonyl enolate. In the preparation of **3t** it was observed that, after the addition of sodium hydroxide to the reaction mixture, the exothermic reaction was followed by the precipitation of a colourless solid which was shown by ^{1}H-N.M.R. to contain no aromatic proton. Signals were seen at $\delta = 3.46$ (s, 2H) and at $\delta = 3.98$, 4.2 (dd, 2H). A structure consistent with these data is the hydrate **4**. A sample which crystallised from ethyl acetate/chloroform as white flakes, m.p. 116–118°, rapidly became oily on standing at room temperature.



4

Hydrates of type **4** have previously been reported in the preparation of 1,3-oxazoles from ureas and bromoketones[5], and also from the addition of water to 2-amino-1,3-oxazoles in dilute acid[5]. A mechanism consistent with these data is shown in the following scheme.



2 **1** **3**

Further support for this mechanism is provided by the fact that dialkylcyanamides, where the corresponding anion cannot be generated, are unreactive in alkaline solution[6].

The effect of the reaction conditions (pH and temperature) on the yield of **3** was studied for the case of 2-amino-4-methyl-1,3-oxazole (**3b**). The results are shown in Figures 1 and 2.

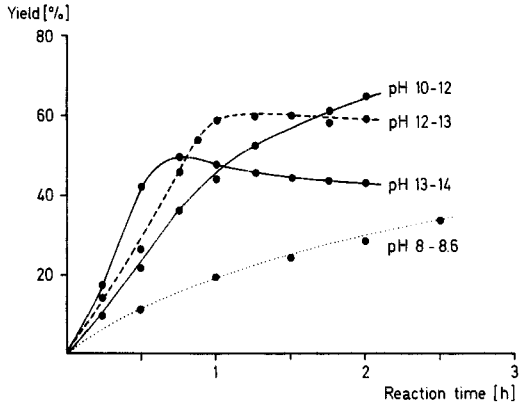


Figure 1. The variation in yield (G.L.C. of reaction solution) of 2-amino-4-methyl-1,3-oxazole (**3b**) with pH of reaction medium at 20°

All compounds prepared were characterised by N.M.R.- and I.R.-spectral studies, and elemental analyses were in good accordance with theoretical values.

Preparation of Substituted Cyanamides (2); General Procedure:

A primary amine (0.1 mol) is added to a stirred, cooled solution (−10° to −20°) of cyanogen bromide (10.6 g, 0.1 mol) in tetrahydrofuran (50 ml) containing anhydrous sodium carbonate (20.8 g, 0.2 mol). The mixture is stirred at the same temperature for 2 h, allowed to warm to 0°, and then filtered. The filtrate (tetrahydrofuran solution of **2**) can be used in the cyclocondensation without further purification. If isolation of the cyanamide **2** is required, diethyl ether is used in place of tetrahydrofuran. Yields of isolated cyanamides **2** are generally >90%.

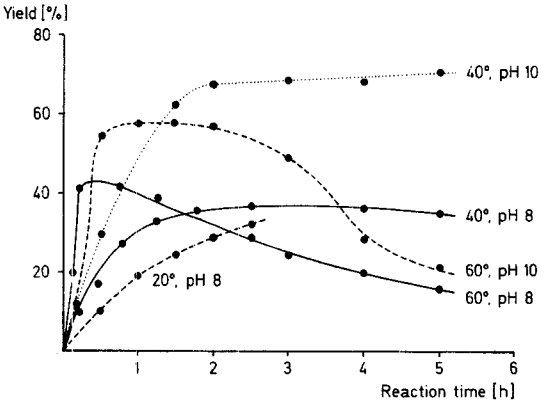


Figure 2. The effect of reaction temperature on yield (G.L.C. of reaction solution) of 2-amino-4-methyl-1,3-oxazole (**3b**) at pH 8 and pH 10

Preparation of 2-Amino-1,3-oxazoles (3); General Procedures:

2-Alkylamino-1,3-oxazoles: A solution of the alkylcyanamide (**2**; 0.1 mol) in tetrahydrofuran (50 ml) is diluted with water (50 ml) and an aqueous solution (54%) of the α-hydroxyaldehyde or -ketone (**1**; 0.1 mol) is added with stirring, followed by the dropwise addition of aqueous 2*N* sodium hydroxide (10 ml, 0.02 mol). The temperature rises to 40–45° and two phases separate. Stirring is continued for a further 2 h, the mixture is diluted with water, and the product is extracted with ether. The extract is dried with sodium sulfate, the solvent evaporated, and the residue distilled in vacuo or recrystallised from ethyl acetate/petroleum ether (b.p. 40–60°) or petroleum ether (40–60°).

N-Unsubstituted 2-Amino-1,3-oxazoles: These compounds are prepared from cyanamide and an α-hydroxycarbonyl compound as described above but the temperature of the solution is maintained at 20° and the pH adjusted to 10.

Table. 2-Amino-1,3-oxazoles (**3**) from α-Hydroxyaldehydes or -ketones (**1**) and Cyanamides (**2**)[d]

3	R^1	R^2	R^3	Yield [%]	b.p. or m.p.	Brutto formula[a]		b.p. or m.p. of *N*-acetyl derivative
a	H	H	H	40	m.p. 91–94°	$C_3H_4N_2O$	(84.1)	b.p. 89–91°/1 torr
b	CH_3	H	H	78[b]	b.p. 66–67°/0.5 torr	$C_4H_6N_2O$	(98.1)	m.p. 127°
c	CH_3	H	CH_3	65	m.p. 61–63°	$C_5H_8N_2O$	(122.1)	
d	CH_3	H	*i*-C_3H_7	55	m.p. 46–48°	$C_7H_{12}N_2O$	(140.2)	b.p. 56°/0.8 torr
e	CH_3	H	*n*-C_4H_9	85	b.p. 70–72°/0.1 torr	$C_8H_{14}N_2O$	(154.2)	
f	CH_3	H	*sec*-C_4H_9	71	b.p. 68–70°/1.0 torr	$C_8H_{14}N_2O$	(154.2)	b.p. 64°/0.6 torr
g	CH_3	H	*n*-C_6H_{13}	67	b.p. 86–88°/0.03 torr	$C_{10}H_{18}N_2O$	(182.3)	b.p. 90–92°/0.08 torr
h	CH_3	H	$-CH_2-CH=CH_2$	73	b.p. 68°/0.3 torr	$C_7H_{10}N_2O$	(138.2)	b.p. 67°/0.8 torr
i	CH_3	H	$-CH_2-CH_2-OCH_3$	75	b.p. 72–73°/0.7 torr	$C_7H_{12}N_2O$	(156.2)	
j	CH_3	H	$-CH_2-C_6H_5$	78	m.p. 112°	$C_{11}H_{12}N_2O$	(188.2)	
k	CH_3	H	$-CH_2-C_6H_4-Cl$	72	m.p. 110–111°	$C_{11}H_{11}ClN_2O$	(222.7)	
l	CH_3	H	$-CH_2-CH_2-C_6H_5$	43	b.p. 134°/0.7 torr	$C_{12}H_{14}N_2O$	(202.3)	b.p. 122°/0.5 torr
m	$Cl-C_6H_4-$	H	*n*-C_4H_9	58	m.p. 65–67°	$C_{13}H_{15}ClN_2O$	(250.7)	
n	C_2H_5	H	*n*-C_4H_9	73	b.p. 140°/0.5 torr[c]	$C_9H_{16}N_2O$	(168.2)	
o	*c*-C_6H_{11}	H	*n*-C_4H_9	55	m.p. 34–37[c]	$C_{13}H_{22}H_2O$	(222.3)	
p	*i*-C_3H_7	H	*n*-C_4H_9	68	b.p. 130°/0.3 torr[c]	$C_{10}H_{18}N_2O$	(182.3)	
q	C_6H_5	H	*n*-C_4H_9	48	m.p. 52–53[c]	$C_{13}H_{16}N_2O$	(216.3)	
r	CH_3	CH_3	*n*-C_4H_9	90	b.p. 92–94°/0.5 torr[c]	$C_9H_{16}N_2O$	(168.2)	b.p. 89–91°/1.0 torr
s	H	$-CH_2OH$	*n*-C_4H_9	22	m.p. 87–88°	$C_8H_{14}N_2O_2$	(170.1)	
t	$-CH_2OH$	H	*n*-C_4H_9	49	m.p. 59–60°	$C_8H_{14}N_2O_2$	(170.1)	

[a] The elemental analyses were in satisfactory agreement with the calculated values: C, ±0.4%; H, ±0.4%; Cl, ±0.4%; N, ±0.4%.
[b] Ref.[2], 65% yield.
[c] Air-bath temperatures from bulb-to-bulb evaporative distillation.

2-Butylamino-4-hydroxymethyl-1,3-oxazole (3t):

Butylcyanamide: Butanamine (14.6 g, 0.20 mol) is added dropwise to a stirred mixture of cyanogen bromide (21.2 g, 0.20 mol) and anhydrous sodium carbonate (42.4 g, 0.4 mol) in dry ether (150 ml) at −10° to −15°. The mixture is stirred for 2 h at this temperature, allowed to warm to 10°, and filtered. Evaporation of the filtrate without heating gives the cyanamide as a colourless oil; yield: 18.6 g (94%).

2-Butylamino-4-hydroxy-4-hydroxymethyl-4,5-dihydro-1,3-oxazole (**4**; *Hydrate of* **3t**): Butylcyanamide (18.6 g, 0.188 mol) is mixed with a solution of 1,3-dihydroxy-2-propanone dimer (18.0 g, 0.20 mol as monomer) in water (200 ml). The stirred mixture is basified with aqueous 2*N* sodium hydroxide (20 ml) becoming hot despite cooling in ice. The mixture is stirred for 2 h; then, the solid is isolated by filtration and washed with water; yield: 27.1 g (71%); m.p. 116–118° (from ethyl acetate/chloroform).

2-Butylamino-4-hydroxymethyl-1,3-oxazole (**3t**): Compound **4** (27.1 g, 0.144 mol) is suspended in toluene (500 ml) and heated under reflux with a Dean-Stark water trap for 2 h. The brown solution is decanted from a little dark tar, evaporated and the residue is distilled under vacuum; b.p. 126–128°/0.1 torr. The distillate is recrystallised from ethyl acetate/petroleum ether to give colourless crystals; yield: 16.6 g (49%, based on **2**); m.p. 59–60°.

$C_8H_{14}N_2O_2$	calc.	C 56.5	H 8.3	N 16.5
(170.1)	found	56.4	8.2	16.3

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