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3-(2-Alken-1-one-2-yl)indoles through the palladium-catalyzed reaction of 2-alkynyltrifluoroacetanilides with cyclic α-iodoenones

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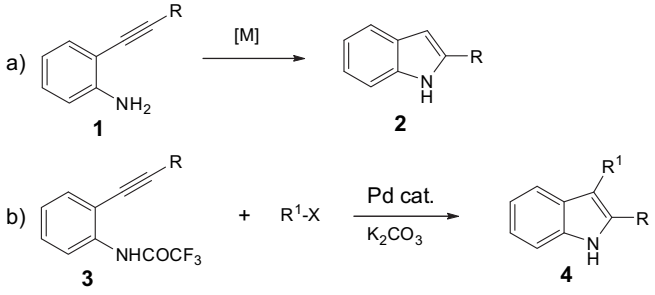
ABSTRACT

α-Iodoenones can be efficiently employed as organic electrophiles in the Pd-catalyzed synthesis of 2,3-disubstituted indoles from 2-alkynyltrifluoroacetanilides. Best results were obtained using the weak ligand $As(Ph)_3$. The methodology reported provides an efficient entry to indoles bearing a 2-alkenon-2-yl moiety linked in the 3-position, that possesses a scarcely reported substitution pattern.

1. Introduction

The indole ring system is one of the most widely distributed heterocycles found in nature, and occurs in many biologically active compounds.[1] Due to their relevance, the development of new and efficient procedures for building up indoles from acyclic precursors is a current challenge in organic synthesis.[2] Besides classical methodologies, the transition metal mediated cyclization of functionalized alkynes[3] has gained increasing attention, allowing the use of mild reaction conditions and, consequently, the introduction of a wide range of functionalities in the target heterocycle. One of the most popular strategies in this context is the cyclization of 2-alkynylaniline derivatives **1** to give 2-substituted indoles **2**. Although this reaction can be carried out in the presence of various reagents, including bases[4] and ammonium fluoride,[5] many procedures rely on the use of transition metal salts[3,6] (Scheme 1, a). Sequential C-3 functionalization of the indole ring can be obtained in some instances, with remarkable improvement in terms of scope and application.[7]

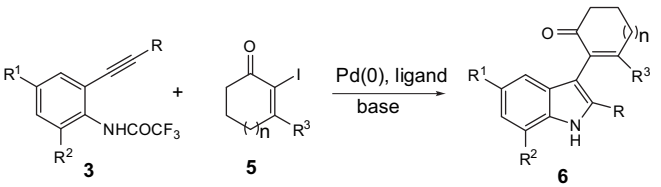


R^1 = Ar, vinyl, alkyl, alkynyl, allyl.
X = -I, -Br, -Cl, -OTf.

Scheme 1.

In the search for strategies towards C-3 functionalized indoles from alkynylanilines, attention was turned to a variety of approaches involving the coordination of the carbon–carbon triple bond by σ-organopalladium(II) complexes, generated in situ through oxidative addition of organic electrophiles R^1-X to Pd(0).[3,8] Sequential aminopalladation/reductive elimination of Pd(0) affords indoles **4**, bearing the R^1 group in the 3-position (Scheme 1, b). This process requires the use of trifluoroacetanilides **3**, able to generate an anionic nitrogen nucleophile in the presence of carbonate bases. The use of suitable electrophiles allowed the introduction of various R^1 fragments including aryl/heteroaryl/vinyl,[9] alkyl,[10] alkynyl,[11] allyl[12] and (running the reaction under a CO atmosphere) acyl groups.[13]

In connection with our current research interests in this area[14] and in order to widen the scope and generality of the methodology, we decided to develop a procedure for the preparation of 3-(2-alken-1-on-2-yl)-indoles **6** through the palladium-catalyzed reaction of 2-alkynyltrifluoroacetanilides with α-iodoenones **5** (Scheme 2).



R = Ar, vinyl, alkyl; R^3 = Me, H;
n = 0-2.

Scheme 2.

α-Iodoenones **5** represent an interesting class of organic electrophile.[15] In spite of their sluggish reactivity and limited stability, these substrates have been successfully employed in some Pd-catalysed cross-coupling reactions[16] with organostannanes,[17]

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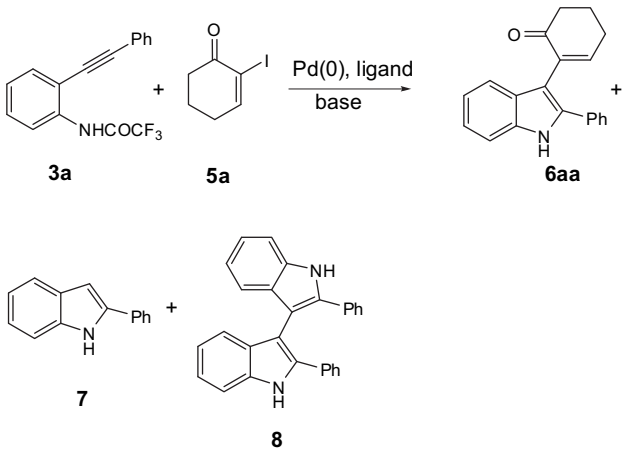
organozinc,[18] organoboranes,[19] organoindium[20] and terminal alkynes,[21] with the aim to achieve challenging α-functionalization of unsaturated carbonyl compounds. However, their efficiency in the Heck reaction was found to be strongly dependent on the structure: while 2-iodo-3-methylcyclopentenone reacted in good yield, other substrates such as 2-iodocyclopentenone (with the 3-position unblocked) and 2-iodocyclohexenone/cycloheptenone derivatives gave unsatisfactory results.[22] This was attributed to competitive Pd-catalyzed dehydration/aromatization to give phenols, kinetically favoured in these cases with respect to the vinylic substitution path.

To date, the use of **5** as precursors of σ-organopalladium (II) complexes in the aminopalladation/reductive elimination methodology described in Scheme 1,b is still unexplored.

2. Results and discussion

The reaction between trifluoroacetanilide **3a** and 2-iodocyclohexenone **5a** was chosen as a model (Scheme 3), and some of our results are reported in Table 1.



Scheme 3.

Table 1
Pd-catalyzed reaction of **3a** with **5a**[a]

Entry	Base	Catalyst (equiv %)	T (°C)	Yield[b]		
				6aa	**7**	**8**
1	K_2CO_3	$Pd(PPh_3)_4$ (5)	80	12	27	32
2	K_2CO_3	$Pd(PPh_3)_4$ (5)	100	40	22	27
3	Cs_2CO_3	$Pd(PPh_3)_4$ (5)	100	44	36	10
4	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)	100	58	16	12
5	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)+ttmpp (10)	100	45	15	21
6	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)+P(cy)$_3$ (10)	100	71	6	9
7	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)+$As(Ph)_3$ (10)	100	78	3	11
8	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)+$As(Ph)_3$ (5)	100	77	5	10
9	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)+$As(Ph)_3$ (5)	100	50[d]	10	9
10	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)+$As(Ph)_3$ (5)	100	52[e]	12	22
11	Cs_2CO_3	$Pd_2(dba)_3$ (2.5)+$As(Ph)_3$ (5)	80	95[c]	—	—
12	Cs_2CO_3	$Pd_2(dba)_3$	80	75[c]	—	—
13	Cs_2CO_3	$Pd(OAc)_2$ (5)+$As(Ph)_3$ (10)	80	51	7	5
14	Cs_2CO_3	$Pd(OAc)_2$ (5)	80	15	45	14
15	K_2CO_3	$Pd_2(dba)_3$ (2.5)+$As(Ph)_3$ (5)	80	88[c]	—	—

[a] Reactions were carried out on a 0.3 mmol scale in 1.5 mL of MeCN for 2 h using the following molar ratios: **3a**:**5a**:base=1:1.1:1.5.
[b] Unless otherwise stated yields were determined by HPLC analysis.
[c] Isolated yield.
[d] Carried out in ethanol.
[e] Carried out in DMF.

Using the reaction conditions that were found suitable for the palladium-catalyzed reaction of **3** with aryl iodides and vinyl triflates,[9c] the target indole **6aa** was obtained in very low yield (entry 1), confirming the sluggish reactivity of α-iodoenones.[16]

According to previous findings,[9b,14] 2-phenyilndole **7** and the dimer **8** were isolated as significant by-products. Raising the temperature to 100 °C (conditions used for the less reactive aryl bromides/triflates[9b]) afforded **6aa** in moderate yield (entries 2 and 3). The use of ligandless $Pd_2(dba)_3$ as catalyst resulted in a further improvement, although the yield was still unsatisfactory (entry 4). A screening of some ligands revealed that tricyclohexyl phosphine and triphenylarsine were the most effective in promoting the present reaction (entries 6 and 7); the latter weak ligand has been used in various Stille cross-coupling of substrates **5**.[17a–d] Good results were also obtained by reducing $AsPh_3$/Pd ratio to 1:1 (entry 8). Changing the solvent from CH_3CN to ethanol or DMF gave worse results (entries 9 and 10), whereas lowering the temperature to 80 °C afforded **6a** in nearly quantitative amount (entry 11). Omitting $AsPh_3$ at this temperature afforded **6aa** in 75% yield (entry 12), proving that $AsPh_3$ plays a significative role in determining the reaction outcome, although the process can be carried out also by using ligandless Pd(0). The presence of the ligand appears more important using a Pd(II) precatalyst: while in the presence of $AsPh_3$ **6aa** was obtained as main product, although in moderate yield (entry 13), the use of $Pd(OAc)_2$ alone resulted in a very different product distribution, and 2-phenylindole **7** was isolated in 45% yield (entry 14).

Finally, we found that under the optimized conditions the use of K_2CO_3 as base instead of Cs_2CO_3 was possible, although the latter afforded a slightly better yield (entries 11 and 15).

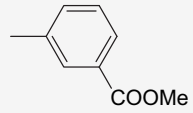
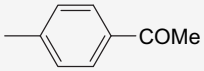
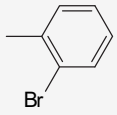
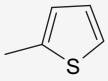
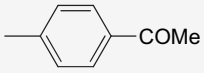
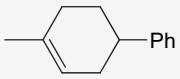
We next extended the process to include various 2-alkynylanilines/α-iodoenones; due to the limited stability and troublesome synthesis of acyclic α-iodoenones,[15] the present study was centred on the use of cyclic substrates **5a**–**d**. Our preparative results are reported in Table 2.

As shown in Table 2, all cyclic α-iodoenones tested, independent from their ring size, afforded target 3-(2-alken-1-on-2-yl) indoles **6** in moderate to good yields (entries 1–4); likely, the lower reactivity observed in the case of **5b** (entry 2) is determined by unfavourable steric effect of the methyl group. It is worth noting that the present reaction tolerates the presence of various functional groups such as ester (entry 5), keto (entry 6), nitro and cyano (entry 11). A vinylic substituent at the 2-position is also allowed, although with moderate results (entry 12). Moreover, indoles substituted on the benzene ring can be obtained starting from substituted 2-alkynyltrifluoroacetanilides (entries 10 and 11).

3. Conclusions

In conclusion, the results reported here widen significantly the scope of the synthesis of 2,3-disubstituted indoles through aminopalladation/reductive elimination, proving that α-iodoenones **5** differing in ring size can be efficiently used as organic electrophiles in such process. Best results were obtained in the presence of the weak ligand $AsPh_3$, although ligandless $Pd_2(dba)_3$ was also effective. The present reaction allows a straightforward entry to 3-(2-alken-1-one-2-yl)indoles **6**, possessing a scarcely reported substitution pattern,[23] and usefully complements the well-known reaction of 3-unsubstituted indoles with 1,3-dicarbonyl compounds,[7b,24] that affords regioisomeric 3-(2-alken-1-one-3-yl)indoles. Moreover, the 2-alken-1-one-2-yl moiety of **6** could allow further functionalization, opening access to more complex indole derivatives; for example, the presence of a suitable *o*-substituted phenyl ring at the 2-posititon (as in **6da**, entry 7) promises to open a new access to polycyclic indole derivatives through sequential palladium-catalyzed processes. This investigation is now under way, and the results will be reported in due course.

Table 2
Pd-catalyzed synthesis of indoles **6** from 2-alkynyltrifluoroacetanilides **3** and cyclic α-iodoenones **5**[a]

Entry	2-alkynyltrifluoroacetanilide **3**				α-Iodoenone **5**			Indole **6**	Yield[b] (%)
		-R	-R^1	-R^2		-R^3	*n*= Time (h)		
1	**3a**	Ph	H	H	**5a**	H	1 2	**6aa**	95
2	**3a**				**5b**	CH_3	1 2	**6ab**	58
3	**3a**				**5c**	H	0 2.5	**6ac**	76
4	**3a**				**5d**	H	2 3	**6ad**	67
5	**3b**		H	H	**5a**		3.5	**6ba**	95
6	**3c**		H	H	**5a**		2	**6ca**	67
7	**3d**		H	H	**5a**		2	**6da**	87
8	**3e**		H	H	**5a**		2	**6ea**	95
9	**3f**	*n*-Butyl	H	H	**5a**		2	**6fa**	77
10	**3g**		F	F	**5a**		3	**6ga**	72
11	**3h**	*n*-Butyl	NO_2	CN	**5a**		3.5	**6ha**	60[c]
12	**3i**		H	H	**5a**		2	**6ia**	40

[a] Reactions were carried out on a 0.3 mmol scale in 1.5 mL of MeCN using the following molar ratios: **3**:**5**:Cs_2CO_3:$Pd_2(dba)_3$:$AsPh_3$=1:1.1:1.5:0.025:0.05.
[b] Isolated yields.
[c] Carried out with 1.5 equiv of **5a**.

4. Experimental

4.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz, unless otherwise stated. IR was recorded with a Perkin–Elmer 683 or with a Varian 100 FT-IR spectrometer. Only the most significant IR absorptions are given. EI mass spectra were recorded with a Saturn 2000T GC/MS apparatus. ESI mass spectra were recorded with a ThermoFinnigan LCQ Deca XP Plus. CHN analyses were recorded with an Eager 200 analyser. α-Iodoenones **5** were obtained according to the literature.[15] The synthesis of 2-alkynyltrifluoroacetanilides **3a**, **3e**, **3f** and **3i** was previously described.[13] Compounds **3b**, **3c**, **3d** and **3g** were obtained using the following typical procedure.

4.2. Representative procedure for the synthesis of 2-alkynyltrifluoroacetanilides 3b–d and 3g from 2-ethynylanilines

*4.2.1. Methyl 3-({2-[(trifluoroacetyl)amino] phenyl} ethynyl) benzoate (**3b**).* To a solution of 2-ethynylaniline (0.700 g, 5.97 mmol) in DMF (1 mL) and triethylamine (2 mL) were added methyl 3-iodobenzoate (1.721 g, 6.57 mmol), $PdCl_2(PPh_3)_2$ (0.084 g, 0.12 mmol) and CuI (0.045 g, 0.24 mmol). The mixture was stirred at room temperature under N_2 atmosphere for 5 h, then extracted with HCl 0.1 M (50 mL) and EtOAc (3×50 mL). The combined organic layers were washed with 10% NaCl, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was connected to a rotary pump for 0.5 h, then dissolved in anhydrous CH_2Cl_2 (5 mL). The flask was cooled with an ice bath, then triethylamine (1.25 mL, 8.96 mmol) and trifluoroacetic anhydride (1.26 mL, 3.47 mmol) were added. The mixture was stirred under N_2 atmosphere for 2 h, then extracted with HCl 0.1 M (100 mL) and EtOAc (3×50 mL). The combined organic layers were washed with 10% NaCl, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 90:10 v/v) to give **3b** (1.303 g, 64% yield) as pale brown solid, mp 110–111 °C (cryst from acetone/hexane). ^{1}H NMR: δ=8.84 (br s, 1H, NH), 8.38 (d, *J*=7.7 Hz, 1H), 8.22–8.20 (m, 1H), 8.06 (dt, *J*=7.9 Hz, *J*=1.5 Hz, 1H), 7.69 (dt, *J*=7.9 Hz, *J*=1.5 Hz, 1H), 7.61–7.52 (m, 1H), 7.50–7.40 (m, 2H), 7.28–7.22 (m, 1H), 3.96 (s, 3H). ^{13}C NMR: δ=166.3 (C=O), 154.6 (q, *J*=37.3 Hz, CF_3C=O), 136.4, 135.6, 132.8, 132.1, 131.1, 130.4, 129.1, 125.8, 122.4, 120.1, 113.4 (Ar), 97.1, 84.0 (C≡C), 52.6. IR (KBr):

ν=3370, 1735, 1725 cm^{-1}. MS (EI): *m*/*z* (%)=347 (10) [M^+], 332 (100). Anal. calcd for $C_{18}H_{12}F_3NO_3$: C 62.25, H 3.48, N 4.03. Found: C 62.38, H 3.50, N 4.01.

*4.2.2. N-{2-[(4-Acetylphenyl)ethynyl]phenyl}-2,2,2-trifluoroacetamide (**3c**).* Yield=62%; pale brown solid, mp 141–142 °C (cryst from acetone/hexane). ^{1}H NMR: δ=8.85 (br s, 1H, NH), 8.32 (d, *J*=8.2 Hz, 1H), 7.96 (d, *J*=8.1 Hz, 2H), 7.60–7.56 (m, 3H), 7.43 (t, *J*=7.1 Hz, 1H), 7.23 (t, *J*=7.6 Hz, 1H), 2.61 (s, 3H). ^{13}C NMR: δ=196.9 (*C*=O), 154.4 (q, *J*=37.4 Hz, CF_3C=O), 137.0, 136.2, 131.9, 131.5, 130.3, 128.5, 126.3, 125.6, 119.9, 113.1 (Ar), 96.9, 85.9 (C≡C), 26.5. IR (KBr): ν=3310, 1710, 1690 cm^{-1}. MS (EI): *m*/*z* (%)=331 (35) [M^+], 316 (100). Anal. calcd for $C_{18}H_{12}F_3NO_2$: C 65.26, H 3.65, N 4.23. Found: C 65.11, H 3.65, N 4.24.

*4.2.3. N-{2-[(2-Bromophenyl)ethynyl]phenyl}-2,2,2-trifluoroacetamide (**3d**)*[25]. Yield=65%; pale brown solid, mp 109–110 °C (cryst from acetone/hexane). ^{1}H NMR: δ=8.88 (br s, 1H, NH), 8.42 (d, *J*=8.2 Hz, 1H), 7.68–7.55 (m, 3H), 7.45–7.23 (m, 4H). ^{13}C NMR: δ=154.2 (q, *J*=37.5 Hz, CF_3C=O), 136.4, 133.3, 132.6, 132.4, 130.3, 130.3, 127.4, 125.6, 125.2, 124.3, 118.6, 113.2 (Ar), 96.0, 87.5 (C≡C). IR (KBr): ν=3440, 1710, 1680 cm^{-1}. MS (EI): *m*/*z* (%)=369 (92), 367 (100) [M^+], 288 (79), 218 (88). Anal. calcd for $C_{16}H_9BrF_3NO$: C 52.20, H 2.46, N 3.80. Found: C 52.06, H 2.47, N 3.78.

*4.2.4. N-{2-[(4-Acetylphenyl)ethynyl]-4,6-difluorophenyl}-2,2,2-trifluoroacetamide (**3g**)*[26]. Yield=56%; pale brown solid, mp 172–173 °C (cryst from acetone/hexane). ^{1}H NMR: δ=8.13 (br s, 1H, NH), 7.94 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 2H), 7.15–7.08 (m, 1H), 7.01–6.86 (m, 1H), 2.61 (s, 3H). ^{13}C NMR: δ=197.2 (*C*=O), 161.6 (dd, *J*=252 Hz, *J*=13 Hz), 157.7 (dd, *J*=241 Hz, *J*=14 Hz), 154.3 (q, *J*=37.4 Hz, CF_3C=O), 137.3, 131.9, 128.4, 126.1, 115.2 (d, *J*=24 Hz), 106.0 (t, *J*=25 Hz) (Ar), 96.7, 85.5 (C≡C), 26.6. IR (KBr): ν=3220, 1725, 1670 cm^{-1}. MS (EI): *m*/*z* (%)=367 (27) [M^+], 352 (100). Anal. calcd for $C_{18}H_{10}F_5NO_2$: C 58.86, H 2.74, N 3.81. Found: C 59.00, H 2.73, N 3.81.

4.3. *N*-(2-Cyano-6-hex-1-ynyl-4-nitrophenyl)-2,2,2-trifluoroacetamide (3h)

To a solution of 2-amino-3-bromo-5-nitrobenzonitrile (1.51 g, 6.25 mmol) in DMF (1 mL) and piperidine (2 mL) were added 1-hexyne (0.912 mL, 8.11 mmol), $PdCl_2(PPh_3)_2$ (0.087 g, 0.12 mmol) and CuI (0.047 g, 0.24 mmol). The mixture was stirred at 50 °C under N_2 atmosphere for 3 h, then extracted with HCl 0.1 M (50 mL) and EtOAc (3×50 mL). The combined organic layers were washed with 10% NaCl, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was connected to a rotary pump for 0.5 h, then dissolved in anhydrous CH_2Cl_2 (7 mL). The flask was cooled with an ice bath, then triethylamine (1.30 mL, 9.38 mmol) and trifluoroacetic anhydride (1.33 mL, 9.38 mmol) were added. The mixture was stirred under N_2 atmosphere for 2 h, then extracted with HCl 0.1 M (50 mL) and EtOAc (3×50 mL). The combined organic layers were washed with 10% NaCl, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc 90:10 v/v) to give **3h** (1.17 g, 55% yield) as pale yellow solid, mp 95–96 °C (cryst from acetone/hexane). ^{1}H NMR: δ=8.86 (br s, 1H, NH), 8.48 (dd, *J*=7.0 Hz, *J*=2.5 Hz, 2H), 2.52 (t, *J*=6.9 Hz, 2H), 1.65–1.35 (m, 4H), 0.96 (t, *J*=7.2 Hz, 3H). ^{13}C NMR: δ=155.1 (q, *J*=39.2 Hz, CF_3C=O), 146.2, 141.9, 131.3, 127.3, 123.7, 111.8 (Ar), 113.9 (C≡N), 104.8, 73.3 (C≡C), 30.3, 22.3, 19.5, 13.7. IR (KBr): ν=3240, 2238, 1732, cm^{-1}. MS (EI): *m*/*z* (%)=339 (36) [M^+], 297 (100). Anal. calcd for $C_{15}H_{12}F_3N_3O_3$: C 53.10, H 3.57, N 12.39. Found: C 53.22, H 3.57, N 12.35.

4.4. Representative procedure for the synthesis of indoles 6

*4.4.1. 2-(2-Phenyl-1H-indol-3-yl)cyclohex-2-en-1-one (**6aa**).* To a solution of **3a** (0.100 g, 0.35 mmol) in MeCN (1.5 mL) were added 2-iodocyclohex-2-en-1-one **5a** (0.085 g, 0.38 mmol), Cs_2CO_3 (0.169 g, 0.52 mmol), $Pd_2(dba)_3$ (0.008 g, 0.009 mmol) and $AsPh_3$ (0.006 g, 0.019 mmol). The mixture was stirred at 80 °C under N_2 atmosphere for 1.5 h, then extracted with H_2O (50 mL) and EtOAc (3×40 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc 85:15 v/v) obtaining 0.094 g (95% yield) of 2-(2-phenyl-1*H*-indol-3-yl)cyclohex-2-en-1-one **6aa** as pale yellow solid, mp 93–94 °C (cryst from diethyl ether/hexane). ^{1}H NMR: δ=8.58 (br s, 1H, N–H), 7.42–7.34 (m, 4H), 7.30–7.20 (m, 3H), 7.12–7.06 (m, 2H), 7.00 (t, *J*=4.2 Hz, 1H), 2.59 (t, *J*=6.2 Hz, 2H), 2.53–2.45 (m, 2H), 2.18–2.12 (m, 2H). ^{13}C NMR: δ=198.4 (*C*=O), 150.5, 135.8, 135.3, 134.8, 133.0, 129.1, 128.5, 128.3, 127.3, 122.1, 119.8, 119.2, 111.2, 39.0, 26.6, 23.0. IR (KBr): ν=3330, 1670 cm^{-1}. MS (EI): *m*/*z* (%)=287 (100) [M^+], 258 (28), 230 (28). Anal. calcd for $C_{20}H_{17}NO$: C 83.59, H 5.96, N 4.87. Found C 83.91, H 5.97, N 4.89.

*4.4.2. 3-Methyl-2-(2-phenyl-1H-indol-3-yl)cyclohex-2-en-1-one (**6ab**).* Yield=58%; 93 mg of pale brown solid, mp 89–90 °C (cryst from diethyl ether/hexane), were obtained from 154 mg of **3a** and 138 mg of **5b**. ^{1}H NMR: δ=8.52 (br s, 1H, N–H), 7.43–7.35 (m, 2H), 7.30–7.23 (m, 4H), 7.21–7.19 (m, 1H), 7.13–7.05 (m, 2H), 2.56 (t, *J*=6.4 Hz, 2H), 2.53–2.45 (m, 2H), 2.20–2.03 (m, 2H), 1.64 (s, 3H). ^{13}C NMR: δ=198.2 (*C*=O), 160.6, 136.1, 135.3, 133.3, 128.7, 127.9, 127.4, 126.7, 122.3, 119.9, 119.5, 111.1, 38.4, 32.8, 22.4. IR (KBr): ν=3320, 1660 cm^{-1}. MS (EI): *m*/*z* (%)=301 (100) [M^+], 258 (31), 230 (22). Anal. calcd for $C_{21}H_{19}NO$: C 83.69, H 6.35, N 4.65. Found C 83.99, H 6.37, N 4.64.

*4.4.3. 2-(2-Phenyl-1H-indol-3-yl)cyclopent-2-en-1-one (**6ac**).* Yield=76%; 79 mg of pale brown solid, mp 175–176 °C (cryst from diethyl ether/hexane), were obtained from 110 mg of **3a** and 87 mg of **5c**. ^{1}H NMR: δ=8.54 (br s, 1H, N–H), 7.68 (t, *J*=2.5 Hz, 1H), 7.53–7.39 (m, 3H), 7.35–7.25 (m, 4H), 7.20–7,12 (m, 2H), 2.81–2.74 (m, 2H), 2.60–2.55 (m, 2H). ^{13}C NMR: δ=208.3 (*C*=O), 161.3, 140.5, 136.3, 136.2, 133.2, 128.9, 128.8, 128.2, 127.9, 122.9, 120.6, 120.0, 111.2, 35.2, 27.5. IR (KBr): ν=3320, 1680 cm^{-1}. ESI-MS *m*/*z* (%): 274 (100) [M^++1]. Anal. calcd for $C_{19}H_{15}NO$: C 83.49, H 5.53, N 5.12. Found C 83.21, H 5.53, N 5.10.

*4.4.4. 2-(2-Phenyl-1H-indol-3-yl)cyclohept-2-en-1-one(**6ad**).* Yield=67%; 74 mg of pale yellow oil were obtained from 106 mg of **3a** and 95 mg of **5d**. ^{1}H NMR: δ=8.48 (br s, 1H, N–H), 7.47–7.34 (m, 3H), 7.32–7.23 (m, 4H), 7.12–7.05 (m, 2H), 6.78 (t, *J*=6.4 Hz, 1H), 2.72 (t, *J*=6.2 Hz, 2H), 2.55–2.46 (m, 2H), 1.94–1.81 (m, 4H). ^{13}C NMR: δ=205.3 (*C*=O), 145.5, 138.3, 135.8, 135.3, 133.1, 129.1, 128.6, 127.7, 127.6, 122.3, 120.1, 119.3, 111.1, 42.9, 28.3, 25.2, 22.1. IR (KBr): ν=3350, 1660 cm^{-1}. MS (EI): *m*/*z* (%)=301 (100) [M^+]. Anal. calcd for $C_{21}H_{19}NO$: C 83.69, H 6.35, N 4.65. Found C 83.30, H 6.33, N 4.67.

*4.4.5. Methyl 3-[3-(6-oxocyclohex-1-en-1-yl)-1H-indol-2-yl]benzoate (**6ba**).* Yield=95%; 107 mg of yellow solid, mp 142–143 °C (cryst from diethyl ether/hexane), were obtained from 113 mg of **3b** and 80 mg of **5a**. ^{1}H NMR: δ=9.03 (br s, 1H, N–H), 8.11 (s, 1H), 7.78 (d, *J*=7.8 Hz, 1H), 7.43–7.35 (m, 2H), 7.09 (t, *J*=4.7 Hz, 1H), 7.08–7.04 (m, 4H), 3.88 (s, 3H), 2.65–2.50 (m, 4H), 2.20–2.14 (m, 2H). ^{13}C NMR: δ=198.5 (*C*=O), 166.9 (*C*=O), 150.8, 136.1, 134.8, 133.8, 133.3, 131.0, 130.2, 129.1, 128.7, 128.3, 128.1, 122.6, 120.1, 119.2, 111.3, 52.2, 39.1, 26.8, 23.1. IR (KBr): ν=3325, 1710, 1680 cm^{-1}. MS (EI): *m*/*z*

(%)=345(20) [M$^+$], 330 (100). Anal. calcd for $C_{22}H_{19}NO_3$: C 76.42, H 5.54, N 4.06. Found C 76.63, H 5.52, N 4.08.

*4.4.6. 2-[2-(4-Acetylphenyl)-1H-indol-3-yl]cyclohex-2-en-1-one (**6ca**).* Yield=67%; 58 mg of brown solid, mp 194–195 °C (cryst from acetone/hexane), were obtained from 90 mg of **3c** and 67 mg of **5a**. ^{1}H NMR: δ=9.09 (br s, 1H, N–H), 7.60 (d, J=8.2 Hz, 2H), 7.45–7.40 (m, 1H), 7.34 (d, J=8.2 Hz, 2H), 7.16 (t, J=3.9 Hz, 1H), 7.12–7.00 (m, 3H), 2.66–2.57 (m, 4H), 2.48 (s, 3H), 2.26–2.17 (m, 2H). ^{13}C NMR: δ=198.3, 197.6 (*C*=O), 151.0, 137.7, 136.4, 135.5, 134.7, 133.9, 128.7, 128.5, 126.9, 123.0, 120.3, 119.4, 111.2, 39.1, 26.8, 26.5, 23.1. IR (KBr): ν=3330, 1670 cm^{-1}. MS (EI): m/z (%)=329 (100) [M$^+$], 286 (17), 272 (72). Anal. calcd for $C_{22}H_{19}NO_2$: C 80.22, H 5.81, N 4.25. Found C 80.47, H 5.82, N 4.27.

*4.4.7. 2-[2-(2-Bromophenyl)-1H-indol-3-yl]cyclohex-2-en-1-one (**6da**).* Yield=87%; 109 mg of pale yellow solid, mp 180–181 °C (cryst from diethyl ether/hexane) were obtained from 126 mg of **3d** and 84 mg of **5a**. ^{1}H NMR: δ=8.23 (br s, 1H, N–H), 7.64 (d, J=7.7 Hz, 1H), 7.45–7.30 (m, 3H), 7.24–7.07 (m, 4H), 6.85 (t, J=4.1 Hz, 1H), 2.54 (t, J=6.2 Hz, 2H), 2.44–2.35 (m, 2H), 2.11–2.02 (m, 2H). ^{13}C NMR: δ=198.0 (*C*=O), 149.8, 135.5, 134.6, 134.2, 133.3, 132.6, 129.7, 128.9, 128.4, 127.4, 127.2, 123.3, 122.6, 120.2, 120.1, 111.0, 39.0, 26.7, 23.0. IR (KBr): ν=3350, 1650 cm^{-1}. MS (EI): m/z (%)=367 (87), 365 (87) [M$^+$], 286 (100), 272 (72). Anal. calcd for $C_{20}H_{16}BrNO$: C 65.59, H 4.40, N 3.82. Found C 65.65, H 4.42, N 3.81.

*4.4.8. 2-(2-Thien-2-yl-1H-indol-3-yl)cyclohex-2-en-1-one (**6ea**).* Yield=95%; 94 mg of brown solid, mp 144–145 °C (cryst from acetone/hexane), were obtained from 100 mg of **3e** and 83 mg of **5a**. ^{1}H NMR: δ=8.93 (br s, 1H, N–H), 7.31–7.27 (m, 1H), 7.12–7.08 (m, 2H), 7.04–7.00 (m, 2H), 6.90–6.84 (m, 1H), 6.72–6.70 (m, 1H), 6.62 (t, J=4.6 Hz, 1H), 2.64 (t, J=6.2 Hz, 2H), 2.56–2.51 (m, 2H), 2.23–2.10 (m, 2H). ^{13}C NMR: δ=198.7 (*C*=O), 152.2, 135.9, 134.6, 134.4, 129.7, 129.2, 127.3, 124.8, 124.3, 122.5, 119.9, 118.9, 111.1, 39.1, 26.8, 23.0. IR (KBr): ν=3320, 1670 cm^{-1}. MS (EI): m/z (%)=293 (100) [M$^+$], 264 (22), 236 (42). Anal. calcd for $C_{18}H_{15}NOS$: C 73.69, H 5.15, N 4.77. Found C 73.43, H 5.13, N 4.77.

*4.4.9. 2-(2-Butyl-1H-indol-3-yl)cyclohex-2-en-1-one (**6fa**).* Yield=77%; 81 mg of pale yellow solid, mp 91–93 °C (cryst from diethyl ether/hexane), were obtained from 106 mg of **3f** and 96 mg of **5a**. ^{1}H NMR: δ=8.10 (br s, 1H, N–H), 7.33–7.28 (m, 1H), 7.24–7.19 (m, 1H), 7.09–7.00 (m, 3H), 2.68–2.53 (m, 6H), 2.21–2.09 (m, 2H), 1.65–1.49 (m, 2H), 1.40–1.22 (m, 2H), 0.88 (t, J=7.2 Hz, 3H). ^{13}C NMR: δ=198.5 (*C*=O), 149.5, 137.5, 135.2, 134.5, 129.0, 128.4, 121.0, 119.4, 118.6, 110.5, 39.1, 31.6, 29.7, 26.7, 23.3, 22.4, 13.8. IR (KBr): ν=3310, 1660 cm^{-1}. MS (EI): m/z (%)=267 (100) [M$^+$], 224 (98), 196 (41). Anal. calcd for $C_{18}H_{21}NO$: C 80.86, H 7.92, N 5.24. Found C 81.11, H 7.88, N 5.22.

*4.4.10. 2-[2-(4-Acetylphenyl)-5,7-difluoro-1H-indol-3-yl]cyclohex-2-en-1-one (**6ga**).* Yield=72%; 95 mg of pale yellow solid, mp 195–195 °C (cryst from acetone/hexane), were obtained from 132 mg of **3g** and 88 mg of **5a**. ^{1}H NMR: δ=8.59 (br s, 1H, N–H), 7.93 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 7.06 (t, J=4.0 Hz, 1H), 6.84 (d, J=8.6 Hz, 1H), 6.77–6.67 (m, 1H), 2.66–2.52 (m, 4H), 2.60 (s, 3H), 2.22–2.15 (m, 2H). ^{13}C NMR (500 MHz): δ=197.2, 196.6 (*C*=O), 156.6 (dd, J_1=238.1 Hz, J_2=10.0 Hz), 150.7, 147.8 (dd, J_1=247.0 Hz, J_2=13.9 Hz), 135.9, 135.53, 135.49, 133.2, 130.8 (dd, J_1=10.6 Hz, J_2=5.9 Hz), 128.1, 126.2, 120.4 (d, J=13.5 Hz), 99.7 (dd, J_1=23.9 Hz, J_2=4.0 Hz), 97.6 (dd, J_1=30.2 Hz, J_2=20.3 Hz). IR (KBr): ν=3310,1670 cm^{-1}. MS (EI): m/z (%)=365 (100) [M$^+$], 308 (79). Anal. calcd for $C_{22}H_{17}F_2NO_2$: C 72.32, H 4.69, N 3.83. Found C 72.08, H 4.69, N 3.85.

*4.4.11. 2-Butyl-5-nitro-3-(6-oxocyclohex-1-en-1-yl)-1H-indole-7-carbonitrile (**6ha**).* Yield=60%; 63 mg of yellow solid, mp>230 °C (dec) (cryst from acetone/hexane), were obtained from 106 mg of **3f** and 104 mg of **5a**. ^{1}H NMR: δ=10.04 (br s, 1H, N–H), 8.40 (s, 1H), 8.29 (s, 1H), 7.11 (t, J=3.8 Hz, 1H), 2.75–2.64 (m, 6H), 2.29–2.20 (m, 2H), 1.72–1.60 (m, 2H), 1.41–1.29 (m, 2H), 0.92 (t, J=7.2 Hz, 3H). ^{13}C NMR: δ=198.1 (*C*=O), 151.7, 143.6, 141.0, 138.1, 132.5, 129.2, 120.8, 120.2, 115.5, 112.2, 93.5, 38.8, 31.2, 26.7, 26.6, 23.0, 22.4, 13.7. IR (KBr): ν=3330, 2230, 1670 cm^{-1}. MS (EI): m/z (%)=337 (100) [M$^+$], 295 (48), 294 (88). Anal. calcd for $C_{19}H_{19}N_3O_3$: C 67.64, H 5.68, N 12.46. Found C 67.91, H 5.66, N 12.41.

*4.4.12. 2-[2-(4-Phenylcyclohex-1-en-1-yl)-1H-indol-3-yl]cyclohex-2-en-1-one (**6ia**).* Yield=40%; 46 mg of pale grey solid, mp 120–122 °C (cryst from diethyl ether/hexane), were obtained from 115 mg of **3g** and 76 mg of **5a**. ^{1}H NMR: δ=8.06 (br s, 1H, N–H), 7.36–7.21 (m, 7H), 7.17–7.00 (m, 3H), 6.08 (br s, 1H), 2.90–2.75 (m, 1H), 2.65–2.52 (m, 4H), 2.50–2.35 (m, 4H), 2.30–1.95 (m, 4H). ^{13}C NMR: δ=198.2 (*C*=O), 149.3, 146.6, 136.8, 135.4, 135.0, 131.5, 130.6, 129.2, 128.4, 126.7, 126.4, 126.2, 122.0, 119.8, 119.0, 110.6, 39.5, 39.1, 33.7, 29.9, 28.0, 26.7, 23.2. IR (KBr): ν=3335,1660 cm^{-1}. ESI-MS m/z (%): 368 (100) [M$^+$+1]. Anal. calcd for $C_{26}H_{25}NO$: C 84.98, H 6.86, N 3.81. Found C 85.23, H 6.89, N 3.80.

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25. Diisopropylamine was used in place of triethylamine.
26. Starting 2-ethynyl-4,6-difluoroaniline was obtained according to Ref. 6d.