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29. ^{15}N Labelling: Potassium Azide, Tetrazoles and Imidazoles

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(30. IV. 75)

Summary. A simplified high-yield preparation of end-labelled potassium azide from $K^{15}NO_3$ is described. Treatment of 4-chloropyrimidines with $K^{15}NN_2$ and subsequent gas-phase pyrolysis gives ring-labelled 1-cyanoimidazoles in 80–100% yields. The cyano-groups in the latter are easily removed by hydrolysis.

^{15}N labelling of *inter alia* heterocyclic compounds is of importance for the elucidation of chemical and biochemical reaction pathways. Such labellings usually require lenghty and/or expensive syntheses. A simple way to introduce ^{15}N-labelled substituents in (hetero)aromatic molecules is *via* nucleophilic substitution with azide ion. Labelled azide is, however, very expensive and not widely distributed.

We now report a simple and inexpensive preparation of end-labelled potassium azide from commercial potassium nitrate, as well as its use in an efficient synthesis of ^{15}N-labelled imidazoles.

1. *Potassium Azide.* End-labelled KN_3 has been prepared by *Clusius & Hürzeler* [1] by the sequence $NaNO_2 \rightarrow C_2H_5ONO \rightarrow KN_3$. The sodium nitrite was obtained by *Clusius & Hoch* [2] by reduction of KNO_3 with mercury. We have adopted these procedures for use with a standard vacuum line, and modified the reaction in such a way that the conversion of KNO_3 to KN_3 is a two-flask operation. The apparatus is shown in Fig. 1, and the procedure is described in detail in the Experimental Part.

Commercial $K^{15}NO_3$ is reduced to ^{15}NO according to *Clusius* [2] in flask A. The ^{15}NO is condensed into the side-arm H of flask G and allowed to react with the required amount of O_2. The $^{15}N_2O_3$ formed is again condensed into the side-arm H. Flask G is then detached, ethanol is added through the mouth K, the content of the side-arm H is allowed to evaporate, the ethyl nitrite formed is condensed back into the side-arm H, and a mixture of hydrazine hydrate and potassium methylate is added through K. Potassium [1-^{15}N]-azide precipitates in a yield up to 77% and a purity of *ca.* 90%. Thus, the major reactions may be written:

$$2\,{}^{15}NO + 1/2\,O_2 \rightleftarrows {}^{15}N_2O_3$$

$${}^{15}N_2O_3 + 2\,C_2H_5OH \longrightarrow 2\,C_2H_5O^{15}NO$$

$$N_2H_4 + KOCH_3 + C_2H_5O^{15}NO \longrightarrow K^{15}NN_2 + CH_3OH + C_2H_5OH + H_2O$$

The yields of subsequent reaction using this azide were usually as good as those obtained in test-runs with commercial unlabelled KN_3.

2. *Imidazoles from pyrimidines.* 4-Chloropyrimidines (**1**) are converted with KN_3 under anhydrous conditions to tetrazolo[1,5-*c*]pyrimidines (**2**). The yields are 80–100%. Gas-phase pyrolysis of the tetrazoles (**2**) yields exclusively ring-labelled

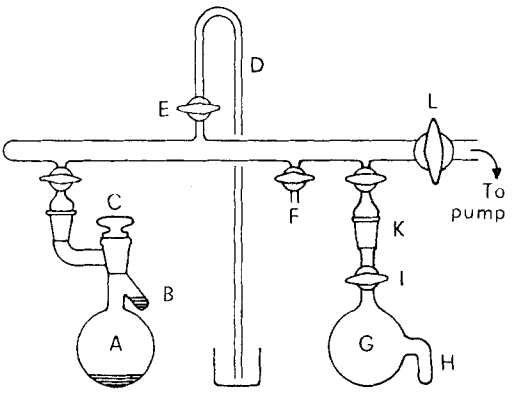
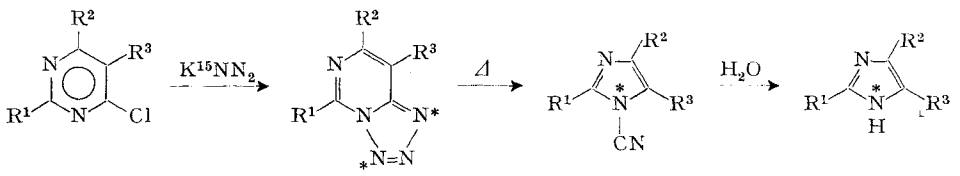


Fig. 1. *Apparatus for production of* $K^{15}NN_2$

1-cyanoimidazoles (**3**) in yields of 99%. The mechanism of this reaction has been described elsewhere [3] [4]. The cyanoimidazoles (**3**) are easily hydrolyzed to imidazoles (**4**).



1 **2** **3** **4**

1–4 **a**: $R^1 = R^2 = CH_3$, $R^3 = H$
b: $R^1 = CH_3S$, $R^2 = CH_3$, $R^3 = H$
c: $R^1 = C_6H_5$, $R^2 - R^3 =$ benzo

This transformation therefore represents a simple two-step ^{15}N-labelling of imidazoles, with an overall yield of 80–100%. The rearrangement **2** → **3** also takes place in solution [4], but the yields are lower.

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Experimental Part

Potassium [1-^{15}N]-azide. – The apparatus (Fig. 1) requires a standard vacuum line and two specially constructed flasks, A and G. The volumes of flask A and G are *ca.* 500 ml for 2 g portions of KNO_3. The volumes of the side-arms B and H are *ca.* 20 and 10 ml, respectively.

2 g KNO_3 and 35.4 g Hg were placed in flask A. 9.3 ml conc. H_2SO_4 was carefully introduced into the arm B. The flask was evacuated, closed, and the content of arm B slowly added by tilting and shaking. After 2 h with occasional shaking flask A was attached to the vacuum line, the pressure of NO measured on the manometer D (C open, I closed), I opened, the NO condensed into H, and I closed. Pure oxygen was introduced through F (C and E open) and an amount corresponding to a quarter of the original NO pressure was admitted into flask G. After closing I, the content of H was allowed to evaporate. The brown gas formed was condensed back into H (blue liquid). The flask was detached, and 2.2 ml ethanol was added through the mouth K by gently opening I. (The ethanol may also be distilled into G *via* the vacuum line.) The content of H was vapourized and the colourless gas formed condensed back into H. A solution of 1.15 g potassium in 7 ml methanol, 14 ml ether, and 1.4 ml hydrazine hydrate was now added through K and I. The content of flask G became warm and colourless. After several hours, the precipitated KN_3 was washed out with methanol/ether, filtered off, washed with methanol/ether, and dried in a desiccator. The yields of several preparations were 67–77%. The purity of the product was 88–94% by titration and IR. spectroscopy. The impurities were potassium nitrite and nitrate according to the IR. spectra.

[1(3)-^{15}N]-5,7-Dimethyltetrazolo[1,5-c]pyrimidine (**2a**). 4-Chloro-2,6-dimethylpyrimidine (297.5 mg; 2.085 mmol) and potassium [1-^{15}N]-azide (50 atom-% ^{15}N; 175.1 mg; 2.15 mmol) were mixed with 20 ml dry dimethylformamide in a 50 ml flask. The flask was stoppered, the stopper secured, and the mixture stirred magnetically at 80° for 22 h. After cooling and filtering, the solvent was distilled *in vacuo*, and the residue recrystallized from petroleum ether/benzene, yielding 250 mg (78% based on $K^{15}NN_2$) of colourless prisms, m.p. 83–84° (lit. [5] 84–85°). The mass spectrum indicated 49.8% of one nitrogen atom as ^{15}N.

[1-^{15}N]-2,4-Dimethylimidazole-1-carbonitrile (**3a**). **2a** (191.3 mg; 1.28 mmol) was pyrolyzed [6] at 375°/0.05 Torr, being sublimed into the pyrolysis tube from a flask at 75° during 1 h. The product was dissolved in dry ether and the solvent evaporated, yielding 153.7 mg (99%) of **3a**, m.p. 63–64° (lit. [6] 63–64°), 24.8 atom-% ^{15}N by mass spectrometry.

[1(3)-^{15}N]-2,4-Dimethylimidazole (**4a**). A mixture of **3a** (1 mmol) and 0.1 N NaOH (10 ml) was allowed to stand for 13 h. The product was isolated after neutralization with 0.1 N HCl, extraction with boiling $CHCl_3$, removal of the solvent, and drying *in vacuo*. The NMR. spectrum was identical with that of authentic 2,4-dimethylimidazole. The mass spectrum indicated 24 atom-% ^{15}N (one nitrogen atom labelled).

5-Phenyltetrazolo[1,5-c]quinazoline. A mixture of 4-chloro-2-phenylquinazoline (**1c**; 3.0 g; 12 mmol) and sodium azide (0.9 g; 14 mmol) in 125 ml absolute ethanol was heated in a closed vessel at 55–60° for 6 h with magnetic stirring, and then at 20° for a further 15 h. After removal of the solvent *in vacuo*, the residue was taken up in dry benzene, filtered off, and the filtrate evaporated. The resulting solid was washed with petroleum ether and recrystallized from methanol, yielding 3.0 g (97%), m.p. 162–163° (Lit. [7] 162–163°).

The labelled compound (**2c**) (90 atom-% ^{15}N) was prepared in a similar manner from **1c** and $K^{15}NN_2$ (yield: *ca.* 80% on a 50 mg scale).

[1-^{15}N]-2-Phenylbenzimidazole-1-carbonitrile (**3c**). **2c** (39 mg; 0.16 mmol; 90 atom-% ^{15}N) was pyrolyzed [6] at 450°/0.001 Torr, being sublimed in at 130–140°. The yield of **3c** was 34.3 mg (99%), m.p. 110° (45 atom-% ^{15}N).

In a similar pyrolysis of unlabelled **2c** (450 mg) the yield of 2-phenylbenzimidazole-1-carbonitrile was 99.9%; m.p. 110° (sharp); subl. 60° (0.001 Torr); very soluble in ether.

$C_{14}H_9N_3$ (219.09) Calc. C 76.7 H 4.14 N 19.18% Found C 76.8 H 4.30 N 19.16%

2-Phenyl-[1(3)-^{15}N]-benzimidazole (**4c**) was obtained in quantitative yield after heating **3c** (30 mg) with 5 ml 1N NaOH at 100° for 3 h. The product, extracted with ethyl acetate, had m.p. 305° (45 atom-% ^{15}N). An unlabelled specimen prepared similarly was identical with an authentic sample [8].

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30. Tetrazoloazines. ^{15}N Nuclear Magnetic Resonance and Infrared Absorption Spectroscopy

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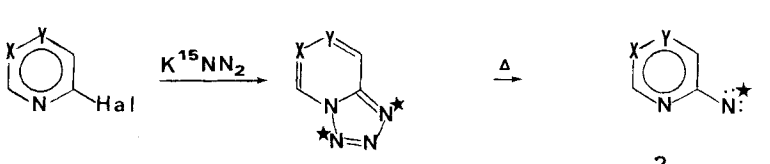
Summary. The reaction of 4-chloro-2-phenylquinazoline with $K^{15}NN_2$ has been studied by ^{15}N-NMR. spectroscopy. ^{15}N-chemical shifts in 5-phenyl-1(3)-[^{15}N]-tetrazolo[1,5-*c*]quinazoline and -$N_\alpha(N_\gamma)$-[^{15}N]-4-azido-2-phenylquinazoline are reported. The characteristic IR. absorption frequencies of the tetrazole group have been determined in a series of annelated ^{15}N-labelled compounds. From these studies and the chemistry of the labelled tetrazoles, it is concluded that all haloazines examined react with KN_3 by the direct nucleophilic substitution mechanism. An addition of nucleophile-ring opening-ring closure (ANRORC) mechanism was not observed. The synthesis of several ^{15}N-labelled tetrazoloazines is described.

The ready availability of ^{15}N-labelled potassium azide [1] has allowed the synthesis of a number of labelled tetrazoloazines with the general formula **1**.



X and Y = CH or N; ★ = $^1/_2$ ^{15}N

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