A General Strategy for the Synthesis of 2,2′-, 2,3′-, and 2,7′-Bi-indolyls

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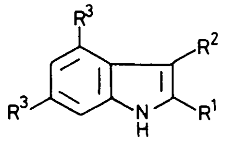
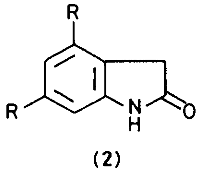
Various substituted indoles undergo electrophilic substitution with indolin-2-one or 4,6-dimethoxyindolin-2-one and phosphoryl chloride to afford 2,2′-, 2,3′-, or 2,7′-bi-indolyls, depending on the initial substitution pattern.

There has been considerable recent interest in general methods for the synthesis of 2,2′-[1a,2] and 2,3′-bi-indolyls.[1b,3] In particular, the formation of the latter bi-indolyls by an electrophilic substitution involving 3-bromoindolinium cations as electrophiles has just been reported.[3] We therefore wish to describe our own results in a similar area, which lead to 2,2′-, 2,3′-, and 2,7′-bi-indolyls. In our case, the operative electrophile is the Vilsmeier-type intermediate derived from indolin-2-one (**2a**) and phosphoryl chloride. For example, addition of 2-phenylindole (**1a**) in chloroform to a mixture of (**2a**) and phosphoryl chloride, followed by several hours gentle heating, basification, extraction, and chromatography on silica gel, gave the 2,3′-bi-indolyl (**3a**) in 60% yield, together with the terindolyl (**4**) in 19% yield. The yield of compound (**4**) can be increased to 60% when excess of reagent (**2a**) is used (see Table 1). An isolated example of a similar reaction involving 1-methylindole and 1-methylindolin-2-one has been reported.[1b].



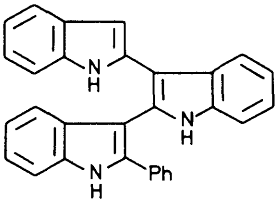
(1)

a; R^1 = Ph R^2 = R^3 = H,
b; R^1 = R^2 = H, R^3 = OMe
c; R^1 = R^2 = Ph, R^3 = OMe
d; R^1 = Ph, R^2 = H, R^3 = OMe
e; R^1 = H, R^2 = Me, R^3 = OMe

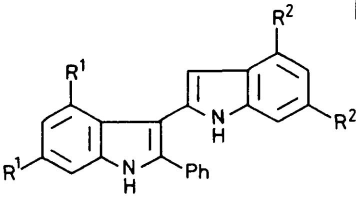


(2)

a; R = H
b; R = OMe

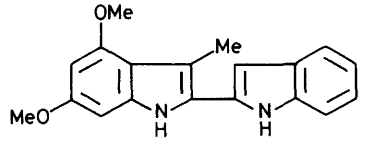


(4)

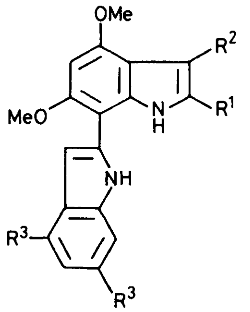


(3)

a; R^1=R^2=H
b; R^1= OMe, R^2=H
c; R^1 = R^2= OMe

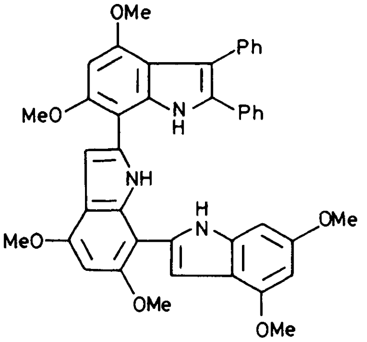


(6)



(5)

a; R^1 = R^2=Ph, R^3 = H
b; R^1= Ph, R^2= R^3= H
c; R^1 = H, R^2=Me, R^3= H
d; R^1 = R^2= Ph, R^3 = OMe
e; R^1= Ph, R^2= H, R^3= OMe



(7)

We have been particularly interested in the application of the above general method to the synthesis of the previously unknown 2,7′-bi-indolyls. The unusually high reactivity of 4,6-dimethoxyindole (**1b**)[4] towards Vilsmeier formylation at C-7 compared with C-3 prompted us to investigate the Vilsmeier-type reactions of the 4,6-dimethoxyindoles (**1c**),† (**1d**),[5] and (**1e**)[6] with indolin-2-one and phosphoryl chloride. The diphenylindole (**1c**) yielded only the 2,7′-bi-indolyl (**5a**) but the related 4,6-dimethoxy-2-phenylindole (**1d**) gave a mixture of the 2,3′-bi-indolyl (**3b**) and the 2,7′-bi-indolyl (**5b**). The 3-methylindole (**1e**) similarly underwent reaction at C-2 and C-7 to yield the 2,2′-bi-indolyl (**6**) and the 2,7′-bi-indolyl (**5c**). The parent dimethoxyindole (**1b**) gave a mixture of bi- and ter-indolyls which have not been separated and characterized. Phosphoryl chloride was found to be a more effective reagent than either oxalyl chloride[7] or benzoyl chloride,[8] which have been used in Vilsmeier reactions.

The reaction has been extended to include the use of the previously unreported 4,6-dimethoxyindolin-2-one (**2b**), which was prepared by the Wolff–Kishner reduction of the hydrazone of 4,6-dimethoxyisatin. In combination with the indole (**1c**), this gave good yields of the bi-indolyl (**5d**) and the terindolyl (**7**) in separate experiments. Furthermore, indole

Table 1. Synthesis of bi- and ter-indolyls from indoles and indolin-2-ones.

Indole	Indolin-2-one	Product[a]	M.p./°C	% Yield[b]
(**1a**)	(**2a**) (1 equiv.)	(**3a**)	208—209	60
(**1a**)	(**2a**) (2.6 equiv.)	(**4**)	264—265	60
(**1c**)	(**2a**)	(**5a**)	222—223	56
(**1d**)	(**2a**)	(**3b**)	113—114	56
		(**5b**)	144—146	25
(**1e**)	(**2a**)	(**6**)	134—136	33
		(**5c**)	153	27
(**1c**)	(**2b**) (1 equiv.)	(**5d**)	217—218	50
(**1c**)	(**2b**) (2.6 equiv.)	(**7**)	238	35
(**1d**)	(**2b**)	(**3c**)	228	30
		(**5e**)	243—245	10

[a] All products have been characterized by elemental analyses and spectra. [b] Yields are those of isolated products.

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† Indole (**1c**) has been prepared by Dr. L. C. H. Wong from 3,5-dimethoxyaniline by means of the Bischler reaction, ref. 5.

(**1d**) and indolinone (**2b**) gave a mixture of the 2,3′-bi-indolyl (**3c**) and the 2,7′-bi-indolyl (**5e**).

In general, the characterization of the products has been based on ^{1}H n.m.r. and mass spectra, together with a comparison of these data with those of the products of normal Vilsmeier formylation.[9]

The 2,7′-bi-indolyl series comprises a potentially important new class of compounds since the pyrrole rings occupy the same relationship to each other as they do in the porphyrins. Hence the possible use of (**2b**) to extend the 2,7′-linkage beyond the terindolyl stage offers exciting chelation potential.

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