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F-Tag Induced Acyl Shift in the Photochemical Cyclization of *o*-Alkynylated *N*-Alkyl-*N*-acylamides to Indoles**

Helena Simek Tosino,[a] André Jung,[a] Olaf Fuhr,[b, c] Claudia Muhle-Goll,[d] Nicole Jung,*[a, c] and Stefan Bräse*[a, c]

A photochemical cyclization of F-tagged, *o*-alkynylated *N*-alkylamides to indoles catalyzed by $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ is presented. This straightforward and efficient reaction involves an intramolecular rearrangement due to the presence of an electron withdrawing group in the acyl moiety and is the first example of photochemically induced 1,3-acyl shift in the cyclization towards 3-acylindoles. A four-step reaction sequence including the photoreaction as a key step to the desired indoles has been developed and optimized. The compatibility of differently substituted F-tagged precursors with the photocyclization step was investigated and the robustness of this step towards modifications could be shown. In total, 16 so far unknown derivatives with diverse modifications in positions N1 and C2, bearing a pentadecafluorooctanoyl moiety as F-tag, were synthesized in very good yields and fully characterized.

Introduction

Developing new synthetic approaches for the synthesis of nitrogen-containing heterocyclic compounds from readily available starting materials is an important topic in modern organic chemistry.[1,2] Of special interest for mimicking natural processes is the synthesis of indole-containing systems as indoles are one of the most widely distributed heterocycles in nature.[3–5] In particular, 3-acylindoles and their derivatives are ubiquitous in natural products, biologically active compounds and pharmaceuticals,[6–9] expressing diverse benefits such as hypocholesterolemic, analgesic,[7,10] anti-inflammatory, immunomodulatory, antiemetic, antivirus and anticancer activities (Figure 1).[10] Indoles are also versatile precursors for the synthesis of alkaloids and other related heterocycles.[6–9,11]

Common methods to synthesize 3-acylindoles include the Friedel-Crafts acylation,[5,6,8–12,14] Vilsmeier-Haack reaction[5,6,8,9,11,12,14] and indole Grignard reaction.[5,6,8,9,11,12] Generally, these often suffer from side reactions,[5,6,8,9] like *N*1-acylation or oligomerisation in the case of the Friedel-Crafts acylation,[5,6] and involve harsh reaction conditions, such as the use of $POCl_3$ in the Vilsmeier-Hack reaction.[5,9] As a consequence, the development of new, more efficient methods for the synthesis of 3-acylated indoles is encouraged.[5,8,9] In the last years, excellent methods for the synthesis of 3-acylindoles using preformed indoles have been developed.[12,14,15] In contrast, approaches for their assembly from readily-available non-indole starting materials using a simple and expedient procedure still remain scarce[12,16] with only very few examples involving visible light.[1,12,17–20] Examples for successful photochemical reactions are, for example, the direct coupling of anilines with alkynes[20] or Langlois' reagent[19] under visible-light irradiation, as well as visible-light induced cyclizations of 2-alkynylated aniline derivatives,[1,17,18] Aiming for a fast and efficient process to gain novel 3-acylindoles with diverse modifications in positions *N*1 and *C*2, we investigated the visible-light photoredox synthesis previously reported by Zhang et al.[12] The proposed mechanism of this reaction involves a deprotonation step in the benzylic position of compound **4**, resulting in the formation of a more stable α-amino benzyl radical which can undergo cyclization (Scheme 1a) to compounds of type **6**. The most similar approach to the synthesis of 3-acylated indoles induced by a thermal process was realized by cyclization of alkynylated anilines involving 1,3-acyl shift (Scheme 1b).[21,22]

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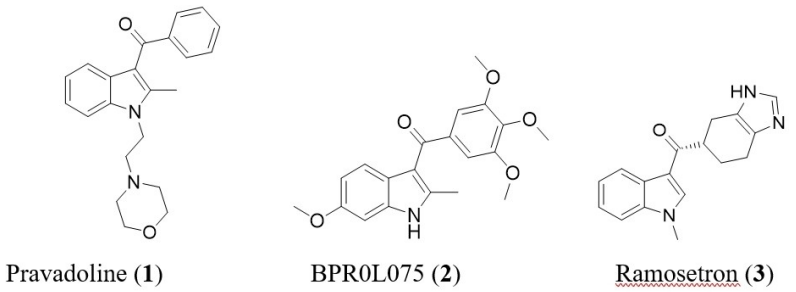
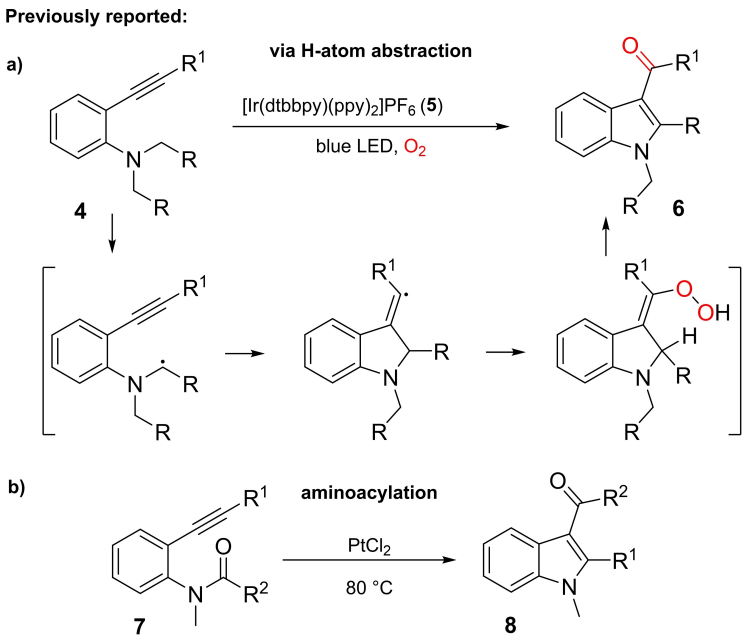


Figure 1. Selected examples of 3-acylindoles. Anti-inflammatory and analgesic Pravadoline (**1**),[4,10,12] anticancer BPR0 L075 (**2**),[13] and antiemetic Ramosetron (**3**).[10]



Scheme 1. Examples for syntheses of 3-acylindoles. a) Visible light-induced intramolecular oxidative cyclization of *o*-alkynylated *N,N*-dialkylamines;[12] b) Thermally induced, platinum-catalysed cyclization through 1,3-acyl shift.[21,22]

Results and Discussion

Using the previously described method by Zhang et al.[12] (Scheme 1a), we envisaged the synthesis of compounds **6** with an acyl-fluorous tag, introduced by replacement of one of the *N*-bound alkyl substituents R in compound **4**. The desired F-tagged (fluorine-tagged) alkynyl-functionalized aniline precursors **15a**–**15u** were obtained from 2-iodoaniline (**9**) through a three-step procedure (Scheme 2). The order of the reaction steps and the conditions were varied in the attempt to optimize the outcome of the target compounds. Scheme 2 summarizes the results with respect to an optimization of the order of the reaction steps and the reaction conditions in detail, highlighting the results of the optimization for compound **15a**. First attempts with a variation of the order of the reaction steps resulted in different findings: The alkylation of 2-iodoaniline (**9**) in a first step results in the formation of a double-alkylated by-product, indicating that alkylation should be conducted after the introduction of the desired electron-withdrawing F-tag. Furthermore, full conversion of the Sonogashira reaction was not achieved if the substrate bore both the F-tag and the R^2 on the nitrogen atom. The optimal order of the reaction steps was therefore found to be: (1) a Sonogashira cross-coupling reaction, (2) an *N*-acylation, and (3) an *N*-alkylation. The conditions of the Sonogashira coupling, as well as the acylation reaction, both involved the use of diisopropylethyl amine (DIPEA) as a base and acetonitrile as a solvent, and resulted in a full conversion of the starting material after short time (2–5 h). Finally, the alkylation reaction in the presence of K_2CO_3 in refluxing acetonitrile yielded the desired precursor **15a**. All other compounds **15** shown in Scheme 2 were synthesized according to the same, optimized pathway in mostly very good yields for the single steps and the whole sequence. DIPEA also turned out to be a well-performing base in the alkylation step and could be used as an organic alternative for K_2CO_3 except

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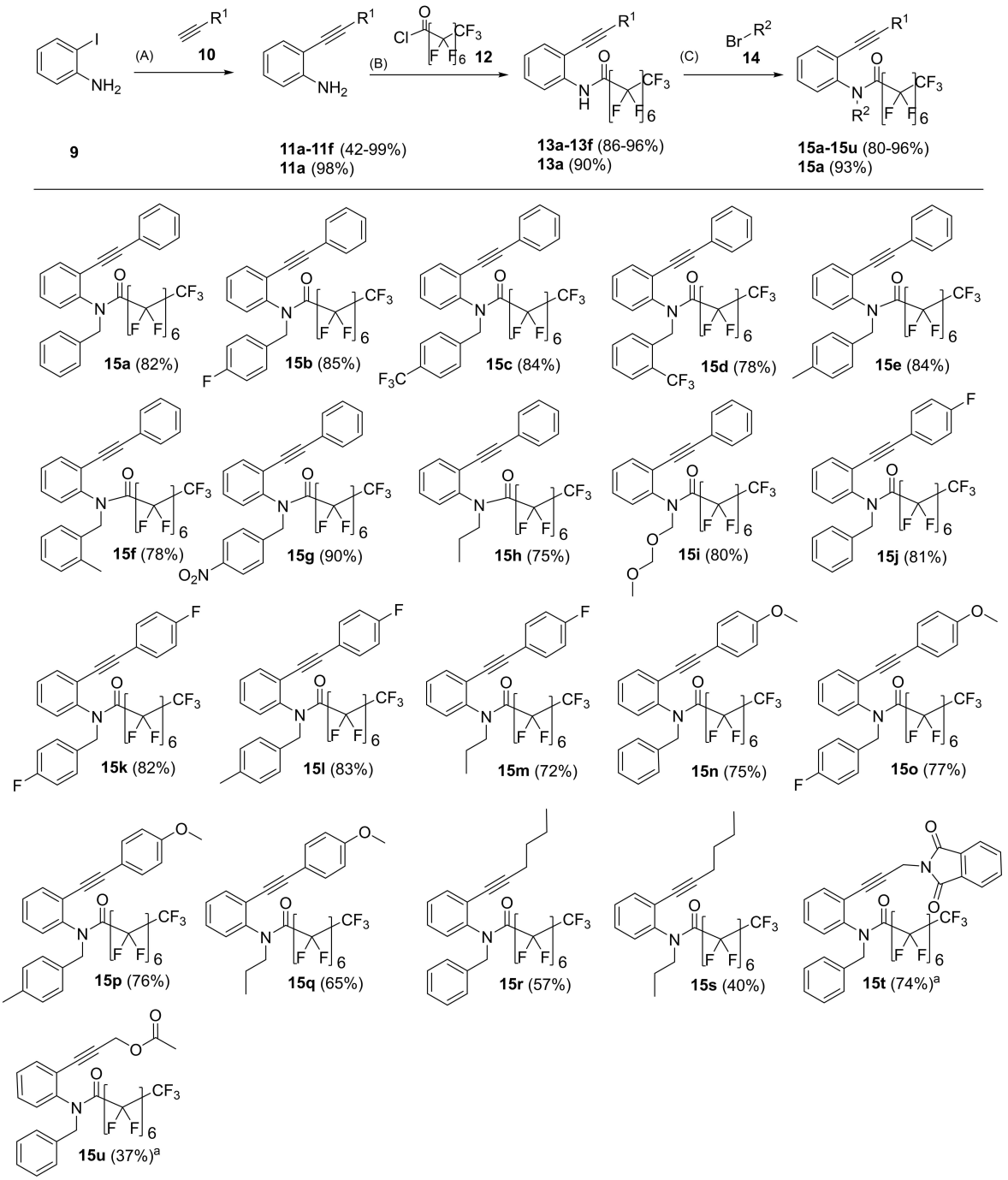

Scheme 2. Optimized reaction route and structures of the synthesized F-tagged alkynyl-functionalized cyclization precursors **15a**–**15u** with yields of the sequence including three reaction steps. (A) 0.02 equiv. $Pd(PPh_3)_2Cl_2$, 0.04 equiv. CuI, 2.50 equiv. DIPEA, 1.25 equiv. alkyne (**10**), MeCN, 21 °C, 4–48 h; (B) 4.0 equiv. DIPEA, 1.1 equiv. R_FCOCl (**12**), MeCN, 0–21 °C, 2.5-3 h; (C) 1.5 equiv. K_2CO_3, 1.5 equiv. R^2Br (**14**), MeCN, 80 °C, 24 h. [a] DIPEA was used for alkylation.

when using iodopropane as a reagent, where it led to diminished yields (see Supporting Information Table S1 for the comparison of yields).

In our model system, the photoinduced cyclization of the F-tagged aniline derivative **15a** under previously reported conditions using $[Ir(dtbbpy)(ppy)_2]PF_6$ (**5**) as a photocatalyst[12] did not lead to any conversion. Other catalysts commonly used in related literature,[12,17] such as ruthenium complexes and the organic dyes Eosin Y and Rose Bengal, were also examined, but gave no conversion of the starting material. Among all tested catalysts, only $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$ (**16**) was found to convert the starting material, at least to a small extend, under conditions as reported by Zhang et al.[12] (Scheme 3). Interestingly, the photoinduced cyclization of the F-tagged substrate did not yield the expected product. Instead, a rearrangement of the fluorous acyl moiety to the

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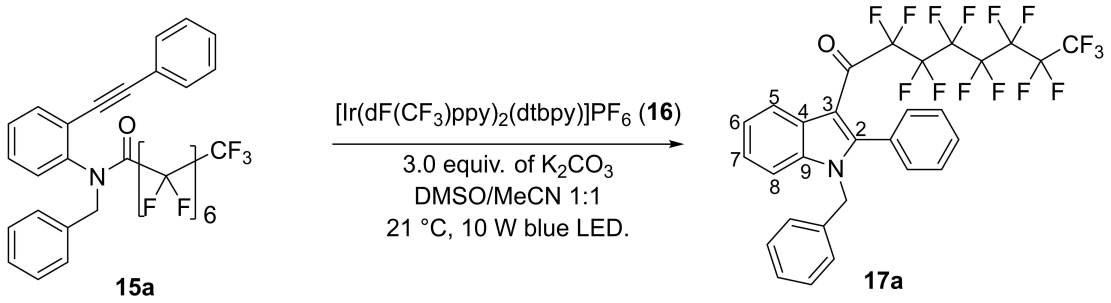

Scheme 3. Synthesis of the 3-acylated indole derivative by photochemically induced 1,3-acyl shift of the perfluorinated acyl group.

compound **17a** was observed (Scheme 3). The 1,3-acyl shift in the cyclization of alkynylated anilines to form 3-acylindoles was reported in literature but could so far, to the best of our knowledge, only be achieved thermally in the presence of metals like platinum,[21,22] zinc[23] and palladium,[24] like exemplarily shown on Scheme 1b for the platinum catalysed cyclization of **7** to the 3-acylindole derivative **8**.

Initially, the structure of **17a** was investigated by ^{1}H NMR (nuclear magnetic resonance), which confirmed that a cyclization to the indole scaffold had occurred. Furthermore, the presence of the perfluorinated chain in the sample was confirmed by ^{19}F NMR and the product mass could be confirmed using FAB-MS (fast atom bombardment-mass spectroscopy) and HRMS (high resolution mass spectroscopy) measurements. However, at this point, it was still not clear at which position the fluorinated acyl moiety was attached to the indole core. The structure of **17a** was further examined and confirmed by 2D NMR spectroscopy and single crystal X-ray diffraction (Figure 2b; please see Supporting Information for further data). The NMR-based characterization of the obtained structure included some interesting aspects due to presence of the fluorous tag and the need to exactly determine its attachment point to the indole core. The ^{13}C NMR signal corresponding to the *C*-5 carbon atom occurs as a triplet in the spectrum, while on the other hand, quaternary *C*-4 and *C*-3 carbons with less bond distance to the first CF_2-group appear as singlets in the ^{13}C NMR spectrum. This effect can be explained by the non-bonded proximity through space of the carbon and fluorine nuclei.[25] Additional challenges were observed in the attempt to determine the centre of the ^{13}C signals in the fluorine tag which occur with complex multiplicity and a very low intensity due to the coupling of ^{13}C atoms to multiple ^{19}F nuclei. To circumvent this and to understand the connectivity of ^{13}C to ^{19}F nuclei, a ^{19}F{1H}-^{13}C{1H}-HSQC (heteronuclear single quantum coherence) NMR spectrum was measured (Figure 2a). The spectrum clearly showed coupling of seven carbon nuclei with fluorine over one bond and chemical shifts of the involved carbon atoms could be determined, although the signals could not be clearly separated from each other and were difficult to identify in the 1D ^{13}C NMR spectra. The ^{19}F{1H}-^{13}C{1H}-HSQC NMR measurement was used to characterize all final compounds and was identified as a fast and reliable method to gain the required information on the centre of all ^{13}C nuclei in the isolated compounds.

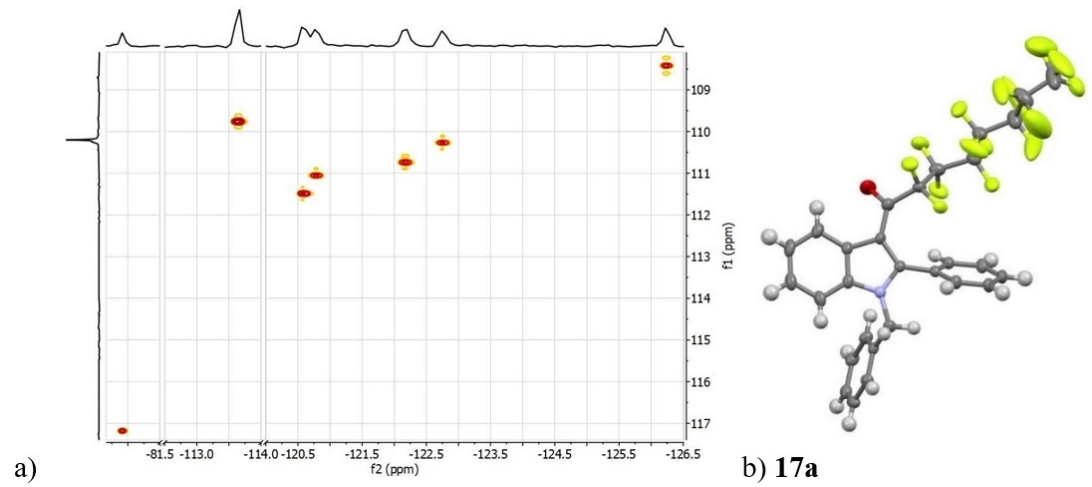

Figure 2. Characterization of the compound **17a**. a) ^{19}F{1H}–^{13}C{1H} HSQC spectrum allowing the identification of ^{19}F-coupled ^{13}C NMR signals through correlation to ^{19}F NMR signals; b) Molecular structure determined by single crystal X-ray diffraction.

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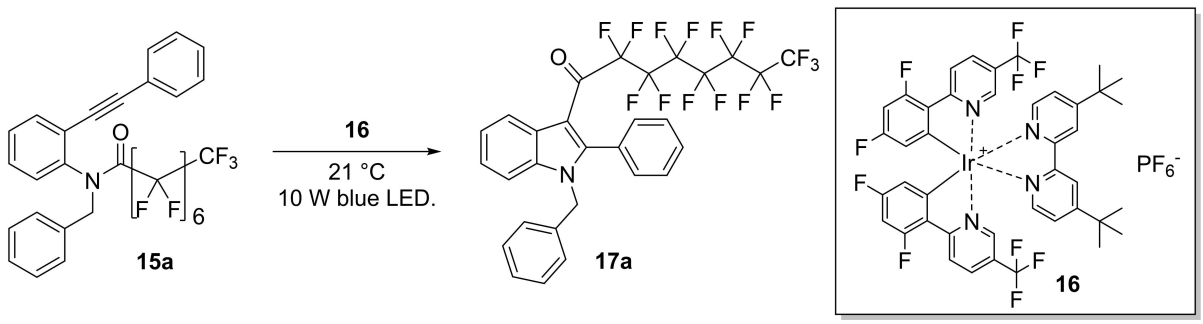
To improve the yield of the reaction from compound **15a** to **17a**, the conditions of the photoinduced indole formation step catalysed by **16** were altered including the testing of different solvents, bases, catalyst loadings and concentrations of the starting material under 48 h irradiation with blue LED (light emitting diode) light (λ = 465 nm). The key results are summarized in Table 1 (please see Supporting Information for all tested conditions). Initial solvent screenings revealed dimethylsulfoxide (DMSO)/acetonitrile (MeCN) 1:1 to be the best option when using K_2CO_3 as a base and with a catalyst loading of 1.5 mol%. Using the organic base collidine instead of inorganic K_2CO_3 resulted in a higher yield (Table 1, Entry 2). Further investigations showed that DMSO as sole solvent gives the best results (Table 1, Entry 3), and that the addition of a base was not necessary to gain comparable yields to reactions with base (Table 1, Entry 4). Increasing the catalyst loading resulted in slightly increased yields (Table 1, Entries 5–7), but the highest improvement was made by lowering the molarity of the reaction. Using a concentration of 0.01 M (with respect to the starting material **15a**) led to the full conversion of the starting material in 24 h (Table 1, Entry 8). The best conditions for the conversion of **15a** into indole **17a** were found to be a catalyst loading of 3 mol% and a 0.01 M concentration of **15a** in DMSO. Control experiments revealed that both visible light irradiation as well as the presence of a photocatalyst are obligatory for the reaction to take place (Table S2, Supporting Information).

The scope of the reaction was tested with the synthesis of a small library of indole derivatives by irradiating the precursors **15a**–**15u** in the presence of the iridium catalyst **16** with 15 W blue LED light (λ = 465 nm). The details of the photoreactor used for derivative synthesis are described by Li et al.[26] In total, 16 so far unknown F-tagged derivatives were synthesized successfully with yields ranging from 52% to 80%, showing the compatibility of this transformation with differently substituted precursors (Scheme 4). Cyclization of the compounds with benzylic R^2 was successful and both electron-withdrawing (–F, $–CF_3$) and electron-donating ($–CH_3$) substituents of this benzyl moiety were well-tolerated in the photoreaction, giving the desired products **17b**–**17f** in yields ranging from 69% to 79%. The only exception was found for $R^2 = p\text{-}NO_2–Bn$, for which the cyclization did not yield the desired product and the starting material could be regained. The cyclization of the precursors with aliphatic R^2 and with phenylic R^1 also yielded the desired products **17h**–**17q** in very good yields, showing the robustness of this reaction towards modifications. On the other hand, aliphatic alkynes, bulky isoindolinone alkyne and the methylacetyl alkyne were not tolerated and could not be converted to the desired products **17r**–**17u** under the applied conditions (please see Supporting Information for unsuccessful experiments).

To investigate the tolerance of the reaction with respect to different acyl-moieties instead of the fluorous tag in compounds **15**, derivatives bearing an electron withdrawing group (EWG) such as trifluoromethyl, pentafluorophenyl and *p*-CF_3-phenyl group were prepared and reacted under optimized conditions as described in Scheme 5. The pentafluorobenzoyl-substituted product **17v** was obtained in 79% yield, while the trifluoroacetyl product **17x** could only be isolated in 9% yield while most of the starting material (56%) was recovered. Interestingly, the *p*-CF_3-benzoyl derivative **17w**, having a phenyl group between the acyl and trifluoromethyl group in comparison to the derivative **17x**, could also be successfully synthesized and isolated in 54% yield. Furthermore, *p*-cyanobenzoyl substituted precursor **15y**, bearing a non-fluorine electron-withdrawing group, was successfully converted to the product **17y** in 68% yield after 21 h. This opens up the possibility to transfer the method to other fluorine-containing groups, as well as to non-fluorine, strongly electron-withdrawing acyl groups, leading to extension of the

Table 1. Optimisation of the photoreaction.



Entry	Conc of **15a** [M]	Solvent	Base[a]	16 [mol%]	Time [h]	Yield of **17a** [%]
1	0.05	DMSO/MeCN 1:1	K_2CO_3	1.5	24	12
2	0.05	DMSO/MeCN 1:1	collidine	1.5	48	33
3	0.05	DMSO	collidine	1.5	48	45
4	0.05	DMSO	–	1.5	48	46
5	0.05	DMSO	–	3	48	55
6	0.05	DMSO	–	5	48	59
7	0.05	DMSO	–	7	48	62
8	0.01	DMSO	–	3	24	80

All reactions were performed at 21 °C under irradiation with λ = 465 nm. [a] 3 equiv. of base were added.

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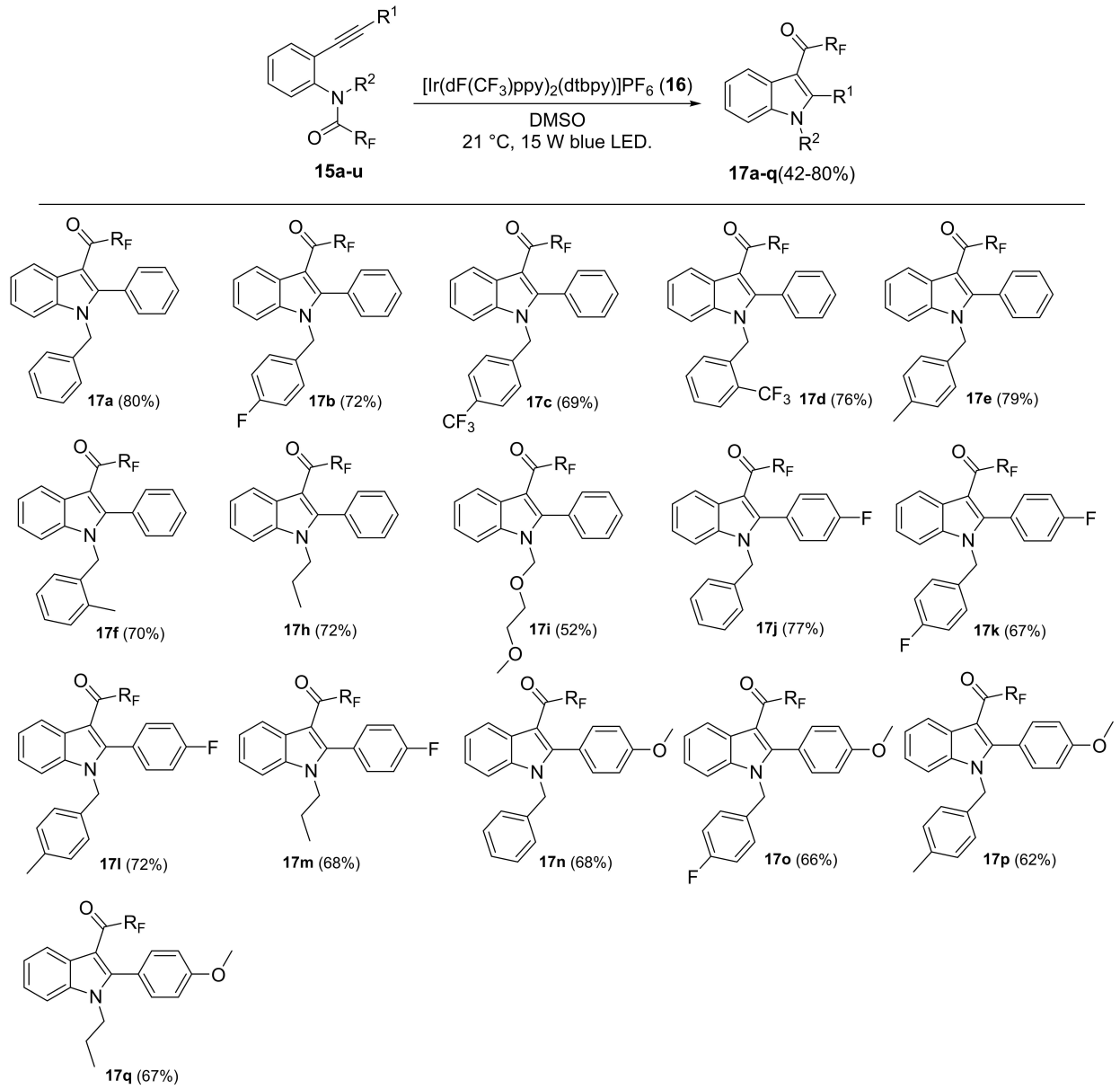

Scheme 4. Synthesized F-tagged indole derivatives **17a**–**17q** with corresponding yields for the photoinduced cyclization step.

developed approach. Cyclization precursors bearing different other groups such as benzoyl, pentanoyl and 2,4,6-trichlorobenzoyl moieties did not react under described conditions (see Supporting Information for unsuccessful experiments with compounds **15aa**–**15af**).

Additional investigations were made with the attempt to gain insights into the mechanism of this reaction. For a crossover experiment, a solution of equimolar amounts of **15e** and **15v** was irradiated with blue LED light under standard conditions (Scheme 6). No evidence for crossover products **17ev** and **17ve** was found and only **17e** and **17v** could be isolated in yields of 64% and 39%, respectively, suggesting that the cyclization occurs in an intramolecular manner.

The initiation of the cyclization reaction from **15a** to **17a** (Scheme 4) with the radical starters AIBN (azobis(isobutyronitril)) and DBPO (dibenzoylperoxide) under thermal conditions was not successful and no product could be isolated, indicating that the conversion can only be achieved photochemically. Radical quenching experiments with TEMPO (2,2,6,6-tetramethylpiperidinyloxyl) and BHT (butylated hydroxytoluene) showed diminished yields depending on the amount of scavenger used (Table S4, Supporting Information) with 3 equiv. of TEMPO being sufficient for the complete suppression of the reaction. These findings suggest that the reaction might proceed through a radical pathway, even though the respective quenching products could not be isolated and no direct chemical evidence could be obtained. To investigate the redox behavior of the compounds **15**, cyclic voltammetry experiments were conducted with compound **15a**. Neither oxidation nor reduction signals could be

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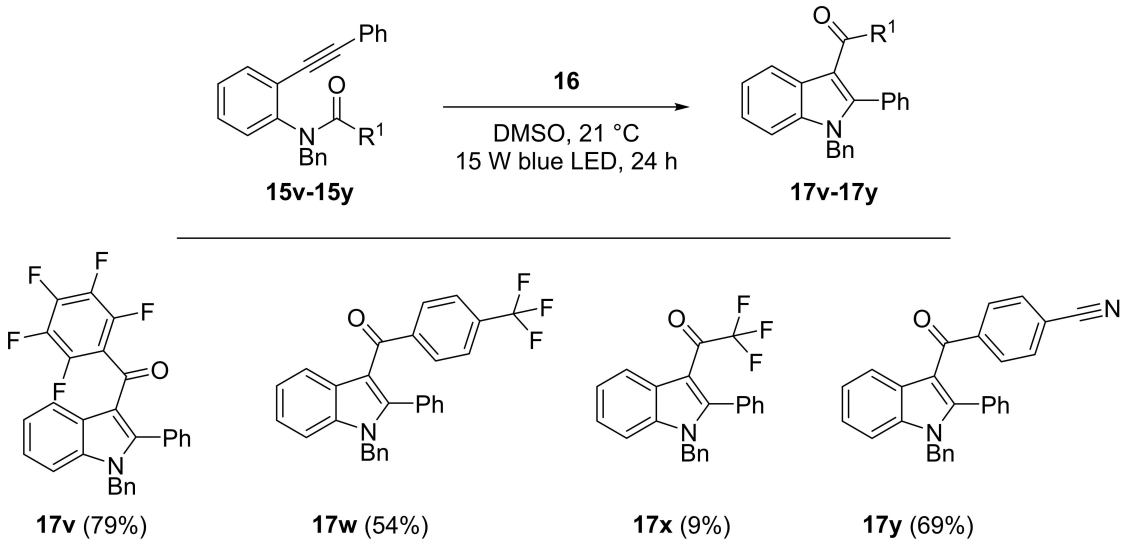
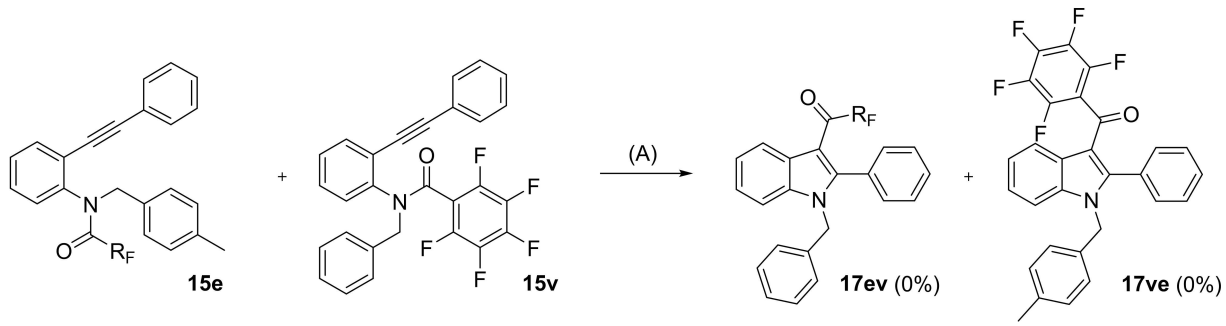


Scheme 5. Synthesized derivatives **17 v**, **17 w**, **17 x** and **17 y** bearing different acyl moieties.



Scheme 6. Crossover experiment as proof for an intramolecular process. (A) 6.0 mol % $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$, DMSO, 21 °C, 15 W blue LED, 27 h.

observed in the cyclic voltammogram in the range of −2 V to +2 V, indicating a high ground state redox stability of the cyclization precursor. Also experiments repeated under blue LED light gave no clear indication of a redox potential of compound **15 a**. As the mechanism of the reaction could not be proven in this study, further investigations will be part of future work.

Conclusion

We discovered and optimized a new photochemical cyclization reaction to synthesize indole derivatives from F-tagged *o*-alkynylated *N*-alkyl-*N*-acylamides and a few other EWG-substituted *o*-alkynylated *N*-alkyl-*N*-acylamides. The reaction involves the 1,3-acyl shift of the fluorous (or EWG-containing) acyl moiety from position *N*1 to the position *C*3 and experiments have shown that both visible light irradiation as well as the presence of electron withdrawing groups in the acyl moiety are necessary for this kind of rearrangement to occur. Additionally, an efficient reaction route toward the cyclization precursors from commercially available and non-expensive 2-iodoaniline was developed. The order of reaction steps and conditions of each step were optimized to gain optimal results with respect to the yield and purity of the compounds. The combination of the developed reaction route towards F-tagged precursors with the new cyclization reaction resulted in a fast and expedient process to synthesize novel indole derivatives with diverse modifications in positions *N*1 and *C*2. Using this process, a small library of 16 novel, F-tagged 3-acylindole derivatives, as well as four additional derivatives bearing other EWG-containing acyl moieties, was synthesized. The results of this study were confirmed by X-ray crystallography of crystal structures gained after different steps of the reaction sequence. In addition, $^{19}F\{1H\}$–$^{13}C\{1H\}$–HSQC NMR measurements were used to characterize all 16 F-tagged target compounds, providing a fast and reliable method to gain the required information on the centre of all ^{13}C nuclei in the isolated compounds. The fluorine tag should be easily cleavable from the products, yielding 3-carboxylic acid[27] or 3-ester derivatives[28] of the synthesized substituted indoles. This would make them valuable candidates for different biological screenings, since the indole core is an important building block present in many biologically active compounds.

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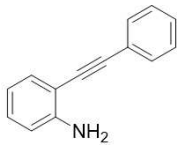
Experimental Section

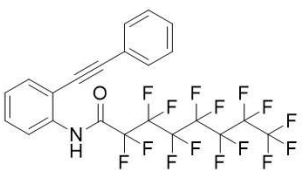
Exemplarily selected experiments describing the main steps of the process are described in the experimental section. All further reactions are available in the Supplemental Information.

2-(2-phenylethynyl)aniline (11 a)



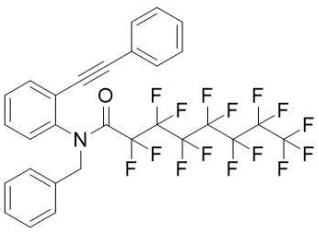
In a flask, 2-iodoaniline (1.00 g, 4.57 mmol, 1.00 equiv.) was dissolved in anhydrous MeCN (10 mL), followed by the subsequent addition of copper(I) iodide (35.3 mg, 185 μmol, 0.0406 equiv.), bis(triphenylphosphine)palladium(II) dichloride (64.8 mg, 92.3 μmol, 0.0202 equiv.) and N,N-diisopropylethylamine (1.77 g, 2.39 mL, 13.7 mmol, 3.00 equiv.). Then ethynylbenzene (725 mg, 780 μL, 6.96 mmol, 1.52 equiv.) was added dropwise and the mixture was stirred at 21 °C. After 4 h, the solvent was removed under reduced pressure to afford the crude product. The obtained crude product was purified via flash-chromatography (Interchim devices puriFLASH 4125) on silica gel (PF-15SIHP-F0080) using cyclohexane/ethyl acetate 0% to 5% ethyl acetate in 10 column volumes to afford 2-(2-phenylethynyl)aniline (861 mg, 4.46 mmol) as an orange solid in 98% yield. R_f = 0.59 (cHex:EtOAc = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$ [7.26 ppm] ppm) δ = 7.56–7.51 (m, 2H), 7.41–7.30 (m, 4H), 7.15 (ddd, J = 8.1, 7.3, 1.6 Hz, 1H), 6.74 (td, J = 7.7, 0.9 Hz, 2H), 4.20 (br.s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$ [77.16 ppm] ppm) δ = 147.9, 132.3 (+, CH), 131.6 (+, CH, 2 C), 129.9 (+, CH), 128.5 (+, CH, 2 C), 128.4 (+, CH), 123.5, 118.1 (+, CH), 114.5 (+, CH), 108.1, 94.8, 86.0; MS (EI, 70 eV, 30 °C), m/z (%): 194 (16) $[M+1]^+$, 193 (100) $[M]^+$, 192 (9), 181 (43), 165 (26), 131 (45), 119 (12), 100 (11), 90 (10), 69 (83). HRMS ($C_{14}H_{11}N$): calcd 193.0885, found 193.0866; IR (ATR, ṽ) = 3463 (w), 3381 (w), 3367 (w), 3048 (w), 3029 (w), 2953 (vw), 2921 (w), 2871 (vw), 2854 (w), 2204 (w), 1611 (m), 1592 (w), 1567 (w), 1494 (w), 1482 (m), 1453 (m), 1439 (w), 1391 (vw), 1310 (m), 1275 (w), 1258 (w), 1150 (w), 1068 (w), 1024 (w), 941 (w), 914 (w), 858 (w), 744 (vs), 688 (vs), 622 (w), 582 (w), 560 (m), 526 (m), 516 (m), 479 (s), 448 (m), 438 (w), 422 (w), 415 (w), 401 (m), 387 (s), 377 (s) cm^{-1}.

2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-(2-(phenylethynyl)phenyl)octanamide (13 a)



2-(2-Phenylethynyl)aniline (501 mg, 2.54 mmol, 1.00 equiv.) was dissolved in dry MeCN (15 mL) under inert atmosphere and N,N-diisopropylethylamine (1.34 g, 1.80 mL, 10.3 mmol, 4.07 equiv.) was added. The solution was cooled to 0 °C using an ice bath and after 10 minutes of stirring, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoyl chloride (1.22 g, 700 μL, 2.74 mmol, 1.08 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 10 minutes, then the cooling was removed and the mixture allowed to warm up to 21 °C. Once all the starting material was consumed (monitored by TLC), the solvent was removed under reduced pressure to afford the crude product. The obtained crude product was purified via flash-chromatography (Interchim devices puriFLASH 4125) on silica gel (PF-15SIHP-F0080) using cyclohexane/ethyl acetate 0% to 2% ethyl acetate in 10 column volumes (1 column volume = 173.2 mL, flowrate 34 mL/min) to afford 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-(2-(phenylethynyl)phenyl)octanamide (1.35 g, 2.29 mmol) as an colorless solid in 90% yield. R_f = 0.34 (cHex:EtOAc = 50:1). ^{1}H NMR (400 MHz, $CDCl_3$ [7.26 ppm] ppm) δ = 8.96 (br.s, 1H), 8.37 (dd, J = 8.4, 1.1 Hz, 1H), 7.58 (dd, J = 7.7, 1.5 Hz, 1H), 7.54–7.49 (m, 2H), 7.47–7.36 (m, 4H), 7.23 (td, J = 7.6, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ [77.16 ppm] ppm) δ = 155.0 (t, J = 25.8 Hz), 136.3, 131.9 (+, CH), 131.6 (+, CH, 2 C), 130.0 (+, CH), 129.5 (+, CH), 128.8 (+, CH, 2 C), 125.8 (+, CH), 121.8, 119.8 (+, CH), 113.7, 98.2, 82.9, carbons of the F-chain (7 C) are not visible in the spectra; ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = [(−77.15)–(−84.18) (m)], [(−119.05)–(−119.92) (m)], [(−120.95)–(−121.56) (m)], [(−121.79)–(−122.04) (m)], [(−122.04)–(−122.38) (m)], [(−122.49)–(−123.33) (m)], [(−125.59)–(−126.80) (m)]; MS (FAB, 3-NBA), m/z (%): 591 (17) $[M+2]^+$, 590 (73) $[M+1]^+$, 589 (100) $[M]^+$, 307 (16), 193 (52), 155 (22), 154 (67), 139 (16), 138 (30), 137 (42), 136 (49), 107 (16), 105 (21). HRMS (C22H10F15NO): calcd 589.0517, found 589.0516; IR (ATR, ṽ) = 3322 (w), 1714 (m), 1579 (w), 1534 (m), 1493 (w), 1448 (w), 1367 (w), 1324 (w), 1306 (w), 1278 (vw), 1227 (s), 1196 (vs), 1163 (s), 1143 (vs), 1106 (s), 1071 (w), 1041 (w), 1016 (s), 989 (vw), 950 (w), 912 (w), 849 (vw), 751 (vs), 738 (m), 722 (s), 688 (s), 677 (m), 657 (m), 636 (m), 620 (vs), 598 (w), 584 (w), 567 (s), 554 (m), 544 (s), 528 (vs), 504 (m), 492 (m), 475 (s), 380 (vw) cm^{-1}.

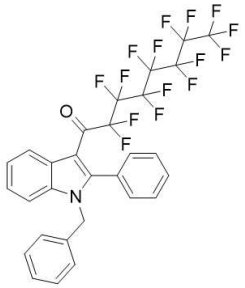
N-benzyl-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-(2-(phenylethynyl)phenyl)octanamide (15 a)



In a vial, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-(2-(phenylethynyl)phenyl)octanamide (300 mg, 509 μmol, 1.00 equiv.) was dissolved in MeCN (10 mL). Potassium carbonate (106 mg, 763 μmol, 1.50 equiv.) and benzyl bromide (129 mg, 90.0 μL, 742 μmol, 1.46 equiv.) were added and the mixture was stirred at 80 °C. After 24 h, the solvent was removed under reduced pressure to afford the crude product. The obtained crude product was purified via flash-chromatography (Interchim devices puriFLASH 4125) on silica gel (PF-15SIHP-F0040) using cyclohexane/ethyl acetate 0% to 2% ethyl acetate in 10 column volumes (1 column volume = 91.9 mL, flow rate 26 mL/min) to afford N-benzyl-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-(2-(phenylethynyl)phenyl)octanamide as a colorless oil in 93% yield (323 mg, 475 μmol). R_f = 0.54 (cHex:EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$ [7.26 ppm] ppm) δ = 7.61 (dd, J = 7.7, 1.5 Hz, 1H), 7.52–7.46 (m, 2H), 7.40–7.32 (m, 4H), 7.28–7.23 (m, 3H), 7.21 (dd, J = 7.9, 1.6 Hz, 1H), 7.19–7.16 (m, 2H), 6.76 (dd, J = 8.0, 1.2 Hz, 1H), 5.65 (d, J = 14.0 Hz, 1H), 4.37 (d, J = 14.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ [77.16 ppm] ppm) δ = 158.3 (t, J = 25.0 Hz), 140.3, 135.2, 132.8 (+, CH), 131.8 (+, CH, 2 C), 129.8 (+, CH, 2 C), 129.3 (+, CH), 129.1 (+, CH), 129.0 (+, CH), 128.7 (+, CH, 2 C), 128.7 (+, CH), 128.6 (+, CH, 2 C), 128.3 (+, CH), 123.3, 122.5, 95.7, 84.6, 55.0 (−, CH_2). C-atoms of the F-chain (7 C) are not visible; ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = [(−80.45)–(−80.98) (m)], [(−110.64)–(−111.18) (m)], [(−120.38)–(−120.42) (m)], [(−120.53)–(−120.62) (m)], [(−121.91)–(−122.36) (m)], [(−122.54)–(−123.19) (m)], [(−125.97)–(−126.81) (m)]; MS (FAB, 3-NBA), m/z

(%): 681 (13) $[M+2]^+$, 680 (45) $[M+1]^+$, 679 (34) $[M]^+$, 678 (27), 177 (12), 133 (46), 89 (100), 87 (41). HRMS ($C_{29}H_{16}F_{15}NO$): calcd 680.1065, found 680.1067; IR (ATR, $\tilde{\nu}$) = 1680 (s), 1672 (s), 1594 (vw), 1496 (w), 1482 (w), 1452 (w), 1441 (w), 1434 (w), 1417 (w), 1367 (w), 1330 (w), 1320 (w), 1298 (vw), 1235 (m), 1197 (vs), 1179 (s), 1145 (vs), 1132 (vs), 1102 (s), 1078 (w), 1069 (w), 1043 (w), 1024 (m), 994 (vw), 986 (vw), 967 (m), 953 (w), 916 (w), 884 (vw), 874 (vw), 854 (vw), 839 (vw), 819 (vw), 803 (vw), 781 (vw), 766 (w), 754 (s), 730 (s), 714 (w), 697 (s), 688 (m), 673 (s), 654 (m), 643 (m), 619 (w), 602 (w), 577 (m), 552 (s), 520 (vs), 479 (m), 466 (w), 448 (m), 422 (vw), 404 (w), 384 (w) cm^{-1}; UV-VIS (absorption, DMSO), λ_{max} = 304, 286 nm.

1-(1-benzyl-2-phenyl-1H-indol-3-yl)-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctan-1-one (17a)



N-Benzyl-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-N-(2-(phenylethynyl)phenyl)octanamide (50.0 mg, 73.6 µmol, 1.00 equiv.) was dissolved in deutered DMSO (7.3 mL). $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (2.60 mg, 2.20 µmol, 0.0299 equiv.) was added and the mixture was put under irradiation of 15 W blue LED light. After 20 h, the TLC shows complete consumption of the starting material. The reaction was quenched with water (15 mL) and extracted with ethyl acetate (3*15 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford the crude product. The obtained crude product was purified via flash-chromatography (Biotage Isolera Four) on silica gel (PF-15SIHP–F0012) using cyclohexane/ethyl acetate 0% to 2% ethyl acetate in 10 column volumes (1 column volume = 39.3 mL; flow-rate = 15 mL/min) to afford 1-(1-benzyl-2-phenyl-1H-indol-3-yl)-2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctan-1-one as colorless oil in 80% yield (39.8 mg, 58.6 µmol). R_f = 0.38 (cHex : EtOAc = 10 : 1). ^{1}H NMR (400 MHz, $CDCl_3$ [7.26 ppm] ppm) δ = 8.22 (d, J = 8.0 Hz, 1H), 7.53–7.45 (m, 1H), 7.45–7.38 (m, 2H), 7.38–7.34 (m, 1H), 7.33–7.21 (m, 7H), 6.91 (dd, J = 6.8, 2.7 Hz, 2H), 5.18 (s, 2H). Impurities: spectrum contains grease signals at 1.27 and 0.08 ppm; ^{13}C NMR (101 MHz, $CDCl_3$ [77.16 ppm], ppm) δ = 180.4 (t, J = 28.3 Hz), 149.4, 136.6, 136.2, 130.6, 130.2 (+, CH, 2 C), 123.0 (+, CH), 129.1 (+, CH, 2 C), 128.5 (+, CH, 2 C), 127.9 (+, CH), 126.8, 126.1 (+, CH, 2 C), 124.4 (+, CH), 123.9 (+, CH), 122.1 (t, J = 3.4 Hz), 111.4, 111.4 (+, CH), 48.2 (−, CH_2). Missing signals: carbons of the perfluorinated alkyl chain (7 C) are not visible in the regular ^{13}C NMR spectrum and can be found in the ^{19}F^{13}C HSQC spectrum; ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ = −80.74, −113.56, −120.49, −120.67, −122.06, −122.63, −126.12; MS (EI, 70 eV), m/z (%): 681 (30) [M + 2] +, 680 (96) [M + 1] +, 679 (70) [M] +, 678 (16), 602 (15), 311 (14), 310 (60), 283 (9), 282 (8), 281 (14), 280 (15), 207 (17), 205 (10), 204 (8), 193 (10), 191 (11), 147 (43), 133 (17), 92 (8), 91 (100). HRMS ($C_{29}H_{16}F_{15}NO$): calcd 680.1065, found 680.1065; IR (ATR, $\tilde{\nu}$) = 3061 (vw), 3031 (vw), 2961 (vw), 2922 (vw), 2853 (vw), 1662 (w), 1643 (w), 1605 (vw), 1527 (w), 1496 (w), 1477 (w), 1462 (m), 1453 (w), 1446 (w), 1404 (s), 1366 (m), 1351 (w), 1337 (w), 1319 (w), 1295 (w), 1275 (w), 1241 (s), 1197 (vs), 1162 (s), 1143 (vs), 1108 (vs), 1078 (m), 1058 (m), 1030 (m), 1018 (w), 1004 (m), 983 (w), 931 (w), 901 (w), 867 (w), 847 (w), 841 (w), 823 (w), 815 (m), 807 (w), 795 (w), 776 (m), 765 (m), 749 (s), 734 (s), 722 (vs), 705 (vs), 690 (s), 662 (s), 639 (s), 620 (w), 601 (m), 589 (w), 561 (s), 551 (s), 528 (s), 514 (m), 466 (w), 453 (m), 446 (m), 425 (w), 408 (w), 387 (w), 375 (w) cm^{-1}; UV-VIS (absorption, DMSO, 10 µM, 20 °C) λ_{max} (log ε in $M^{-1}cm^{-1}$) = 340 (4.039), 264 (4.037) nm.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The Supporting Information covers detailed material on the conducted experiments and their results, including the description of unsuccessful experiments. Data that refers to the herein described experiments were submitted to the repository Chemotion (https://www.chemotion-repository.net/). All DOIs minted for the data are linked in to the specific experiments in the Supporting Information and a summary of all new data obtained in this study can be gained with the collection DOIs as follows:[29] https://dx.doi.org/10.14272/collection/HMS 2021-11-05, https://dx.doi.org/10.14272/collection/AJ 2021-01-11 and https://dx.doi.org/10.14272/collection/HMS 2022-12-06.

Keywords: acyl-shift · fluorous-tag · indoles · visible-light photochemistry

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[29] Research data of this publication can be accessed as Open Access in the repository Chemotion. The data is assigned to the following DOIs: https://dx.doi.org/10.14272/collection/HMS_2021-11-05, https://dx.doi.org/10.14272/collection/AJ_2021-01-11 and https://dx.doi.org/10.14272/collection/HMS_2022-12-06.

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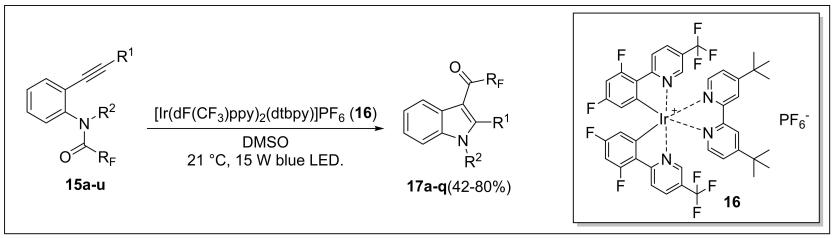

H. Simek Tosino, A. Jung, Dr. O. Fuhr, Dr. C. Muhle-Goll, Dr. N. Jung, Prof. Dr. S. Bräse**

1 – 11

F-Tag Induced Acyl Shift in the Photochemical Cyclization of *o*-Alkynylated *N*-Alkyl-*N*-acylamides to Indoles

3-Acylindoles with different substituents in positions N-1 and C-2 were successfully synthesized by cyclization of *o*-substituted *N*-alkyl-*N*-acylamides by photochemically induced 1,3-acyl shift.