Novel Reaction of Indoles and Pyrrole with Pyrillium Catalyzed by Ceric Ammonium Nitrate (CAN)

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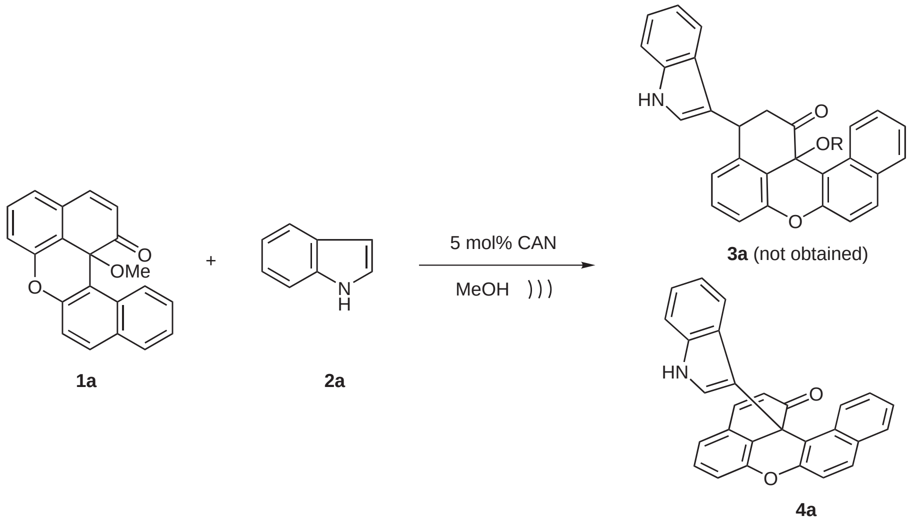
Abstract: The reaction of xanthene derivatives with indoles and pyrrole catalyzed by CAN in methanol through S_N1 reaction of pyrillium with a nucleophilic reagent afforded the corresponding indole- and pyrrole-substituted xanthene derivatives in high yields, respectively.

Key words: CAN, indole, pyrrole, xanthen, pyrillium

The xanthenes and benzoxanthenes are natural or synthetically important compounds, which were used as dyes, fluorescent materials for visualization of biomolecules and in laser technologies due to their useful spectroscopic properties.[1] Among these compounds, santalin pigments, as they are known, have been isolated from a number of plant species.[2] Xanthene-based compounds have also been investigated for agricultural bactericidal activity,[3] photodynamic therapy,[4] anti-inflammatory effects,[5] antiviral activity,[6] and for antagonism of the paralyzing action of zoxazolamine.[7] However, few literature procedures are available concerning the synthesis and reaction of 1-oxo-13c-alkyloxy-1,13c-dihydrodibenzo[*a*,*kl*]-xanthene from 1,1′-bi-2-naphthol.[8]

We have previously reported that ceric ammonium nitrate (CAN) efficiently catalyzes the Michael addition of indole to α,β-unsaturated ketones under ultrasonic irradiation to afford the corresponding adducts in excellent yields.[9] As an extension of this study, we decided to investigate the Michael addition of indole **2a** with α,β-unsaturated compounds like **1a** (Scheme 1). These homologues were expected to provide 1-oxo-(3-indolyl)-13c-methyloxy-1,2,3,13c-dihydrodibenzo[*a*,*kl*]-xanthene (**3a**) as the target product.[10] However, as discussed herein, when compounds **1a** and **2a** were mixed together in the presence of 5 mol% CAN in methanol under ultrasonic conditions, an unexpected product 1-oxo-13c-(3-indolyl)-1,13c-dihydrodibenzo[*a*,*kl*]-xanthene (**4a**) was obtained with high regioselectivity.

First, the reaction of 1-oxo-13c-methoxy-1,13c-dihydrodibenzo[*a*,*kl*]-xanthene (**1a**) with **2a** (1.0 equiv) was studied. The reaction was catalyzed by CAN under ultrasonic irradiation. It was found that reaction of **1a** with **2a** in methanol proceeded smoothly under sonic waves to give the unexpected product **4a** in 95% yield after 3 hours (Table 1, entry 1).[11] When the amount of **2a** was changed



Scheme 1 Reaction of **1a** with indole

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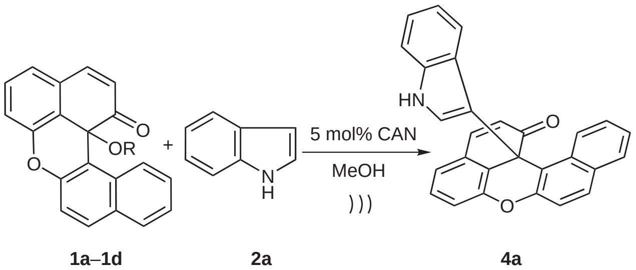
from 1.0 to 2.0 equivalents, the reaction still furnished compound **4a** as the sole product in high yield without further Michael addition of the indole to the cyclohexenone (Table 1, entry 2). The structure of compound **4** was confirmed by NMR and IR spectroscopy.

Table 1 Reactions of **1a**–**d** with Indole **2a**[a]



Entry	R (Subst.)		Time (h)	Yield (%)[b]
1	Me	**1a**	3	95 (88)[c]
2	Me	**1a**	3	95[d]
3	Et	**1b**	2	95
4	*i*-Bu	**1c**	2	82
5	*n*-Bu	**1d**	2	82

[a] The reactions were carried out under sonication conditions.
[b] Isolated yields.
[c] The reaction was carried out without ultrasound irridiation.
[d] 2.0 Equiv of **2a** was used under the identical conditions.

When compounds **1b**–**d** were used as the starting materials in the reactions under the identical conditions using CAN as the catalyst, the same product **4a** was obtained in good yields (Table 1, entries 3–5).

A variety of indoles **2b**–**j** were then tested (Table 2). Compound **1a** reacted smoothly with various substituted indoles **2b**–**f** in the presence of a catalytic amount of CAN under sonic waves to afford 1-oxo-13c-(3-indolyl)-1,13c-dihydrodibenzo[*a*,*kl*]-xanthenes **4b**–**f** in high yields (Table 2, entries 2–6). However, reactions of **1a** with **2g**–**i** did not give the desirable products, which might be due to steric restriction (Table 2, entries 7–9). The less reactive nitroindole derivate **2j** also did not react under the same reaction conditions (Table 2, entry 10). In addition, the structure of the product **4e** was ascertained by spectroscopic methods, and the conclusive proof of the assigned structure was confirmed by single-crystal X-ray analysis (Figure 1).[12]

The reaction occurred predominantly at 2-position of pyrrole **5**, while the regioisomeric 3-substituted adduct could hardly be detected by NMR analysis of the final reaction mixture. The reaction of **1a** and **5** was examined to generate the desired product **6** in 90% yield under sonic conditions (Scheme 2).

A possible mechanism of the reaction was shown in Scheme 3. First, CAN promoted the cleavage of the alkoxy group in compound **1** to give the intermediate

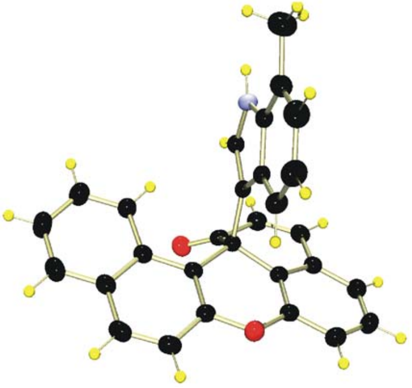
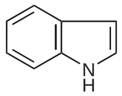
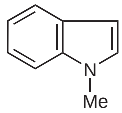
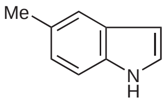
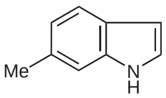
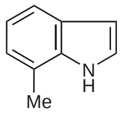
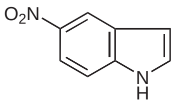
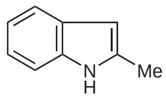
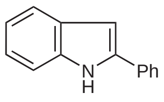
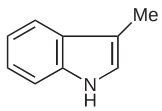
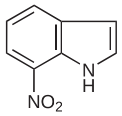
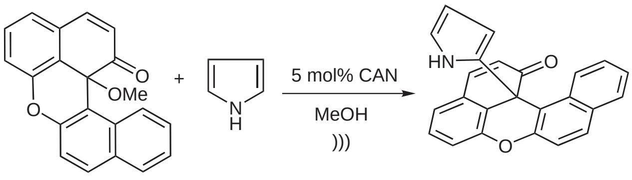


Figure 1 X-ray structure of compound **4e**

Table 2 Reactions of **1a** with Indoles **2a**–**k** Catalyzed by CAN[a]

Entry	Indoles		Product	Time (h)	Yield (%)[b]
1		**2a**	**4a**	3	95
2		**2b**	**4b**	4	89
3		**2c**	**4c**	3	95
4		**2d**	**4d**	6	87
5		**2e**	**4e**	4	84
6		**2f**	**4f**	5	80
7		**2g**	–	5	n.r.
8		**2h**	–	5	n.r.
9		**2i**	–	5	n.r.
10		**2j**	–	5	n.r.

[a] All reactions were performed under sonication conditions.
[b] Isolated yields.



1a **5** **6**

Scheme 2 Reaction of **1a** with pyrrole **5** catalyzed by CAN

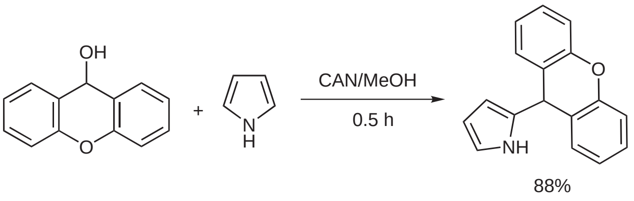
pyrillium species, it was then attacked by the nucleophilic indole and pyrrole regioselectively to give the desired product.

Considering the structural similarities between **1a** and 9*H*-xanthen-9-ol (**7**), we also tried reactions of compound **7** with indole or pyrrole catalyzed by CAN under similar conditions.[13] It was found that the reaction of **7** with indole **2a** in the presence of anhydrous MeOH proceeded smoothly at room temperature, giving **8a** in 90% yield even without ultrasound irradiation (Scheme 4).

As shown in Table 3, xanthen-9-ol **7** reacted well with various substituted indoles such as **2c**, **2d**, and **2g**, and the desired 3-(9*H*-xanthen-9-yl)-1*H*-indole derivatives were formed in good yields (Table 3, entries 3, 4, and 7). It was interesting to note that the reaction of the passivated indole derivate **2f** could also be perform under the same conditions to give the desired product **8f** in 90% yield (Table 3, entry 6). The migration of groups from the 3- to the 2-position of indole was also observed in the alkylation of 3-substituted indoles. By analogy, reaction of **7** with indole **2i** proceeded smoothly at the 2-position giving the 3-indolyl-3-(3-methyl-1*H*-indol-2-yl)indolin-2-one **8i** in 96% yield under identical conditions (Table 3, entry 9). In all cases, the reactions proceeded smoothly at ambient temperature to give the desired products in good to excellent yields with high regioselectivity without any side products. All products were characterized by ^{1}H NMR, IR, and mass spectrometry and also by comparison with values reported in literature.[14]

For pyrrole **5**, the alkylation reaction occurred predominantly at 2-position, while the 3-substituted adduct could not be detected by NMR analysis of the product mixture. Hence, the desired product 2-(9*H*-xanthen-9-yl)-1*H*-pyrrole (**9**) was formed in 88% yield in the presence of 5 mol% CAN (Scheme 5).

In conclusion, we have described a novel and convenient method for the alkylation of indoles and pyrrole through the CAN-mediated S_N1 reaction. This method offers several advantages including high product yields, clean reaction profiles, higher selectivity, and simple experimental/product isolation procedures, which makes it a useful and attractive strategy for the synthesis of indoles and pyrroles bearing xanthen substituents.



7 **5** **9**

Scheme 5 Reaction of **7** with **5** catalyzed by CAN

Acknowledgment

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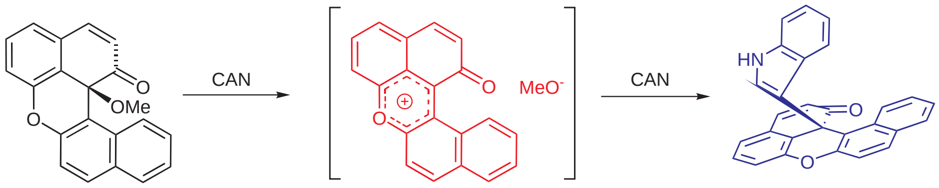
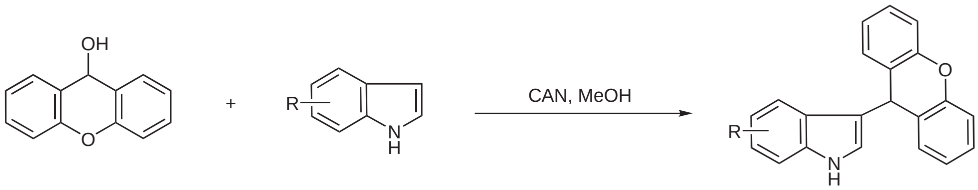


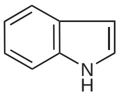
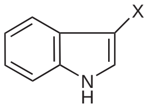
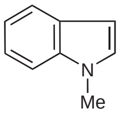
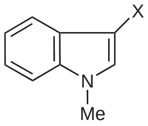
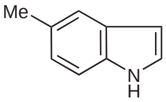
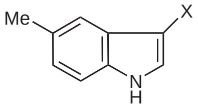
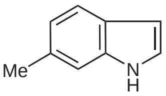
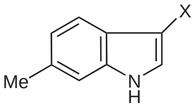
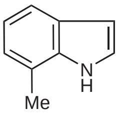
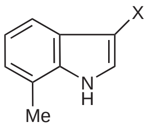
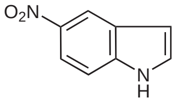
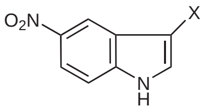
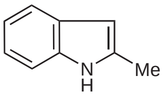
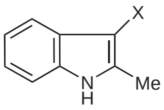
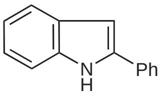
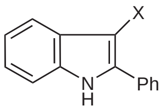
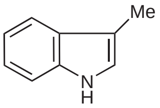
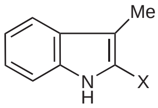
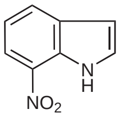
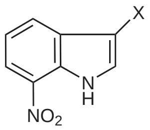
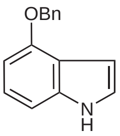
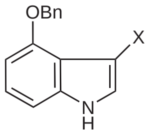
Scheme 3 Proposed reaction mechanism



7 **2** **8**

Scheme 4 Reaction of **7** with **2** catalyzed by CAN

Table 3 Reactions of Indoles **2a–k** with **7** Catalyzed by CAN[a]

Entry	Indoles		Product[c]		Time (h)	Yield (%)[b]
1		**2a**		**8a**	1	90 (93)[d]
2		**2b**		**8b**	0.5	75
3		**2c**		**8c**	0.5	76
4		**2d**		**8d**	3	80
5		**2e**		**8e**	0.5	91
6		**2f**		**8f**	0.5	90
7		**2g**		**8g**	0.7	88
8		**2h**		**8h**	1	90
9		**2i**		**8i**	1	96
10		**2j**		**8j**	0.5	95
11		**2k**		**8k**	1	76

[a] All reactions were carried out using a catalytic amount of CAN (5 mol%) at r.t.
[b] Isolated yields.
[c] X = 9-xanthenyl.
[d] The reaction was carried out under sonication conditions.

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(10) Compound **1a** with 3.0 equiv morpholine proceeded smoothly under sonic waves to give the **3′** after 3 h under neat conditions.

(11) **General Procedure for the Reaction of Indoles with 1-Oxo-13c-alkyloxy-1,13c-dihydro-dibenzo[*a,kl*]-xanthene**
A mixture of 1-oxo-13c-methoxy-1,13c-dihydro-dibenzo[*a,kl*]-xanthene (**1a**, 0.157 g, 0.5 mmol), indole **2a** (0.059 g, 0.5 mmol), CAN (0.014 g, 5 mol%), and anhyd MeOH (2 mL) was irradiated with ultrasound in an open vessel at r.t. until the indole was completely consumed (3 h, monitored by TLC). Then the reaction mixture was washed with cold H_2O (3 × 15 mL) and cold EtOH (3 × 0.5 mL), respectively. The crude mixture was purified by flash chromatography to afford the pure product **4a** (0.190 g, yield: 95%).
1-Oxo-13c-3-indoly-1,13c-dihydro-dibenzo[*a,kl*]-xanthene (4a)
Kelly needles (chartreuse, acicular crystals) mp 192–194 °C. IR (KBr): ν = 3465, 3056, 1697 (C=O), 1458, 1227, 1026, 810, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.43 (d, 1 H, *J* = 9.6 Hz), 6.84–6.88 (m, 2 H), 6.97–7.21 (m, 4 H), 7.78–7.81 (m, 7 H), 7.35–7.40 (m, 3 H), 7.65 (d, 1 H, *J* = 8.0 Hz), 7.75 (d, 1 H, *J* = 8.8 Hz), 7.89 (d, 1 H, *J* = 8.0 Hz), 8.08 (br, s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.1, 111.8, 112.8, 115.8, 117.3, 117.4, 117.9, 118.8, 120.8, 122.2, 123.2, 123.6, 124.4, 124.5, 125.5, 127.4, 127.7, 128.0, 129.0, 130.6, 130.9, 132.3, 132.4, 135.3, 138.3, 147.6, 148.6, 201.0. HRMS: *m/z* calcd for $C_{28}H_{17}NO_2$: 399.1259; found: 399.1240 [M^+].

(12) Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 268046 for compound **4e**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [e-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; fax: +44 (1223)336033]. Crystal data for **4e**·C_3H_6O: $C_{29}H_{19}NO_2 \cdot C_3H_6O$, *Mr* = 471.53, triclinic, space group *P*–1, *a* = 9.7116(16) Å, *b* = 10.9061(18) Å, *c* = 11.572(2) Å, α = 95.996(5)°, β = 101.305(5)°, γ = 96.887(5)°, *V* = 1182.8(4) $Å^3$, *Z* = 2, *D*calc = 1.324 g cm^{-3}, (MoKα) = 0.085 mm^{-1}; 11701 reflections collected, 4286 unique reflections, *R* = 0.0196.

(13) In the last 20 years, reactions of xanthen-9-ol with indole, promoted by AcOH and $BF_3 \cdot OEt_2$, have been reported. See: (a) Deschner, R.; Pindur, U. *J. Heterocycl. Chem.* **1984**, *21*, 1485. (b) Pindur, U.; Deschner, R. *Arch. Pharm.* **1988**, *321*, 427. (c) Bratton, L. D.; Roth, B. D.; Trivedi, B. K.; Unangst, P. C. *J. Heterocycl. Chem.* **2000**, *37*, 1103.

(14) **General Experimental Procedure**
A mixture of indole **2a** (0.059 g, 0.5 mmol), **7** (0.099 g, 0.5 mmol), CAN (0.014 g, 0.025 mmol), and anhyd MeOH (2 mL) was stirred in flask at r.t. until **2a** was completely consumed (1 h, checked by TLC). After standing 0.5 h, the reaction mixture was washed with cold H_2O (3 × 15 mL). The crude mixture was purified by flash chromatography to afford the pure product **3a** (0.134 g, yield: 90%).
3-(9*H*-Xanthen-9-yl)-1*H*-indole (8a)
Mp 143–145 °C (lit.[13a] 145 °C). IR (KBr): ν = 3429 (NH), 3051, 2920, 2850, 1254, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.55 (s, 1 H, CH), 6.90–7.36 (m, 13 H), 8.02 (br, s, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.8, 111.2, 116.3, 119.6, 119.6, 120.3, 122.1, 122.8, 123.1, 124.4, 125.8, 127.7, 129.4, 136.7, 151.3. HRMS: *m/z* calcd for $C_{21}H_{15}NO$: 297.1154; found: 297.1157 [M+].