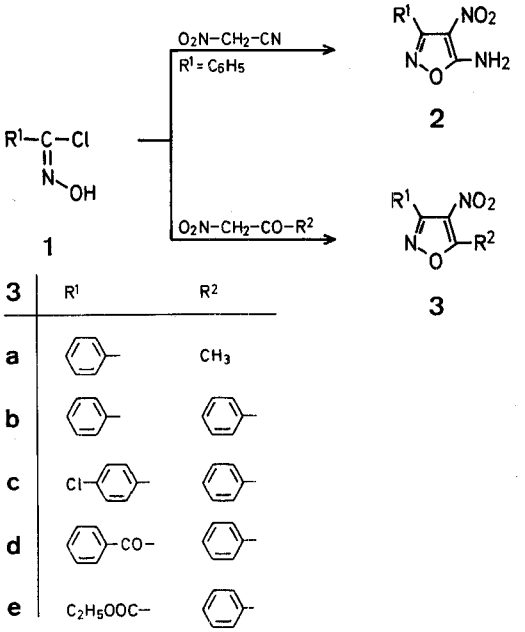
4-Nitro-1,2-oxazoles from Hydroximic Acid Chlorides

Vittorio Dal Piaz, Sergio Pinzauti, Pasquale Lacrimini

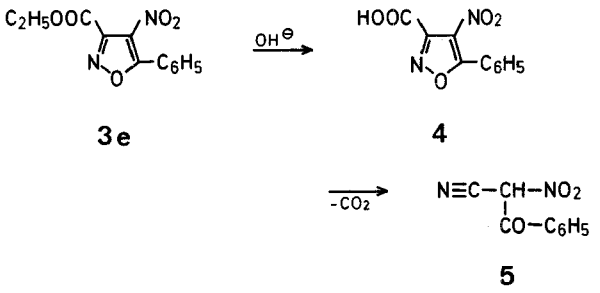
Istituto di Chimica Farmaceutica dell'Università, Via G. Capponi 9, 50121 Firenze, Italy

Direct nitration of the free 4-position in 1,2-oxazoles (isoxazoles) is the method most widely employed to synthesise 4-nitroisoxazoles. The nitration of 5-arylisoxazoles is independent of the reaction medium and occurs only on the phenyl nucleus[1,2]. 3-Arylisoxazoles in sulphuric acid medium are also nitrated on the phenyl nucleus; in acetic anhydride medium the isoxazole ring undergoes the substitution but sometimes other nitro-derivatives are formed as by-products[2,3]. If electron-accepting substituents are present, a complete deactivation of the 4-position takes place and the isoxazole ring cannot be nitrated. Other synthetic methods, i.e. the reaction between unsaturated aldehydes and nitrous gases or the cyclisation of intermediates containing the nitro group, have been reported in a few cases[4].

In order to obtain a new convenient one-step synthesis of 4-nitroisoxazoles, we have investigated the reaction between hydroximic acid chlorides (**1**) and alkyl (aryl) nitromethyl ketones or nitroacetonitrile[5]. When the reaction is carried out in alcoholic medium in presence of triethylamine, the 4-nitroisoxazoles (**2** and **3a–e**) are obtained in good yields. Compound **3b** was also prepared by the reaction between dibenzoylnitromethane[6] and hydroxylamine.



Compounds **3b, c** give the corresponding amines by reduction with amalgamated aluminium. Mild hydrolysis of **3e** yields the carboxylic acid **4**. The previously unknown benzoylnitroacetonitrile (**5**) was obtained as a result of decarboxylation of **4** and subsequent ring opening.



All melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer Infracord 337 using a thin film of nujol mull. Column chromatographic separations were performed with neutral alumina(eluent cycloexane/methyl ethyl ketone 9:1, then 7:3). Analytical results for C,H,N,Cl wer within ±0.3% of the theoretical values. The samples from different experiments were identified by mixture m.p.s and superimposable I.R. spectra.

3-Phenyl-4-nitro-5-methylisoxazole[7] **(3a)**:
Triethylamine (2.95 ml, 0.021 mol) in dry ethanol was added dropwise at 0° to a stirred solution of nitroacetone[8] (2.16 g, 0.021 mol) in dry ethanol. A solution of benzhydroximic acid chloride[9] (**1**, $R^1 = C_6H_5$; 3.26 g, 0.021 mol) was then added dropwise at −10°. After 1 h the mixture was concentrated under reduced pressure, the residue was washed with water and recrystallized from methanol; yield: 72%; m.p. 48°.

3-Phenyl-4-nitro-5-aminoisoxazole[10] **(2)**:
The above described method (0.021 mol scale) was followed using nitroacetonitrile instead of nitroacetone as starting material. Column chromatography afforded **2**; yield: 38%; m.p. 111–113° (from diisopropyl ether).

3,5-Diphenyl-4-nitroisoxazole (3b):
Procedure A: The same method (0.021 mol scale) employing ω-nitroacetophenone[11] and benzhydroximic acid chloride was used; yield: 56%; m.p. 174–176° (from methanol).

Procedure B: Dibenzoylnitromethane and hydroxylamine hydrochloride (0.021 mol scale) were refluxed for 1.5 h in dry ethanol. After cooling the cristalline product was collected and recrystallised from methanol; yield: 65%; m.p. 174–176°.

I.R. (nujol): ν_{max} = 1520 (NO_2), 828 cm^{-1} (C—N).

Reduction of 3,5-Diphenyl-4-nitroisoxazole:
A solution of **3b** (1.25 g) in ether (20 ml) and water (2 ml) was refluxed under nitrogen with an excess of amalgamated aluminium (1.5 g) for 3 h. After filtration the precipitate was washed with ether. Evaporation of the solution gives 3,5-diphenyl-4-aminoisoxazole; yield: 82%; m.p. 123–124° (from light petroleum b.p. 75–120°).

I.R. (nujol): ν_{max} = 3418 and 3350 cm^{-1} (NH_2).

3-(*p*-Chlorophenyl)-4-nitro-5-phenylisoxazole (3c):
From *p*-chlorobenzhydroximic acid chloride[12], ω-nitroacetophenone, and triethylamine (a 0.021 mol scale reaction) in dry methanol: yield: 77%; m.p. 165° (from ethanol).

I.R. (nujol): ν_{max} = 1540 (NO_2), 832 cm^{-1} (C—N).

Reduction of 3-(*p*-Chlorophenyl)-4-nitro-5-phenylisoxazole:
Treatment analogous to that described for **3b** leads to 3-(*p*-chlorophenyl)-4-amino-5-phenylisoxazole; yield: 75%; m.p. 157–158° (from benzene).

I.R. (nujol): ν_{max} = 3418 and 3348 cm^{-1} (NH_2).

3-Benzoyl-4-nitro-5-phenylisoxazole (3d):
From ω-nitroacetophenone, ω-chloroisonitrosoacetophenone[13], and triethylamine (a 0.021 mol scale reaction) in dry ethanol; yield: 53%; m.p. 100–101° (from methanol).

I.R. (nujol): ν_{max} = 1680 (CO), 835 cm^{-1} (C—N).

3-Ethoxycarbonyl-4-nitro-5-phenylisoxazole (3e):
The 0.021 mol scale reaction between ω-nitroacetophenone and ethyl chlorooximinoacetate[14] was carried out as described for **3a–d**. Column chromatography afforded **3e**; yield: 46%; m.p. 42–43° (from light petroleum b.p. 40–70°).

I.R. (nujol): ν_{max} = 1740 (CO), 1530 (NO_2), 1280 (C—O), 815 and 840 cm^{-1} (C—N).

Hydrolysis of 3e:
The ester **3e** (1.2 g) was stirred in aqueous alcoholic sodium hydroxide solution at 10° for 2 h. The mixture was then added dropwise under stirring to a cooled (−10°) solution of concentrated hydrochloric acid. The precipitated carboxylic acid **4** was recrystallised from 6*M* hydrochloric acid (gently heating); yield: 54%; m.p. 126° (decomp.).

I.R. (nujol): ν_{max} = 3300–2500 (OH), 1710 (CO), 1530 (NO_2), 822 cm^{-1} (C—N).

Decarboxylation of 3-Carboxy-4-nitro-5-phenylisoxazole:
Carboxylic acid **4** (0.5 g), heated at 55° in vacuo (0.02 torr), gives the product **5** as a white sublimate; yield: 74%; m.p. 104°.

I.R. (nujol): ν_{max} = 2225 (CN), 1600 (CO), 1550 cm^{-1} (NO_2).

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