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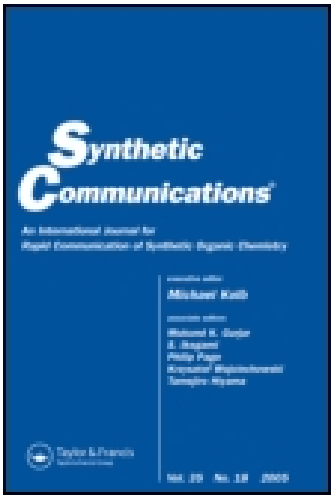

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Synthesis of Bulky 2,2-Diaryl-1,2-dihydro-3H-indol-3-ones via Singlet Oxygenation of 2-Arylindoles

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SYNTHETIC COMMUNICATIONS, 26(1), 149-152 (1996)

SYNTHESIS OF BULKY 2,2-DIARYL-1,2-DIHYDRO-3H-INDOL-3-ONES *VIA* SINGLET OXYGENATION OF 2-ARYLINDOLES

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Abstract: 2,2-Diaryl-1,2-dihydro-3H-indol-3-ones (**2a-2j**) have been synthesized *via* singlet oxygenation of 2-arylindoles (**1a-1d**), followed by acid-catalyzed nucleophilic substitution of the resulting 2-aryl-2-methoxy-1,2-dihydro-3H-indol-3-ones (**3a-3d**) with aryl nucleophiles in one pot in good yields.

1,2-Dihydro-3H-indol-3-ones are useful synthetic intermediates for the synthesis of biologically active compounds such as indomethacine,[1] serotonin[2] and ellipticine.[3] The direct C-2 arylation of 1,2-dihydro-3H-indol-3-ones with aryllead (IV) triacetate was recently reported.[4] This reaction provided a convenient route for the synthesis of aryl substituted 1,2-dihydro-3H-indol-3-ones, but in the case of bulky 2,2-diaryl derivative, the yield was exceptionally low.[4] We now wish to describe a facile synthesis of 2,2-diaryl-1,2-dihydro-3H-indol-3-ones *via* singlet oxygenation of 2-arylindoles.

General procedure: A solution of 2-arylindoles (**1a-1d**, 2.5 mmol), methylene blue (MB, 0.25 mmol) and pyridine (2 ml) in methanol (250 ml) was irradiated internally with a 1000 W tungsten halogen lamp operated at 180 V through a cutoff light filter (1% aqueous $K_2Cr_2O_7$, λ > 500 nm) in a typical immersion apparatus at 20℃ under oxygen bubbling for 1.5-2 h (TLC monitering). To the reaction mixture were added acetic acid (20 ml) and aryl nucleophiles (HAr, 2.5-3.0 mmol). The mixture was then refluxed for 1-2 h to complet the nucleophilic substitution reaction (TLC monitering). After removal of solvent *in vacuo*, the residue was chromatographed over silica gel column, elution with petroleum ether (60-90℃)-ethyl acetate gave the 2,2-diaryl-1,2-dihydro-3H-indol-3-ones (**2a-2j**).

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Table 1 summarizes the results obtained with several 2-arylindoles and aryl nucleophiles. In the synthesis of **2a-2d**, the aryl nucleophiles used in the second step were the same as the starting 2-arylindoles and the yields were based on the total consumption of 2-arylindoles, whereas in the synthesis of **2e-2j**, the aryl nucleophiles were different and the yields were thus based on 2-arylindoles consumed in the first step. Considering the high yields of **2a-2j**, especially those of **2c** and **2d**, the bulk of 2-arylindoles and aryl nucleophiles seems to have no significant effect on the reaction.

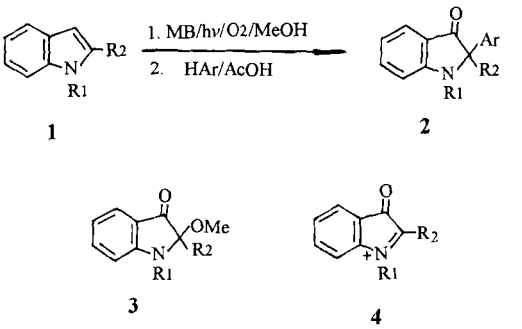

Table1 2,2-Diaryl-1,2-dihydro-3H-indol-3-ones from 2-arylindoles and aryl nucleophiles

1			**2**[5]		Isolated yield (%)	mp[c] (prev) (℃)
	R_1	R_2		Ar		
a	H	Ph	**a**	2-Ph-3-indolyl	90[a]	246-247 (247[6])
b	Me	Ph	**b**	1-Me-2-Ph-3-indolyl	88[a]	243-244 (241[7])
c	H	2,4-diMeC_6H_3	**c**	2-(2,4-diMeC_6H_3)-3-indolyl	93[a]	199-201
d	H	2-naphthyl	**d**	2-(2-naphthyl)-3-indolyl	92[a]	244-245
a	H	Ph	**e**	1-Me-2-Ph-3-indolyl	82[b]	200-202 (202[6])
a	H	Ph	**f**	2-(4-$MeOC_6H_4$)-3-indolyl	83[b]	207-208
b	Me	Ph	**g**	2-Ph-3-indolyl	80[b]	234-235
b	Me	Ph	**h**	2-Me-3-indolyl	77[b]	252-253
b	Me	Ph	**i**	1,2-diMe-3-indolyl	78[b]	195-197
b	Me	Ph	**j**	4-$MeNHC_6H_4$	76[b]	184-185

a. Based on total consumption of 2-arylindoles. b. Based on starting 2-arylindoles. c. Crystalized from methanol or benzene-methanol.

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The first step of the procedure involves sensitized photooxygenation of 2-arylindoles. We previously reported that MB-sensitized photooxygenation of 2-phenylindoles (**1a, 1b**) in methanol gave oxidative coupling products (**2a, 2b**) and solvent trapping products (**3a, 3b**) with varying proportions in high total yields.[8] Similar results were also observed with **1c** and **1d**. No reaction occured either in the absence of MB or in the dark. The photo-reactions were also inhibited by singlet oxygen quenchers such as β -carotene and 1,4-diazabicyclo[2,2,2]octane, indicating that singlet oxygen ($^1O_2$) was the possible active intermediate.[9] We found that, under the conditions selected in this paper, the oxidative coupling of **1a-1d** in singlet oxygenation may be completely retarded and the reaction gave **3a-3d** as main products, among which, **3a** and **3b** have been isolated in 85% and 81% yields respectively. In the presence of acid and without isolation, **3a-3d** underwent facile nucleophilic substitution with aryl nucleophiles leading to the final products **2a-2j** probably *via* iminium intermediates **4a-4d**.[6,10,11]

Compound **2a** has previously been prepared by chemical oxidative coupling of **1a**,[12,13,14] whereas **2b** was prepared by indirect oxidative coupling of **1b**.[15,7] On the other hand, compound **2a** and **2e** were both synthesized *via* nucleophilic addition of 2-phenyl-3H-indol-3-one with **1a** and **1b** respectively.[6] However, the starting 2-phenyl-3H-indol-3-one may previously be prepared from **1a** only by peracid oxidation in low yield,[12] or by stepwise indirect procedures in low overall yield.[16] In contrast to these reported approaches, the present method, by using methanol trapping reaction in singlet oxygenation, divides the oxidative coupling reaction of 2-arylindoles in two steps but combines the singlet oxygenation and nucleophilic substitution in one pot and offers a general and convenient route for preparing 2,2-diaryl-1,2-dihydro-3H-indol-3-ones from easily available 2-arylindoles under mild conditions in good yields.

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5. All new compounds gave consistent elemental and spectral data. **Compound 2d**: yellow plates. IR (KBr): 3368, 3274 (NH), 1689 (C=O), 1613 (Ph-N-C-)^6 , 747 cm^{-1}. MS (EI) m/z: 500 (M^+). Anal. calcd. for $C_{36}H_{24}N_2O$: C, 86.37; H, 4.83; N, 5.60. Found: C, 86.42; H, 5.00; N, 5.51. **Compound 2g**: yellow prisms. IR (KBr): 3225 (NH), 1671 (C=O), 1612 (Ph-N-

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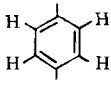
Ç-)[6]. 741, 700 cm^{-1}. ^{1}HNMR (DMSO-d_6 /TMS): 2.87 (3H, s, CH_3), 6.35-8.00 (18H, m, ArH), 8.34 (1H, s, NH) ppm. MS (EI) m/z: 414 (M^+). Anal. calcd. for $C_{29}H_{22}N_2O$: C, 84.03; H, 5.35; N, 6.76. Found: C, 83.91; H, 5.34; N, 6.77. **Compound 2j:** yellow plates. IR (KBr): 3415 (NH), 1680 (C=O), 1612 (Ph-N-Ç-)[6], 805, 749, 706 cm^{-1}. ^{1}HNMR ($CDCl_3$): 2.81 (3H, s, CH_3), 2.83 (3H, s , CH_3), 3.45 (1H, s, NH), 6.50, 7.03 (4H, AA'BB', 

), 6.69- 7.65 (9H, m, Ph and indole ArH) ppm. MS (EI) m/z: 328 (M^+). Anal. calcd. for $C_{22}H_{20}N_2O$: C, 80.46 ; H, 6.14; N, 8.53. Found: C, 80.62; H, 6.17; N, 8.59.

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