Thioacetamide catalysed transformation of nitriles to 2-substituted imidazolines

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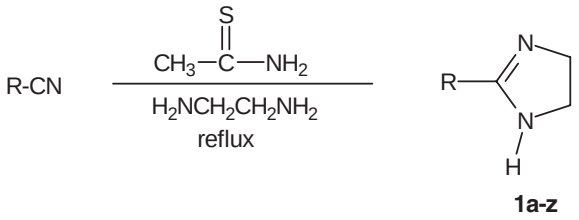
The reaction of various nitriles with ethylenediamine in presence of thioacetamide as catalyst has been studied.

Keywords: 2-imidazoline; tolazoline; naphazoline; cyclocondensation; thioacetamide

The wide biological activities such as anti-histaminic,[1] anti-hyperglycemic,[2] anti-inflammatory,[3] anti-nociceptive,[3] immunomodulating,[3] anti-oxidant,[3] anti-tumour,[3] and anti-cancer activity[3] associated with 2-imidazoline derivatives have stimulated considerable synthetic work on this heterocycle. Moreover 2-imidazolines have also been used as the precursosr for the preparation of 1*H*-imidazoles.[4] Some previous studies suggested the use of esters,[5,6] iminoalkyl ethers,[7] thioamides,[8] *N*-substituted amidines,[9,10] thioesters[11] and *N*-ethyl carboxylate thioesters[12] as the precursors for the preparation of 2-imidazolines. However, all these methods are tedious and/ or require expensive catalysts[5,6] or rather harsh conditions, often giving less than satisfactory conversions. According to other reported procedures, 2-imidazolines have been prepared from the nitriles in the presence of ammonium polysulfide,[13,14] H_2S[15] or P_2S_5.[16,17] We now report the thioacetamide catalysed transformation of various nitriles into 2-imidazolines. Although the reaction[18] of benzyl cyanide with ethylenediamine in the presence of thioacetamide is reported for the synthesis of tolazoline, it has surprisingly not been explored fully for the different substituted nitriles with respect to their position on the phenyl ring, *ortho*, *meta* and *para* position, as well as to their electronic effects.

Towards this end a series of different nitriles were reacted with ethylenediamine in the presence of a catalytic amount of thioacetamide for the formation of the corresponding 2-imidazolines (Scheme 1, Table 1). In the first series, the reaction of substituted benzonitriles was investigated (entries 1–13). The choice of the substituent was made with respect to their position on the phenyl ring, *ortho*, *meta* and *para* position, as well as to their electronic effects. We found



Scheme 1 Reaction of nitriles with ethylene diamine in the presence of thioacetamide.

that the position of the substituent on the phenyl ring does not greatly affect the yield. The benzonitrile with a substituent such as CH_3, OH, $N(CH_3)_2$, $NHCH_3$, OCH_3 (electron donating), Cl and Br (electron withdrawing) underwent smoothly the cyclocondensation to afford the corresponding 2-imidazolines in good yield (entries 1–13). However the reaction is not applicable to the nitriles with dipolar substituents such as NO_2, $OCOCH_3$, $NHCOCH_3$, COOH and $COOCH_3$ (entries 14–18), presumably due to side reactions with nitro and acid/ester/amide groups. Attempts to isolate any pure compound(s) were thwarted by the complex nature of the crude product. In the next series the reaction of substituted benzyl nitriles was investigated (entries 19–26). Here again the choice of the substituent was made with respect to their position on the phenyl ring, *ortho*, *meta* and *para* position and on the methylene group (entry 23), as well as to their electronic effects. However, the same observations were obtained as those, which we observed with the benzonitrile series. In the next series nitriles such as naphthonitriles

Table 1 Reaction of nitriles with ethylenediamine in the presence of thioacetamide

Entry	*R*	M.p.[a] /°C	Yield[b] /%	Entry	*R*	M.p.[a] /°C	Yield[b] /%
1	C_6H_5	100	87	19	$C_6H_5CH_2$	67	86
2	4-$CH_3C_6H_4$	182	88	20	4-$CH_3OC_6H_4CH_2$	120	85
3	4-$CH_3OC_6H_4$	139	84	21	3,4-$(CH_3O)_2C_6H_3CH_2$	78	81
4	4-$H_3CHNC_6H_4$	122	81	22	3,4,5-$(CH_3O)_3C_6H_2CH_2$	76	79
5	4-$(H_3C)_2NC_6H_4$	109	79	23	$C_6H_5CHC_6H_5$	156	77
6	4-HOC_6H_4	> 300	87	24	2-$ClC_6H_4CH_2$	117	82
7	4-BrC_6H_4	198	86	25	4-$(H_3C)_2NC_6H_4CH_2$	100	79
8	4-ClC_6H_4	187	83	26	4-$O_2NCH_2C_6H_4$	–	–
9	3,4-$(CH_3O)_2C_6H_3$	157	80	27	1-Naphthyl	134	84
10	3,4,5-$(CH_3O)_3C_6H_2$	183	82	28	2-Naphthyl	118	81
11	3-$CH_3C_6H_4$	99	87	29	1-Naphthylmethyl	118	83
12	2-ClC_6H_4	Oil	81	30	2-Thienyl	176	87
13	2-OH C_6H_4	208	87	31	3-Pyridyl	104	84
14	4-$O_2NC_6H_4$	–	–	32	3-Indolylmethyl	132	80
15	4-$HO_2CC_6H_4$	–	–	33	8-Quinolylmethyl	92	81
16	4-$H_3CO_2CC_6H_4$	–	–	34	Cyclohexylmethyl	109	85
17	4-$CH_3CONHC_6H_4$	–	–	35	1-Cyclohexenyl	Oil	77
18	4-$CH_3COOC_6H_4$	–	–	36	1-Cyclohexenylmethyl	Oil	75

[a]Melting points are uncorrected.
[b]Yields are unoptimised and refer to purified product.

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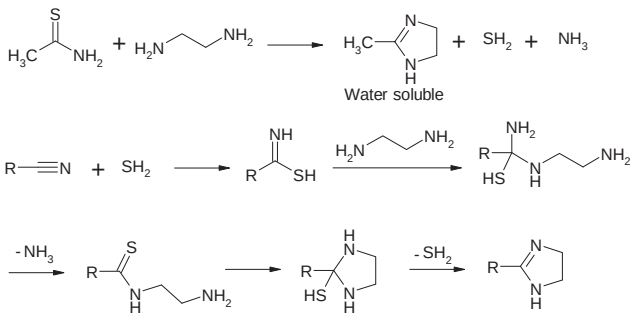

Scheme 2 Thioacetamide catalysed transformation of nitriles to 2-sustituted imidazolines.

(entries 27 and 28), naphthylmethyl nitriles (entry 29), heterocyclic nitriles (entries 30–33) and aliphatic nitriles (entries 34–36) were investigated and the results obtained are shown in the Table 1.

When we analysed the reaction mix of entry 1 on GC, it showed the presence of 2-methyl-2-imidazoline and absence of thioacetamide (based on comparison with the authentic samples). This was not surprising as the conversion of thioamides to 2-sustituted imidazolines is well reported in the literature.[8] Hence, we propose that an initial reaction of thioacetamide with ethylenediamine produces water soluble 2-methyl-2-imidazoline and H_2S, the latter then acts as the actual catalyst[15] for cyclocondensation of nitriles to form imidazolines. A mechanistic pathway for the thioacetamide catalyzed transformation of nitriles to 2-sustituted imidazolines is outlined in the Scheme 2.

In conclusion a series of different nitriles (aromatic, heterocyclic and aliphatic) have been cyclocondensed with ethylenediamine in presence of thioacetamide as a H_2S source to give the corresponding 2-imidazoline in high yield. Unfortunately nitriles with dipolar functional groups such as NO_2, $OCOCH_3$, $NHCOCH_3$, COOH and $COOCH_3$ were not found to be suitable for this transformation.

Experimental

A mixture of nitrile (10 mmole), thioacetamide (1 mmole) in ethylenediamine (7 cm^3) was refluxed with stirring for 3–3.5 h. The reaction mixture was poured onto ice, the solid obtained was filtered, washed thoroughly with water and dried. Where solid was not obtained the aqueous layer was extracted with $CHCl_3$ (4×50 cm^3). The combined $CHCl_3$ extracts were washed with water (3×50 cm^3) and then dried (anhydrous Na_2SO_4). Evaporation of the solvent followed by trituration of the residue obtained with pet. ether (60 : 80) afforded the corresponding analytically pure 2-imidazoline **1** which was then further purified by recrystallisation with acetone and hexane (in case of solid) or column chromatography [alumina, pet. ether:chloroform (80:20)] (in case of oil). All the compounds synthesised gave satisfactory elemental analyses and spectral data consistent with the assigned structures.

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