Advanced Synthesis & Catalysis

Accepted Article

Title: Two-step Synthesis of Polysubstituted 6-Nitroindoles under Flow Chemical and Microwaves conditions

Authors: Alessandro Palmieri, Serena Gabrielli, Roberto Ballini, and Susanna Sampaolesi

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700790

Link to VoR: http://dx.doi.org/10.1002/adsc.201700790

10.1002/adsc.201700790

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Two-step Synthesis of Polysubstituted 6-Nitroindoles under Flow Chemical and Microwaves conditions

Susanna Sampaolesi,[a] Serena Gabrielli,[a] Roberto Ballini[a] and Alessandro Palmieri[a,*]

[a] Green Chemistry Group, School of Sciences and Technology, Chemistry Division, University of Camerino, Via S. Agostino n. 1, 62032 Camerino (MC), Italy.
Phone: (+39)-0737-402262; Fax: (+39)-0737-402297; e-mail: alessandro.palmieri@unicam.it

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A new simple and efficient synthesis of 6-nitroindoles, starting from *N*-carboxylalkyl pyrrole-2-carboxaldehydes and protected β-nitro ketones, has been developed. The method involves two distinct domino processes, respectively performed under flow chemical conditions and microwaves irradiations. 6-Nitroindoles were produce from good to excellent overall yields.

Keywords: heterocycles; flow chemistry; microwaves; nitro compounds; domino reactions.

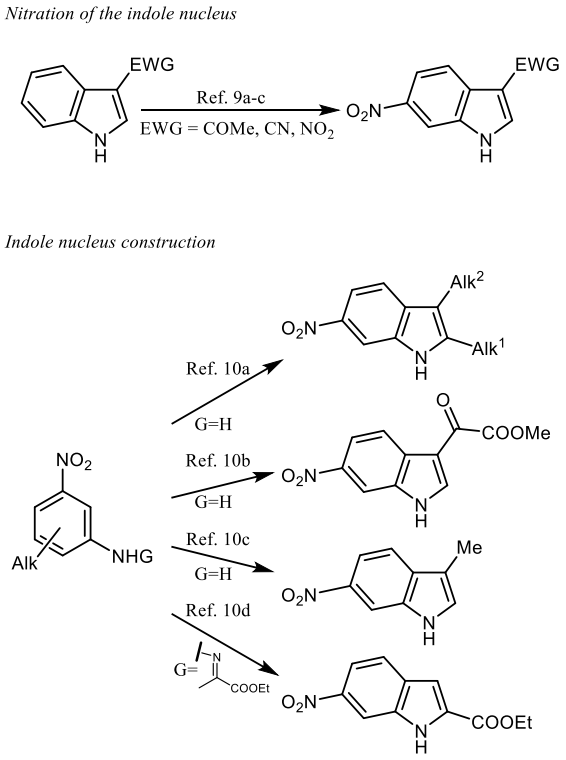
Introduction

The indole nucleus is probably the most ubiquitous heterocyclic system in nature.[1] It is widely present in many biological active molecules,[2] is extensively used as synthetic precursor of strategic targets,[3] as well as investigated in agrochemistry, essential oils, material science, pigments and dyes.[4] For all these reasons, since its discovery in 1866 by Adolf von Baeyer,[5] the preparation and derivatization of functionalized indoles are the research focus of many chemists.[6] In this context, the nitro functionalized indoles are valuable precursors of other important 6-substituted derivatives,[7] due to the possibility to convert the nitro group into many other functionalities.[8]

However, although their importance, only few synthetic procedures are present in the literature for their preparation, which can be classified in two main approaches: *(i)* direct nitration of the indole nucleus, and *(ii)* the *ex-novo* indole nucleus construction starting from nitro functionalized arenes (Scheme 1).

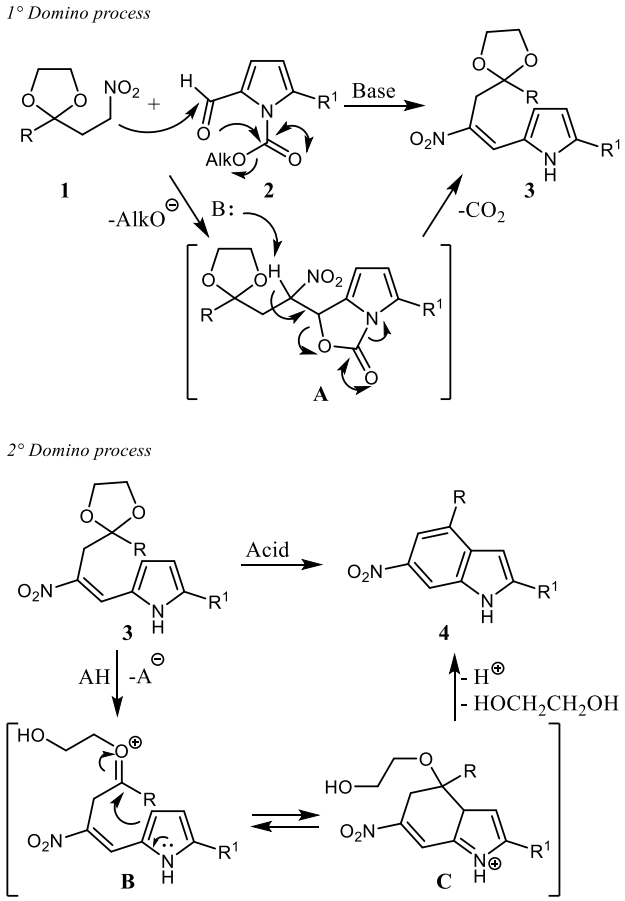
The former approach often requires harsh reaction conditions and provides good results only with specific substituted indoles, shows a low functional group tolerance and generally produces a mixture of nitroindole isomers.[9] The second approach is based on the reactivity of nitro arenes (mainly *m*-nitro anilines and their derivatives) in combination with carbonyl compounds, it involves the assembly of the pyrrole moiety, providing the target compounds in moderate yields, as a mixture of nitroindole regioisomers as well.[10]

In this regard, with the aim to overcome these limitations and following our studies concerning the *ex-novo* synthesis of heterocycles,[11] we developed a new general, simple and efficient protocol for synthesizing 6-nitroindoles starting from β-protected nitro ketones **1** and *N*-protected pyrrolyl-2-carboxaldehydes **2** (Scheme 2).



Scheme 1. Some synthetic examples of 6-nitroindoles

The method involves two distinct steps: *(i)* a base promoted flow chemical *nitroaldol-transesterification-decarboxylation* domino process, which presumably passes *via* the intermediate **A** (as analogously reported for Grignard reagents),[12] that provides the adduct **3** by an elimination-decarboxylation process; and *(ii)* a microwave assisted *deprotection-cyclization-aromatization* cascade process, achieved under acidic conditions.



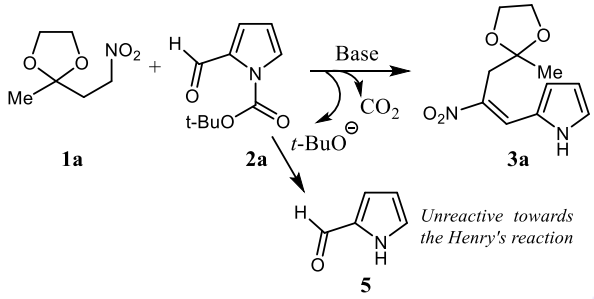
Scheme 2. Two-step approach

Results and Discussion

In order to optimize the whole process, we firstly focused our efforts to the first step (Scheme 3). In this context, due to the low reactivity of **1a** with the unprotected pyrrole derivative **5**,[13] we moved our attention to the *N*-BOC protected derivative **2a** (R^1=H, R^2=*t*-Bu).

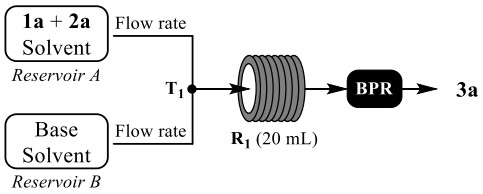
Unfortunately, even after a wide series of tests (for more details see SI), the adduct **3a** was isolated only in 39% yield. This unsatisfactory result is probably due to the competitive decarboxylation of **2a** (giving **5**), promoted by the *tert*-butoxyde (*t*-BuO^-) generated during the reaction.[14]

At this point, with the purpose to remedy this problem, we switched from batch to flow chemical conditions (FCC). In this regard, exploiting the peculiarity of flow chemistry,[15] the *tert*-butoxyde species can be continuously removed from the reaction system, thus minimizing its interaction with **2a** and preventing the formation of **5**.



Scheme 3. Competitive *N*-decarboxylation

For this aim, we implemented a flow equipment constituted of two different reservoirs, respectively containing **1a** and **2a** (*Reservoir A*), and a base (*Reservoir B*), a T-mixing piece ($\mathbf{T_1}$), a PTFE coil reactor ($\mathbf{R_1}$, 20 mL, I.D. = 0.8 mm, O.D. = 1.58 mm), and a back pressure regulator (Scheme 4).



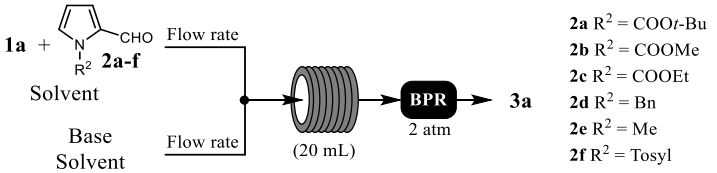
Scheme 4. Flow Chemical approach

The solutions were pumped through the system by two HPLC pumps and, after a deep screening in terms of base, stoichiometry, temperature, concentration and solvent (Table 1), the best yield of **3a** (*entry i*, 61%) was obtained using a 0.15 M dioxane solution of **1a** and **2c**, a 0.15 M dioxane solution of DBU (1,5-diazabiciclo[5.4.0]undec-5-ene), a flow rate of 2 mL/h for each pump (residence time 5 hours), at room temperature and in the presence of a back pressure regulator (BPR) set at 2 atmospheres.

In order to confirm the generality of our approach, we extended the reaction conditions used in *entry i* to a wide range of β-protected nitro ketones and *N*-ethyl carboxylate pyrrole-2-carboxaldehydes (Table 2).

In all cases, adducts **3** were obtained, as single *E* diastereoisomer, in good yields. In particular, the 5-substituted aldehydes **2g-j** furnished the corresponding adducts **3b**, **3d**, **3f-h** and **3j** in an excellent range of yields from 70 to 95%.

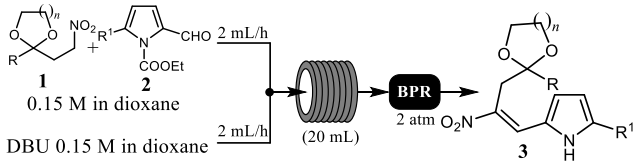
Table 1. Optimization of the step I under FCC.



Entry	2 (eq.)		Base(eq.)	Solvent (M)	Total Flow Rate (mL/h)	Yield (%) of **3a**[a]
a	**2a**	(1)	DBU (1)	2-MeTHF (0.1 M)	5	44
b	**2a**	(1)	DBU (1)	CPME (0.1 M)	5	38
c	**2a**	(1)	DBU (1)	DMF (0.1 M)	5	31
d	**2a**	(1)	DBU (1)	MeCN (0.1 M)	5	37
e	**2a**	(1)	DBU (1)	Dioxane (0.1 M)	5	48
f	**2a**	(1)	DBU (1)	Dioxane (0.15 M)	5	51
g	**2a**	(1)	DBU (1)	Dioxane (0.2 M)	---	---[b]
h	**2b**	(1)	DBU (1)	Dioxane (0.15 M)	5	11
i	**2c**	(1)	DBU (1)	Dioxane (0.15 M)	5	61
j	**2d**	(1)	DBU (1)	Dioxane (0.15 M)	5	---[c]
k	**2e**	(1)	DBU (1)	Dioxane (0.15 M)	5	---[c]
l	**2f**	(1)	DBU (1)	Dioxane (0.15 M)	5	27
m	**2c**	(1)	TMG (1)	Dioxane (0.15 M)	5	42
n	**2c**	(1)	TBD (1)	Dioxane (0.15 M)	5	46
o	**2c**	(1)	DBU (1.5)	Dioxane (0.15 M)	5	54
p	**2c**	(1)	DBU (1)	Dioxane (0.15 M)	4	56
q	**2c**	(1)	DBU (1)	Dioxane (0.15 M)	6.6	58
r	**2c**	(1)	DBU (1)	Dioxane (0.15 M)	5	42[d]
s	**2c**	(1)	DBU (1)	Dioxane (0.15 M)	5	35[e]

[a] Yield of pure isolated products. [b] Clogging of the reactor coil due to precipitate formation. [c] Recovery of starting materials [d] Reaction performed at 0°C. [e] Reaction performed at 50°C

Table 2. Synthesis of adducts **3a-j**.

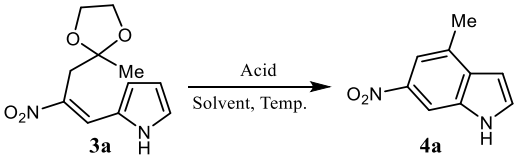


	R	*n*		R^1		Yield (%) of **3**[a]
1a	Me	1	**2c**	H	**3a**	61
1a	Me	1	**2g**	$CH_3(CH_2)_8$	**3b**	70
1b	Et	1	**2c**	H	**3c**	54
1b	Et	1	**2h**	$Ph(CH_2)_4$	**3d**	90
1c	*p*-^{t}Bu-C_6H_4	1	**2c**	H	**3e**	55
1d	*p*-Me-C_6H_4	1	**2h**	$Ph(CH_2)_4$	**3f**	95
1e	$Ph(CH_2)_2$	1	**2i**	$Cl(CH_2)_6$	**3g**	89
1e	$Ph(CH_2)_2$	1	**2j**	$CH_3(CH_2)_3$	**3h**	79
1f	H	2	**2c**	H	**3i**	52
1f	H	2	**2g**	$CH_3(CH_2)_8$	**3j**	88

[a] Yield of pure isolated products.

Once confirmed the goodness of the first step, we moved our attention to optimize the conversion of adducts **3a-j** into the title targets **4a-j**. Hence, based on our previous experiences,[16] we investigated the transformation of **3a** into **4a** under a variety of acidic conditions. As shown in Table 3, we found the best result (*entry m*, 74%), under microwave irradiation, at 100°C, in the presence of Amberlyst 15 (200 mg/mmol) as acid promoter, and using 2-MeTHF as the solvent.

Table 3. Optimization studies of the step II.

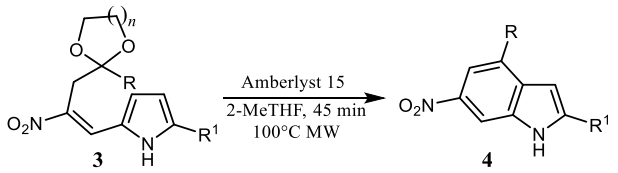


Entry	Acidic species (mg/mmol)	Solvent	Time (min)	Yield of **4a**[a]
a	Amberlyst 15 (400)	EtOAc	30	58[b]
b	Amberlyst 15 (200)	EtOAc	30	57[b]
c	Amberlyst 15 (100)	EtOAc	30	42[b]
d	Amberlyst 15 (200)	2-MeTHF	30	66[b]
e	Amberlyst 15 (200)	^{i}PrOH	30	44[b]
f	Amberlyst 15 (200)	Dioxane	30	40[b]
g	*p*-TsOH·H_2O (190)	2-MeTHF	30	45[b]
h	AcOH (1000)	---	30	---[b]
i	Amberlyst 15 (200)	2-MeTHF	30	69[c]
j	Amberlyst 15 (200)	2-MeTHF	30	68[d]
k	Amberlyst 15 (200)	2-MeTHF	30	52[e]
l	Amberlyst 15 (200)	2-MeTHF	15	64[c]
m	Amberlyst 15 (200)	2-MeTHF	45	74[c]
n	Amberlyst 15 (200)	2-MeTHF	60	72[c]

[a] Yield of pure isolated products. [b] Reaction performed at 80°C, MW irradiation. [c] Reaction performed at 100°C, MW irradiation. [d] Reaction performed at 120°C, MW irradiation. [e] Batch reflux conditions.

Finally, we extended the method to all adducts **3**, always obtaining very good results (Table 4).

Table 4. Synthesis of 6-nitroindoles **4a-j**.



3 **4**

	R	R^1	*n*	Yield (%) of **4**[a]	
3a	Me	H	1	**4a**	74
3b	Me	$CH_3(CH_2)_8$	1	**4b**	77
3c	Et	H	1	**4c**	87
3d	Et	$Ph(CH_2)_4$	1	**4d**	78
3e	*p*-^{t}Bu-C_6H_4	H	1	**4e**	67
3f	*p*-Me-C_6H_4	$Ph(CH_2)_4$	1	**4f**	62
3g	$Ph(CH_2)_2$	$Cl(CH_2)_6$	1	**4g**	75
3h	$Ph(CH_2)_2$	$CH_3(CH_2)_3$	1	**4h**	81
3i	H	H	2	**4i**	70
3j	H	$CH_3(CH_2)_8$	2	**4j**	68

[a] Yield of pure isolated products.

Conclusion

In conclusion, we have developed a new, general, convenient and mild synthetic protocol for the preparation of 6-nitroindoles, which are key intermediates for synthesizing more complex biologically active molecules. The method is based on the peculiarity of the flow chemistry and the effectiveness of the microwave technology. By our approach it has been possible to synthesize a large variety of title targets in satisfactory to good overall yields, hardly obtainable by the conventional batch synthesis. Moreover, the accurate selection of starting materials gave the opportunity to introduce specific substituents in 2- and 4-positions, avoiding any problem due to the formation of a mixture of nitroindole isomers, which, as reported in the literature, is very common about the preparation of these derivatives.

Experimental Section

General remarks. ^{1}H-NMR analyses were recorded at 400 MHz on a Varian Mercury Plus 400. ^{13}C-NMR analyses were recorded at 100 MHz. IR spectra were recorded with a PerkineElmer FT-IR spectrometer Spectrum Two UATR. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. GS-MS analyses were obtained by a Hewlett-Packard GC/MS 6890N that works with the EI technique (70 eV). Microwave irradiations were performed by Biotage® Initiator+.

General procedure for the synthesis of compounds 3a-j.

The flow equipment was set up according to Scheme 3. Protected β-nitro ketones **1a-j** (1.5 mmol) and *N*-ethyl carboxylate 2-pyrrole carboxaldehydes **2c**, **2g-h** (1.5 mmol) were taken up in dioxane (10 mL) and filled into the *reservoir A*. DBU (1.5 mmol) was taken up in dioxane (10 mL) and filled into *reservoir B*. The two solutions were simultaneously pumped with a flow rate of 2 mL/h for each pump into the T-connector before passing through a 20 mL reactor coil pressurised by back pressure regulator set at 2 atm. The outflow was collected and, after the removal of the solvent under vacuum, the crude adducts **3a-j** were purified by flash column chromatography (toluene:EtOAc=98:2).

Compound **3a**. Yellow waxy solid; IR (neat): ν = 756, 948, 1042, 1273, 1491, 1626, 2977, 3299 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.5 (s, 3H), 3.47 (bs, 2H), 3.86-3.94 (m, 2H), 3.95-4.02 (m, 2H), 6.36-6.38 (m, 1H), 6.67 (m, 1H), 7.07 (bs, 1H), 8.13 (s, 1H), 10.75 (bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 25.1, 37.6, 65.3, 110.5, 112.1, 120.2, 125.3, 125.5, 128.0, 140.0; EI-MS (70eV): *m/z* = 238 ([M$^+$], 2%), 105 (7%), 104 (11%), 87 (100%), 43 (32%); Anal. Calcd. for $C_{11}H_{14}N_2O_4$ (238.24): C, 55.46; H, 5.92; N, 11.76; Found: C, 55.51; H, 5.95; N, 11.73.

Compound **3b**. Yellow waxy solid; IR (neat): ν = 916, 1038, 1187, 1251, 1274, 1477, 1501, 1626, 2854, 2924, 3266 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.8 Hz), 1.27-1.39 (m, 12H), 1.50 (s, 3H), 1.56-173 (m, 2H), 2.66 (t, 2H, *J* = 7.3 Hz), 3.47 (bs, s, 2H), 3.88-3.96 (m, 2H), 3.96-4.03 (m, 2H), 6.11 (t, 1H, *J* = 2.99 Hz), 6.62 (t, 1H, *J* = 2.99 Hz), 8.12 (s, 1H), 10.58 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.2, 22.8, 24.9, 28.5, 29.2, 29.4, 29.5, 29.6, 32.0, 37.8, 65.1, 110.3, 110.8, 122.1, 124.4, 128.3, 137.9, 142.2; EI-MS (70eV): *m/z* = 364 ([M$^+$], 1%), 118 (18%), 87 (100%), 43 (14%). Anal. Calcd. for $C_{20}H_{32}N_2O_4$ (364.49): C, 65.91; H, 8.85; N, 7.69; Found: C, 65.86; H, 8.82; N, 7.72.

Compound **3c**. Yellow solid; mp 127-129°C; IR (neat): ν = 754, 945, 1041, 1275, 1493, 1628, 2976, 3294 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.05 (t, 3H, *J* = 7.3 Hz), 1.82 (q, 2H, *J* = 7.5 Hz), 3.44 (bs, 2H), 3.85-3.98 (m, 4H), 6.37 (dd, 1H, *J* = 2.6, 6.0 Hz), 6.65-6.67 (m, 1H), 7.06-7.07 (m, 1H), 8.10 (s, 1H), 10.75 (bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 8.3, 32.2, 35.7, 65.8, 112.0, 112.7, 120.0, 125.2, 125.5, 127.8, 140.4; EI-MS (70eV): *m/z* = 252 ([M$^+$], 1%), 104 (9%), 102 (5%), 101 (100%), 57 (26%), 29 (5%). Anal. Calcd. for $C_{12}H_{16}N_2O_4$ (252.27): C, 57.13; H, 6.39; N, 11.10. Found: C, 57.18; H, 6.36; N, 11.13.

Compound **3d**. Yellow waxy solid; IR (neat): ν = 700, 734, 785, 951, 1039, 1186, 1265, 1476, 1498, 1562, 1627, 2858, 2934, 3263 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.04 (t, 3H, *J* = 7.3 Hz), 1.69-1.73 (m, 4H), 1.80 (t, 2H, *J* = 7.3 Hz), 2.64-2.72 (m, 4H), 3.41 (bs, s, 2H), 3.79-3.92 (m, 4H), 6.11 (t, 1H, *J* = 2.6 Hz), 6.6 (dd, 1H, *J* = 2.6, 3.4 Hz), 7.16-7.20 (m, 3H), 7.25-7.30 (m, 2H), 8.08 (s, 1H), 10.58 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 8.5, 28.4, 28.8, 31.2, 32.2, 35.7, 35.9, 65.7, 110.5, 112.8, 121.9, 124.6, 126.1, 128.3, 128.5, 128.6, 138.2, 141.8, 142.3. EI-MS (70eV): *m/z* = 118 (10%), 101 (100%), 57 (19%), 29 (6%). Anal. Calcd. for $C_{22}H_{28}N_2O_4$ (384.48): C, 68.73; H, 7.34; N, 7.29. Found: C, 68.69; H, 7.36; N, 7.32.

Compound **3e**. Yellow solid; mp 42-44°C; IR (neat): ν = 753, 972, 1042, 1281, 1473, 1500, 1629, 2861, 2935, 3287 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.34 (s, 9H), 3.65 (s, bs, 2H), 3.82-3.86 (m, 2H), 3.98-4.01 (m, 2H), 6.41 (dt, 1H, *J* = 2.6, 3.4 Hz), 6.7 (q, 1H, *J* = 1.7 Hz), 7.14-7.16 (m, 1H), 7.42-7.44 (m, 2H), 7.51-7.55 (m, 2H), 8.18 (s, 1H), 10.87 (s, bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 31.6, 34.9, 38.6, 65.1, 110.4, 112.1, 120.3, 125.3, 125.4, 125.6, 128.1, 138.5, 139.7, 151.9; EI-MS (70eV): *m/z* = 206 (17%), 205 (100%), 190 (5%), 161 (21%), 118 (6%), 105 (6%); Anal. Calcd. for $C_{20}H_{24}N_2O_4$ (356.42): C, 67.40; H, 6.79; N, 7.86; Found: C, 67.45; H, 6.82; N, 7.90.

Compound **3f**. Yellow waxy oil; IR (neat): ν = 751, 971, 1038, 1278, 1476, 1498, 1626, 2858, 2931, 3283 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.75-1.77 (m, 4H), 2.37 (s, 3H), 2.69 (t, 2H, *J* = 6.6Hz), 2.76 (t, 2H, *J* = 6.6Hz), 3.61 (bs, 2H), 3.70-3.79 (m, 2H), 3.85-3.96 (m, 2H), 6.13 (bs, 1H), 6.63 (bs, 1H), 7.19 (t, 4H, *J* = 7.3Hz), 7.23-7.29 (m,

3H), 7.39 (m, 2H), 8.12 (s, 1H), 10.68 (bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 21.4, 28.5, 28.8, 31.2, 35.9, 38.7, 64.8, 110.5, 110.6, 122.1, 124.7, 125.6, 126.1, 128.4, 128.6, 128.7, 129.4, 137.5, 138.3, 138.8, 141.8, 142.2; EI-MS (70eV): *m/z* = 163 (100%), 119 (25%), 91 (14%), 65 (3%); Anal. Calcd. for $C_{27}H_{30}N_2O_4$ (446.55): C, 72.62; H, 6.77; N, 6.27; Found: C, 72.66; H, 6.81; N, 6.24.

Compound **3g**. Orange oil; IR (neat): ν = 700, 1039, 1185, 1275, 1476, 1497, 1626, 2858, 2932, 3266 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.37-1.45 (m, 2H), 1.45-1.54 (m, 2H), 1.66-1.81 (m, 4H), 2.10-2.16 (m, 2H), 2.70 (t, 2H, *J* = 7.7 Hz), 2.81-2.87 (m, 2H), 3.50-3.54 (m, 4H), 3.90-3.94 (m, 2H), 3.98-4.02 (m, 2H), 6.12 (dd, 1H, *J* = 2.1, 3.4 Hz), 6.62 (dd, 1H, *J* = 2.3, 3.6 Hz), 7.19-7.25 (m, 3H), 7.27-7.33 (m, 2H), 8.10 (s, 1H), 10.54 (bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 26.8, 28.3, 28.7, 29.0, 30.4, 32.6, 36.3, 41.1, 45.2, 65.8, 110.5, 112.2, 122.1, 124.5, 126.3, 128.3, 128.5, 128.8, 138.0, 141.5, 141.9; EI-MS (70eV): *m/z* = 446 ([M$^+$], 0.1%), 217 (12%), 177 (87%), 112 (73%), 104 (24%), 91 (100%), 77 (17%), 68 (26%); Anal. Calcd. for $C_{24}H_{31}ClN_2O_4$ (446.97): C, 64.49; H, 6.99; N, 6.27; Found: C, 64.45; H, 7.03; N, 6.30.

Compound **3h**. Orange oil; IR (neat): ν = 733, 1039, 1185, 1263, 1284, 1476, 1498, 1626, 2929, 2956, 3266 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.98 (t, 3H, *J* = 7.3 Hz), 1.42 (tq, 2H, *J* = 7.3, 7.7 Hz), 1.62-1.76 (m, 2H), 2.12-2.17 (m, 2H), 2.71 (t, 2H, *J* = 7.7 Hz), 2.83-2.88 (m, 2H), 3.51 (bs, 2H), 3.89-4.05 (m, 4H), 6.14 (dd, 1H, *J* = 2.6, 3.4 Hz), 6.64 (dd, 1H, *J* = 2.6, 3.0 Hz), 7.20-7.34 (m, 5H), 8.12 (s, 1H), 10.57 (bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.1, 22.6, 28.1, 30.4, 31.3, 36.4, 41.1, 65.8, 110.5, 112.2, 122.2, 124.4, 126.3, 128.4, 128.5, 128.8, 137.8, 141.5, 142.4; EI-MS (70eV): *m/z* = 384 ([M$^+$], 0.1%), 177 (100%), 118 (18%), 91 (47%); Anal. Calcd. for $C_{22}H_{28}N_2O_4$ (384.48): C, 68.73; H, 7.34; N, 7.29; Found: C, 68.68; H, 7.30; N, 7.32.

Compound **3i**. Yellow waxy solid; IR (neat): ν = 782, 974, 1019, 1036, 1269, 1479, 1499, 1628, 2858, 2921, 3292 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.38-1.49 (m, 1H), 2.11-2.16 (m, 1H), 3.2 (d, 2H, *J* = 5.1 Hz), 3.87 (dt, 2H, *J* = 2.6, 12.4 Hz), 4.18 (dd, 2H, *J* = 1.3, 5.1 Hz), 4.91 (t, 1H, *J* = 5.1 Hz), 6.35-6.39 (m, 1H), 6.67-6.71 (m, 1H), 7.05-7.09 (m, 1H), 8.19 (s, 1H), 10.48 (s, bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 25.8, 34.5, 67.4, 100.5, 112.2, 120.2, 120.8, 125.4, 125.7, 129.0, 138.3; EI-MS (70eV): *m/z* = 238 ([M$^+$], 6%), 105 (14%), 104 (21%), 87 (100%), 77 (6%), 59 (22%), 41 (8%), 31 (13%); Anal. Calcd. for $C_{11}H_{14}N_2O_4$ (238.24): C, 55.46; H, 5.92; N, 11.76; Found: C, 55.50; H, 5.96; N, 11.72.

Compound **3j**. Yellow waxy oil; IR (neat): ν = 780, 976, 1016, 1039, 1266, 1477, 1498, 1627, 2854, 2924, 3288 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.8Hz), 1.27-1.40 (m, 12H), 1.46 (dt, 1H, *J* = 1.2, 13.7 Hz), 1.62-1.72 (m, 2H) 2.10-2.22 (m, 1H), 2.66 (t, 2H, *J* = 7.7 Hz), 3.20 (t, 2H, *J* = 5.1Hz), 3.87 (td, 2H, *J* = 2.1, 12.4 Hz), 4.17 (dd, 2H, *J* = 6.0, 11.1 Hz), 4.9 (t, 1H, *J* = 5.1 Hz), 6.09-6.11 (m, 1H), 6.62-6.64 (m, 1H), 8.15 (s, 1H), 10.35 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.4, 22.9, 25.9, 28.5, 29.1, 29.5, 29.6, 29.7, 32.1, 34.7, 67.4, 100.7, 110.6, 122.6, 124.4, 129.2, 136.1, 142.8; EI-MS (70eV): *m/z* = 364 ([M$^+$], 1%), 118 (10%), 87 (100%), 59 (8%), 31 (6%); Anal. Calcd. for $C_{20}H_{32}N_2O_4$ (364.49): C, 65.91; H, 8.85; N, 7.69; Found: C, 65.96; H, 8.88; N, 7.66.

General procedure for the synthesis of compounds 4a-j.

A solution of the intermediate **3a-j** (1 mmol) in 2-MeTHF (10 mL) was treated with Amberlyst 15 (0.200 g) and irradiated by Biotage® Initiator$^+$ at 100°C for 45 minutes. Then, the Amberlyst 15 was filtered off washing with fresh 2-MeTHF (10 mL) and, after the removal of the solvent at reduced pressure, the crude products **4a-j** were purified by flash chromatography column (toluene).

Compound **4a**. Yellow solid; mp 145-147°C; IR (neat): ν = 727, 745, 770, 866, 1064, 1293, 1314, 1482, 1509, 3338 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 2.61 (s, 3H), 6.65-6.67 (m, 1H), 7.50 (t, 1H, *J* = 2.4 Hz), 7.83 (d, 1H, *J* = 0.87 Hz), 8.25 (s, 1H), 8.77 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 19.0, 102.4, 106.3, 115.4, 129.6, 131.1, 133.1, 134.0, 143.5; EI-MS (70eV): *m/z* = 176 ([M$^+$], 100%), 146 (20%), 130 (55%), 128 (16%), 118 (12%), 103 (24%), 102 (16%), 91 (8%), 77 (28%), 63 (5%), 51 (6%); Anal. Calcd. for $C_9H_8N_2O_2$ (176.17): C, 61.36; H, 4.58; N, 15.90; Found: C, 61.41; H, 4.55; N, 15.87.

Compound **4b**. Yellow solid; mp 66-68°C; IR (neat): ν = 747, 780, 1073, 1310, 1331, 1259, 1466, 1513, 1537, 2851, 2921, 3360 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.88 (t, 3H, *J* = 6.8Hz), 1.26-1.42 (m, 12H), 1.71-1.81 (m, 2H), 2.55 (s, 3H), 2.82 (t, 2H, *J* = 7.3 Hz), 6.34 (t, 1H, J = 0.9 Hz), 7.79-7.81 (m, 1H), 8.16 (s, 1H), 8.62 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.4, 18.9, 22.9, 28.8, 29.2, 29.4, 29.5, 29.6, 29.7, 32.1, 99.6, 105.6, 115.4, 129.6, 134.0, 134.3, 142.4, 146.6; EI-MS (70eV): *m/z* = 302 (21%), 203 (30%), 190 (100%), 157 (15%), 143 (42%), 131 (15%), 115 (15%), 41 (9%); Anal. Calcd. for $C_{18}H_{26}N_2O_2$ (302.42): C, 71.49; H, 8.67; N, 9.26; Found: C, 71.44; H, 8.63; N, 9.28.

Compound **4c**. Red solid, mp 114-117°C; IR (neat): ν = 665, 726, 742, 756, 975, 1057, 1118, 1297, 1481, 1504, 2905, 2977, 3341 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.37 (t, 3H, *J* = 7.7 Hz), 2.97 (q, 2H, *J* = 7.7 Hz), 6.65-6.67 (m, 1H), 7.50 (t, 1H, *J* = 2.8 Hz), 7.85-7.86 (m, 1H), 8.28-8.29 (m, 1H), 9.02 (bs, s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.5, 26.4, 102.1, 106.5, 113.5, 129.9, 132.6, 134.3, 137.2, 143.6; EI-MS (70eV): *m/z* = 190 ([M$^+$], 100%), 176 (8%), 175 (80%), 160 (6%), 144 (22%), 143 (24%), 130 (9%), 129 (34%), 128 (13%), 117 (35%), 115 (28%), 102 (12%), 89 (10%), 75 (7%), 63 (9%), 51 (6%); Anal. Calcd. for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73; Found: C, 63.19; H, 5.33; N, 14.77.

Compound **4d**. Orange waxy solid; IR (neat): ν = 699, 749, 879, 1073, 1301, 1447, 1485, 1512, 1540, 2858, 2932, 3361 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.38 (t, 3H, *J* = 7.3 Hz), 1.73-1.86 (m, 4H), 2.7 (t, 2H, *J* = 7.7 Hz), 2.85 (t, 2H, J = 7.7Hz), 2.93 (q, 2H, *J* = 7.7 Hz), 6.36 (s, 1H), 7.19-7.23 (m, 3H), 7.29-7.33 (m, 2H), 7.85-7.86 (m, 1H), 8.17 (s, 1H), 8.63 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.5, 26.4, 28.6, 28.7, 31.2, 35.9, 99.5, 105.8, 113.7, 126.1, 128.6, 128.7, 133.6, 134.3, 135.9, 142.4, 142.6, 146.2; EI-MS (70eV): *m/z* = 322 (45%), 217 (42%), 204 (100%), 171 (20%), 157 (45%), 142 (19%), 130 (27%), 115 (27%), 91 (54%), 65 (12%); Anal. Calcd. for $C_{20}H_{22}N_2O_2$ (322.41): C, 74.51; H, 6.88; N, 8.69; Found: C, 74.46; H, 6.85; N, 8.67.

Compound **4e**. Yellow solid; mp 61-63°C; IR (neat): ν = 751, 836, 1070, 1311, 1327, 1492, 2961, 3374 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.40 (s, 9H), 6.85-6.86 (m, 1H), 7.53-7.56 (m, 3H), 7.64-7.67 (m, 2H), 8.11 (d, 1H, *J* = 2.1 Hz), 8.36-8.37 (m, 1H), 8.84 (s, bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 31.6, 34.9, 103.7, 106.9, 115.0, 126.0, 128.6, 130.2, 131.3, 134.9, 135.0, 136.5, 143.8, 151.3; EI-MS (70eV): *m/z* = 294 ([M$^+$], 49%), 279 (100%), 251 (11%), 233 (11%), 217 (10%), 204 (9%), 191 (9%), 165 (6%), 139 (5%), 125 (5%), 111 (7%), 102 (8%), 161 (21%), 118 (5.9%), 105 (5.9%); Anal. Calcd. for $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52; Found: C, 73.48; H, 6.19; N, 9.49.

Compound **4f**. Yellow solid; mp 154-156°C; IR (neat): ν = 753, 828, 1071, 1291, 1317, 1500, 1535, 2933, 3367 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.69-1.83 (m, 4H), 2.45 (s, 3H), 2.69 (t, 2H, *J* = 7.5 Hz), 2.76 (t, 2H, *J* = 7.5 Hz), 6.50 (s, 1H), 7.15-7.22 (m, 3H), 7.25-7.34 (m, 4H), 7.58 (dt, 2H, *J* = 1.7, 8.1 Hz), 8.06 (d, 1H, *J* = 1.7 Hz), 8.22 (dd, 1H, *J* = 0.8, 2.1 Hz), 8.49 (bs,1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 21.5, 28.6, 28.7, 31.2, 35.8, 101.0, 106.2, 115.0, 126.1, 128.6, 128.7, 128.7, 129.7, 132.4, 133.7, 134.9, 136.7,

137.9, 142.2, 142.9, 146.7; EI-MS (70eV): *m/z* = 384 ([M^+], 100%), 341 (12%), 179 (33%), 219 (54%), 208 (45%), 204 (37%), 91 (46%), 65 (11%); Anal. Calcd. for $C_{25}H_{24}N_2O_2$ (384.48): C, 78.10; H, 6.29; N, 7.29; Found: C, 78.14; H, 6.26; N, 7.27.

Compound **4g**. Orange solid; mp 65-66°C; IR (neat): ν = 698, 751, 1069, 1301, 1446, 1476, 1510, 1541, 2859, 2935, 3351 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 1.39-1.57 (m, 4H), 1.75-1.84 (m, 4H), 2.83 (t, 2H, *J* = 7.7 Hz), 3.02-3.08 (m, 2H), 3.17-3.23 (m, 2H), 3.52 (t, 2H, *J* = 6.6 Hz), 6.34 (d, 1H, *J* = 0.86 Hz), 7.19-7.26 (m, 3H), 7.27-7.33 (m, 2H), 7.83 (d, 1H, *J* = 1.7 Hz), 8.15 (d, 1H, *J* = 1.3 Hz), 8.40 (bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 26.8, 28.6, 28.7, 29.0, 32.6, 35.4, 36.6, 45.2, 99.5, 105.8, 114.8, 126.4, 128.6, 128.7, 133.5, 133.7, 134.3, 141.7, 142.7, 146.0; EI-MS (70eV): *m/z* = 384 ([M^+], 25%), 293 (100%), 188 (12%), 142 (60%), 115 (14%), 91 (39%); Anal. Calcd. for $C_{22}H_{25}ClN_2O_2$ (384.90): C, 68.65; H, 6.55; Cl, 9.21; N, 7.28; Found: C, 68.61; H, 6.52; N, 9.23.

Compound **4h**. Orange solid; mp 148-149°C; IR (neat): ν = 575, 697, 748, 883, 1286, 1312, 1447, 1495, 1540, 2858, 2926, 3334 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.99 (t, 3H, *J* = 7.3 Hz), 1.40-1.49 (m, 2H), 1.70-1.82 (m, 2H), 2.83 (t, 2H, *J* = 7.7 Hz), 3.03-3.09 (m, 2H), 3.18-3.23 (m, 2H), 6.35 (m, 1H), 7.20-7.35 (m, 5H), 7.84 (d, 1H, *J* = 1.7 Hz), 8.17 (m, 1H), 8.55 (bs, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.1, 22.7, 28.5, 31.2, 35.4, 36.6, 99.4, 105.9, 114.7, 126.4, 128.6, 128.7, 133.4, 133.8, 134.3, 141.8, 142.6, 146.6; EI-MS (70eV): *m/z* = 322 ([M^+], 17%), 231 (100%), 185 (11%), 142 (36%), 115 (10%), 91 (20%); Anal. Calcd. for $C_{20}H_{22}N_2O_2$ (322.41): C, 74.51; H, 6.88; N, 8.69; Found: C, 74.55; H, 6.91; N, 8.66.

Compound **4i**. Yellow solid; mp 141-143°C; IR (neat): ν = 725, 747, 773, 867, 1061, 1298, 1318, 1485, 1512, 3335 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 6.67-6.68 (m, 1H), 7.52 (t, 1H, *J* = 2.7 Hz), 7.68 (d, 1H, *J* = 9.0 Hz), 8.03 (dd, 1H, *J* = 2.14, 9.0 Hz), 8.40 (d, 1H, *J* = 2.1 Hz), 8.73 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 103.9, 108.2, 115.6, 120.8, 130.0, 133.0, 134.5, 143.7; EI-MS (70eV): *m/z* = 162 ([M^+], 100%), 132 (39%), 116 (82%), 104 (29%), 89 (70%), 77 (9%), 63 (30%), 51 (10%), 39 (8%), 30 (9%); Anal. Calcd. for $C_8H_6N_2O_2$ (162.04): C, 59.26; H, 3.73; N, 17.28; Found: C, 59.22; H, 3.75; N, 17.31.

Compound **4j**. Orange solid; mp 59-61°C; IR (neat): ν = 733, 779, 819, 1061, 1293, 1464, 1501, 1540, 1592, 2851, 2926, 2953, 3358 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.8Hz), 1.18-1.44 (m, 12H), 1.72-1.80 (m, 2H), 2.82 (t, 2H, *J* = 7.7 Hz), 6.36 (s, 1H), 7.53 (d, 1H, *J* = 9.0 Hz), 7.99 (dd, 1H, *J* = 2.1, 8.5 Hz), 8.29 (d, 1H, *J* = 2.1 Hz), 8.48 (bs, s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$): δ = 14.4, 22.9, 28.7, 29.1, 29.5, 29.6, 29.7, 32.1, 101.1, 107.5, 115.7, 119.5, 134.3, 134.4, 142.5, 147.2; EI-MS (70eV): *m/z* = 288 ([M^+], 13%),189 (30%), 176 (100%), 175 (50%), 143 (15%), 129 (37%), 115 (15%), 41 (15%); Anal. Calcd. for $C_{17}H_{24}N_2O_2$ (288.39): C, 70.80; H, 8.39; N, 9.71; Found: C, 70.84; H, 8.42; N, 9.68.

Acknowledgements

The authors thank the University of Camerino for the financial support.

References

[1] a) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73-103; b) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045-1075; c) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, 105, 2873-2920.

[2]a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M.; Freidinger, W. L. Whitter, G. F. Lundell, D. F. Verber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. H. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirhfield, *J. Med. Chem.* **1988**, *31*, 2235-2246; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893-930.

[3] G. W. Gribble in *Indole Ring: Synthesis from Natural Products to Drug Discovery*, *1st ed.*, Wiley, Chichester, **2016**.

[4] a) J. Bergman, *Studies in Natural Products Chemistry*, *Vol. 1*, Part A (Ed.; A. Rahman), Elsevier, New York, **1988**, pp 3-30; b) K. S. J. Stapleford, *The Indole Alkaloids*; *Chemistry of Carbon Compounds*, *Vol. 4*, Part B (Ed.; S. Coffey), Elsevier, New York, **1977**, pp 63-163.

[5] a) A. Baeyer, *Justus Liebigs Ann. Chem.* **1866**, *140*, 295-296; b) A. Baeyer, A. Emmerling, *Chem. Ber.* **1869**, *2*, 679-682.

[6] M. Inman, C. J. Moddy, *Chem. Sci.* **2013**, *4*, 29-41.

[7] a) F. J. Brown, L. A. Cronk, D. Aharony, D. W. Snyder, *J. Med. Chem.* **1992**, *35*, 2419-2439; b) H. Deng, A. N. Gifford, A. M. Zvonok, G. Cui, X. Li, P. Fan, J. R. Deschamps, J. L. Flippen-Anderson, S. J. Gatley, A. Makriyannis, *J. Med. Chem.* **2005**, *48*, 6386-6392; c) I. Borza, É. Bozo´, G. Barta-Szalai, C. Kiss, G. Tárkányi, Á. Demeter, T. Gáti, V. Háda, S. Kolok, A. Gere, L. Fodor, J. Nagy, K. Galgóczy, I. Magdó, B. Ágai, J. Fetter, F. Bertha, G. M. Keserü, C. Horváth, S. Farkas, I. Greiner, G. Domány, *J. Med. Chem.* **2007**, *50*, 901-914; d) Y. Jia, M. Bois-Choussy, J. Zhu, *Org. Lett.* **2007**, *9*, 2401-2404; e) S. C. Annedi, S. P. Maddaford, G. Mladenova, J.Ramnauth, S. Rakhit, J. S. Andrews, D. K. H. Lee, D. Zhang, F. Porreca, D. Bunton, L. Christie, *J. Med. Chem.* **2011**, *54*, 7408-7416.

[8] a) N. Ono, *The nitro group in organic synthesis*, Wiley-VCH, New York, **2001**; b) R. Ballini, S. Gabrielli, A. Palmieri, M. Petrini, *Curr. Org. Chem.* **2011**, *15*, 1482-1506; c) R. Ballini, M. Petrini, *Adv. Synth. Catal.* **2015**, *357*, 2371-2402.

[9] a) W. E. Noland, K. R. Rush, L. R. Smith, *J. Org. Chem.* **1966**, *31*, 65-69; b) W. E. Noland, K. R. Rush, *J. Org. Chem.* **1966**, *31*, 70-77; c) O. Ottoni, R. Cruz, N. H. Krammer, *Tetrahedron Lett.* **1999**, *40*, 1117-1120; d)

[10] a) N. Moskalev, M. Makosza, *Tetrahedron Lett.* **1999**, *40*, 5395-5398; b) J. Bergman, P. Sand, *Tetrahedron* **1990**, *46*, 6085-6112; c) A. R. Katritzky, S. Rachwal, S. Bayyuk, *Org. Prep. Proced. Int.* **1991**, *23*, 357-363; d) B. Narayana, B. V. Ashalatha, K. K. Vijaya Raj, J. Fernandes, B. K. Sarojini, *Bioorg. Med. Chem.* **2005**, *13*, 4638-4644;

[11] a) R. Ballini, S. Gabrielli, A. Palmieri, *Synlett* **2010**, 2468-2470; b) S. Gabrielli, R. Ballini, A. Palmieri, *Monatsh. Chem.* **2013**, *144*, 509-514; c) S. Gabrielli, A. Giardinieri, S. Sampaolesi, R. Ballini, A. Palmieri, *Molecules* **2016**, *21*, 776.

10.1002/adsc.201700790

[12] a) H. Muratake, M. Natsume, *Heterocycles* **1989**, *29*, 783-794.

[13] Acceptable results were described in the literature only using nitromethane. a) J. -P. Strachan, D. F. O'Shea, T. Balasubramanian, J. S. Lindsey, *J. Org. Chem.* **2000**, *65*, 3160-3172; b) G. J. T. Kuster, R. H. J. Steeghs, H. W. Scheeren, *Eur. J. Org. Chem.* **2001**, 553-560; c) W. E. Noland, G. Pardi, J. *Heter. Chem.* **2005**, *42*, 1149-1154; d) M. Wessling, H. J. Schäfer, *Beilstein J. Org. Chem.* **2015**, *11*, 1163-1174.

[14] a) I. Hasan, E. R. Marinelli, L. -C. Chang Lin, F. W. Fowler, A. B. Levy, *J. Org. Chem.* **1981**, *46*, 157-164; b) C. S. Schwalm, I. B. D. De Castro, J. Ferrari, F. L. De Oliveira, R. Aparicio, C. R. D. Correia, *Tetrahedron Lett.* **2012**, *53*, 1660-1663.

[15] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2015**, *11*, 1194-1219 and references cited therein.

[16] a) A. Palmieri, S. Gabrielli, R. Ballini, *Chem. Commun.* **2010**, 6165-6167; b) A. Palmieri, S. Gabrielli, D. Lanari, L. Vaccaro, R. Ballini, *Adv. Synth. Catal.* **2011**, *353*, 1425-1428; c) A. Palmieri, S. Gabrielli, M. Parlapiano, R. Ballini, *RSC Adv.* **2015**, *5*, 4210-4213.

10.1002/adsc.201700790

FULL PAPER

Two-step Synthesis of Polysubstituted 6-Nitroindoles under Flow Chemical and Microwaves conditions

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Susanna Sampaolesi, Serena Gabrielli, Roberto Ballini and Alessandro Palmieri*