HETEROCYCLES, Vol. 31, No. 12, 1990

SYNTHESIS OF 1,4,5-TRISUBSTITUTED IMIDAZOLES

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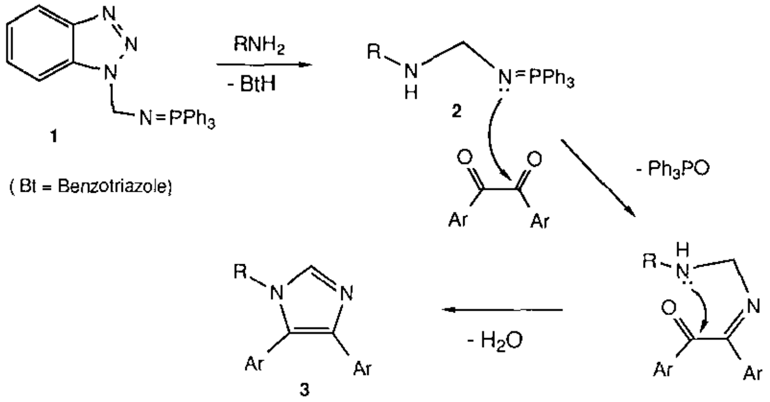
Abstract - 1-Substituted 4,5-diarylimidazoles are prepared in high yields by the reaction of 1-(benzotriazol-1-yl)-*N*-triphenylphosphorylidenemethylamine with primary amines and the treatment of the resulting intermediates with α-diaryl ketones.

Betmip [1-(benzotriazol-1-yl)-*N*-triphenylphosphorylidenemethylamine] (1) is a new synthon of considerable utility. In previous communications we have demonstrated the usefulness of Betmip in a novel synthesis of primary amines,[1] and in the preparation of carbodimides, imines, isothiocyanates, aziridines and secondary amines.[2] The present paper is concerned with the application of Betmip to the synthesis of 1-substituted 4,5-diarylimidazoles from primary amines and α-diketones.

Substituted imidazoles, many of which play important roles in biologically significant processes, have been prepared by a variety of synthetic methods.[3] Although most substitution patterns can be realized by these methods, few simple, straightforward routes to 1,4,5-trisubstituted imidazoles have been reported. Such imidazoles have been synthesized by novel cycloadditions, exemplified by reactions of TosMIC derivatives, tosylbenzyl isocyanide and α-tosylbenzyl isocyanide with aldimines,[4] and by the dimerization of *N*-methyl-*C*-phenylnitrone in the presence of potassium cyanide to give 1-methyl-4,5-diphenylimidazole.[5]

Many methods of imidazole synthesis, such as the classical Radziszewski reaction, involve the use of α-functionalized carbonyl compounds such as α-diketones and ammonia with or without added aldehyde.[6] Formamide is a convenient substitute for ammonia, and in the presence of formic acid 4,5-disubstituted imidazoles are formed[7] from diaryl ketones, although ketones possessing α-hydrogens undergo self-condensation reactions.

We have shown that the Betmip molecule undergoes displacement of benzotriazole by primary amines and the resulting intermediates (**2**), on treatment with α-diaryl ketones, give 1,4,5-trisubstituted imidazoles (**3**) in good yields (see Table 1). The reaction can be carried out in one pot, without isolation of **2**, and the work up and isolation procedures are straight-forward. The use of various primary aliphatic amines, Betmip, and α-diketones such as benzil and phenanthrenequinone gave good results, and the reaction was successfully extended to include 4-dimethylaminoaniline. The activation by the strongly electron donating dimethylamino group was essential. Use of the less nucleophilic *p*-toluidine, with Betmip and phenanthrenequinone, resulted in the isolation of the known phenanthro[9,10]oxazole,[8] without incorporation of the amine moiety.



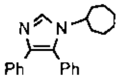
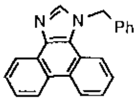
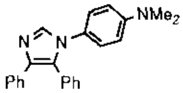
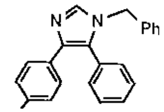
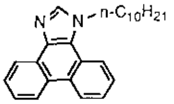
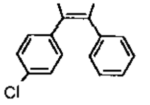
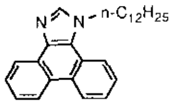
	Amine α-Diketone	Imidazole 3		Amine α-Diketone	Imidazole 3
a	Cycloheptylamine Benzil		**e**	Benzylamine 9,10-Phenanthrenequinone	
b	4-Dimethylaminoaniline Benzil				
c	Benzylamine 4-Chlorobenzil		**f**	Decylamine 9,10-Phenanthrenequinone	
d	Dodecylamine 4-Chlorobenzil		**g**	Dodecylamine 9,10-Phenanthrenequinone	

Table 1 Preparation of 1,4,5-Trisubstituted Imidazoles **3**

No	Yield (%)	Molecular Formula	mp (°C)	C(%)	H(%)	N(%)
				Required	(Found)	
3a	81	$C_{22}H_{24}N_2$	132.0-133.5	83.50 (83.50)	7.64 (7.68)	8.85 (8.74)
3b	84	$C_{23}H_{21}N_3$	177.5-179.5	81.39 (81.43)	6.24 (6.24)	12.38 (12.49)
3c	55	$C_{22}H_{17}N_2Cl$	144.0-147.0	76.63 (76.83)	4.97 (4.94)	8.12 (8.00)
3d	53	$C_{27}H_{35}N_2Cl$	183.0-185.0	76.66 (76.30)	8.34 (8.39)	6.62 (6.47)
3e	79	$C_{22}H_{16}N_2$	218.0-220.0	85.69 (85.55)	5.23 (5.29)	9.08 (8.90)
3f	72	$C_{25}H_{30}N_2$	73.5-75.0	83.75 (83.35)	8.43 (8.63)	7.81 (7.60)
3g	75	$C_{27}H_{34}N_2$	75.0-77.0	83.89 (83.47)	8.87 (8.97)	7.25 (7.04)

Use of the unsymmetrical α-diketone, *p*-chlorodibenzoyl, led to the exclusive formation of 4-(*p*-chlorophenyl)-5-phenylimidazole (**3c**), as confirmed by an X-ray analysis. This corresponds to the expected initial attack of the more nucleophilic iminophosphorane nitrogen at the activated carbonyl. Figure 2 shows a perspective view and atom labelling of the crystal structure. Atom coordinates, bond lengths and bond angles are given in Tables 2-4. The imidazole ring is planar with geometry comparable with that of other imidazole structures except for a slight stretching of the C(4) - C(5) bond; such stretching has been observed with similarly substituted imidazoles. The three phenyl rings are planar to within 0.01Å and their meanplanes inclined to the imidazole meanplane at angles of 82.0° (benzyl), 29.8° (4-phenyl) and 62.5° (5-phenyl). The two adjacent phenyl rings at C(4) and C(5) are mutually inclined at an angle of 58.6°. There are no unusually short (<3.4Å) intermolecular contacts between non-hydrogen atoms.

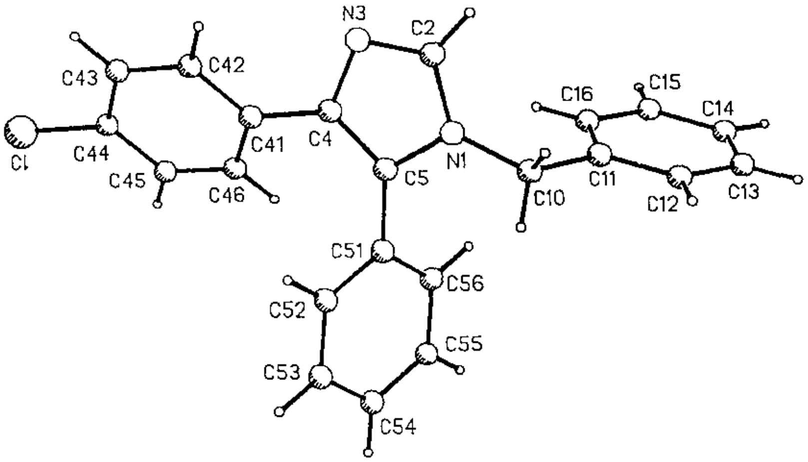


Figure 1 Perspective view and atom labelling of the X-ray structure of 4-(*p*-chlorophenyl)-5-phenylimidazole **3c**

EXPERIMENTAL

Column chromatography was carried out on MCB silica gel (230-400 mesh). Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^{1}H and, ^{13}C nmr spectra were recorded on a Varian VXR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal reference for ^{1}H spectra and $CDCl_3$ for ^{13}C nmr spectra (abbreviations used: s singlet; d doublet; t triplet; q quartet; qu quintet; m multiplet; bs broad singlet and dd doublet of doublets). Elemental analyses were performed on a Carlo Erba-1106 instrument under the supervision of Dr. D. Powell.

Representative Procedure For The Preparation Of Imidazoles 3

To a solution of betmip[2] (2.5 g, 6.1 mmol) in THF (100 ml) was added cycloheptylamine (0.69 g, 6.1 mmol). After refluxing the resulting solution for 12 h, benzil (1.3 g, 6.1 mmol) was added and the mixture refluxed for a further

16 h. The reaction mixture was cooled, diluted with ether (100 ml) and washed twice with aqueous potassium *hydroxide (2N, 25 ml) to remove the benzotriazole byproduct.* The crude product was column chromatographed on silica gel eluted with ether, to remove the triphenylphosphine oxide and some impurities and gave 1-cycloheptyl-4,5-diphenylimidazole **(3a)** (1.57 g, 81%) as colourless needles. ^{1}H Nmr 1.22-1.38 (m, 2H), 1.49-1.60 (m, 4H), 1.62-1.70 (m, 2H), 1.70-1.95 (m, 2H), 1.97-2.10 (m, 2H), 7.05-7.22 (m, 3H), 7.28-7.34 (m, 2H), 7.41-7.49 (m, 5H), 7.70 (s, 1H). ^{13}C NMR 24.4, 27.3, 36.4, 56.4, 125.9, 126.3, 127.7, 127.8, 128.8, 129.8, 130.8, 131.0, 133.7, 134.6, 137.2.

1-(p-Dimethylaminophenyl)-4,5-diphenylimidazole (3b): ^{1}H Nmr 2.90 (s, 6H), 6.55-6.56 (d, J=9Hz, 2H), 6.93-6.96 (d, J=9Hz, 2H), 7.53-7.56 (d, J=8Hz, 2H), 7.15-7.24 (m, 8H), 7.70 (s, 1H). ^{13}C Nmr 40.3, 111.9, 125.1, 126.3, 126.6, 127.1, 127.7, 128.0, 128.3, 130.0, 130.4, 130.7, 134.7, 137.6, 138.2, 149.7.

1-Benzyl-4-(4-chlorophenyl)-5-phenylimidazole (3c): ^{1}H Nmr 4.95 (s, 2H), 6.93-6.98 (m, 2H), 7.12-7.23 (m, 4H), 7.24-7.32 (m, 3H), 7.33-7.46 (m, 5H), 7.63 (s, 1H). ^{13}C Nmr 48.6, 126.9, 127.7, 127.9, 128.3, 128.8, 128.9, 128.95, 129.0,130.2, 130.8, 132.0, 133.1, 136.4, 137.2, 137.3.

1-Dodecyl-4-(4-chlorophenyl)-5-phenylimidazole (3d): ^{1}H Nmr 0.88 (t, J=7Hz, 3H), 1.2 (m, 18H), 1.56 (quint, J=7Hz, 2H), 3.77 (t, J=7Hz, 2H), 7.13-7.18 (m, 2H), 7.29-7.41 (m, 2H), 7.45-7.49 (m, 3H), 7.59 (s, 1H). ^{13}C Nmr 14.1, 22.6, 26.4, 28.9, 29.27, 29.29, 29.4, 29.5, 29.55, 29.55, 30.7, 31.9, 127.7, 128.2, 128.7, 128.8, 129.1, 130.4, 130.6, 131.8, 133.2, 136.6, 137.0.

1-Benzylphenanthro[9,10-*d*]imidazole (3e): ^{1}H Nmr 5.72 (s, 2H), 7.07-7.09 (d, J=7Hz, 2H), 7.23-7.28 (m, 3H), 7.39 (t, J=7Hz, 1H), 7.49 (t, J=7Hz, 1H), 7.60 (t, J=7Hz, 1H), 7.71 (t, J=7Hz, 1H), 7.88-7.98 (m, 2H), 8.62-8.75 (m, 3H). ^{13}C Nmr 51.2, 121.1, 122.4, 122.8, 123.1, 124.1, 124.9, 125.5, 126.0, 126.6, 127.3, 127.4, 128.0, 128.1, 129.0, 129.1, 135.8, 138.8, 140.2, 142.3.

1-Decylphenanthro[9,10-*d*]imidazole (3f): ^{1}H Nmr 0.86 (t, J=7Hz, 3H), 1.23 (m, 14H), 1.97 (qu, J=7Hz, 2H), 4.51 (t, J=7Hz, 2H), 7.61 (m, 3H), 7.70 (t, J=7Hz, 1H), 7.90 (s, 1H), 8.13 (d, J=7Hz, 1H), 8.65 (d, J=8Hz, 1H), 8.77 (d, J=7Hz, 1H), 8.75 (m, 1H). ^{13}C Nmr 14.1, 22.6, 26.6, 29.1, 29.2, 29.40, 29.43, 30.3, 31.6, 48.1, 120.8, 122.3, 123.0, 123.3, 124.3, 124.8, 125.0, 125.3, 126.7, 127.3, 128.0, 129.0, 138.9, 141.8.

1-Dodecylphenanthro[9,10-*d*]imidazole (3g): ^{1}H Nmr 0.88 (t, J=7Hz, 3H), 1.22 (m, 18H), 1.92 (qu, J=7Hz, 2H), 4.43 (t, J=7Hz, 2H), 7.56-7.62 (m, 3H), 7.70 (t, J=8Hz, 1H), 7.82 (s, 1H), 8.09 (m, 1H), 8.64 (d, J=8Hz, 1H), 8.70 (d, J=8Hz, 1H), 8.75 (m, 1H). ^{13}C Nmr 14.1, 22.6, 26.5, 29.0, 29.3, 29.37, 29.44, 29.44, 29.5, 30.2, 31.8, 48.0, 120.7, 122.3, 123.0, 123.2, 124.2, 124.8, 124.9, 125.3, 126.6, 126.2, 127.5, 127.9, 128.9, 138.7, 141.7.

Crystallography

Crystal data at -125°C : $C_{22}H_{17}N_2Cl$, Mr = 309.4, tetragonal, space group $P4_3$, $a = b = 9.465(4)$, $c = 19.538(8)$ Å, U=1750(2) Å^3, F(000) = 720, Z = 4, $D_c = 1.31$ g cm^{-3}, μ(MoKα) = 2.21 cm^{-1}, ω-scan, $2\theta_{max} = 60°$, N = 2627, N_0 = 2128, 225 parameters, S = 1.31, R = 0.046, R_W = 0.050.

Intensity data were collected at -125°C with a Nicolet R3m four-circle diffractometer by using monochromatized MoKα (λ = 0.71069Å) radiation. Cell parameters were determined by least squares refinement, the setting angles of 25 accurately centred reflections ($2\theta > 15°$) being used. Throughout data collection the intensities of three standard reflections (008, 040, 400) were monitored at regular intervals and this indicated no significant crystal decomposition. The space groups $P4_1$ and $P4_3$ were distinguished by collecting all Friedel equivalents and merging and refining in both space groups. The intensities were corrected for Lorentz and polarization effects and for absorption by a procedure based on azimuthal ψ-scans. Reflections with $I > 3\sigma(I)$ were used for structure solution and refinement.

The structure was solved by direct method, and refined by blocked cascade least-squares procedures. All non-hydrogen atoms were refined with anisotopic thermal parameters. Hydrogen atoms were included in calculated positions with isotropic thermal parameters equal to the isotropic equivalent of their carrier atoms. The function minimized was $\Sigma w(|F_o|-|F_c|)^2$, with $w = [\sigma^2(F_o)+0.00096(F_o)^2]^{-1}$. All calculations (including diagrams) were performed on a Nova 4X computer using SHELXTL.[9] Final atom coordinates, bond lengths and bond angles are listed in Tables 2-4. Tabulations of hydrogen atomic coordinates, anisotropic thermal parameters, structure factors and equations of meanplanes are available from the author P. J. S.

Table 2. Atomic coordinates (x10^4) and isotropic thermal parameters (Å^{2}x10^3)

	x	y	z	Ueq[a]
N(1)	3615(2)	1579(3)	4866[b]	24(1)
C(2)	3089(3)	2915(3)	4944(2)	26(1)
N(3)	2905(3)	3241(3)	5597(1)	26(1)
C(4)	3328(3)	2077(3)	5960(2)	23(1)
C(5)	3776(3)	1019(3)	5520(1)	22(1)
C(10)	4049(3)	941(3)	4216(1)	28(1)
C(11)	2840(3)	417(3)	3784(2)	23(1)
C(12)	3121(3)	27(4)	3108(2)	29(1)
C(13)	2059(4)	-490(4)	2689(2)	32(1)
C(14)	680(4)	-627(3)	2940(2)	30(1)
C(15)	392(3)	-211(3)	3608(2)	29(1)
C(16)	1465(3)	292(3)	4031(2)	25(1)
C(41)	3321(3)	2069(3)	6717(2)	22(1)
C(42)	3514(3)	3350(3)	7068(2)	26(1)
C(43)	3520(3)	3391(3)	7776(2)	29(1)
C(44)	3358(3)	2146(3)	8145(2)	27(1)
Cl	3428(1)	2210(1)	9037(1)	42(1)
C(45)	3151(3)	867(3)	7813(2)	28(1)
C(46)	3139(3)	837(3)	7100(2)	26(1)
C(51)	4381(3)	-404(3)	5654(2)	25(1)
C(52)	5631(3)	-524(3)	6020(2)	31(1)
C(53)	6176(4)	-1841(4)	6178(2)	38(1)
C(54)	5890(4)	-3057(4)	5957(2)	39(1)
C(55)	4254(4)	2941(4)	5584(2)	39(1)
C(56)	3688(3)	-1615(3)	5438(2)	30(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor

[b] Origin defining coordinate

Table 3. Bond lengths (Å)

N(1)-C(2)	1.367(4)	N(1)-C(5)	1.391(3)
N(1)-C(10)	1.464(3)	C(2)-N(3)	1.324(4)
N(3)-C(4)	1.369(4)	C(4)-C(5)	1.386(4)
C(4)-C(41)	1.478(4)	C(5)-C(51)	1.487(4)
C(10)-C(11)	1.507(4)	C(11)-C(12)	1.396(4)
C(11)-C(16)	1.392(4)	C(12)-C(13)	1.385(4)
C(13)-C(14)	1.400(5)	C(14)-C(15)	1.390(4)
C(15)-C(16)	1.393(4)	C(41)-C(42)	1.405(4)
C(41)-C(46)	1.396(4)	C(42)-C(43)	1.385(4)
C(43)-C(44)	1.390(4)	C(44)-Cl	1.743(3)
C(44)-C(45)	1.388(4)	C(45)-C(46)	1.394(4)
C(51)-C(52)	1.387(4)	C(51)-C(56)	1.386(4)
C(52)-C(53)	1.383(5)	C(53)-C(54)	1.391(5)
C(54)-C(55)	1.382(5)	C(55)-C(56)	1.394(5)

Table 4. Bond angles (^{0})

C(2)-N(1)-C(5)	106.8(2)	C(2)-N(1)-C(10)	125.5(2)
C(5)-N(1)-C(10)	127.4(2)	N(1)-C(2)-N(3)	111.8(2)
C(2)-N(3)-C(4)	105.8(2)	N(3)-C(4)-C(5)	110.5(3)
N(3)-C(4)-C(41)	121.3(3)	C(5)-C(4)-C(41)	128.2(3)
N(1)-C(5)-C(4)	105.1(2)	N(1)-C(5)-C(51)	123.4(2)
C(4)-C(5)-C(51)	131.5(3)	N(1)-C(10)-C(11)	114.1(2)
C(10)-C(11)-C(12)	118.2(3)	C(10)-C(11)_C(16)	122.9(3)
C(12)-C(11)-C(16)	118.9(3)	C(11)-C(12)-C(13)	120.9(3)
C(12)-C(13)-C(14)	120.2(3)	C(13)-C(14)-C(15)	119.0(3)
C(14)-C(15)-C(16)	120.7(3)	C(11)-C(16)-C(15)	120.4(3)
C(4)-C(41)-C(42)	118.9(3)	C(4)-C(41)-C(46)	122.7(3)
C(42)-C(41)-C(46)	118.4(3)	C(41)-C(42)-C(43)	120.8(3)
C(42)-C(43)-C(44)	119.7(3)	C(43)-C(44)-Cl	119.0(2)
C(43)-C(44)-C(45)	120.8(3)	Cl-C(44)-C(45)	120.2(2)
C(44)-C(45)-C(46)	119.1(3)	C(41)-C(46)-C(45)	121.2(3)
C(5)-C(51)-C(52)	119.6(3)	C(5)-C(51)-C(56)	120.8(3)
C(52)-C(51)-C(56)	119.5(3)	C(51)-C(52)-C(53)	120.5(3)
C(52)-C(53)-C(54)	120.1(3)	C(53)-C(54)-C(55)	119.6(3)
C(54)-C(55)-C(56)	120.3(3)	C(51)-C(56)-C(55)	120.0(3)

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Received, 28th September, 1990