Selective and Efficient Formylation of Indoles (C3) and Pyrroles (C2) Using 2,4,6-Trichloro-1,3,5-Triazine/Dimethylformamide (TCT/DMF) Mixed Reagent

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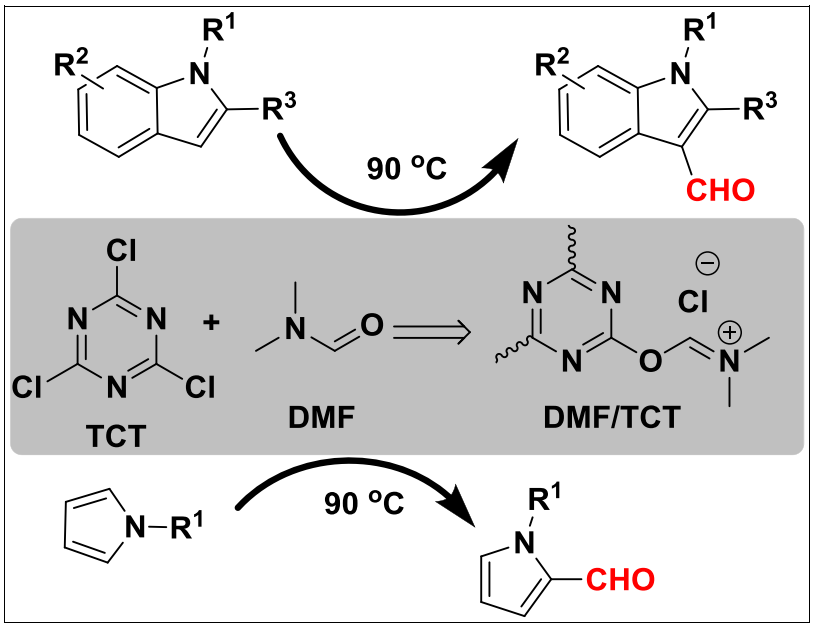


This study introduces an efficient method for the selective formylation of indoles and pyrroles at the positions of C(3) and C(2), respectively. The mixture of three equivalents of *N*,*N*-dimethylformamide and one equivalent of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) generates an easy handling formylating agent for the efficient formylation of these classes of compounds to give the corresponding aldehydes under mild reaction conditions. This procedure was highly efficient, and a range of formylated indoles and pyrroles were obtained in good to excellent yields.

INTRODUCTION

Formylation of aromatic compounds for the generation of aromatic aldehydes is one of the imperative methods in the synthesis of many materials. Because of the possibility of transformation of a formyl group to other functionalities, there is widespread interest in the development of new and efficient methods for the formylation of aromatic compounds [1]. Moreover, during the multistep synthesis of many natural products, formylation reaction is often necessary, and the selectivity, simplicity, and efficiency of this step are highly critical [2]. Some of the widely used formylating agents that have been reported up to now are $POCl_3$/*N*,*N*-dimethylformamide (DMF) [3], HCO_2H/*N*,*N*′-Dicyclohexylcarbodiimide (DCC) [4], 2,2,2-trifluoroethyl formate [5], formic acid/1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDAC) [6], acetic formic anhydride [7], formyl-pivaloyl anhydride [8], cyanomethylformate [9], pentafluorophenyl formate [10], imidazole/DMF [11], MeOH/Ru [12], CO_2/$PhMe_2SiH$ [13], AgOTf/Cl_2CHOMe [14], tetramethylethylenediamine/O_2/visible light [15], $FeCl_3$/DMSO [16], CO/acid [17], 2-benzotriazolyl-1,3-dioxolane [18], *N*-methyl aniline/Ru [19], Pd/CO/H_2 [20], *tert*-butyl isocyanide [21], Pd/CH_3NO_2 [22], etc. In spite of the diversity of formylating agents, there are serious restrictions for the preparation of some of them, such as harsh experimental conditions, the use of unusual reagents, formation of unwanted or toxic byproducts, use of expensive procedures for their synthesis, and thermal instability of the reagents.

2,4,6-Trichloro-1,3,5-triazine (TCT) has been introduced as an efficient reagent or catalyst in many organic transformations [23]. This reagent is a stable, nonvolatile, and inexpensive substrate that highlighted it in organic synthesis as an applicable reagent. Synthesis of benzopyran [24], synthesis of thiiranes [25], functionalization of glycosides [26], synthesis of 2-substituted benzofurans [27], oxidation of alcohols

[28], synthesis of sulfonamides [29], Beckmann rearrangement [30], synthesis of quinazolinones [31], synthesis of homoallylic alcohols [32], Friedel–Crafts acylations [33], synthesis of indole derivatives [34], synthesis of α-amino nitriles [35], and preparation of hydroxamic acids [36] are only part of the applications of this valuable reagent in organic synthesis.

Combination of TCT and DMF generates an efficient reagent that has been used for the formyl protection of primary hydroxyl groups by Luca *et al.* for the first time [37]. This reagent was also used for formylation of enol ethers [38]. Also, TCT/DMF was used as reagent in the synthesis of alkyl chlorides and *N*-alkylphthalimides from alcohols [39]. The use of this reagent for formylation of some reactive aromatic compounds has also been reported, but the generality of the method is limited [40]. In the continuation of our program on the formylation reactions [41] and the use of TCT in organic transformations [42], we report herein a novel methodology for the efficient and selective formylation of indoles and pyrroles under mild conditions. The method looks efficient for introduction of the formyl group into such systems and, therefore, can be of interest for broad circles of synthetic chemists, particularly having in mind the importance of pyrrole/indole carbaldehydes as building blocks for heterocyclic chemistry [43].

RESULTS AND DISCUSSION

The TCT/DMF mixed reagent as formylating reagent is produced simply using the reaction of TCT and DMF at room temperature. DMF immediately reacts with TCT and forms a white solid powder, which is stable under ambient conditions. The possible chemical structures of this salt are shown in Scheme 1.

All of the chemical structures can act as formylating agent [44]. It should be mentioned that these chemical structures are proposed for this reagent formed at room temperature and there are other suggested structures at higher temperatures [44a,45].

At first, we studied the applicability of using TCT/DMF mixed reagent for the C(3) formylation of indoles. This reaction is one of the important methods for direct C(3) functionalization of indoles; however, the used protocols suffer from harsh conditions, low selectivity, and lack of functionality tolerance [46]. Also, the C3 formylation of indoles is an important step in multistep synthesis of many natural products and biologically active compounds [47]. From this point of view, it seems that the elaboration of an efficient method that avoids these difficulties is highly needed. As a result, we set out to optimize the reaction conditions for the formylation of indole as a simple model substrate using TCT/DMF mixed reagent. The results of optimization study are tabulated in Table 1.

As demonstrated in Table 1, entry 12 shows the most suitable conditions for the efficient formylation of indole using TCT/DMF mixed reagent. At ambient temperature, no product was observed. Also, in the case of using PEG, THF, acetonitrile, and toluene as solvents, no increase in the yield was observed. The amount of indole was also checked, and it was observed that 1 Eq of mixed reagent is enough for formylation of at least 1.2 Eq of indole. With the optimal conditions in hand, we examined the scope of the reaction for formylation of different indoles (Scheme 2).

Indole gave indole-3-carbaldehyde (**2a**) in 90% isolated yield. The lower yield obtained for 2-methyl-*1H*-indole (**2b**) may be because of the presence of some steric hindrance. 5-Bromo-*1H*-indole (**2c**) was less active to some extent, and only 62% of the product was obtained. 1-Methyl-*1H*-indole-3-carbaldehyde (**2d**) was produced in 74% isolated yield under optimized conditions. Next, few indole derivatives were synthesized and formylated under the optimized condition. These results demonstrated that the TCT/DMF mixed reagent is an efficient, mild, and easy handling reagent for C3 formylation of indole derivatives (**2e–k**). The potential utility of this method in organic synthesis was established in the synthesis of a new cholesterol-indole derivative (Scheme 3).

As shown in Scheme 3, compound **2l** was synthesized in a three-step process. Compound **1i** was synthesized from indole in a controlled experiment. Addition of cholesterol to **1i** resulted in the production of a cholesterol-indole derivative (**1l**) [48]. Then, **1l** was formylated using our procedure, and compound **2l** was obtained in 68% isolated yield.

In the synthesis of many biologically active compounds and natural products containing the pyrrole moiety, C(2) formylation is significant, and for this reason, the introduction of efficient methodology for this transformation was

Scheme 1. Four possible forms of DMF/TCT as formylating agent. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

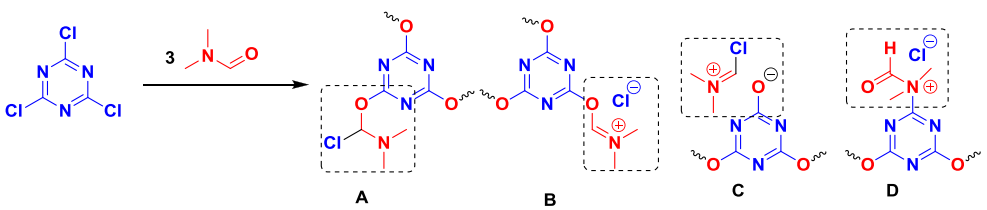
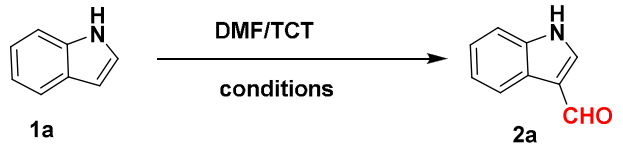


Table 1

Optimization of the reaction conditions.[a]



Entry	Solvent	T (°C)	Time (h)	Yield (%)[b]
1	None	RT	24	0
2	None	90	2	50
3	DMF	90	2	90
4	DMF	RT	12	0
5	DMF	100	2	90
6	DMF/PEG-600	90	12	0
7	DMF/THF	Reflux	12	40
8	DMF/CH_3CN	Reflux	12	60
9	DMF/toluene	90	12	0
10	DMF/dioxane	90	12	20
11	DMF	90	5	82[c]
12	DMF	90	2	90[d]

[a]Reaction conditions: TCT (1 mmol), DMF (0.5 mL), solvent (1.0 mL), and indole (1 mmol).
[b]Yield of the isolated product.
[c]1.5 mmol of indole was used.
[d]1.2 mmol of indole was used.

considered [49]. Formylation of pyrrole derivatives is highly sensitive to the conditions used and also the formylating agent, because under unsuitable conditions, polymerization and diformylation occur and the target molecule could not be formed [50]. Thus, we checked the activity of some pyrrole derivatives with our method, and the obtained results are shown in Scheme 4.

As shown in the preceding texts, the TCT/DMF mixed reagent is efficient for formylation of both indole and pyrrole derivatives.

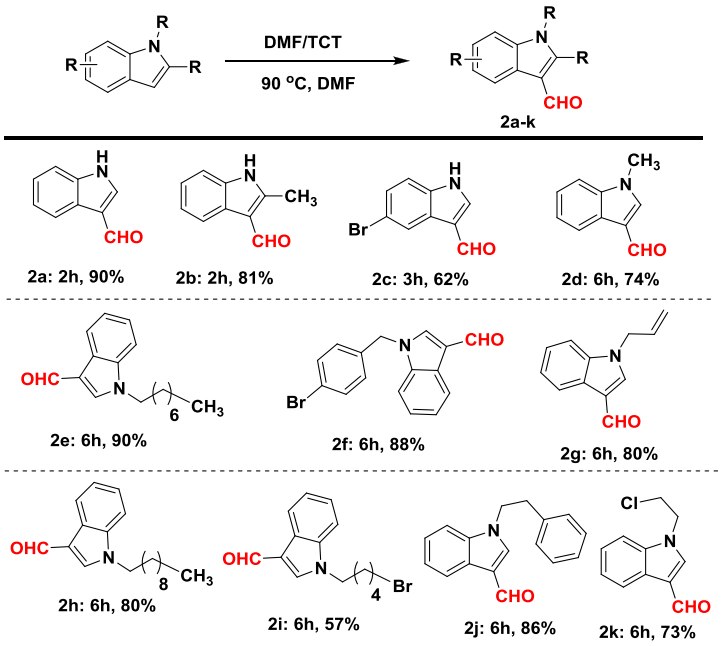
In order to show the merit and applicability of our procedure for formylation of indoles related to other methods, a comparison with some other reported methodologies is presented in Table 2. The results show that our method is superior to some of the previously reported conditions in terms of reaction condition, reaction time, and yield.

In conclusion, we have developed an efficient method for the C(3) formylation of indole and C(2) formylation of pyrrole derivatives using TCT/DMF reagent. The synthetic usefulness of this methodology for the synthesis of aldehydes was demonstrated, and the target products ranging from **2a** to **2z** were obtained in moderate to good yields and short reaction times. The method is characterized by its simplicity, easy handling of the reagents, and the availability of the formylating agent employed.

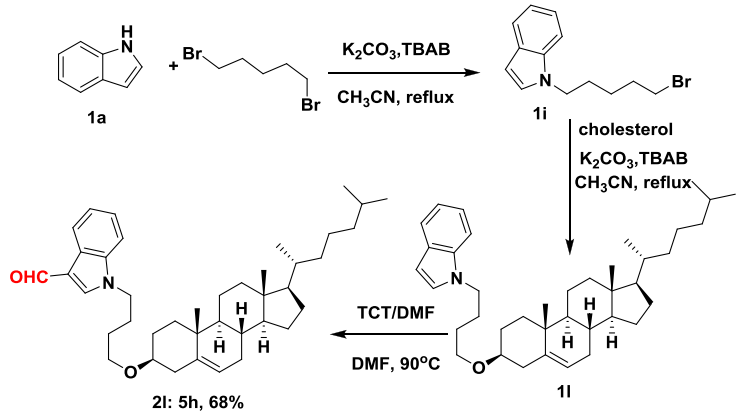
EXPERIMENTAL

General experimental details. Chemicals were purchased from Merck and Aldrich chemical companies and used without further purification. ^{1}H NMR (250 MHz) and ^{13}C NMR (62.9 MHz) spectra were recorded on a Bruker

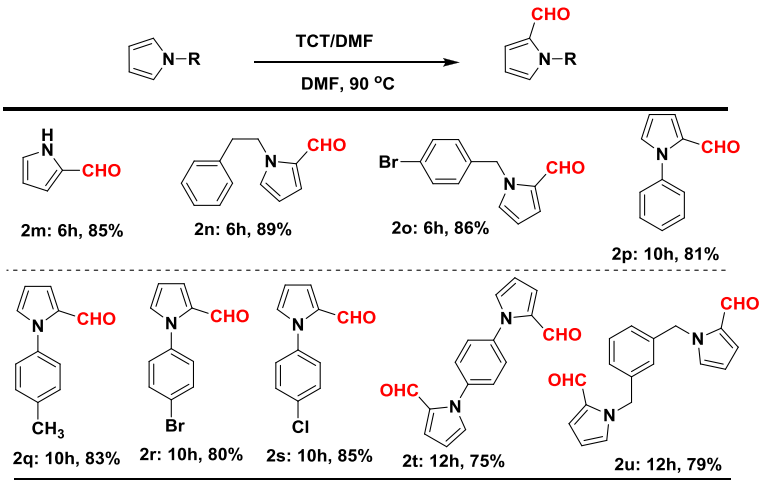
Scheme 2. Products of C3 formylation of indole derivatives by DMF/TCT reagent. Reaction conditions: TCT (1 mmol), DMF (0.5 mL), solvent (1.0 mL), and indole (1.2 mmol). All yields are isolated products. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Scheme 3. C3 formylation of a cholesterol-indole derivative using TCT/DMF reagent. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Scheme 4. Formylation of some pyrrole derivatives using TCT/DMF reagent. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Avance spectrometer in deuterated chloroform ($CDCl_3$) solution with tetramethylsilane as an internal standard. Fourier-transform infrared spectroscopy with a Shimadzu FTIR-8300 spectrophotometer was employed for characterization of products. GC/MS was performed using a Shimadzu GC MS-QP1000 EX instrument, and results are given in m/z (rel%). Melting points were determined in open capillary tubes using a Barnstead electrothermal 9100 BZ circulating oil melting point apparatus. Reaction monitoring was accomplished with thin-layer chromatography on silica gel PolyGram SILG/UV254 plates. Column chromatography was carried out on columns of silica gel 60 (70–230 mesh).

General procedure for the formylation of indoles and pyrroles using TCT/DMF reagent. Into a reaction tube, TCT [52] (1 mmol, 0.189 g) and DMF (0.5 mL) was added and permit is to stir for 1 h at room temperature. Then, the mixture was charged with either pyrrole or indole substrates (1.2 mmol) and 1 mL of DMF as solvent and stirred for appreciate time specified in Schemes 2–4 at 90°C. When the reaction was completed (monitored by thin-layer chromatography), a saturated solution of Na_2CO_3 (25 mL) was add to the mixture in order to hydrolyze the iminium salt for the formation of formyl group. Then, EtOAc (25 mL) was added to the reaction mixture. After separation of ethyl acetate layer from H_2O, the aqeous phase was extracted with EtOAc (25 mL) again. The combined organic layers were then dried anhydrous Na_2SO_4, filtered, and concentrated in vacuum to yield the crude product. The crude product was purified by column chromatography (*n*-hexane/EtOAc) to obtain the desired purity.

Indole-3-carbaldehyde (2a). Yield: 90% (157 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.27–7.33 (m, 3H), 7.84–7.86 (m, 1H), 8.26–8.29 (m, 1H), 10.03 (s, 1H), 11.08 (brs, 1H). ^{13}C NMR (62.5 MHz, acetone-d_6): δ

Table 2

Comparison of the results of formylation of indole using TCT/DMF reagent and other methods.

Entry	Conditions	Yield of product (%)	Ref.
1	TCT/DMF, 90°C, 2 h	**2a**: 90 **2b**: 81 **2c**: 62 **2g**: 80	This work
2	AgOTf, Cl_2CHOMe, CH_2Cl_2, −78 to 0°C, 0.5 h	**2a**: 66	[14]
3	Rose bengal, KI, O_2, hv, MeCN/H_2O, 60°C, 48 h	**2d**: 70 **2g**: 55	[15]
4	$RuCl_3$, TBHP, PivOH, *N*-methyl acetamide, 25°C, 24 h	**2a**: 81 **2b**: 34 **2c**:73	[19]
5	DMSO, H_2O, NH_4OAc, 150°C, N_2, 30 h	**2d**: 79	[46h]
6	TMEDA, O_2, $CuCl_2$, DMSO/H_2O, 120°C, 4 h	**2a**: 74 **2g**: 77	[46b]
7	TMEDA, O_2, $CuCl_2$, K_2CO_3, 120°C, 1–3 h	**2a**: 43 **2d**: 93	[46c]
8	DMF, $POCl_3$, 0°C, NaOH, H_2O,	**2a**: 97	[51]
9	nBu_4NI, TBPB, PivOH, DMSO, 80°C, 8 h	**2a**: 82 **2b**: 42 **2c**: 57	[52]

(ppm) = 111.5, 117.2, 117.3, 126.5, 127.3, 128.8, 142.4, 142.6, 189.8. MS: m/z 145 (41, M^+). *Anal*. Calcd for C_9H_7NO (145.16): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.38; H, 4.75; N, 9.53.

2-Methylindole-3 carbaldehyde (2b). Yield: 81% (155 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.74 (s, 3H), 6.96–7.26 (m, 3H), 8.21–8.25 (m, 1H), 8.75 (brs, 1H), 10.19 (s, 1H). ^{13}C NMR (62.5 MHz, acetone-d_6): δ (ppm) = 12.0, 112.3, 116.4, 121.6, 123.1, 123.9, 127.8, 136.7, 145.6, 185.1. MS: m/z 159 (36, M^+). *Anal*. Calcd for $C_{10}H_9NO$ (159.18): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.36; H, 5.61; N, 8.73.

5-Bromoindole-3-carbaldehyde (2c). Yield: 62% (167 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 7.17–7.36 (m, 2H), 7.78 (s, 1H), 8.42 (s, 1H), 8.77 (brs, 1H), 9.98 (s, 1H). MS: m/z 224 (21, M^+). *Anal*. Calcd for C_9H_6BrNO (224.05): C, 48.25; H, 2.70; N, 6.25. Found: C, 48.17; H, 2.61; N, 6.15.

1-Methylindole-3-carbaldehyde (2d). Yield: 74% (141 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.56 (s, 3H), 7.14–7.38 (m, 4H), 8.13 (m, 1H), 9.72 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 33.5, 110.0, 117.8, 121.8, 122.8, 123.9, 125.1, 137.9, 139.7, 184.4. *Anal*. Calcd for $C_{10}H_9NO$ (159.18): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.36; H, 5.63; N, 8.69.

1-Octylindole-3-carbaldehyde (2e). Yield: 90% (277 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.78–0.79 (m, 3H), 1.17–1.23 (m, 10H), 1.75–1.83 (m, 2H), 4.01–4.07 (t, *J* = 7.4 Hz, 2H), 7.20–7.28 (m, 3H), 7.68 (s, 1H), 8.20–8.24 (m, 1H), 9.98 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 13.9, 14.1, 22.6, 26.8, 29.1, 29.7, 31.7, 47.3, 110.1, 117.9, 122.1, 122.8, 123.8, 125.4, 137.2, 138.4, 184.5. MS: m/z 257 (28, M^+). *Anal*. Calcd for $C_{17}H_{23}NO$ (257.37): C, 79.33; H, 9.01; N, 5.44. Found: C, 79.21; H, 8.92; N, 5.40.

1-(4-Bromobenzyl)indole-3-carbaldehyde (2f). Yield: 88% (331 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 5.10 (s, 2H), 6.84–6.87 (d, *J* = 7.2 Hz, 2H), 7.12–7.16 (m, 2H), 7.26–7.30 (m, 5H), 7.52 (s, 1H), 8.17–8.21 (m, 1H), 9.80 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 50.2, 110.4, 118.5, 122.1, 122.3, 123.2, 124.3, 128.8, 132.2, 134.5, 137.2, 138.7, 184.7. MS: m/z 314 (31, M^+). *Anal*. Calcd for $C_{16}HBrNO$ (314.18): C, 61.17; H, 3.85; N, 4.46. Found: C, 61.08; H, 3.79; N, 4.40.

1-Allylindole-3-carbaldehyde (2g). Yield: 80% (177 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 4.56–4.58 (m, 2H), 4.98–5.17 (m, 2H), 5.78–5.89 (m, 1H), 7.17–7.20 (m, 3H), 7.52 (s, 1H), 8.18–8.20 (m, 1H), 9.82 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 49.4, 110.4, 118.2, 118.9, 122.0, 123.0, 124.0, 125.3, 131.7, 137.2, 138.7, 184.6. MS: m/z 185 (27, M^+). *Anal*. Calcd for $C_{12}H_{11}NO$ (185.22): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.73; H, 5.94; N, 7.51.

1-Decylindole-3-carbaldehyde (2h). Yield: 80% (273 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.79–0.81 (m, 3H), 1.17–1.23 (m, 14H), 1.79–1.81 (m, 2H), 4.02–4.08 (t, *J* = 7.5 Hz, 2H), 7.20–7.27 (m, 3H), 7.60 (s, 1H), 8.21–8.25 (m, 1H), 9.82 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 14.1, 22.6, 26.8, 29.1, 29.2, 29.4, 29.5, 29.7, 31.8, 47.3, 110.0, 120.8, 121.9, 122.1, 122.8, 123.9, 135.4, 138.2, 184.5. MS: m/z 285 (30, M^+). *Anal*. Calcd for $C_{19}H_{27}NO$ (285.42): C, 79.95; H, 9.53; N, 4.91. Found: C, 79.88; H, 9.44; N, 4.82.

1-(5-Bromopentyl)indole-3-carbaldehyde (2i). Yield: 57% (201 mg). ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.27–1.39 (m, 2H), 1.58–1.68 (m, 2H), 1.69–1.80 (m, 2H),

3.33–3.37 (t, J = 6.2, 2H), 3.97–4.02 (t, J = 7.0, 2H), 7.17–7.22 (m, 3H), 7.54 (s, 1H), 8.18–8.21 (m, 1H), 9.82 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 24.1, 29.0, 32.0, 44.6, 47.0, 110.1, 118.0, 122.1, 122.9, 124.0, 125.4, 137.1, 138.5, 184.5. MS: m/z 294 (21, M^+). *Anal*. Calcd for $C_{14}H_{16}BrNO$ (294.19): C, 57.16; H, 5.48; N, 4.76. Found: C, 57.08; H, 5.39; N, 4.71.

1-Phenethyl-1H-indole-3-carbaldehyde (2j). Yield: 86% (256 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.01–3.07 (t, J = 7.4 Hz, 2H), 4.26–4.32 (t, J = 7.5 Hz, 2H), 6.90–7.29 (m, 9H), 8.21–8.24 (m, 1H), 9.78 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 36.1, 48.9, 110.0, 117.9, 122.2, 122.9, 124.0, 125.4, 127.1, 128.7, 128.9, 136.6, 137.4, 138.8, 184.5. MS: m/z 249 (44, M^+). *Anal*. Calcd for $C_{17}H_{15}NO$ (249.31): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.78; H, 6.00; N, 5.49.

1-(2-Chloroethyl)-1H-indole-3-carbaldehyde (2k). Yield: 73% (181 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 3.85–3.90 (t, J = 6.0 Hz, 2H), 4.49–4.54 (t, J = 5.0 Hz, 2H), 7.32–7.36 (m, 3H), 7.79 (s, 1H), 8.32–8.35 (m, 1H), 10.02 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 42.1, 48.7, 109.5, 118.5, 119.4, 122.5, 123.2, 124.3, 136.7, 138.9, 184.7. MS: m/z 207 (25, M^+). *Anal*. Calcd for $C_{11}H_{10}ClNO$ (207.66): C, 63.63; H, 4.8; N, 6.75. Found: C, 63.63; H, 4.85; N, 6.75.

1-(4-(((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)butyl)-1H-indole-3-carbaldehyde (2l). Yield: 68% (478 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.78–1.94 (m, 41H), 2.84–2.90 (d, J = 18.0 Hz, 1H), 3.23–3.28 (t, J = 6.5 Hz, 1H), 3.92–4.07 (m, 5H), 6.98–7.57 (m, 5H), 9.54 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 19.7, 20.2, 22.6, 23.2, 23.4, 24.4, 26.4, 26.7, 26.8, 28.2, 29.3, 29.8, 30.0, 35.8, 36.2, 37.2, 37.7, 38.8, 39.1, 46.2, 47.7, 56.9, 63.1, 64.1, 71.8, 101.0, 109.3, 119.1, 119.2, 121.0, 121.4, 122.2, 127.7, 134.2, 136.5, 151.9, 183.0. MS: m/z 585 (39, M^+). *Anal*. Calcd for $C_{40}H_{59}NO_2$ (585.90): C, 82.00; H, 10.15; N, 2.39. Found: C, 81.91; H, 10.06; N, 2.32.

Pyrrole-2-carbaldehyde (2m). Yield: 85% (96 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 6.34–6.36 (t, J = 2.5 Hz, 1H), 7.01–7.02 (m, 1H), 7.18–7.19 (d, J = 1.0 Hz, 1H), 9.51 (s, 1H), 10.68 (brs, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 111.3, 122.1, 127.2, 123.9, 179.6. *Anal*. Calcd for C_5H_5NO (95.10): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.07; H, 5.25; N, 14.66.

1-Phenethyl-1H-pyrrole-2-carbaldehyde (2n). Yield: 89% (212 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.85–2.91 (t, J = 7.6 Hz, 2H), 4.32–4.38 (t, J = 7.2 Hz, 2H), 5.96–5.99 (m, 1H), 6.52 (s, 1H), 6.78–6.79 (m, 1H), 6.95–6.98 (d, J = 7.5 Hz, 1H), 7.06–7.15 (m, 5H), 9.42 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 23.9, 50.8, 109.4, 125.1, 126.6, 128.5, 129.0, 131.1, 131.7, 138.2, 179.2. MS: m/z 199 (32, M^+). *Anal*. Calcd for $C_{13}H_{13}NO$ (199.25): C, 78.36; H, 6.58; N, 7.03. Found: C, 78.27; H, 6.52; N, 6.91.

1-(4-Bromobenzyl)--pyrrole-2-carbaldehyde (2o). Yield: 86% (272 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 5.74 (s, 2H), 6.26–6.28 (t, J = 2.5 Hz, 1H), 6.96–67.01 (m, 4H), 7.38–7.41 (d, J = 7.5 Hz, 2H), 9.52 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 51.38, 110.4, 121.7, 125.1, 129.0, 131.5, 131.8, 136.8, 179.5. MS: m/z 264 (29, M^+). *Anal*. Calcd for $C_{12}H_{10}BrNO$ (264.12): C, 54.57; H, 3.82; N, 5.30. Found: C, 54.49; H, 3.76; N, 5.25.

1-Phenyl-H-pyrrole-2-carbaldehyde (2p). Yield: 81% (166 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 6.32–6.34 (t, J = 2.5, 1H), 6.98–7.39 (m, 7H), 9.59 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 110.9, 122.0, 126.07, 128.2, 129.10, 131.0, 132.6, 138.75, 179.0. MS: m/z 171 (28, M^+). *Anal*. Calcd for $C_{11}H_9NO$ (171.20): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.10; H, 5.24; N, 8.11.

***1-(p*-Tolyl)-1H-pyrrole-2-carbaldehyde (2q).** Yield: 83% (184 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.35 (s, 3H), 6.32–6.34 (t, J = 2.0 Hz, 1H), 6.97–7.20 (m, 6H), 9.49 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 21.1, 110.7, 121.6, 125.8, 129.7, 131.0, 132.6, 135.1, 136.7, 179.1. MS: m/z 185 (19, M^+). *Anal*. Calcd for $C_{12}H_{11}NO$ (185.22): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.72; H, 5.93; N, 7.50.

1-(4-Bromophenyl)-1H-pyrrole-2-carbaldehyde (2r). Yield: 80% (240 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 6.28–6.30 (t, J = 2.2 Hz, 1H), 6.97–7.23 (m, 5H), 7.45–7.50 (m, 1H), 10.01 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 111.2, 123.7, 129.2, 131.2, 132.3, 134.2, 137.7, 178.8. MS: m/z 250 (24, M^+). *Anal*. Calcd for $C_{11}H_8BrNO$ (250.09): C, 52.83; H, 3.22; N, 5.60. Found: C, 52.74; H, 3.17; N, 5.52.

1-(4-Chlorophenyl)-1H-pyrrole-2-carbaldehyde (2s). Yield: 85% (209 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 6.33–6.36 (t, J = 3.2 Hz, 1H), 6.96–7.39 (m, 6H), 9.50 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 111.1, 123.6, 127.2, 129.2, 131.3, 132.1, 134.1, 137.4, 178.7. MS: m/z 205 (41, M^+). *Anal*. Calcd for $C_{11}H_8ClNO$ (205.64): C, 64.25H, 3.92; N, 6.81. Found: C, 64.17; H, 3.85; N, 6.73.

1,1′-(1,4-Phenylene)bis(1H-pyrrole-2-carbaldehyde) (2t). Yield: 75% (237 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 6.32–6.34 (t, J = 2.5 Hz, 2H), 6.96–7.16 (m, 6H), 7.48–7.51 (d, J = 7.7 Hz, 2H), 9.48 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 111.2, 123.7, 127.5, 127.7, 131.3, 132.2, 138.1, 178.7. MS: m/z 264 (16, M^+). *Anal*. Calcd for $C_{16}H_{12}N_2O_2$ (264.28): C, 72.72; H, 4.58; N, 10.60. Found: C, 72.64; H, 4.51; N, 10.53.

1,1′-(1,3-Phenylenebis(methylene))bis(1H-pyrrole-2-carbaldehyde) (2u). Yield: 79% (277 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 5.50 (s, 4H), 6.24–6.26 (t, J = 2.5 Hz, 2H), 6.92–7.25 (m, 8H), 9.52 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) = 51.7, 110.2, 124.9, 125.9, 126.4, 129.1, 131.5, 138.1, 179.5. MS: m/z 292 (27, M^+). *Anal*. Calcd for $C_{18}H_{16}N_2O_2$ (292.33): C, 73.95; H, 5.52; N, 9.58. Found: C, 73.86; H, 5.45; N, 9.51.

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[52] Please see the MSDS of TCT (MSDS ICSC 1231) because it is a lachrymator and causes burns on contact with the skin.