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Reactions of electron-rich indoles with triflic anhydride

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ABSTRACT

The reaction of electron-rich 3-aryl-substituted 4,6-dimethoxyindoles in the presence of base with triflic anhydride results in biaryl coupling, producing both 2,2′- and 2,7′-biindoles. Further, if acetone is present, the corresponding vinyl triflate is formed and subsequent reaction yields the known indolylpyrroloindoles and dimeric spiroindoles. This is the first reported synthesis of these compounds under basic conditions.

1. Introduction

As part of our ongoing investigations into the biological activities of homo- and hetero-dimeric aromatic systems,[1] we have been investigating biindoles as bioisosteres of binaphthyl units. We previously reported the synthesis of 2,2′-biindoles under thallium(III) trifluoroacetate-mediated oxidative coupling conditions,[2] and as part of the mechanistic investigations, we required access to indoles that were N-protected with non-aromatic electron-withdrawing protecting groups. While these mechanistic studies were successfully completed,[2] our initial attempts to generate *N*-triflylindole monomers yielded unexpected results. Therefore, our investigations into the reactions of electron-rich indoles with triflic anhydride are reported here.

2. Results and discussion

Initial treatment of 3-aryl-4,6-dimethoxyindoles with NaH followed by addition of triflic anhydride yielded both the corresponding 2,2′-dimer and/or the 2,7′-dimer in overall reasonable yield (Scheme 1) with no requirement for chromatography when sole products were formed. There was no indication of the formation of the *N*-triflylindole. The optimisation of this dimerisation is summarised in Table 1. Interestingly, the 3-(*p*-bromophenyl)indole **2** gave the 2,2′-dimer as well as the 2,7′-dimer, whereas the 3-(*p*-nitrophenyl)indole derivative and the 3-phenylindole derivative gave only 2,7′-dimers. These results clearly show that the *p*-OMe group is strongly 2,2′-directing whereas the mildly deactivating bromo group favoured the formation of 2,7′ and 2,2′-dimers, with *p*-NO_2 indole and the derivative having no *para* substituent on the 3-aryl indole giving only the 2,7′-dimer. This demonstrates the influence of the 3-aryl *para* substituent in the formation of the 2,7′- over the 2,2′-dimer, and has been observed previously during the thallium(III) trifluoroacetate oxidative coupling of these monomers.[2]

Although no experiments were performed investigating the mechanism, we speculate that the initial step involves the known electron transfer from substrate to triflic anhydride (Scheme 2).[3] The longer reaction times and poorer yields in the absence of NaH could possibly be attributed to a greater ease of this electron transfer from the indole anion versus the neutral form. The electron transfer is also clearly influenced by the presence of substituents of differing electronic nature. The basic mechanism outlined in Scheme 2 also suggests the possibility of the formation of 7,7′-dimers, even though these were not isolated from the reactions. Presumably, the balance of electron distribution of the two proposed intermediates favoured the use of the radical in the C2 position for subsequent reaction. Alternatively, the electrophilic radical intermediates could react with the indole anion at the activated C2 position giving rise to both dimers. Although both indole C2 and C7 positions are activated, the later by the presence of the two methoxy groups, higher yields are generally observed in these indole system by reaction at C2.[2]

During the previously mentioned optimisation reactions, contamination of the solvent led to the observation of the formation

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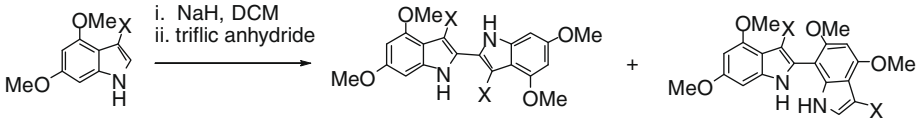


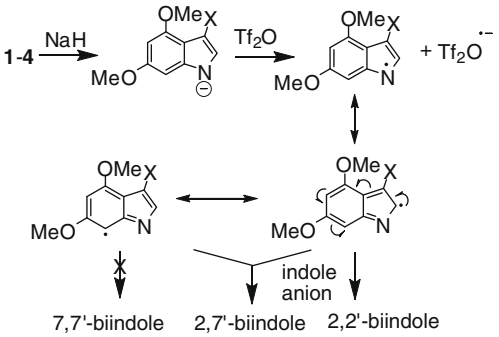
1: X = *p*-$MeOC_6H_4$
2: X = *p*-BrC_6H_4
3: X = Ph
4: X = *p*-$O_2NC_6H_4$

	2,2′-dimer Yield %	X		2,7′-dimer Yield %
5	70	*p*-$MeOC_6H_4$	**9**	0
6	15	*p*-BrC_6H_4	**10**	55
7	0	Ph	**11**	60
8	0	*p*-$O_2NC_6H_4$	**12**	47

Scheme 1. Dimerisation of dimethoxyindoles using triflic anhydride yielding 2,2′- and 2,7′-biindoles.

Table 1
Optimisation of the formation of 2,2′- and 2,7′-indole dimers

3-Aryl unit	NaH (equiv)	Tf_2O (equiv)	Isolated yield (%)		Time (h)
			2,2′-Dimer	2,7′-Dimer	
p-$MeOC_6H_4$	0	1	25	0	96
	1	1	40	0	72
	2	2	70	0	72
p-BrC_6H_4	0	1	0	15	72
	1	1	5	30	72
	2	2	15	55	48
p-$O_2NC_6H_4$	0	1	0	10	72
	1	1	0	30	96
	2	2	0	47	72
Ph	0	1	0	15	72
	1	1	0	50	72
	2	2	0	60	48



Scheme 2. Proposed mechanism for the triflic anhydride-mediated dimerisation of electron-rich indoles in the presence of NaH leading to a 7,7′-biindole and a 2,2′-biindole.

of a different product. Investigation of this reaction revealed that treatment of 4,6-dimethoxy-3-arylindoles **1** and **3** with triflic anhydride in acetone produced the pyrroloindole spirodimer **13** and the indolylpyrroloindoles **14** and **16** (Scheme 3).[4,5] These heterocyclic scaffolds have been previously reported starting from analogous 4,6-dimethoxyindoles and various aldehydes and ketones, but under acidic conditions. We report here that the corresponding heterocycles are accessible under basic conditions with the likely mechanism involving the generation of a vinyl triflate[6] from acetone. The structure of **14** was confirmed by an X-ray crystallographic study (Fig. 1).[7]

The indole dimers synthesised in this study were screened for their anti-malarial activity (Table 2) with most 2,2′- and 2,7′-indoles showing moderate activity. Surprisingly, the 2,7′-derivative **11** containing an unsubstituted 3-phenyl ring showed no anti-malarial activity in this assay. In contrast, when tested for their anti-tuberculosis activity, **11** was the only compound to show any activity, albeit only weakly.

In conclusion, this is the first report of triflic anhydride-mediated dimerisation of 3-substituted-4,6-dimethoxyindoles with the formation of 2,2′- and 2,7′-dimers. We report here for the first time the anti-malarial activity of this compound class with the 2,2′-dimer **5**, the 2,7′-dimer **10** and the indolylpyrroloindole **16** found to have moderate activity. Only one spiro compound with the same carbon skeleton has been previously reported[8] albeit containing two ketone moieties. The reactions can be controlled to a degree to produce the 2,2′ or 2,7′-dimers by using the appropriate *para*-substituted 3-phenyl substituents.

3. Experimental

3.1. Biological assays

The assay used the microculture radioisotope technique at a starting concentration of 10 μg/ml and was performed at the National Centre for Genetic Engineering and Biotechnology (BIOTEC), Pathumthani, Thailand.

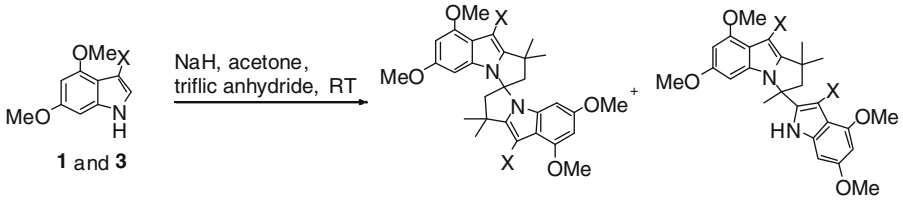
The parasite *Plasmodium falciparum* (K1, multidrug-resistant strain) was cultured continuously according to the method of Trager and Jensen.[9] Quantitative assessment of anti-plasmodial activity in vitro was undertaken by means of the microculture radioisotope technique based upon the method described by Desjardins et al.[10] Inhibition concentration (IC_{50}) represents the concentration which causes 50% reduction in parasite growth as indicated by uptake of [3*H*]-hypoxanthine by *P. falciparum*.

The anti-mycobacterial activity was assessed against *Mycobacterium tuberculosis* H37Ra using the Microplate Alamar Blue Assay (MABA) according to Collins.[11] Standard drugs, isoniazid (MIC of 0.40–0.090 μg/ml) and kanamycin sulfate (MIC of 2.0–5.0 μg/ml) were used as reference compounds for the anti-mycobacterial assay.

4. General procedures

4.1. Synthesis of dimers

To a solution of 4,6-dimethoxy-3-(4-methoxyphenyl)indole (1 mmol) in CH_2Cl_2 (10 ml) was added sodium hydride (2 mmol, 60% dispersion in mineral oil) and the suspension stirred for 5 min. Triflic anhydride (2 mmol) was then added to the reaction mixture. After stirring for 72 h at 25 °C, ice cold water (50 ml) was added carefully. The resulting mixture was partitioned with CH_2Cl_2 (3 × 50 ml) and the combined organic layers dried ($MgSO_4$) and concentrated. The residue was either subjected to crystallisation from methanol to give the dimer **9** or was subjected to flash



	Yield %	X		Yield %
13	20	*p*-MeOC$_6$H$_4$	**14**	70
15	0	Ph	**16**	70

Scheme 3. Formation of spiropyrroloindoles and indolopyrroloindoles using NaH and triflic anhydride.

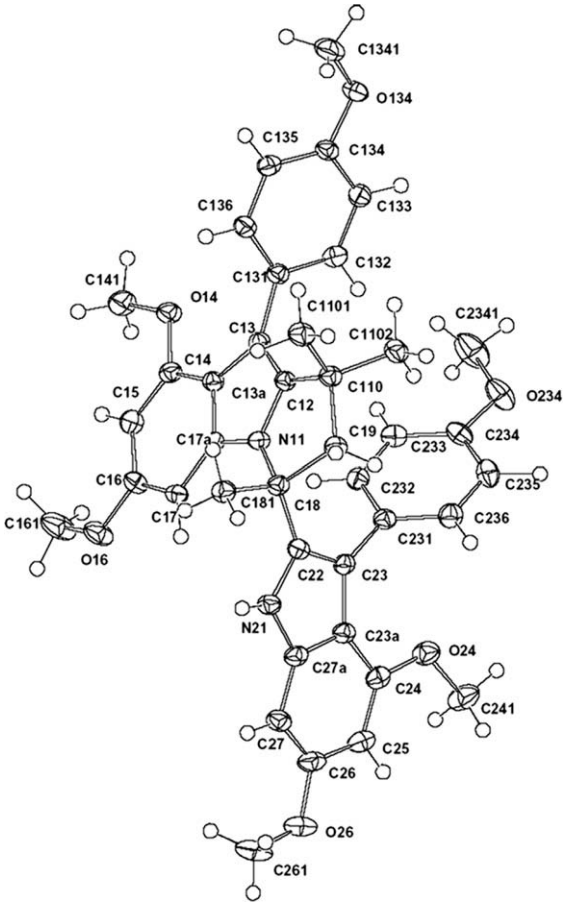


Figure 1. X-ray structure of 5,7-dimethoxy-2,3-dihydro-1-[4,6-dimethoxy-3-(4-methoxyphenyl)indol-2-yl]-1,3,3-trimethyl-4-(4-methoxyphenyl)-1*H*-pyrrolo[1,2-*a*]indole **14**.

Table 2
Anti-malarial and anti-tuberculosis activity of 2,2′- and 2,7′-biindoles and indolopyrroloindole **16**

Indole	Anti-malarial activity IC_{50}	Anti-tuberculosis activity IC_{50}
5	2.8 μg/ml	Inactive
10	4.5 μg/ml	Inactive
16	11.2 μg/ml	Inactive
11	Inactive	200 μg/ml

All other derivatives tested showed no activity in these assays.

column chromatography (hexane/EtOAc, 4:1 up to 1:1) for the separation of **6** and **10** and for the isolation of **11** and **12**. Spectral data for dimers **5**–**12** were identical to that previously reported.[2]

4.2. Synthesis of spiropyrroloindoles and indolylpyrroloindoles 13 and 14

To a solution of 4,6-dimethoxy-3-(4-methoxyphenyl) indole (1 mmol) in acetone (15 mL) was added sodium hydride (2 mmol) and the suspension was stirred for 5 min. Triflic anhydride (2 mmol) was then added slowly. The reaction mixture was heated at reflux for 12 h. Ice cold water (50 ml) was added carefully, and the resultant mixture was partitioned with CH_2Cl_2 (3 × 50 ml). The combined organic layers were dried ($MgSO_4$), then concentrated and the residue was subjected to silica gel flash chromatography and elution with 80:20, hexane/ethyl acetate gave **13** as an off-white powder in 20% yield; further elution gave **14** in 70% yield as a pale yellow powder.

4.2.1. 2,2′-Spirobi(1,2-dihydro-3,3-dimethyl-5,7-dimethoxy-4-(4-methoxyphenyl)-1*H*-pyrrolo[1,2-*a*]indole) 13

White solid, mp 232–234 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (4H, d, J = 5.1 Hz, C4-ArH3, ArH5 and C4′-ArH3′, ArH5′), 6.92 (4H, d, J = 5.1 Hz, C4-ArH2 and C4′-ArH6, ArH6′), 6.06 (2H, d, J = 1.5 Hz, H6 and 6′), 5.47 (2H, d, J = 1.5 Hz, H8 and H8′), 3.87 (6H, s, C4-ArC4-OCH_3 and C4′-ArC4′-OCH_3'), 3.59 (6H, s, C5-OCH_3 and C5′-OCH_3), 3.51 (6H, s, C7-OCH_3 and C7′-OCH_3), 3.28 (2H, d, J = 13.2 Hz, $H2_a$ and $H2'_a$), 2.77 (2H, d, J = 13.2 Hz, $H2_b$ and $H2'_b$), 1.51 (6H, s, C3(CH_{3a})$_2$ and C3′(CH_{3a})$_2$), 1.40, (6H, s, C3(CH_{3b})$_2$ and C3′(CH_{3b})$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.1 (ArC4′), 156.6 (C7), 155.0 (C5), 143.8 (C3a), 132.1 (2 × C, ArC3′ and 5′), 131.0 (C8a), 128.4 (ArC1′), 116.8 (C4a), 108.3 (C4), 92.6 (C8), 85.4 (C6), 79.7 (C2 spiro), 58.3 (C1), 55.4 (3 × C, ArC4′-OCH_3, C5-OCH_3, C7-OCH_3); 38.5 (C3), 31.5 (C3(CH_{3a})$_2$), 28.3 (C3(CH_{3b})$_2$)$_2$. ES-MS m/z: 687 $[M+1]^+$ (35), 364 (100%), 350 (20), 324 (70), 312 (10) 257 (10), 123 (20), 101 (40). ES-HRMS m/z: calcd for $[M+1]^+$ $C_{43}H_{47}N_2O_6$ 687.3425; found 687.3434.

4.2.2. 5,7-Dimethoxy-2,3-dihydro-1-[4,6-dimethoxy-3-(4-methoxyphenyl)indol-2-yl]-1,3,3-trimethyl-4-(4-methoxyphenyl)-1*H*-pyrrolo[1,2-a]indole 14

White solid, mp 229–231 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (1H, s, NH′), 7.35 (4H, d, J = 8.7 Hz, ArH3′ and 5′ and ArH3″ and 5″), 6.84 (4H, d, J = 8.7 Hz, ArH2′ and 6′ and ArH2″ and 6″), 6.34 (1H, d, J = 1.8 Hz, H6), 6.31 (1H, d, J = 1.8 Hz, H7′), 6.22 (1H, d, J = 1.8 Hz, H5′), 6.14 (1H, d, J = 1.8 Hz, H8), 3.86 (3H, s, ArC4″-OCH_3), 3.84 (3H, s, ArC4′-OCH_3), 3.78 (3H, s, C4′-OCH_3), 3.72, (3H, s, C5-OCH_3), 3.66, (3H, s, C7-OCH_3), 3.57 (3H, s, C6′-OCH_3), 2.84 (1H, d, J = 7.8 Hz, H2), 2.39 (1H, d, J = 7.8 Hz, H2), 1.77 (3H, s, C1-CH_3), 1.18 (3H, s, C3-(CH_3)$_2$), 1.12 (3H, s, C3-(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.4 (ArC4″), 158.0 (ArC4′), 157.4 (C6′), 156.7 (C7), 155.2 (C5), 155.0 (C4′), 146.1 (C3a), 135.9 (C7a′), 135.2 (C8a), 132.4 (ArC1″), 132.2 (ArC1′), 128.4 (C2′), 118.0 (C4a), 114.5 (C3a′), 112.8 (C3′), 112.5 (C4), 92.5 (C7′), 92.1 (C8), 87.1 (C6), 86.8 (C5′), 62.4 (C1), 56.6 (C2), 55.1 (ArC4″-OCH_3), 55.8

(ArC4′-OCH_3), 55.5 (C5-OCH_3), 55.5 (C4-OCH_3'), 54.1 (C7-OCH_3), 55.3 (C6-OCH_3'), 38.2 (C3), 30.4 (C3-(CH_3)$_2$), 29.1 (C3 (CH_3)$_2$), 28.2 (C1-CH_3). ES-MS *m/z*: 647.2 $[M+1]^+$ (15%), 546, (40), 364 (4), 264 (2), 147 (50), 103.9 (100). ES-HRMS *m/z*: calcd for $[M+1]^+$ $C_{40}H_{43}N_2O_6$ 647.3141; found 647.3121.

4.2.3. 5,7-Dimethoxy-2,3-dihydro-1-[4,6-dimethoxy-3-phenylindol-2-yl]-1,3,3-trimethyl-4-phenyl-1*H*-pyrrolo[1,2-a]indole 16

White solid, mp 199–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (1H, s, NH′), 7.46–7.26 (10H, Ar′ and Ar″ H2, 3, 4, 5 and 6), 6.38 (1H, d, *J* = 1.2 Hz, H7′), 6.34 (1H, d, *J* = 1.2 Hz, H8), 6.25 (1H, d, *J* = 1.2 Hz, H6), 6.16 (1H, d, *J* = 1.2 Hz, H5′), 3.79 (3H, s, C4-OCH_3'), 3.75, (3H, s, C5-OCH_3), 3.67, (3H, s, C7-OCH_3), 3.57, (3H, s, C6-OCH_3'), 2.86, (1H, d, *J* = 7.8 Hz, H2), 2.41, (1H, d, *J* = 7.8 Hz, H2), 1.78, (3H, s, C1-CH_3), 1.21 (3H, s, C3-(CH_3)$_2$), 1.13, (3H, s, C3-(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.5 (C6′), 155.8 (C7), 155.0 (C5), 154.8 (C4′), 146.6 (3a), 137.3 (ArC1″, ArC1′), 136.1 (C2′), 135.7 (C7a′), 135.2 (C8a), 132.0 (ArC1′), 132.1 (ArC2″ and 6″), 127.4 (ArC3′), 127.0 (ArC3″), 126.6 (C4′ and C5′), 126.0 (C4″ and C5″), 126.7 (C3′), 117.9 (C4a), 114.3 (C3a′), 113.7 (C9), 108.0 (C4), 92.5 (C7′), 92.1 (C8), 87.1 (C6), 86.8 (C5′), 62.4 (C1), 61.9 (C2′), 56.6 (C2), 50.8 (C5-OCH_3), 50.5 (C4′-OCH_3), 50.19 (C7-OCH_3), 50.1 (C6′-OCH_3), 38.9 (C3), 33.2 (C3), 25.2 (C3-(CH_3)$_2$), 23.8 (C3-CH_3)$_2$), 22.8 (C1-CH_3). ES-MS *m/z*: 587.4 $[M+1]^+$ (90%). ES-HRMS *m/z*: calcd for $[M+1]^+$ $C_{38}H_{39}N_2O_4$ 587.2933; found 587.2950.

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7. Crystals of **14** ($C_{40}H_{42}N_2O_6$, *M* = 646.8) are triclinic, space group $P\bar{1}$ (C_i^1, No. 2), *a* = 9.486(2), *b* = 12.416(2), *c* = 14.833(2) Å, α = 92.824(2)°, β = 107.427(2)°, γ = 95.291(2)°, *V* = 1654 Å.^{3} D_c (*Z* = 2) = 1.29 g cm^{-3}. μ_{Mo} = 0.087 mm^{-1}; specimen: 0.32 × 0.07 × 0.05 mm; '$T'_{min,max}$ = 0.82 ('empirical'/multiscan 'correction'). $2\theta_{max}$ = 50°; N_{total} = 16018, *N* = 6789 (R_{int} = 0.029), N_o ($I > 2\sigma(I)$) = 4945; R_1 = 0.056, wR_2 = 0.15. *T* ca. 153 K. CCDC 711437.
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