A Practical Synthesis of 2-Azidophenylisocyanide

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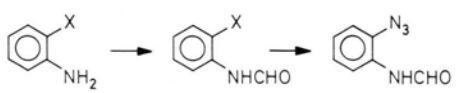
2-Azidophenylisocyanide is useful for the synthesis of β-lactams by four-component-condensation. Its preparation by various methods is compared. The synthesis starting with 2-aminobenzoic acid *via* Hofmann degradation of 2-aminobenzamide is the method of choice.

The four-component-condensation of a carbonyl compound with a β-amino acid and an isocyanide is a method of high synthetic potential for the preparation of β-lactam antibiotics [1]. However, a carbonamide group is formed at the site where a carboxylic acid is found in most β-lactam antibiotics. The cleavability of the amide group under conditions which do not affect the β-lactam, is therefore essential for applications of this technique.

Special isocyanides have been developed [2, 3] which allow the amide/acid conversion *via* *o*-hydroxy or *o*-amino anilides under very mild conditions. Among other isocyanides, 2-azidophenylisocyanide is a highly promising candidate [2]. Up to now, it has been prepared *via* 2-azidoaniline using a six-step procedure starting with 2-nitroaniline [2, 4]. The overall yield varies and does generally not exceed 16%.

We therefore sought for a more viable synthesis of this compound.

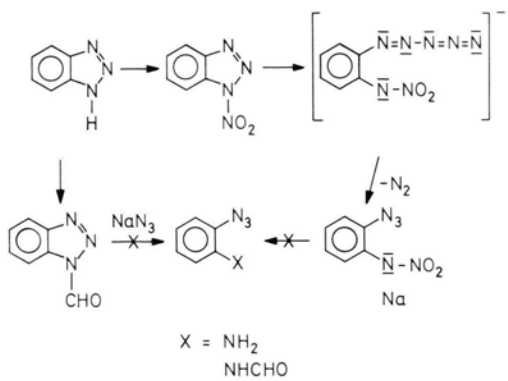
The most straigthforward approach is the nucleophilic replacement of a halogene by azide in a suitable precursor (*e.g.* 2-bromoformanilide), followed by dehydration.



Schema 1

Indeed, we found that under catalysis by CuBr and KI, such a nucleophilic substitution proceeds in DMF or propylene carbonate at 130 °C, but not in other solvents often used for such reactions (HMPA, DMPU, DMSO, N-methylpyrrolidone, tetramethylurea, sulfolane, acetonitrile, 2-methylpyridine). However, the conversions halide azide gave only low yields (about 20%, even in the presence of large excesses of NaN_3), as observed in similar cases [5]. In addition, the separation of product and starting material turned out to be very difficult. This method was therefore abandoned.

Another approach uses benzotriazole as precursor. A facile ring opening of 1-nitrobenzotriazole with secondary amines, leading to imino-diazobenzene derivatives, has been reported [6]. As these reactions proceed *via* diazonium cations, we tried the reaction of substituted benzotriazoles with NaN_3. On mixing 1-nitrobenzotriazole and NaN_3 in the ratio 1:1 in ethanol at room temperature, a gentle evolution of N_2 occurs, indicating the formation of 2-azidonitroaniline salt:



Schema 2

The presence of a azido group is confirmed by IR. However, it was not possible to transform the nitroamino group to the free amine or the formamide. 1-Formylbenzotriazole, which would directly yield 2-azidoformanilide, does not react at all with NaN_3. Obviously, a formyl group is not sufficiently electron withdrawing to promote the ring opening.

Finally, we checked the least expensive precursor, 2-aminobenzoic acid (anthranilic acid). Diazotation and treatment with NaN_3 gives 2-azidobenzoic acid in 84% yield. This acid is converted *via* mixed anhydride to its amide which – without isolation – is treated with aqueous NaOBr. The product of a normal Hofmann degradation, 2-azidoaniline, is isolated in 45–49% yield. Formylation by mixed formic acid/

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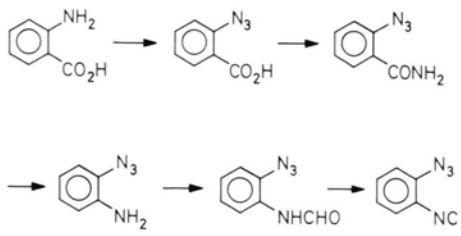
acetic acid anhydride, followed by dehydration with $POCl_3$, gives about 70% 2-azidophenylisocyanide.



Schema 3

The overall yield of this four-step procedure, based on anthranilic acid, is 25–31%, which compares favourably with previous results [2].

Experimental

2-Aminobenzoic acid is diazotised [7] and treated with aqueous NaN_3 according to a known procedure [8]; yield of 2-azidobenzoic acid: 84% (lit. [8]: 75%).

2-Azidoaniline

To a solution of 60.0 g (0.37 mol) 2-azidobenzoic acid and 37.4 g (0.37 mol) triethylamine in 300 ml dichloromethane, 40.1 g (0.37 mol) of ethyl chloroformate are added dropwise with stirring at 0 °C. Stirring at this temperature is continued for 2 h. Dry gaseous ammonia is introduced into the mixture at a slow rate until saturation (about 10 h). After evaporation of the solvent, the residue is treated at 0 °C with 0.44 mol of a freshly prepared solution of NaOBr in 850 ml of water. Stirring at room temperature for 6 h and heating to 60 °C for 30 min completes the Hofmann degradation. After cooling to room temperature, the mixture is extracted with ether (three times 700 ml). Evaporation of the ether gives crude 2-azidoaniline which is recrystallised from methanol/water 1:20. Yield: 22.3–24.3 g (45–49%), m.p. 60–62 °C (lit. [9]: 62 °C).

2-Azidophenylisocyanide

2-Azidoaniline is converted to its formamide by the mixed anhydride method [10], yield: 84–90%, m.p. 119–120 °C. The isocyanide is prepared from the formamide by dehydration with $POCl_3$/KO*t*Bu [2] or $POCl_3$/HN*i*Pr_2 [11], yield: 80–83%.

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