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Synthesis of 2-aryl-imidazo[4,5-*d*][1,2,3]triazoles from a 4-nitro-imidazol-5-yl phosphoramidate and aryl isocyanates

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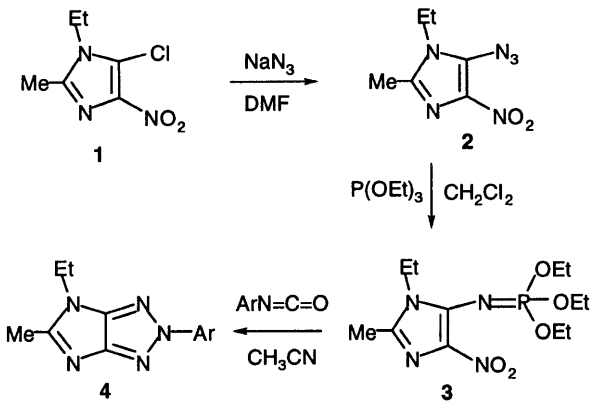
Abstract

The synthesis of a series of 2-aryl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazoles is reported. These compounds are obtained in moderate to good yield by reaction of triethyl *N*-1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl phosphoramidate with aryl isocyanates.

As part of our continuing investigations into new heterocyclisation reactions,[1] we have been investigating reactions of iminophosphorane and phosphoramidate compounds for the construction of nitrogen containing rings. In this paper we report our initial studies on the reactivity of triethyl *N*-4-nitroimidazol-5-yl phosphoramidate **3** towards aryl isocyanates (Scheme 1). Iminophosphoranes and related phosphoramidates are useful reagents in heterocyclic synthesis[2] and are widely used in aza-Wittig reactions[3] with carbonyl compounds to form carbon–nitrogen double bonds. Reaction with isocyanates has been used to synthesise carbodiimides;[4] the



Scheme 1.

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resulting heterocumulene frequently being designed to react further in a tandem cyclisation process to generate a new heterocyclic ring. We were interested in synthesising heterocyclic carbodiimides with an adjacent nitro substituent to investigate the possibility of intramolecular cyclisation between the carbodiimide and nitro groups. Such a cyclisation could be employed to generate triazole or triazene rings. Nitro compounds are known to react with carbodiimides and other heterocumulenes.[5] Rees has demonstrated[6] that the thermolysis of phenyl 2-nitrophenylcarbodiimide leads to formation of phenyl benzotriazole. In this paper we report a new route for the preparation of a number of aryl substituted imidazo[4,5-*d*][1,2,3]triazoles.

The required 4-nitroimidazol-5-yl phosphoramidate **3** was easily prepared by reaction of the azide **2** with triethyl phosphite (Scheme 1). The reaction proceeded smoothly in dichloromethane at room temperature to form the phosphoramidate **3** in high yield. The azide **2** was in turn readily prepared in high yield by treatment of the corresponding chloro compound[7] **1** with sodium azide in dimethylformamide. The nitro compound **3** was obtained as a yellow oil and had analytical and spectroscopic properties fully in accord with the phosphoramidate structure. The phosphoramidate **3** is a stable compound and shows no tendency to undergo rearrangement to the corresponding *N*-ethyl phosphoramidate.

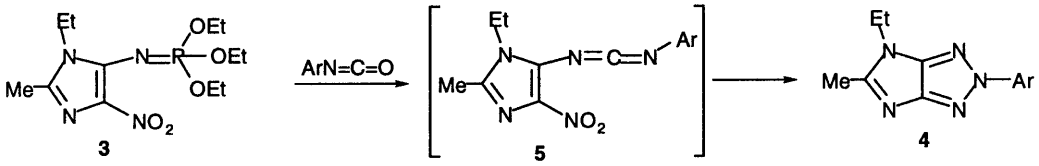
On heating the phosphoramidate **3** with phenyl isocyanate in acetonitrile at 60°C rapid consumption of the phosphoramidate occurred, and the fused imidazo[4,5-*d*][1,2,3]triazole **4a** (Scheme 1) was isolated as a crystalline solid in good yield, simply by evaporating the solvent and triturating with ethanol to remove the triethyl phosphate formed. Acetonitrile was also the most effective solvent for carrying out the reaction with a range of other aryl isocyanates, with the 5-aryl imidazotriazoles **4b**–**h** being formed in moderate to good yield as the only identifiable product in each case (Table 1). Work-up again simply involved trituration and chromatography was not required. The triethyl phosphoramidate reagent thus has the advantage over the corresponding triphenyl iminophosphoranes often used in aza-Wittig reactions, where the triphenylphosphine oxide by-product formed usually requires removal by chromatography. The structures of the triazole products were supported by NMR spectroscopy and mass spectrometric and analytical data.† There has been little synthetic work[8,9] on the construction of imidazo[4,5-*d*][1,2,3]triazole derivatives, and there are no general methods available for the synthesis of this ring system. The route described in this paper now allows preparation of compounds with aryl substituents on the triazole ring.

Table 1
Imidazo[4,5-*d*][1,2,3]triazoles **4a**–**h** prepared from **3**

4	Ar	Yield(%)
a	Ph	63
b	4-MeO–C_6H_4	64
c	4-CF_3–C_6H_4	66
d	4-O_2N–C_6H_4	79
e	4-EtO_2C–C_6H_4	62
f	4-F–C_6H_4	62
g	2,4,6-$Me_3C_6H_2$	57
h	3-NC–C_6H_4	61

† The location of the aryl substituent on the central nitrogen of the [1,2,3]triazole ring has been confirmed by X-ray crystallography. Full structural assignment will be reported in due course.

The formation of the fused triazole rings in this reaction indicates a complex reaction pathway, and one possible mechanism to account for their formation involves initial aza-Wittig reaction to generate the carbodiimide **5** (Scheme 2). At the temperature of the reaction, this compound immediately undergoes further reaction by intramolecular reaction with an adjacent nitro group. A series of ring opening and ring closure reactions analogous to those proposed by Rees[6] then leads to formation of the [1,2,3]triazole ring with extrusion of carbon dioxide. We have not yet been able to isolate a carbodiimide of the type **5** by conducting the reaction at lower temperature, and are currently trying to synthesise one by alternative methods to study if it can be independently converted into the triazole **4**. Further studies on the mechanism of this reaction will be reported in due course.



Scheme 2.

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