Cyanation using the Combined Reagent, Triphenylphosphine–Thiocyanogen (TPPT): A New General Route to Indole and Pyrrole Carbonitriles

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Various types of indoles, pyrroles, and enamines react with the combined reagent, Ph_3P–$(SCN)_2$ (TPPT) under mild conditions to give the corresponding cyanated compounds in high yields. The reaction mechanism of the cyanation is discussed.

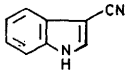
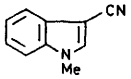
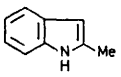
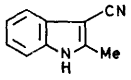
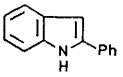
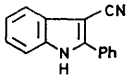
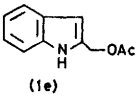
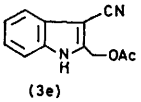
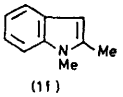
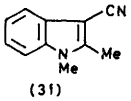
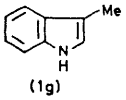
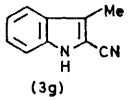
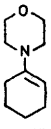
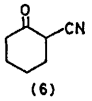
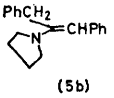
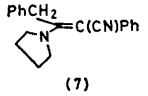
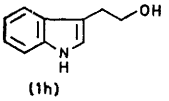
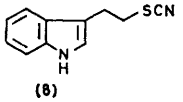
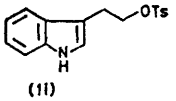
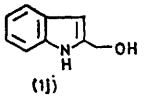
INDOLE and pyrrole carbonitriles are very important intermediates in organic synthesis and have been prepared from the following reactions: (*i*) 3-indolecarbaldehyde with *ON*-bis(trifluoroacetyl)hydroxylamine [1] or *p*-(*NN*-dimethylamino)benzaldehyde in the presence of ammonium dihydrogen phosphate; [2] (*ii*) aldoximes of indoles or pyrroles with 2,4,6-trichloro-*s*-triazine,[3] acetic anhydride,[4] or thionyl chloride; [5] (*iii*) *N*-indolylmagnesium iodide with cyanogen chloride;[6] (*iv*) indoles or pyrroles with ethoxycarbonylimino-triphenylphosphorane in the presence of boron trifluoride; [7] (*v*) pyr-

In our recent communication,[14] we have briefly reported extremely useful cyanation of indoles (1) and pyrroles (2) utilising the combined reagent, Ph_3P–$(SCN)_2$ (TPPT),[15] and now report here a full account of the preliminary work and additional studies concerning the reaction mechanism, scope, and limitation of this cyanation.

RESULTS AND DISCUSSION

Treatment of indoles (1) or pyrroles (2) with TPPT in dry methylene chloride at −40 °C for several hours gave

Results of cyanation reactions with TPPT

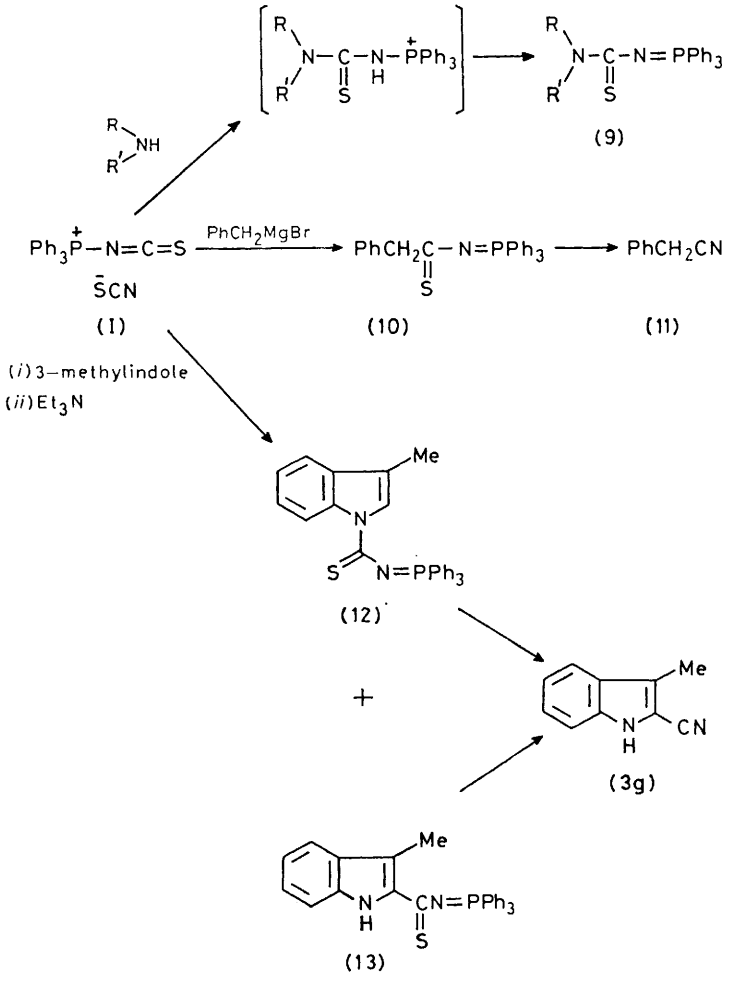
Run	Starting compound	Product	Yield (%)	M.p. (°C) (solvent) [b.p. (°C) (mmHg)]	Lit. M.p. or b.p. (°C)	$\nu_{max.}$/cm^{-1} (KBr disc)	δ (in $CDCl_3$) (J/Hz)
1	 (1a)	 (3a)	93	183—184 ($CHCl_3$)	181 [7] 178—180 [11]	3 240; 2 200	8.20 (1 H, d, J 3); 7.7—7.5 (2 H, m) 7.4—7.1 (2 H, m) [a]
2	 (1b)	 (3b)	64	65 (C_6H_6–n-hexane)	115 (5) [12]	2 220	7.8—7.1 (5 H, m); 3.80 (3 H, s)
3	 (1c)	 (3c)	99	204—206 ($CHCl_3$)	205—208 [10]	3 230; 2 210	7.6—7.0 (5 H, m); 3.55 (3 H, s)
4	 (1d)	 (3d)	88	246—248 (CH_3OH)	240 [13]	3 200; 2 210	12.55 (1 H, br s); 8.1—7.2 (9 H, m) [a]
5	 (1e)	 (3e)	66	149.5—151.5 (benzene–n-hexane)		3 225; 2 225; 1 735	7.7—7.1 (5 H, m); 5.34 (2 H, m), 3.6 (3 H, s); 2.45 (3 H, s)
6	 (1f)	 (3f)	70	104—105 (benzene–n-hexane)	104—105 [12]	2 200	7.7—7.24 (5 H, m); 7.3—7.0 (3 H, m), 3.6 (3 H, s); 2.45 (3 H, s)
7	 (1g)	 (3g)	85	103—104 (benzene–n-hexane)	102—103.5 [12] 104—106 [b]	3 325; 2 215	8.65 (1 H, br s); 7.65—7.0 (4 H, m), 2.4 (3 H, s)
8	 (2a)	 (4a)	50	[113—115 (11)]	115—120 (10) [8] 112—115 (14) [17]	3 440; 2 230 [c]	7.0—6.8 (2 H, m); 6.3—6.1 (1 H, m)
9	 (2b)	 (4b)	61	[120—125 (20)]	101—103 (27) [12]	2 235 [c]	6.74 (2 H, d, J 3); 6.13 (1 H, t, J 3), 3.70 (3 H, s)
10	 (5a)	 (6)	24	[125—130 (10)]	120—122 (5) [d]	2 255; 2 200, 1 720 [c]	
11	 (5b)	 (7)	61	130—131 ($CHCl_3$–n-hexane)		2 190; 1 550	7.3—7.2 (10 H, m); 4.1 (2 H, s); 3.1—2.8 (4 H, m); 1.9—1.4 (4 H, m)
12	 (1h)	 (8)	43	40—41 (n-hexane–light petroleum)		3 420; 2 160 [c]	8.2—7.8 (1 H, br s); 7.6—6.8 (5 H, m), 3.2 (4 H, s)
13	 (1i)	(8)	32				
14	 (1j)	*e*					

[a] In $[^2H_6]$DMSO. [b] C. Kaneko and S. Yamada, *Chem. Pharm. Bull (Tokyo)*, 1966, **14**, 555. [c] In $CHCl_3$. [d] M. E. Kuehne, *J. Amer. Chem. Soc.*, 1959, **81**. 5400. [e] Gave complex mixtures.

conditions to give the compounds (6) and (7), respectively (runs 10 and 11). A serious limitation of this cyanation is that indoles having electron-withdrawing groups such as ethoxycarbonyl or benzoyl at N-1 or C-2, and 2,3-dialkyl-substituted indoles, do not react with TPPT at all.

There are two possible routes for the cyanation of (1), (2), and (5) by TPPT, *i.e.* common addition of the electron-rich carbon of (1), (2), or (5) to the –N=C=S carbon of form (I) of TPPT (route A) or to the –S–C≡N carbon of form (II) of TPPT (route B) as shown in Scheme 1. The path A has been observed in the reaction of indole or pyrrole with acyl isothiocyanate,[16] chlorosulphonyl isocyanate,[11,13] or ethoxycarbonyliminotriphenylphosphorane in the presence of boron trifluoride,[7] path B has been observed in the reaction of pyrrole with aryl cyanate [8] or thiocyanate with Grignard reagent.[17,18]

Although the corresponding phosphinimine (III) could not be isolated in runs 1—11 under ordinary condition, the following results outlined in Scheme 2 strongly support route A for the cyanation of (1), (2), and (5); (*i*) various amines [15] and Grignard reagents [19] were shown to react predominantly with form (I) of TPPT, and the corresponding phosphinimine [(9) and (10)] were isolated in both reactions; (*ii*) thermolysis of phosphinimine (10) in toluene produced benzyl cyanide (11) in high yield with the liberation of $Ph_3P{=}S$; and (*iii*) reaction of the 3-substituted indole (1g) with TPPT at low temperature and subsequent treatment with triethylamine gave the corresponding phosphinimines (12) and (13) in 36 and 3% yields, respectively, and their quantitative conversion into the carbonitrile (3g) was observed by the treatment with one molar equivalent of thiocyanic acid in methylene chloride at room temperature (checked by t.l.c. and i.r.). Further mechanistic studies and potentialities of this cyanation using TPPT are now under investigation.



SCHEME 2

EXPERIMENTAL

I.r. absorption spectra were recorded on a Hitachi-G 2 spectrometer, and n.m.r. spectra on a Hitachi R-20A spectrometer (with tetramethylsilane as an internal standard). Mass spectra were obtained with a Hitachi RMU-6M instrument with a direct-inlet system operating at 70 eV. Column chromatography was carried out on Merck Silica gel 60. Physical and spectral data of compounds (3), (4), (6), and (7) are given in the Table.

General Procedures for the Preparation of Indole and Pyrrole Carbonitriles (3a—g) and (4a,b).—A solution of indole (1) or pyrrole (2) (2 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of freshly prepared TPPT (*ca.* 5 mmol) in dry CH_2Cl_2 (15 ml) at −40 °C under argon. The mixture was stirred for the requisite period (*ca.* 2—5 h) under the same conditions, allowed to warm to room temperature, stirred overnight, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding indole or pyrrole carbonitrile. Compounds (3a—g) and (4a,b) were identical with the authentic specimens, as determined by comparison of their melting or boiling points and spectral data. The results are listed in the Table. The unknown cyanated compounds (3e) gave satisfactory spectral and analytical data (Found: C, 67.18; H, 4.68; N, 12.85. Calc. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08%).

2-*Cyanocyclohexanone* (6).—This was prepared from *N*-cyclohex-1-enylmorpholine (5a) (334 mg, 2 mmol) and TPPT (*ca.* 5 mmol) in dry CH_2Cl_2 (15 ml).

1-*Cyano*-1,3-*diphenyl*-2-(*pyrrolidino*)*propene* (7).—This was prepared from 1,3-diphenyl-2-(pyrrolidino)propene (5b) (526 mg, 2 mmol) and TPPT (*ca.* 5.3 mmol) in dry CH_2Cl_2 (15 ml) (Found: C, 83.15; H, 6.95; N, 9.66. Calc. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.71%).

2-*Indol*-3-*ylethyl Thiocyanate* (8).—(a) *From* 2-*indol*-3-*ylethanol* (1h). A solution of (1h) (210 mg, 1.3 mmol) in dry CH_2Cl_2 (7 ml) was added dropwise to a stirred solution of freshly prepared TPPT (*ca.* 4.5 mmol) in dry CH_2Cl_2 (12 ml) at −40 °C under argon. The mixture was stirred for 3 h at this temperature and then at room temperature for 24 h. After concentration of the mixture *in vacuo*, the residue was subjected to a column chromatography on silica gel with benzene as an eluant to give a solid. Recrystallisation from the solvent cited in the Table gave the thiocyanate (8) (Found: C, 65.38; H, 4.80; N, 13.57. Calc. for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.99; N, 13.85%).

(b) *From* 2-*indol*-3-*ylethyl Toluene*-p-*sulphonate* (1i). In a similar manner as described above, (1i) (473 mg, 1.5 mmol) was reacted with TPPT (*ca.* 4.5 mmol) in dry CH_2Cl_2 to give the thiocyanate (8).

Thermolysis of Phosphinimine (10) *to Benzyl Cyanide* (11).—A solution of (10) (130 mg, 0.39 mmol) in dry toluene (2 ml) was refluxed for 1 h and evaporated under reduced pressure. The residual oil was distilled to give (11) (29 mg, 86%), b.p. 118—122 °C (20 mmHg) (bath temperature) [lit.,[20] 107 °C (12 mmHg)]; $\nu_{max.}$ ($CHCl_3$) 2 240 cm^{-1}.

Isolation of Phosphinimines (12) *and* (13).—A solution of (1g) (393 mg, 3 mmol) in dry CH_2Cl_2 (7 ml) was added dropwise to a stirred solution of freshly prepared TPPT (*ca.* 7.5 mmol) in dry CH_2Cl_2 (20 ml) at −40 °C under argon. The mixture was stirred for 3 h under the same conditions, allowed to warm to 10 °C, and treated with triethylamine (7 ml). After stirring at room temperature overnight, the mixture was concentrated under reduced pressure to give a residue, which was purified by a column chromatography on silica gel (benzene eluant) to give a mixture of (12) and (13) (617 mg, 46%), which were separated by preparative t.l.c. [silica gel, $CHCl_3$–hexane (4 : 5)]. Compound (12) was isolated in 36% yield, m.p. 169—170 °C (from chloroform-ether) (Found: C, 74.66; H, 5.10; N, 6.37. $C_{28}H_{23}N_2PS$ requires C, 74.65; H, 5.15; N, 6.22%); $\nu_{max.}$ ($CHCl_3$) 1 440, 1 405, 1 325, 1 110, and 970 cm^{-1}; δ ($CDCl_3$) 8.90—8.50 (1 H, m, C-7-H), 8.22 (1 H, d, *J* 2 Hz, C-2-H), 8.10—7.00 (18 H, m, Ar-H), and 2.26 (3 H, d, *J* 2 Hz, Me); *m/e* 450.5 (M^+), 320 (base peak, Ph_3P^+–N=C=S), 294 (Ph_3P=S), 262 (Ph_3P), and 156. Compound (13) was isolated in 3% yield, m.p. 59—77 °C (decomp.). Spectroscopic data of (13) were fully consistent with the proposed structure, although an analytical sample could not be obtained because of its unstability upon recrystallisation; $\nu_{max.}$ ($CHCl_3$) 3 376, 1 430, 1 390, 1 350, 1 110, and 970 cm^{-1}; δ ($CDCl_3$) 9.65—9.42 (1 H, br s, NH), 8.04—6.80 (19 H, m, Ar-H), and 2.87 (3 H, s, Me); *m/e* 450.5 (M^+). The spectral properties of the isomeric (12) and (13) were readily distinguished then.

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