Aspects of heterocyclisation reactions mediated by nucleophilic interaction of aromatic nitro groups with ortho heterocumulene side chains

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Dedicated to Douglas Lloyd on the occasion of his 80th birthday

Abstract

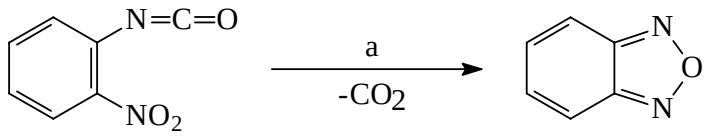
Evidence is presented for the involvement of ketene intermediates in the thermal transformations of ethyl 4-nitro-1*H*-imidazol-5-ylethanoates into 4*H*-imidazo[4,5-*c*]isoxazole derivatives. Direct heterocyclisation of a 1-(4-nitro-1*H*-imidazol-5-yl)-3-phenylcarbodiimide intermediate is proposed to account for the reaction of a triphenyl *N*-(4-nitro-1*H*-imidazol-5-yl)phosphinimine with phenyl isocyanate exemplifying a new, flexible, and potentially general route to 2-aryl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazoles.

Keywords: Heterocyclisation, thermal transformations, ketene, ethyl 4-nitro-1*H*-imidazol-5-ylethanoates, 4*H*-imidazo[4,5-c]isoxazoles

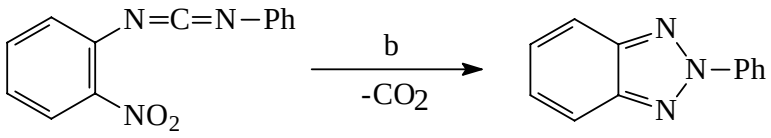
Introduction

Direct interaction of the nitro substituent with electron-rich and electron-poor side-chains in *ortho*-substituted nitroaromatic and nitroheteroaromatic compounds is a well documented[1-3] and fruitful source of novel heterocyclisation reactions. However, among such processes, heterocyclisations initiated by the nucleophilic interaction of aromatic/heteroaromatic nitro groups with *ortho* heterocumulene substituents are relatively rare. Seminal examples include (Scheme 1), the thermolysis[4] of 2-nitrophenyl isocyanate **1** to benzofurazan **2,** and the deep-seated thermal conversion[5] of 1-(2-nitrophenyl)-3-phenylcarbodiimide **3** into 2-phenyl-2H-benzo-1,2,3-triazole **4**. More recent examples, believed to involve nitro-group *ortho*-ketene side-chain interaction, are embodied in efficient methodology for the construction of annelated 2,1-

isoxazole structures valuable as building blocks in heterocyclic synthesis. The synthetic utility and potential general scope of such heterocyclisations are exemplified (Scheme 2) by the efficient solution phase pyrolytic transformations[6,7] of 4-nitro-1H-imidazol-5-ylethanoates **5,** and 3-nitropyridinyl- and 5-nitropyrimidinyl-ethanoates **8** into the respective 3,4-fused isoxazoles **7** and **10**, plausibly through the intermediacy of ketene intermediates **6** and **9**. We now present evidence for the involvement of ketene intermediates **6** in a transformation of the type **5** → **7.** We also describe the first example of a new version of the nitro-group *ortho*-carbodiimide type cyclisation **3** → **4**.



1 **2**



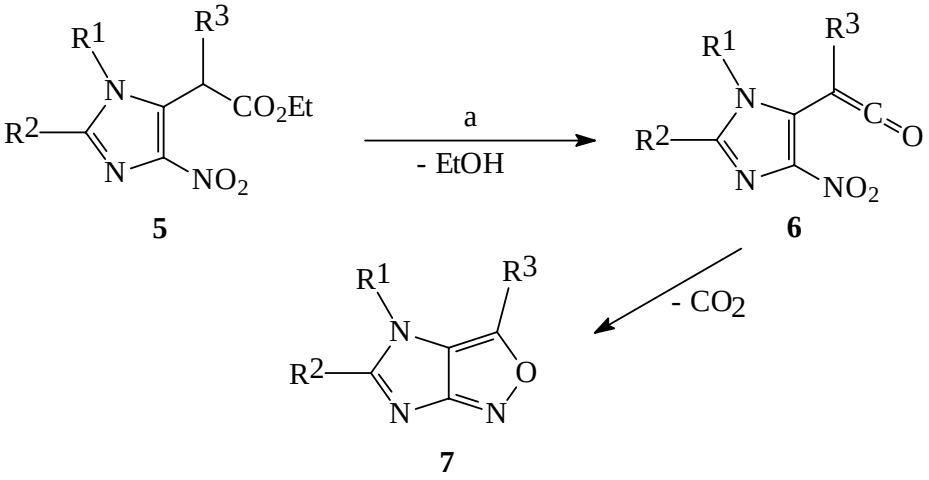
3 **4**

Scheme 1. (a) 255°C; (b) bromobenzene, heat.

Results and Discussion

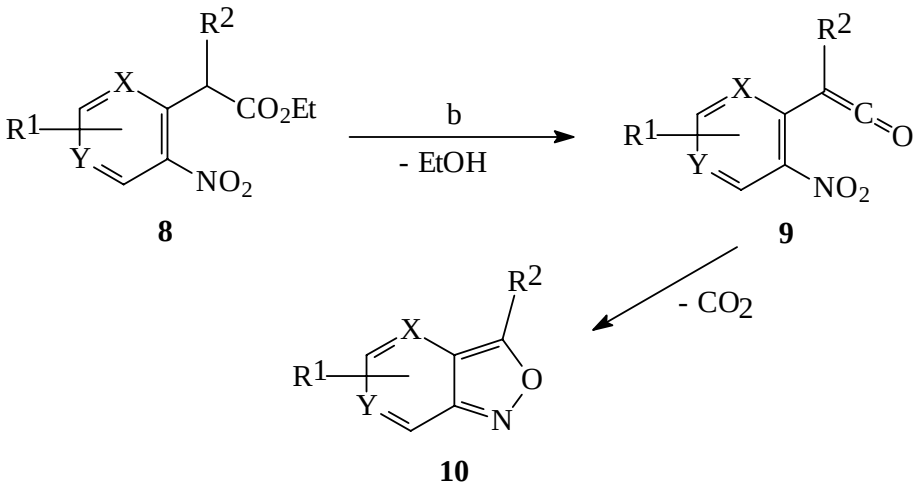
Thermal processes of the type **5** → → **7** can be rationalised by a general mechanism outlined (Scheme 3) for the specific case[6] of the nitroimidazolylmalonate derivative **13.**

Initial thermal elimination of ethanol to give the ketene intermediate **15** is followed by nucleophilic interaction of the nitro group with the *ortho* ketene side-chain affording the cyclic intermediate **17**. Subsequent extrusion of carbon dioxide then leads to the *ortho*-nitroso carbene intermediate **18,** electrocyclisation of which accounts for the formation of the imidazoisoxazole product **19**. The involvement of the ketene intermediate **15** in the transformation **13** → → **19** is now supported by its *in situ* generation by a rational alternative route (Scheme 3) which also leads to the imidazoisoxazole derivative **19** in good yield.



5 **6** **7**

[R^1 = Me, Et; R^2 = H, Me; R^3 = COMe, COPh, CO_2Et, $CONH_2$, CN]

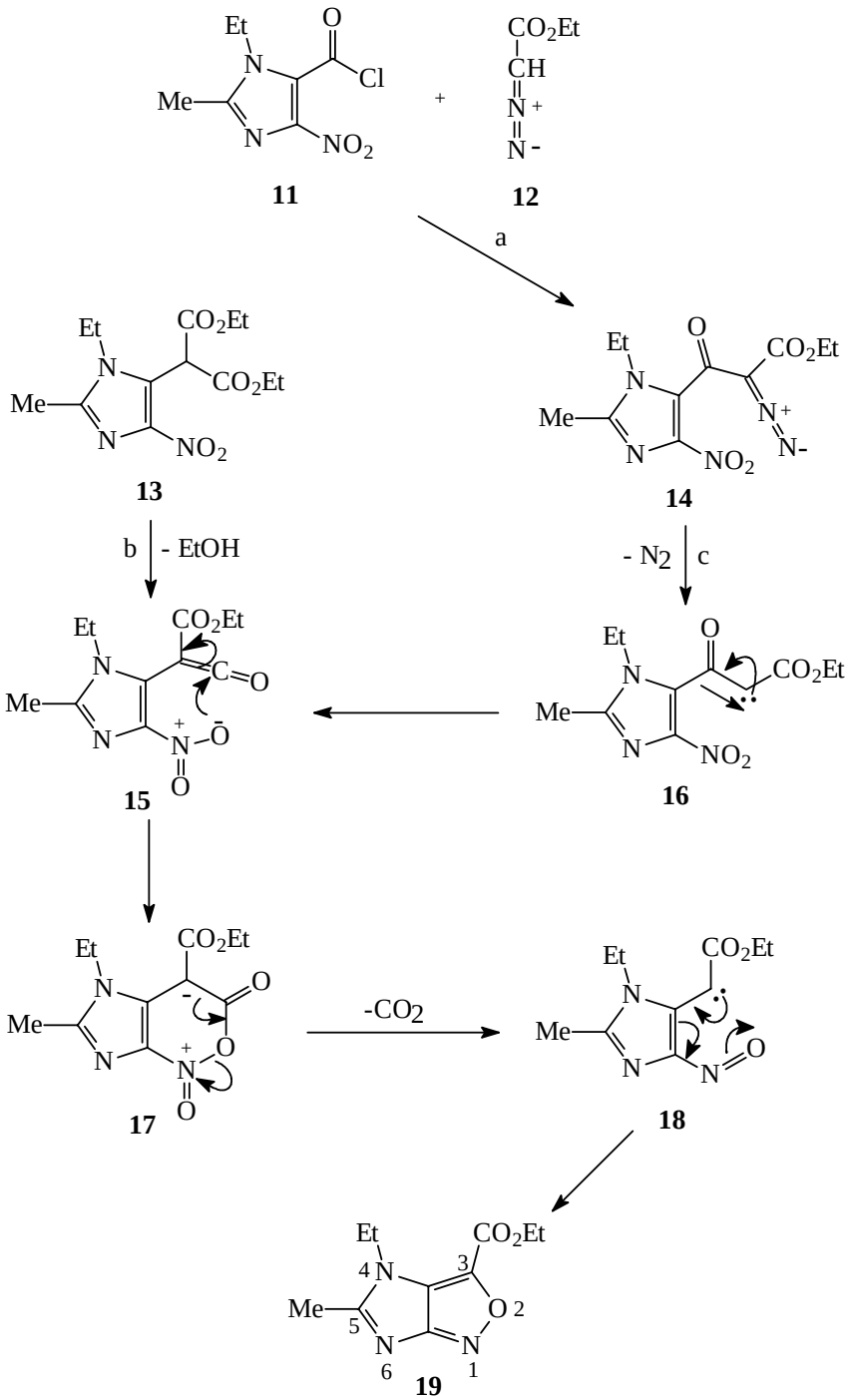


8 **9** **10**

[X = CH, N; Y = CH, N]

[R^1 = Me_2N, MeO; R^2 = CO_2Et, CO_2Me, CO_2Bu^t, CO_2CH_2Ph, COMe, COPh, CN]

Scheme 2. (a) toluene, reflux, 23 h; (b) xylene, 5 Å molecular sieves, reflux, 24 h.



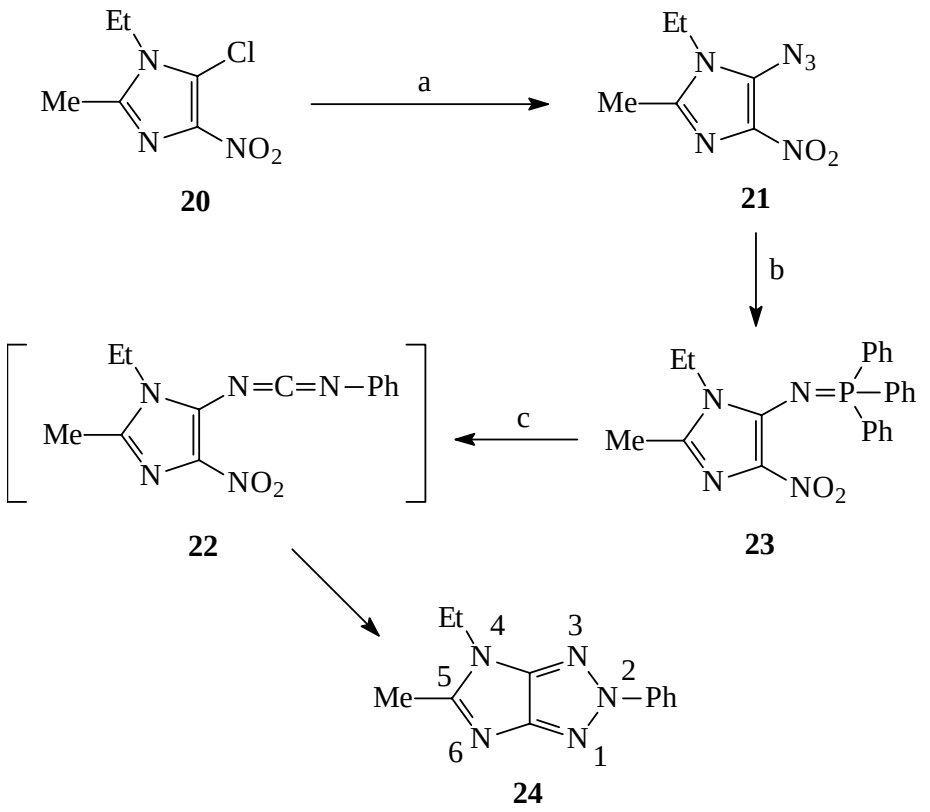
Scheme 3. (a) 10 ^{o}C, 10 min then 50 ^{o}C, 24 h; (b) toluene, reflux, 23 h; (c) toluene, reflux, 5 h.

It was anticipated that formation of the ketene derivative **15** would be the outcome of the spontaneous rearrangement[8] of the acyl carbene **16** generated by thermolysis of the diazo-keto-ester **14**. In practice, the previously undescribed diazo derivative **14** was obtained in excellent yield by condensation of the known[9] nitroimidazole carbonyl chloride **11** with

the readily accessible[10] ethyl 2-diazoethanoate **12** using conditions described by Kimura and his coworkers.[11] Heating the diazo-keto-ester **14** under reflux in toluene resulted in its smooth conversion in good yield into the expected imidazoisoxazole derivative **19.** This result provides compelling evidence for the intermediacy of the ketene derivative **15** in the thermal transformation of the nitroimidazolylmalonate derivative **13** into the imidazoisoxazole **19** and hence supports the general mechanism postulated (Scheme 3) for this type of transformation.

In connection with investigations[12, 13] of the synthesis of hetaryl-fused imidazoles as potential adenosine antagonists, a route (Scheme 4) was required to 1-aryl-3-(4-nitro-1H-imidazol-5-yl)carbodiimides, such as **22**, as key starting materials for the synthesis of imidazo[4,5-*b*]pyrazine derivatives. It was anticipated that the well established[14, 15] reaction of azides with trisubstitued phosphines to give the corresponding phosphinimines and the propensity of the latter to undergo Staudinger (aza-Wittig) reaction with isocyanates to afford carbodiimides[16-18] would provide ready access to the required 1-aryl-3-(4-nitro-1H-imidazol-5-yl)carbodiimides such as **22**.

The previously unknown 5-azido-4-nitro-1H-imidazole **21** required as starting material for the particular synthesis of the carbodiimide derivative **22** was readily obtained in excellent yield by reaction of the known[19, 20] chloronitroimidazole **20** with sodium azide in dimethylformamide. Reaction of the azide **21** with triphenylphosphine proceeded smoothly in 1,2-dimethoxyethane, initially at room temperature then at 60°C, affording the previously undescribed phosphinimine **23** again in high yield. However, reaction of the phosphinimine **23** with phenyl isocyanate in acetonitrile at 60°C gave not the expected carbodiimide **22**, but rather an essentially quantitative yield of an oxygen-free product whose elemental analysis was consistent with the molecular formula $C_{12}H_{13}N_5$. The spectroscopic properties of this product are consistent with its formulation as the 2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole derivative **24** and this structure was firmly established by X-ray diffraction which gave the crystal structure shown in Figure 1. In particular this confirms unambiguously the *N*(2)-position for the phenyl substituent which in turn highlights the extensive molecular rearrangement involved in the reaction of the phosphinimine **23** with phenyl isocyanate which plausibly occurs through the intermediacy of the carbodiimide derivative **22**. On this assumption the formation of the imidazotriazole derivative **24** from the phosphinimine **23** and phenyl isocyanate involves a new version[21] of the thermal heterocyclisation reaction of 1-(2-nitrophenyl)-3-phenylcarbodiimide **3** to 2-phenyl-2*H*-1,2,3-benzotriazole **4** originally reported by Rees and his coworkers.[5] These authors account for the formation of the benzotriazole product **4** through a challenging series of electrocyclic ring-closure/ring-opening reactions. However, the revelation of the detailed mechanism of deep-seated transformations of the types **3** $\rightarrow$ **4** and **23** $\rightarrow \rightarrow$ **24** awaits the outcome of further investigation.



Scheme 4. (a) NaN_3, DMF, room temp, 17 h; (b) Ph_3P, DME, room temp, 30 min then 60°C, 1 h; (c) PhN=C=O, MeCN, 60°C, 6 h.

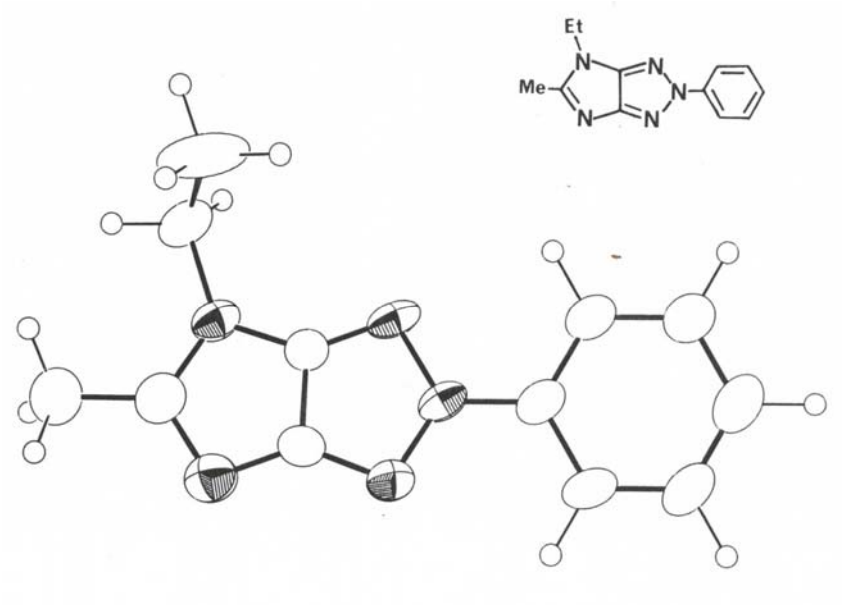


Figure 1

Experimental Section

General Procedures. Infrared spectra were recorded using Perkin-Elmer 298 or Bio-Rad FTS-7 spectrophotometers as nujol mulls. ^{1}H NMR spectra were recorded at 80 or 200 MHz on Bruker WP-80SY and WP-200SY instruments. Electron Impact (EI) mass spectra were recorded at 70 eV on AEI MS-902 and Kratos MS-50TC instruments. X-ray diffraction data were collected using a Stoe-Stadi-4 four circle diffractometer. Microanalyses were carried out using Carlo-Erba Strumentazione 1106 or Perkin-Elmer 2400 elemental analysers. Mps were determined using a Kofler hot stage and are uncorrected.

Materials. All reagents were laboratory grade unless specified. Solvents were of technical grade unless otherwise stated. Dimethylformamide was purified by distillation and stored over molecular sieves. Organic extracts were dried over anhydrous sodium or magnesium sulfate prior to filtration and rotary evaporation under reduced pressure. Wet column flash chromatography was carried out over silica (Merck 9385 or Fluka Kieselgel GF_{254}) and thin layer chromatography was carried out on Polygram SIL G/UV_{254} precoated plastic sheets.

Ethyl 2-diazoethanoate **12**, 1-ethyl-2-methyl-4-nitro-1H-imidazole-5-carbonyl chloride **11**, and 5-chloro-1-ethyl-2-methyl-4-nitro-1H-imidazole **20**, were prepared according to literature procedures.[9, 10, 19, 20]

Ethyl 2-diazo-3-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)-3-oxopropanoate (14). A mixture of 1-ethyl-2-methyl-4-nitro-1H-imidazole-5-carbonyl chloride **11** (2.3 g, 0.01 mol) and ethyl 2-diazoethanoate **12** (2.2 g, 0.02 mol) was stirred at 10 ^{o}C for 10 min then heated at 50 ^{o}C (oil bath) for 24 h. The mixture was rotary evaporated under high vacuum (oil pump) at room temperature and the residual orange oil flash-chromatographed over silica. Elution with hexane-ethyl acetate (4:1) then hexane-ethyl acetate (1:1) successively afforded unreacted ethyl 2-diazoethanoate **12** (0.34 g, 15%) as a yellow oil, identical [IR spectrum and TLC in hexane-ethyl acetate (1:1) over silica] to an authentic sample, and ethyl 2-diazo-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)-3-oxopropanoate **14** (1.8 g, 62%), which formed cream crystals, mp 69-71 ^{o}C (from cyclohexane-ethyl acetate); ν_{max} 2155 ($C=N^+=N^-$), 1725 and 1604 (CO), and 1515 and 1334 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 4.13 (2H, q, J = 7, CH_2), 3.90 (2H, q, J = 7, CH_2), 2.41 (3H, s, CH_3), 1.31 (3H, t, J = 7, CH_3), and 1.15 (3H, t, J = 7, CH_3); (Found: C, 44.6; H, 4.5; N, 23.3%; m/z (EIMS) 295 (M^+), $C_{11}H_{13}N_5O_5$ requires: C, 44.7; H, 4.4; N, 23.7%; M, 295).

Ethyl 4-ethyl-5-methyl-4*H*-imidazo[4,5-*c*]isoxazole-3-carboxylate (19). A solution of ethyl 2-diazo-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)-3-oxopropanoate **14** (1.2 g, 0.004 mol) in anhydrous toluene (20.0 mL) was stirred and heated under reflux with the exclusion of atmospheric moisture for 5 h. Rotary evaporation gave a brown gum which was flash-chromatographed over silica eluting with hexane-ethyl acetate (3:2) to afford ethyl 4-ethyl-5-methyl-4H-imidazo[4,5-*c*]isoxazole-3-carboxylate **19** (0.53 g, 60%) as colourless plates, mp 113-115 ^{o}C (from ethyl acetate) (lit.,[6] 113-115 ^{o}C); ν_{max} 1728 (CO) cm^{-1}; δ_H ($CDCl_3$) 4.43 (2H, q, J = 7, CH_2), 4.18 (2H, q, J = 7, CH_2), 2.53 (3H, s, CH_3), 1.41 (3H, t, J = 7, CH_3), and 1.36 (3H,

t, *J* = 7, CH_3); (Found: C, 53.9; H, 5.8; N, 18.9%; m/z (EIMS) 223 (M^+), Calc. for $C_{10}H_{13}N_3O_3$: C, 53.8; H, 5.8; N, 18.8%; M, 223).

5-Azido-1-ethyl-2-methyl-4-nitro-1*H*-imidazole (21). Sodium azide (1.3 g, 0.02 mol) was added to a solution of 5-chloro-1-ethyl-2-methyl-4-nitro-1H-imidazole **20** (3.8 g, 0.02 mol) in anhydrous dimethylformamide (25.0 mL) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 17 h. The mixture was rotary evaporated and the residue was treated with water (20.0 mL) and the insoluble solid collected to afford the azide **21** (3.9 g, 99%), which formed pale orange needles, mp 72-73 ^oC (decomp) (from tetrachloromethane); ν_{max} 2150 (N_3) and 1550 and 1360 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 3.85 (2H, q, *J* = 7, CH_2), 2.35 (3H, s, CH_3), and 1.30 (3H, t, *J* = 7, CH_3); (Found: C, 36.3; H, 4.0; N, 41.9%; m/z (HREIMS) 196.0719 (M^+), $C_6H_8N_6O_2$ requires: C, 36.7; H, 4.1; N, 42.9%; M, 196.0709).

Triphenyl *N*-(1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl)phosphinimine (23). A solution of the azide **21** (0.78 g, 0.004 mol) in anhydrous 1,2-dimethoxyethane (10.0 mL) was stirred and treated at room temperature with a solution of triphenylphosphine (1.0 g, 0.004 mol) in anhydrous 1,2-dimethoxyethane (5.0 mL) and the mixture was stirred at room temperature for 30 min, then heated at 60 ^oC (oil bath) for 1 h. Filtration afforded the phosphinimine **23** (1.6 g, 92%), which formed bright yellow blades, mp 240-242 ^oC (from ethanol); ν_{max} 1585 and 1340 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 7.78-7.32 (15H, m, ArH), 3.94 (2H, q, *J* = 7, CH_2), 2.29 (3H, s, CH_3), and 1.28 (3H, t, *J* = 7, CH_3); (Found: C, 66.9; H, 5.4; N, 13.0%; m/z (EIMS) 430 (M^+), $C_{24}H_{23}N_4O_2P$ requires: C, 67.0; H, 5.4; N, 13.0%; M, 430).

2-Phenyl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazole (24). A solution of the phosphinimine **23** (0.86 g, 0.002 mol) in anhydrous acetonitrile (30.0 mL) was stirred and treated at room temperature with a solution of phenyl isocyanate (0.24 g, 0.002 mol) in anhydrous acetonitrile (5.0 mL) and the mixture was then stirred and heated at 60 ^oC (oil bath) for
6 h. Rotary evaporation gave a brown solid which was flash-chromatographed over silica eluting with dichloromethane-ethyl acetate (9:1) to afford 4-ethyl-5-methyl-2-phenyl-2H, 4H-imidazo[4,5-*d*][1,2,3]triazole **24** (0.45 g, 99%) which formed colourless rhombs, mp 140-141 ^oC (from ethanol); ν_{max} 1605 (C=N) cm^{-1}; δ_H ($CDCl_3$) 8.12-8.00 (2H, m, ArH), 7.51-7.22 (3H, m, ArH), 4.07 (2H, q, *J* = 7, CH_2), 2.55 (3H, s, CH_3), and 1.53 (3H, t, *J* = 7, CH_3); (Found: C, 63.5; H, 5.4; N, 30.9%; m/z (EIMS) 227 (M^+), $C_{12}H_{13}N_5$ requires: C, 63.4; H, 5.7; N, 30.8%; M, 227).

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References and Notes

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