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$AlMe_3$-Mediated Regio- and Chemoselective Reactions of Indole with Carbamoyl Electrophiles

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Herein, we report the regio- and chemoselective reactions of indole with carbamoyl electrophiles in presence of $AlMe_3$. Indole-3-carboxamide was prepared in one-step from a reaction of indole with tertiary carbamoylimidazole in the presence $AlMe_3$. Under conditions for the formation of an aluminium ate complex, the reaction was diverted to the indole nitrogen. Secondary carbamoyl electrophiles in the presence of $AlMe_3$ regiospecifically yielded trisubstituted ureas. The regiospecificity and chemoselectivity of the indole nitrogen towards ester and tertiary carbamoylimidazole functionalities were also studied.

Introduction

Indoles are very important and attractive structural moieties to both medicinal and synthetic organic chemists. The Friedel–Crafts acylation/alkylation at the C-3 position of indole has been extensively investigated by many researchers.[1a,1b] In continuation of our research,[2a] we attempted to synthesize tetrasubstituted ureas that contain an indole motif by using a tertiary carbamoylimidazole in the presence of $AlMe_3$. As a result, we were pleasantly surprised by the formation of indole-3-carboxamides instead of the expected urea. The use of a carbamoylimidazole as a component in an electrophilic reaction has previously been limited to the synthesis of ureas. The chemical transformation that uses a carbamoylimidazole in a Friedel–Crafts-type carboxamidation has not been reported until now.

Indole-3-carboxamides and ureas that contain an indole motif have received wide attention as potent and selective antagonists of the serotonin 5-HT3 receptor (i.e., **1**),[3a] as platelet activating factor antagonists (i.e., **2**),[3b] as cannabinoid receptor modulators (i.e., **3**),[3c,3d] as p38α MAP kinase inhibitors (i.e., **4**),[4a] as BACE-1 inhibitors,[4b] as Met kinase inhibitors,[4c] and also as useful ligands in organic transformations (see Figure 1).[4d]

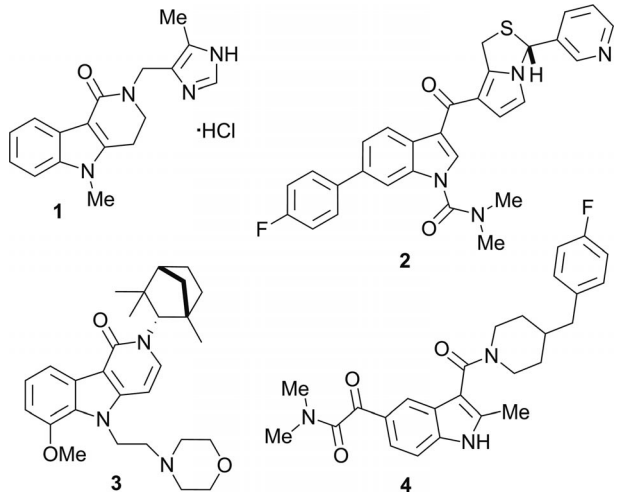

Figure 1. Some bioactive indole-3-carboxamides and an indole urea.

The most frequent methods employed for the preparation of indole-3-carboxamide include (see Scheme 1): (i) the conversion of indole-3-carbaldehyde to its carboxylic acid/ester followed by a coupling reaction with an amine;[5] (ii) the reaction of indole with a Grignard reagent followed by treatment with ethyl chloroformate to give a mixture of C-3- and *N*-ethoxycarbonyl products;[6] (iii) the reaction of indole with Viehe's reagent,[7a] chlorosulfonyl isocyanate,[7b–7d] or isocyanatophosphoryl dichloride[7e] followed by basic hydrolysis; (iv) the treatment of indole with chloroformates[6b] or toxic triphosgene followed by coupling with amines;[8] (v) a Pd-catalyzed carboxamidation of indole by using isocyanide, which was recently reported by Zhu et al.;[9] and (vi) a Friedel–Crafts acylation of indole that was explored in detail by Katritzky et al. by using carbonylbenzotriazole.[10a] However, a Friedel–Crafts carbamoylation with carbamoylazole has not been studied so far. Recently, Sarpong et al.[10b] reported a chemoselective acylation of the indole nitrogen by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and imidazole carbamates.

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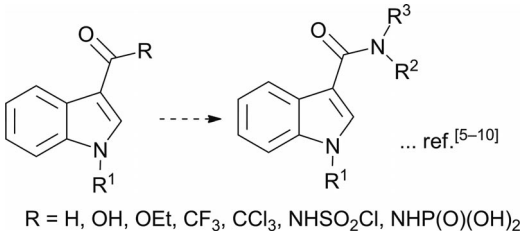


Scheme 1. Some reported methods for C-3 carboxamidation.

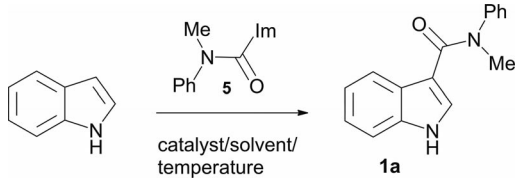
Results and Discussion

We began our study by screening a number of acid catalysts that are commonly employed in a Friedel–Crafts reaction such as Amberlyst 15, $BF_3{\cdot}Et_2O$, trifluoroacetic acid (TFA), $FeCl_3$, $CeCl_3$, $CuCl_2$, $ZnBr_2$, and $ZnCl_2$. Treating indole with a tertiary carbamoylimidazole and any of these catalysts did not lead to the desired carbamoylation. The regioselective C-3 acylation of indole by *N*-chlorozinc complex, which was reported earlier,[10c] did not work with a tertiary carbamoylimidazole. After extensive screening, we determined that $AlMe_3$ was the best catalyst for the C-3 carbamoylation (see Table 1).

Among the several solvents tried (see Table 1) 1,2-dichloroethane (DCE) and toluene were better than the others. Toluene was chosen as the solvent for rest of the study. At a higher reaction temperature with $AlCl_3$, indole-3-carboxamide **1a** was obtained in very low yield (5–15%), and extensive decomposition of carbamoylimidazole **5** occurred. The reaction with $AlMe_3$ was clean, but slow to furnish indole-3-carboxamide **1a**. The yield decreased in solvents such as acetonitrile (ACN) and 1,4-dioxane. The optimal conditions were achieved by using 3 equiv. of $AlMe_3$ in toluene at 110 °C. The preparation and structural characterization by single crystal XRD and NMR spectroscopy of the indole-aluminium amide complex was previously reported.[11] However, the synthetic utility of the reaction remained unexplored until now. Using the optimal conditions, a host of indole-3-carboxamides were synthesized (see Table 2). The yields were moderate to good (45–90%), as the solubility of these indole-3-carboxamides was a concern during the workup and column purification.

All of these compounds were highly soluble in tetrahydrofuran (THF) and were purified by silica gel column chromatography. The carboxamidation reaction was highly sensitive to the nature of the substituent on the benzene ring and indole nitrogen. *N*-substituted indoles such as *N*-methylindole and *N*-benzylindole did not undergo reaction, whereas a smooth reaction occurred using indole with a free N–H. Also, electron-deficient substrates such as 5-cyanoindole and 5-nitroindole failed to react under the above conditions. No reaction was observed when tertiary phenyl carbamates were treated with indole in the presence of $AlMe_3$. This may be attributed to the poor leaving group ability of phenoxide in comparison to a tertiary carbamoylimidazole[2a] (see Scheme 1a in the Supporting Information). 2-Methylindole also underwent C-3 carbamoylation to give product **1j** in 80% yield (see Table 2).

Table 1. Optimization of reaction conditions.[a]



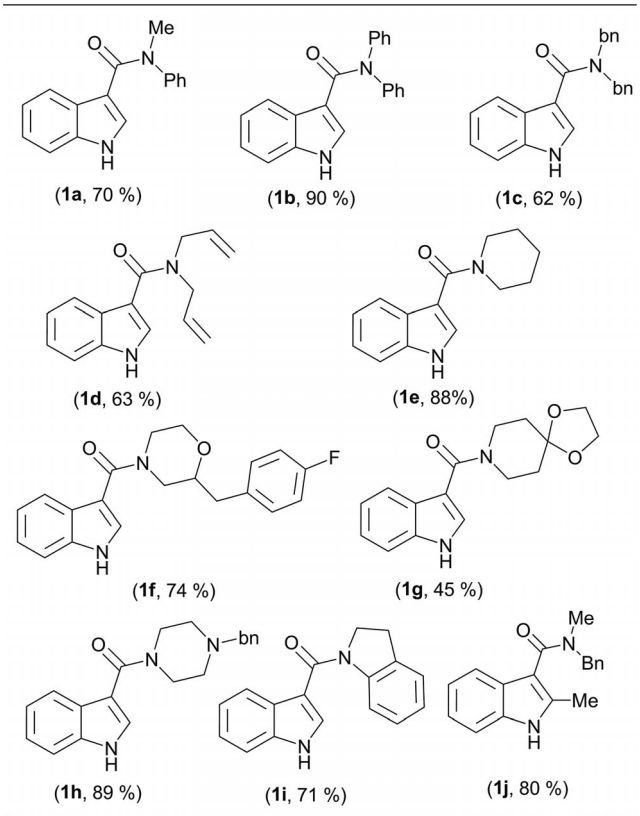
Entry	Lewis acid	Equiv.	Solvent	Time [h]	Temp. [°C][b]	Yield [%][c]
1	Amberlyst 15	wt/wt	ACN	24	86	n.r.[d]
2	Amberlyst 15	wt/wt	DCE	24	86	n.r.
3	Amberlyst 15	wt/wt	toluene	24	86	n.r.
4	$AlCl_3$	1.1	DCM[e]	6	52	n.r.
5	$AlCl_3$	1.1	DCE	24	reflux	5
6	$AlCl_3$	2.1	DCE	24	reflux	9
7	$AlCl_3$	2.1	toluene	24	110	14
8	$BF_3{\cdot}AcOH$	1.5	DCM	6	52	n.r.
9	$FeCl_3$	1.5	DCM	6	52	n.r.
10	$AlMe_3$	1.5	DCM	6	52	n.r.
11	$BF_3{\cdot}Et_2O$	1.5	ACN	24	86	n.r.
12	$CuCl_2$	1.5	ACN	24	86	n.r.
13	$FeCl_3$	1.5	ACN	24	86	n.r.
14	TFA	1.5	ACN	24	86	n.r.
15	$ZnBr_2$	1.5	ACN	24	90	n.r.
16	$CeCl_3$/NaI/silica	1.5	ACN	24	90	n.r.
17	$ZnCl_2$	1.5	DCE	48	90	n.r.
18	$ZnCl_2$/*i*PrMgCl	2.0/1.0	DCE	48	90	n.r.
19	$AlMe_3$	1.5	ACN	24	90	n.r.
20	TFA	1.5	ACN	48	86	n.r.
21	$AlMe_3$	2.5	toluene	24	110	35
22	$AlMe_3$	3.0	toluene	48	110	70
23	$BF_3{\cdot}AcOH$	2.5	toluene	48	110	n.r.
24	$FeCl_3$	2.5	toluene	48	110	n.r.
25	$AlMe_3$	3.0	DCE	48	90	79
26	$AlMe_3$	3.0	ACN	48	90	12
27	$AlMe_3$	3.0	toluene	48	90	68
28	$AlMe_3$	3.0	1,4-dioxane	48	110	45

[a] Reagents and conditions: Indole (1.0 mmol), **5** (1.1 mmol; Im = imidazole). [b] Oil bath temperature. [c] Yield of isolated product. [d] n.r. = no reaction. [e] DCM = dichloromethane.

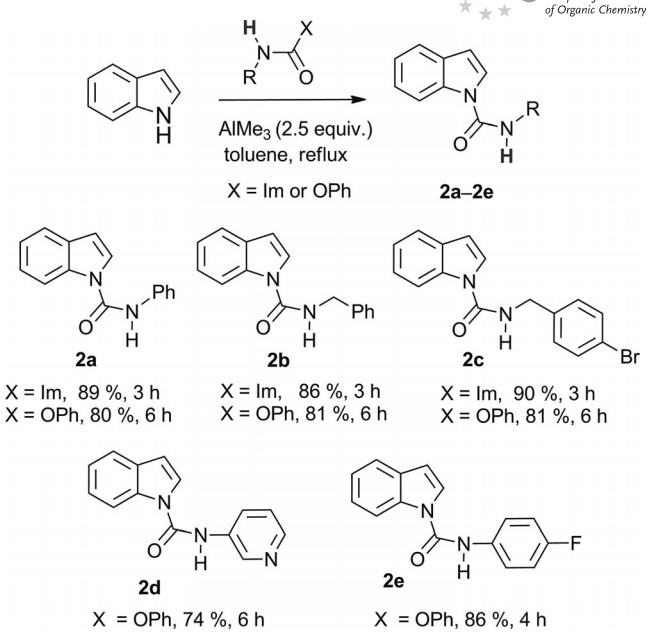
Generally, indole ureas are synthesized from triphosgene derivatives.[12] This method suffers from a disadvantage in that the reaction is always accompanied by the formation of a self-coupled symmetrical urea. Furthermore, electron-deficient indole systems gave low yields, which limited the scope of this methodology. With the purpose of understanding the factors that determine the regiochemical course of the carboxamidation, several secondary carbamoylimidazoles were treated with indole under similar reaction conditions. Interestingly, in the case of secondary carbamoyl electrophiles, the reaction was diverted to the indole nitrogen to give trisubstituted indole ureas **2a**–**2e** (see Scheme 2). Under these conditions, secondary carbamates were reactive unlike tertiary carbamates and furnished the indole ureas. So far, only one example of the formation of an indole urea from a secondary carbamate has been reported under similar conditions.[2b]

As ate complexes are used as switches to tune the regioselectivity of many organometallic reactions,[13] we envisioned

Table 2. C-3 carbamoylation of indole under optimized reaction condition.[a,b]



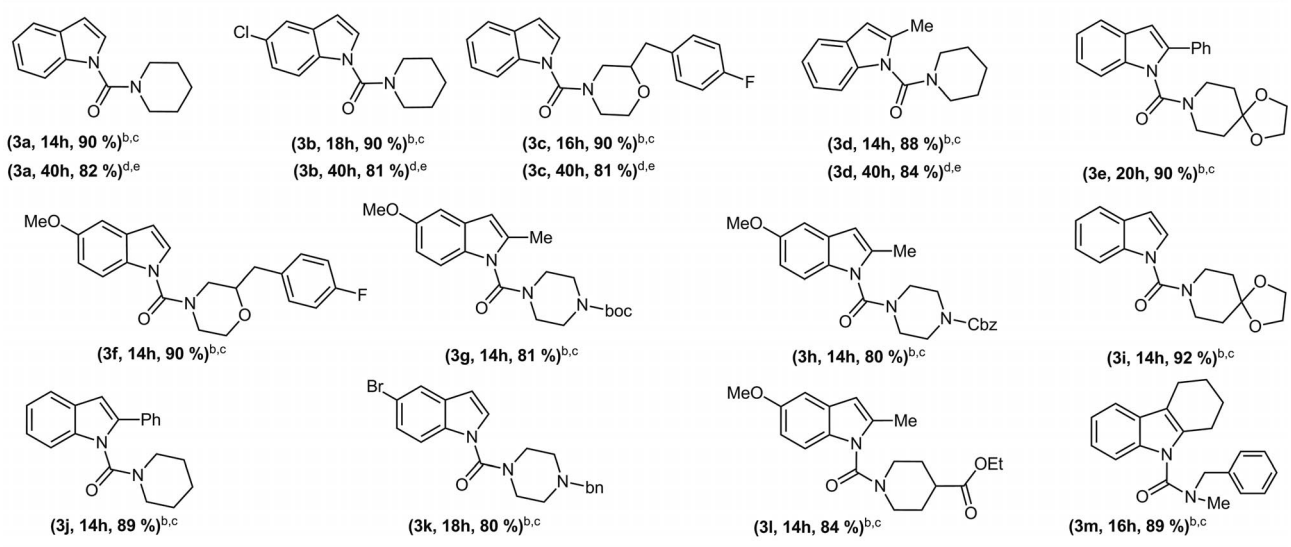
[a] Reagents and conditions: Indole (1.0 mmol), carbamoylimidazole (1.1 mmol), toluene, 110 °C, 48 h. [b] Yield of isolated product.



Scheme 2. Trisubstituted indole ureas from secondary carbamates and carbamoylimidazoles.[a]

that the aluminium ate complex of indole might exhibit not only a higher reactivity towards electrophiles but also a different regiochemical preference. The aluminium ate complex that is derived from tetramethylpiperidine has basic properties and is well-known.[14a] The aluminium ate complex of indole, which is nucleophilic in nature, has not been reported until now, although the synthesis of an indole-aluminium amide complex has been described in the literature.[15] Using the conditions for aluminium ate complex formation, which involves the treatment of indole with lithium hexamethyldisilazide (LiHMDS) followed by the addition of $AlMe_3$, and finally treating with carbamoylimidazole in THF, tertiary carbamoylimidazoles were converted

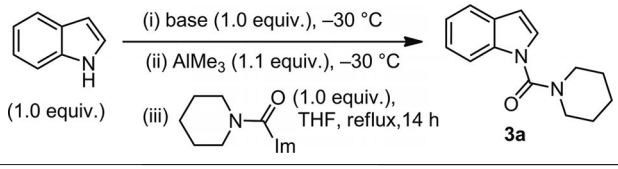
Table 3. *N*-Carbamoylindole synthesis using conditions for aluminium ate complex formation.[a]



[a] Reagents and conditions: Indole (1.0 mmol), THF, –30 °C, LiHMDS (1.0 mmol), then $AlMe_3$ (1.1 mmol), –30 °C, 30 min, carbamoylimidazole (1.025 mmol), 80 °C. [b] Isolated yield. [c] Imidazolide is the leaving group. [d] Ultra performance liquid chromatography (UPLC) conversion. [e] Phenoxide is the leaving group.

exclusively into *N*-carbamoylindoles **3a**–**3m** in good yields (see Table 3). Thus, we achieved the synthesis of a variety of unsymmetrical tetrasubstituted indole ureas under the conditions for aluminium ate complex formation. Tetrahydrocarbazole, which failed to undergo any reaction with tertiary carbamoylimidazole in presence of $AlMe_3$, readily underwent reaction by using the aluminium ate complex conditions to give **3m**. The indole ate complex generated from bases such as *n*BuLi, KHMDS, NaHMDS, and the Grignard reagent *i*PrMgCl also exclusively underwent this *N*-carboxamidation reaction (see Table 4).

Table 4. Combination of different metal bases with $AlMe_3$ for *N*-carbamoylindole synthesis.



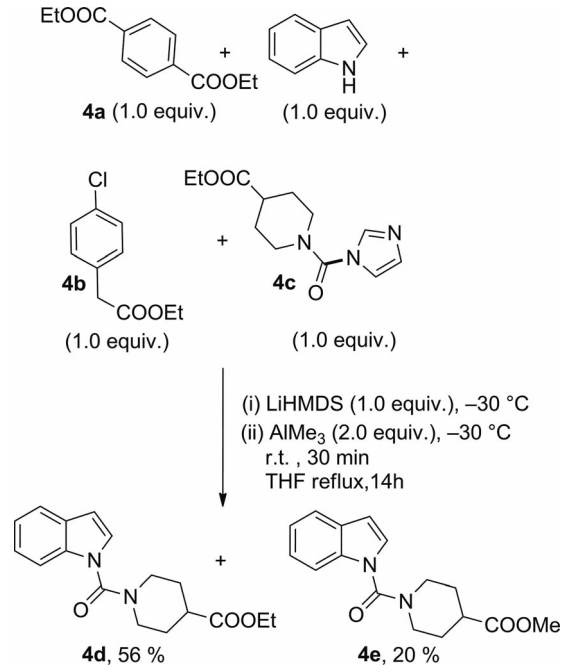
Entry	Base	% Yield[a]
1	LiHMDS	90
2	*i*PrMgCl	89
3	NaHMDS	89
4	KHMDS	90
5	*n*BuLi	91

[a] Yield of isolated product.

Halogenated indoles, which gave **3b** and **3k**, and 2-substituted indoles, which gave **3d**, **3e**, **3g**, **3h**, **3j**, and **3l**, also underwent the reaction very well to form indole ureas. The *N*-(*tert*-butoxycarbonyl) and *N*-benzyloxycarbonyl (Boc and Cbz, respectively) groups were stable under the reaction conditions. An interesting chemoselectivity was observed when indole was treated with a carbamoylimidazole that contained an ester moiety under the conditions for ate complex formation. *N*-carbamoylindole **3l** was prepared without affecting the ester functional group, even with an excess amount of $AlMe_3$ (2.0 equiv.). An equimolar mixture of diethyl terephthalate (**4a**), ethyl (4-chlorophenyl)acetate (**4b**), ethyl 1-(imidazole-1-carbonyl)piperidine-4-carboxylate (**4c**), and indole was subjected to the standard conditions (see Scheme 3). Only the formation of urea was observed as revealed by TLC and LC–MS analysis of the crude product. Workup and purification of this reaction furnished ureas **4d** and **4e**. We also observed the formation of the *trans* esterification product **4e**. The high chemoselectivity in favor of carbamoylimidazole functionality under these conditions is noteworthy.

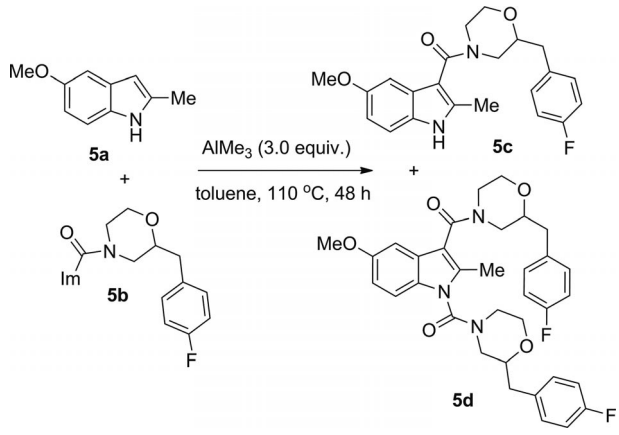
We also attempted a direct one-pot C-3 and *N*-bis(carbamoylation) of indole **5a** by using $AlMe_3$ (see Table 5) in the absence of base and ate complex formation. Although the reaction did not go to completion, the transformation was successful. Products **5c** and **5d** were separated by preparative HPLC. Compound **5c** was also converted into the bis(carbamoylated) product **5d** when treated with $AlMe_3$ and **5b** (see Scheme 4).

The contrasting regiochemical preference that is exhibited by secondary and tertiary carbamoylimidazoles, the



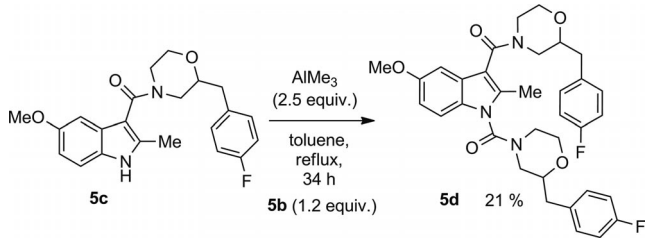
Scheme 3. Regio- and chemoselective competitive reactions of indole with ester and carbamoylimidazole functional groups.

Table 5. One-pot direct bis(carbamoylation) of indole **5a**.



Entry	**5b** [equiv.]	% **5c**[a]	% **5d**[a]
1	1.1	80	12
2	1.6	43 (30)[b]	57 (45)[b]
3	2.3	15	79

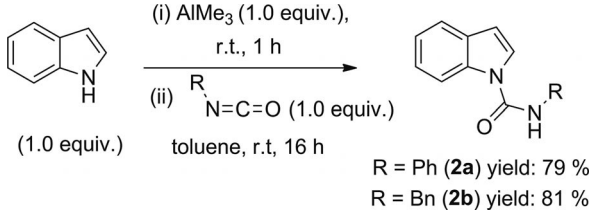
[a] Percent determined by UPLC analysis. [b] Purified by preparative HPLC (isolated yield).



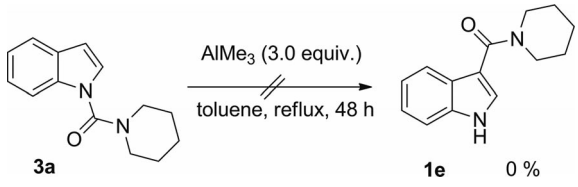
Scheme 4. *N*-acylation of indole-3-carboxamide.

former for nitrogen and the latter for C-3, in this $AlMe_3$-mediated reaction suggests that the two reactions follow different mechanistic pathways. Because secondary carbamoylimidazoles are known to form isocyanates in situ,[12c] it is likely that their reactions proceed through isocyanate intermediates.

A control experiment with indole and phenyl or benzyl isocyanate in presence of $AlMe_3$ (see Scheme 5) yielded exclusively the respective indole ureas, which provided support to this mechanistic proposition. Because the migration of groups from nitrogen to C-3 is known to occur with indoles, we wanted to determine if the C-3 carboxamidation of indole by using a tertiary carbamoylimidazole proceeded through an initial *N*-carbamoylation followed by a migration of the carbamoyl group from the nitrogen to C-3. When urea **3a** was heated in presence of 3 equiv. of $AlMe_3$ at 110 °C for 48 h, the major starting material was recovered (87%) along with minor cleavage products such as *N*-acetyl piperidine and indole. There was no evidence of the formation of **1e**, which ruled out the possibility of this pathway (see Scheme 6). Both electronic and steric factors appear responsible for the preferential C-3 acylation in the case of the tertiary carbamoylimidazoles. Indole dimethylaluminium amide[15] is a covalent compound that is sterically bulky. When it undergoes a reaction with the trimethylaluminium complex of a carbamoylimidazole (i.e., **B**, see Scheme 7), there is considerable steric crowding at the carbonyl reaction centre and also an unfavorable *peri* interaction. As a result, the reaction is diverted to C-3 of the indole, which is a softer centre. Under the conditions for the formation of the aluminium ate complex, we believe that the lithium indole, and not the sterically encumbered ate complex, acts as the nucleophile and attacks the trimethylaluminium complex **B** of the tertiary carbamoylimidazole.

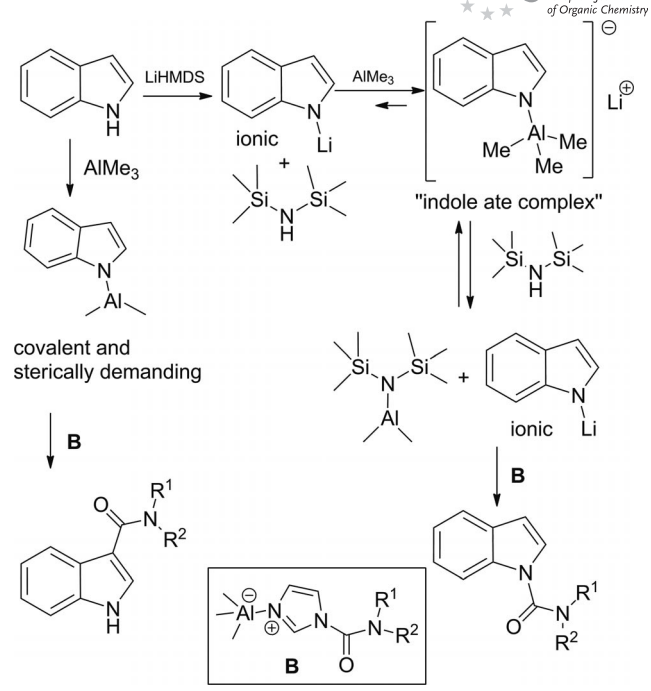


Scheme 5. Reaction of indole with isocyanates in presence of $AlMe_3$.

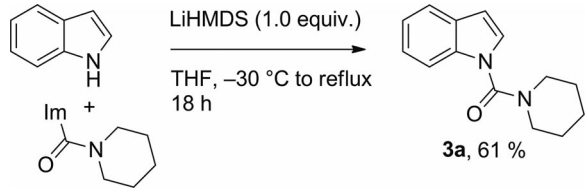


Scheme 6. Possible rearrangement from nitrogen to C-3.

The reaction of the sterically less demanding indolyllithium with complex **B** does not suffer from any *peri* interaction, unlike the indole dimethylaluminium amide. The reaction takes place at the negatively charged nitrogen of indole (hard centre) rather than at the C-3 of indole (soft centre). This line of reasoning is supported by the observation that indolyllithium does react with tertiary carbamoylimidazoles, albeit slowly, to form *N*-indolyl ureas in low yield. In the absence of trimethylaluminium, the tertiary carbamoylimidazole is not activated, and, hence, the slow reaction in this case (see Scheme 8).



Scheme 7. Possible mechanism.



Scheme 8. Tetrasubstituted ureas from simple lithiation.

Conclusions

We have developed an efficient one-step method for the synthesis of indole-3-carboxamide by the reaction of a free N–H indole with tertiary carbamoylimidazoles in the presence of trimethylaluminium. Under these conditions, secondary carbamoyl electrophiles were converted to trisubstituted indole ureas. The combination of base and $AlMe_3$ diverted the reaction from C-3 to *N*-carbamoylation to provide an efficient method for the synthesis of tetrasubstituted indole ureas in excellent yields. This reaction displays high chemoselectivity towards carbamoylimidazoles and is compatible with variety of functional groups. It is interesting that highly reactive isocyanates in presence of $AlMe_3$ gave indole ureas exclusively in good yields, whereas according to earlier literature methods, chloroformates, chlorosulfonylisocyanates, and isocyanatophosphoryl dichloride gave a

mixture of products resulting from *N*- and C-3 acylation. We have also demonstrated a one-pot C-3- and *N*-dicarboxamidation by using $AlMe_3$. The detailed mechanism of these reactions has been investigated.

Experimental Section

General Methods: Purifications were performed with a Combiflash Companion flash column chromatography instrument. Analytical thin layer chromatography was carried out with silica gel (60 F254) plates, which were viewed by exposing them to ultraviolet light. IR spectra were recorded using KBr pellets with a PE-983 infrared spectrometer. The absorption data are reported in cm^{-1}. The NMR spectrocopic data were recorded in $CDCl_3$ or [D_6]DMSO with a Bruker 300 MHz spectrometer. The resonances are reported relative to TMS.

***N*,*N*-Diphenylindole-3-carboxamide (1b):** $AlMe_3$ (2 M solution in toluene, 3 mL, 6.0 mmol) was added dropwise to indole (234 mg, 2.0 mmol) and (diphenylcarbamoyl)imidazole (577 mg, 2.2 mmol) in dry toluene (6 mL) at 0 °C in a flame-dried two-neck flask under nitrogen. The resulting mixture was stirred at r.t. for 30 min and then heated to 110 °C (oil bath temperature) for 48 h. The reaction mixture was cooled to 0 °C and then quenched with a saturated $NaHCO_3$ solution (8 mL). The resulting solution was extracted with THF (3 × 25 mL). Purification of the crude mass by flash column chromatography (hexane/ethyl acetate, 1:9 and then THF/ethanol, 9:1) furnished indole-3-carboxamide **1b** (562 mg, 90%) as an off-white solid.

(1*H*-Indol-1-yl)(piperidin-1-yl)methanone (3a): LiHMDS (1.0 M in hexane, 2.0 mL, 2.0 mmol) was added dropwise to indole (234 mg, 2.0 mmol) in dry THF (2 mL) at –30 °C in a flame-dried two-neck flask under nitrogen. The resulting mixture was stirred for 20 min at –30 °C. Then, $AlMe_3$ (2 M in toluene, 1.1 mL, 2.2 mmol) was added dropwise at –30 °C, and the mixture stirred for 40 min. (Piperidinecarbamoyl)imidazole (367 mg, 2.05 mmol) in THF (5 mL) was added slowly, and the reaction mixture was slowly warmed to r.t. and then heated to 80 °C (oil bath temperature) for 14 h. The reaction mixture was cooled to 0 °C and then quenched with a saturated $NaHCO_3$ solution (4 mL). The resulting solution was extracted with ethyl acetate (2 × 30 mL). Purification by flash column chromatography (hexane/ethyl acetate, 3:97) furnished indole urea **3a** (410 mg, 90%) as a colourless sticky substance.

***N*-(4-Bromobenzyl)imidazole-1-carboxamide :** White solid; m.p. 108–110 °C. R_f = 0.3 (EtOAc/hexane, 1:1). IR (KBr): $\tilde{\nu}$ = 3747, 3130, 2911, 2400, 1920, 1683, 1438, 1288, 1110, 748, 659 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 9.11 (br. s, 1 H), 8.28 (s, 1 H), 7.70 (s, 1 H), 7.54 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.05 (s, 1 H), 4.44 (d, J = 5.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 149.5, 138.4, 136.5, 131.7, 130.1, 130.0, 120.6, 117.0, 43.3 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}BrN_3O$ [M + H] 281.0080; found 281.0085.

{[2-(4-Fluorobenzyl)morpholin-4-yl]imidazol-1-yl}methanone (5b): Off white waxy solid; m.p. 68–70 °C. IR (KBr): $\tilde{\nu}$ = 3748, 3130, 3128, 2910, 2369, 1682, 1602, 1440, 1289, 1262, 1113, 1041, 1012, 822, 659 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.22–7.11 (m, 3 H), 7.08 (s, 1 H), 7.01–6.96 (m, 2 H), 3.99–3.86 (m, 3.2 H), 3.72–3.53 (m, 2.4 H), 3.31–3.22 (m, 1.3 H), 2.99–2.7 (m, 3.6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 160.1, 150.8, 136.8, 132.3, 131.0, 130.9, 130.7, 130.6, 129.9, 117.7, 115.5, 115.2, 76.2, 66.3, 50.3, 46.4, 38.6 ppm. $C_{15}H_{16}FN_3O_2$ (289.31): calcd. C 62.27, H 5.57, N 14.52; found C 62.44, H 6.04, N 14.99.

***N*-Diallylimidazole-1-carboxamide:** Yellow liquid. IR (KBr): $\tilde{\nu}$ = 3386, 3122, 3085, 2985, 2934, 1694, 1644, 1456, 1413, 1355, 1283, 1241, 1198, 1102, 1068, 970, 931, 832, 755, 655 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 8.02 (s, 1 H), 7.46 (s, 1 H), 7.03 (s, 1 H), 5.95–5.83 (m, 2 H), 5.27–5.23 (m, 4 H), 3.93 (d, J = 4.8 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 151.7, 137.3, 133.0, 129.4, 118.7, 118.5, 50.5 ppm. HRMS calcd. for $C_{10}H_{13}N_3ONa$ [M + Na] 214.0951; found 214.0961.

Phenyl Piperidine-1-carboxylate:[16] Yellow solid; m.p. 75–77 °C. IR (KBr): $\tilde{\nu}$ = 3394, 2945, 2667, 2402, 1947, 1705, 1429, 1332, 1026, 907, 804, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.26 (m, 2 H), 7.25–7.08 (m, 3 H), 3.60 (br. s, 2 H), 3.51 (br. s, 2 H), 1.71–1.56 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 151.6, 129.6, 125.0, 121.8, 45.5, 45.1, 25.9, 25.5, 24.3 ppm.

Phenyl 2-(4-Fluorobenzyl)morpholine-4-carboxylate: Yellow sticky mass; R_f = 0.4 (EtOAc/hexane, 3:7). IR (KBr): $\tilde{\nu}$ = 3127, 3008, 2864, 1892, 1718, 1599, 1425, 1204, 1109, 1017, 906, 836, 748, 690, 659 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 7.51–7.22 (m, 6 H), 7.19–7.08 (m, 3 H), 3.97–3.49 (m, 5 H), 2.97–2.75 (m, 4 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 163.0, 159.8, 153.4, 151.5, 134.3, 131.6, 131.5, 130.1, 129.7, 125.7, 122.3, 121.7, 115.4, 115.2, 76.0, 75.9, 48.8, 48.0, 44.4, 43.7, 38.3, 38.2 ppm.

[(2,3-Dihydroindol-1-yl)imidazol-1-yl]methanone:[17] Off-white solid; m.p. 101–103 °C. IR (KBr): $\tilde{\nu}$ = 3128, 3041, 2965, 2854, 2867, 1928, 1681, 1482, 1400, 1260, 1163, 1101, 1022, 997, 951, 902 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.41–7.35 (m, 1 H), 7.24–7.06 (m, 5 H), 4.19 (t, J = 16.5 Hz, 2 H), 3.19 (t, J = 16.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 141.3, 136.6, 132.0, 129.8, 127.6, 125.1, 125.0, 117.5, 116.5, 51.0, 28.3 ppm. $C_{12}H_{11}N_3O$ (213.24): calcd. C 67.59, H 5.20, N 19.71; found C 67.99, H 4.98, N 19.66. Direct mass (LC): m/z = 214.0 [M + 1].

Phenyl (Pyridin-3-yl)carbamate:[18] White solid; m.p. 136–138 °C. IR (KBr): $\tilde{\nu}$ = 3180, 2820, 1940, 1738, 1589, 1551, 1492, 1427, 1343, 1226, 1015, 894, 805, 783 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 10.47 (s, 1 H), 8.71 (s, 1 H), 8.26 (d, J = 4.2 Hz, 1 H), 7.94 (d, J = 7.5 Hz, 1 H), 7.46–7.34 (m, 3 H), 7.29–7.24 (m, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 152.3, 150.8, 144.5, 140.7, 135.9, 129.9, 126.1, 125.8, 124.2, 122.4 ppm. Direct mass (LC): m/z = 215 [M + 1].

Phenyl (4-Fluorophenyl)carbamate:[19] White solid; m.p. 139–140 °C. R_f = 0.5 (EtOAc/hexane. 1:4). IR (KBr): $\tilde{\nu}$ = 3315, 3081, 2748, 2564, 2343, 2226, 2025, 1886, 1715, 1555, 1505, 1411, 1311, 1221, 1102, 1013, 834, 732 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 10.29 (s, 1 H), 7.54–7.50 (m, 2 H), 7.27–7.14 (m, 7 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 152.3, 147.1, 135.4, 124.3, 124.2, 120.6, 116.6, 116.3, 116.1, 115.8, 105.0 ppm.

***N*-Methyl-*N*-phenyl-1*H*-indole-3-carboxamide (1a):** Yellow solid; m.p. 230 °C. R_f = 0.3 (EtOAc/hexane, 1:1). IR (KBr): $\tilde{\nu}$ = 3157, 1897, 1703, 1570, 1478, 1446, 1386, 1317, 1230, 1149, 1110, 1072, 1010, 979, 883, 849, 753, 702, 667 cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 11.28 (br. s, 1 H), 8.05–8.03 (m, 1 H), 7.41–7.27 (m, 6 H), 7.13–7.07 (m, 2 H), 6.35 (m, 1 H) 3.3 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 165.6, 146.0, 135.5, 129.9, 129.3, 128.0, 127.6, 127.3, 122.4, 121.7, 120.8, 112.0, 110.0, 38.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}N_2O$ [M + H] 251.1179; found 251.1165. LC–MS: m/z = 251.07 [M + 1]. UPLC purity: 97.9%.

***N*,*N*-Diphenyl-1*H*-indole-3-carboxamide (1b):** Off-white solid; m.p. 200–202 °C. IR (KBr): $\tilde{\nu}$ = 3238, 2926, 1901, 1737, 1610, 1595, 1490, 1431, 1371, 1318, 1278, 1236, 1139, 1075, 1042, 956, 749 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.45 (s, 1 H), 8.06 (d, J = 7.5 Hz, 1 H), 7.41–7.36 (m, 5 H), 7.3–7.20 (m, 6 H),

7.17–7.08 (m, 2 H), 6.53 (s, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 165.8, 144.9, 135.6, 130.6, 129.6, 128.4, 127.7, 126.7, 122.6, 121.7, 121.1, 112.2, 110.2 ppm. $C_{21}H_{16}N_2O$ (312.37): calcd. C 80.75, H 5.16, N 8.97; found C 80.13, H 5.07, N 8.63. LC–MS: *m*/*z* = 313.17 [M + 1]. UPLC purity: 99.19%.

***N*,*N*-Dibenzyl-1*H*-indole-3-carboxamide (1c):**[20] White solid. M.p 186–187 °C; ref. m.p. 187–188 °C. IR (KBr): $\tilde{\nu}$ = 3382, 3056, 2932, 2342, 1637, 1537, 1339, 1265, 1206, 1131, 1072, 973, 937, 821, 744 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.52 (br. s., 1 H), 7.88–7.84 (m, 1 H), 7.51 (s, 1 H), 7.46–7.33 (m, 5 H), 7.32–7.24 (m, 6 H), 7.22–7.10 (m, 2 H), 4.68 (s, 4 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.5, 137.2, 135.1, 128.2, 127.9, 126.7, 126.2, 121.6, 120.0, 119.9, 111.4, 108.7, 49.3 ppm.

***N*,*N*-Diallyl-1*H*-indole-3-carboxamide (1d):**[21] White solid; m.p. 163 –165 °C. IR (KBr): $\tilde{\nu}$ = 3168, 2690, 2581, 2358, 1932, 1897, 1860, 1778, 1591, 1578, 1508, 1458, 1362, 1341, 1313, 1206, 1136, 1073, 996, 970, 925, 751 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.54 (br. s., 1 H), 7.80 (dd, *J* = 7.0, 0.9 Hz, 1 H), 7.63 (s, 1 H), 7.52–7.39 (m, 1 H), 7.20–7.06 (m, 2 H), 5.98–5.84 (m, 2 H), 5.30–5.16 (m, 4 H), 4.07 (d, *J* = 5.3 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 165.8, 135.2, 133.8, 126.3, 126.0, 121.5, 120.1, 119.7, 116.3, 111.3, 108.8, 48.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}N_2O$ [M + H] 241.1335; found 241.1340.

[(1*H*-Indol-3-yl)piperidin-1-yl]methanone (1e):[22] Brown solid. IR (KBr): $\tilde{\nu}$ = 3190, 2857, 1937, 1896, 1817, 1783, 1725, 1588, 1566, 1523, 1447, 1336, 1139, 1025, 854, 811, 745, 694, 629 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.53 (br. s., 1 H), 7.65–7.61 (m, 2 H), 7.45–7.42 (m, 1 H), 7.17–7.03 (m, 2 H), 3.77–3.42 (br. s, 4 H), 1.65–1.55 (m, 2 H), 1.55–1.47 (m, 4 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 165.0, 135.1, 127.0, 125.4, 121.3, 119.6, 119.5, 111.4, 109.9, 45.0, 25.5, 23.8 ppm. LC–MS: *m*/*z* = 229.19 [M + 1]. UPLC purity: 99.78%.

[2-(4-Fluorobenzyl)morpholin-4-yl](1*H*-indol-3-yl)methanone (1f): White solid; m.p. 181–183 °C. IR (KBr): $\tilde{\nu}$ = 3177, 2867, 1890, 1825, 1721, 1589, 1548, 1530, 1445, 1391, 1339, 1309, 1214, 1154, 1104, 1027, 975, 838, 759 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.58 (br. s, 1 H), 7.64–7.62 (m, 2 H), 7.43–7.40 (m, 1 H), 7.27–7.22 (m, 2 H), 7.16–7.02 (m, 4 H), 4.18–4.14 (m, 1 H), 4.07–4.03 (m, 1 H), 3.84–3.80 (m, 1 H), 3.63–3.57 (m, 1 H), 3.51–3.37 (m, 1 H), 3.15–3.1 (m, 1 H), 2.85–2.71 (m, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 165.7, 162.5, 159.3, 135.7, 134.0, 133.9, 131.1, 131.0, 128.1, 125.9, 121.9, 120.3, 120.2, 115.0, 114.7, 112.0, 109.4, 76.1, 66.2, 48.7, 44.9, 15.2 ppm. $C_{20}H_{19}FN_2O_2$ (338.38): calcd. C 70.99, H 5.66, N 8.28; found C 70.74, H 5.75, N 8.13. LC–MS: *m*/*z* = 339.25 [M + 1]. UPLC purity: 99.78%.

(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)(1*H*-indol-3-yl)methanone (1g):[23] Brown solid; m.p. 195–197 °C. IR (KBr): $\tilde{\nu}$ = 3142, 2962, 1922, 1589, 1567, 1524, 1450, 1366, 1337, 1204, 1105, 1063, 960, 946, 911, 801, 772, 743 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 10.16 (s, 1 H), 7.68 (d, *J* = 4.5 Hz, 1 H), 7.28–7.17 (m, 3 H), 7.08 (s, 1 H), 4.0 (s, 4 H), 3.82 (m, 4 H), 1.76 (m, 4 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 167.4, 135.8, 127.4, 125.4, 122.4, 120.8, 119.9, 112.0, 110.6, 107.1, 64.5, 43.4, 35.4 ppm.

(4-Benzylpiperazin-1-yl)(1*H*-indol-3-yl)methanone (1h):[24] Yellow solid; m.p. 182–185 °C. IR (KBr): $\tilde{\nu}$ = 3130, 2810, 1897, 1731, 1589, 1565, 1524, 1446, 1310, 1148, 1008, 935, 864, 745, 702 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.59 (br. s., 1 H), 7.75–7.58 (m, 2 H), 7.53–7.39 (m, 1 H), 7.37–7.22 (m, 5 H), 7.20–7.04 (m, 2 H), 3.88–3.59 (m, 4 H), 3.56–3.43 (br. s, 2 H), 2.40 (t, *J* = 4.7 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 165.6, 137.9, 135.7, 129.0, 128.3, 128.0, 127.1, 126.0, 122.0, 120.3, 120.2, 112.0, 109.8, 62.0, 52.9, 44.6 ppm.

(2,3-Dihydroindol-1-yl)(1*H*-indol-3-yl)methanone (1i): Brown solid; m.p. 246–248 °C. IR (KBr): $\tilde{\nu}$ = 3380, 3161, 3050, 2570, 1947, 1702, 1693, 1592, 1491, 1389, 1334, 1321, 1312, 1226 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.78 (br. s, 1 H), 8.05–7.98 (m, 3 H), 7.47 (d, 1 H), 7.24–7.11 (m, 4 H), 6.99–6.94 (m, 1 H), 4.36 (t, *J* = 16.8 Hz, 2 H), 3.13 (t, *J* = 16.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 164.9, 144.6, 136.5, 132.9, 129.5, 127.9, 127.5, 125.5, 123.7, 123.0, 122.1, 121.3, 117.5, 112.6, 112.3, 50.8, 28.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N_2O$ [M + H] 263.1179; found 263.1192.

Compound 1j: Brown solid; m.p. 61–63 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.40 (s, 1 H), 7.38–7.32 (m, 6.7 H), 7.06–7.04 (m, 2 H), 4.66 (s, 2 H), 2.86 (s, 3 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 167.5, 137.8, 137.0, 134.62, 128.5, 127.3, 127.0, 126.0, 120.8, 119.7, 118.4, 111.0, 107.7, 51.5, 34.6, 12.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O$ [M + H] 279.1492; found 279.1499.

***N*-Phenylindole-1-carboxamide (2a):**[25] White solid. M.p 120–121 °C; ref. m.p. 124–125 °C. R_f = 0.35 (EtOAc/hexane, 1:9). IR (KBr): $\tilde{\nu}$ = 3244, 3046, 2869, 2785, 1678, 1597, 1529, 1448, 1342, 1258, 1207, 1119, 1011, 884, 811, 744 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.21–7.92 (m, 1 H), 7.65 (d, *J* = 7.2 Hz, 1 H), 7.59–7.46 (m, 3 H), 7.44–7.34 (m, 4 H), 7.32–7.07 (m, 2 H), 6.81–6.55 (m, 1 H) ppm.

***N*-Benzylindole-1-carboxamide (2b):**[26] Pink solid. M.p 85–87 °C; ref. m.p. 85–86 °C. R_f = 0.35 (EtOAc/hexane, 1:4). IR (KBr): $\tilde{\nu}$ = 3371, 3144, 3053, 2935, 2784, 2536, 2342, 1674, 1541, 1338, 1208, 1033, 880, 729, 617 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.10 (dd, *J* = 8.1, 0.9 Hz, 1 H), 7.78–7.53 (m, 1 H), 7.47–7.21 (m, 9 H), 6.63 (dd, *J* = 3.8, 0.8 Hz, 1 H), 5.88 (br. s., 1 H), 4.67 (d, *J* = 5.7 Hz, 2 H) ppm.

***N*-(4-Bromobenzyl)indole-1-carboxyamide (2c):** White solid; m.p. 138–140 °C. R_f = 0.4 (EtOAc/hexane, 3:7). IR (KBr): $\tilde{\nu}$ = 3382, 3057, 2934, 2780, 1673, 1537, 1337, 1207, 1031, 1012, 939, 744, 603 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.76 (t, *J* = 5.9 Hz, 1 H), 8.32–8.18 (m, 1 H), 7.88 (d, *J* = 3.4 Hz, 1 H), 7.68–7.49 (m, 3 H), 7.38–7.31 (m, 2 H), 7.30–7.13 (m, 2 H), 6.70 (dd, *J* = 3.8, 0.8 Hz, 1 H), 4.46 (d, *J* = 5.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 152.0, 138.9, 135.4, 131.3, 129.5, 129.4, 124.7, 123.7, 122.0, 120.7, 120.0, 115.0, 106.4, 42.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}BrN_2O$ [M + H] 330.0284; found 330.0354.

***N*-(Pyridin-3-yl)indole-1-carboxamide (2d):** ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.25 (s, 1 H), 8.86 (s, 1 H), 8.36–8.25 (m, 2 H), 8.11–8.05 (m, 2 H), 7.64 (d, *J* = 7.5 Hz, 1 H), 7.45–7.41 (m, 1 H), 7.34–7.14 (m, 2 H), 6.79 (d, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 150.4, 145.2, 142.8, 135.8, 130.2, 129.8, 128.3, 125.9, 124.4, 124.0, 122.8, 121.3, 115.5, 107.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}N_3O$ [M + H] 238.0975; found 238.0969.

***N*-(4-Fluorophenyl)indole-1-carboxamide (2e):**[26] White fluffy solid. (KBr): $\tilde{\nu}$ = 3240, 3040, 1903, 1674, 1610, 1529, 1537, 1411, 1342, 1298, 1209, 1122, 1012, 827, 745 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.17–7.98 (m, 1 H), 7.73–7.56 (m, 1 H), 7.53–7.40 (m, 4 H), 7.39–7.22 (m, 2 H), 7.11–6.95 (m, 2 H), 6.65 (dd, *J* = 3.4, 0.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 161.4, 158.2, 149.8, 135.1, 132.9, 130.3, 124.5, 123.9, 122.7, 122.6, 122.5, 122.4, 116.1, 115.7, 114.0, 107.9 ppm.

[(Indol-1-yl)piperidin-1-yl]methanone (3a): Colourless sticky mass; R_f = 0.5 (EtOAc/hexane, 1:9). Purified by flash column chromatography (ethyl acetate/hexane, 3:97). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.68–7.65 (m, 1 H), 7.60–7.57 (m, 1 H), 7.37–7.25 (m, 1 H), 7.21–7.15 (m, 2 H), 6.59–6.55 (m, 1 H), 3.67–3.45 (m, 4 H), 1.74–1.56

(br. s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 135.4, 129.4, 126.3, 123.4, 121.6, 120.9, 113.2, 105.5, 47.6, 25.8, 22.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{16}N_2ONa$ [M + Na] 251.1155; found 251.1147. UPLC purity: 99.16%.

[(5-Chloroindol-1-yl)piperidin-1-yl]methanone (3b): Colourless sticky substance; R_f = 0.4 (EtOAc/hexane, 1:9). IR (KBr): $\tilde{\nu}$ = 3331, 3110, 2940, 2857, 1682, 1606, 1569, 1520, 1423, 1316, 1269, 1200, 1066, 987, 870, 789, 761, 718 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.52 (m, 2 H), 7.33–7.18 (m, 2 H), 6.60–6.43 (m, 1 H), 3.52 (d, J = 6.0 Hz, 4 H), 1.55–1.75 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 133.8, 130.5, 125.5, 123.7, 120.4, 120.0, 114.3, 105.0, 47.7, 25.9, 24.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}ClN_2ONa$ [M + Na] 285.0765; found 285.0768.

{[2-(4-Fluorobenzyl)morpholin-4-yl]indol-1-yl}methanone (3c): Colourless sticky substance; R_f = 0.3 (EtOAc/hexane, 1:9). Purified by flash column chromatography (3–4% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3394, 2945, 2891, 1717, 1600, 1430, 1205, 907, 804, 748 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.55 (m, 1 H), 7.55–7.42 (m, 1 H), 7.34–7.19 (m, 1 H), 7.19–7.05 (m, 4 H), 6.99–6.82 (m, 2 H), 6.52 (d, J = 3.4 Hz, 1 H), 3.90–3.52 (m, 5 H), 3.38–3.29 (m, 1 H), 2.90–2.82 (m, 1 H), 2.76–2.62 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3, 160.1, 154.2, 135.2, 132.9, 132.6, 130.7, 130.6, 129.6, 126.0, 123.7, 122.1, 121.9, 121.1, 115.4, 115.1, 113.2, 110.9, 106.3, 76.4, 66.6, 66.5, 50.7, 46.8, 38.8, 38.6 ppm. HRMS (ESI): calcd. for $C_{20}H_{19}FN_2O_2Na$ [M + Na] 361.1323; found 361.1313.

[(2-Methylindol-1-yl)piperidin-1-yl]methanone (3d): Colourless sticky mass; R_f = 0.35 (EtOAc/hexane, 1:9). IR (KBr): $\tilde{\nu}$ = 3345, 3054, 2996, 2938, 1682, 1561, 1455, 1427, 1328, 1302, 1256, 1217, 999, 742, 784 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.42 (m, 1 H), 7.34–7.23 (m, 1 H), 7.21–7.06 (m, 2 H), 6.33 (s,1 H), 3.60–3.26 (m, 4 H), 2.49 (s, 3 H), 1.56–1.71 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.9, 136.2, 135.6, 128.5, 121.9, 120.9, 119.8, 110.7, 103.8, 46.9, 26.1, 24.3, 13.6 ppm. HRMS (ESI): calcd. for $C_{15}H_{19}N_2O$ [M + H] 243.1492; found 243.1503. UPLC purity: 94.28%.

(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)(2-phenylindol-1-yl)methanone (3e): White solid; m.p. 136–138 °C. R_f = 0.3 (EtOAc/hexane, 2:3). IR (KBr): $\tilde{\nu}$ = 3320, 2961, 2879, 2678, 1956, 1896, 1669, 1602, 1427, 1341, 1305, 1146, 1108, 1056, 946, 917, 803, 764, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.60 (m, 1 H), 7.58–7.36 (m, 6 H), 7.32–7.18 (m, 2 H), 6.74 (s, 1 H), 3.89 (s, 4 H), 3.83–2.74 (br. s, 4 H), 1.76–0.82 (br. s, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8, 139.2, 137.0, 131.9, 128.6, 128.4, 128.2, 127.5,123.4, 121.6, 120.6, 111.4, 106.3, 104.5, 64.4, 44.1, 34.4 ppm. HRMS (ESI): calcd. for $C_{22}H_{23}N_2O_3$ [M + H] 363.1703; found 363.1683.

[2-(4-Fluorobenzyl)morpholin-4-yl](5-methoxyindol-1-yl)methanone (3f): Colourless sticky mass; R_f = 0.3 (EtOAc/hexane, 1:4). Purified by flash column chromatography (15% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3394, 2945, 2825, 1717, 1590, 1430, 1205, 907, 804, 747, 690 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.7 Hz, 1 H), 7.22 (d, J = 3.4 Hz, 1 H), 7.19–7.10 (m, 2 H), 7.04 (d, J = 2.6 Hz, 1 H), 7.01–6.87 (m, 3 H), 6.51 (dd, J = 3.8, 0.8 Hz, 1 H), 3.97–3.89 (m, 2 H), 3.86 (s, 3 H), 3.84–3.60 (m, 3 H), 3.26–3.18 (m, 1 H), 2.87–2.77 (m, 1 H), 2.76–2.62 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3, 160.1, 155.5, 154.3, 132.6, 132.6, 130.7, 130.6, 130.3, 130.1, 126.6, 115.4, 115.1, 114.0, 111.6, 106.2, 103.2, 66.6, 55.7, 50.7, 46.8, 38.6 ppm. HRMS (ESI): calcd. for $C_{21}H_{21}FN_2O_3Na$ [M + Na] 391.1416; found 391.1428.

***tert*-Butyl 4-(5-Methoxy-2-methylindole-1-carbonyl)piperazine-1-carboxylate (3g):** Brown solid; m.p. 132–134 °C. IR (KBr): $\tilde{\nu}$ = 3354, 2976, 2928, 2863, 1694, 1618, 1588, 1478, 1454, 1416, 1286, 1247, 1206, 1170, 1147, 1104, 1034, 1002, 925, 859, 840, 788, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, J = 9.1 Hz, 1 H), 6.96 (d, J = 2.6 Hz, 1 H), 6.80 (dd, J = 8.9, 2.5 Hz, 1 H), 6.27–6.25 (m, 1 H), 3.83 (s, 3 H), 3.64–3.35 (m, 8 H), 2.44 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 154.4, 143.4, 137.1, 130.4, 129.4, 111.5, 111.5, 104.6, 102.6, 80.5, 55.7, 46.0, 43.6, 28.3, 13.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{27}N_3O_4Na$ [M + Na] 396.1894; found 396.1883. LC–MS: m/z = 374.17 [M + 1]. UPLC purity: 97.48%.

Benzyl 4-(2-Methyl-5-methoxyindole-1-carbonyl)piperazine-1-carboxylate (3h): Brown solid; m.p. 98–100 °C. IR (KBr): $\tilde{\nu}$ = 3507, 3066, 3033, 2996, 2934, 2863, 1701, 1617, 1587, 1477, 1452, 1420, 1286, 1220, 1206, 1122, 1102, 1035, 1004, 840, 786, 697, 604 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 7.14 (s, 1 H), 6.96 (d, J = 2.3 Hz, 1 H), 6.80 (dd, J = 9.1, 2.6 Hz, 1 H), 6.27–6.25 (m, 1 H), 5.15 (s, 2 H), 3.82 (s, 3 H), 3.71–3.58 (m, 2 H), 3.58–3.41 (m, 6 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 153.4, 137.1, 136.2, 130.3, 129.4, 129.1, 128.6, 128.5, 128.2, 128.0, 127.8, 111.5, 104.8, 102.6, 67.5, 55.7, 45.9, 43.9, 13.6 ppm. HRMS (ESI): calcd. for $C_{23}H_{25}N_3O_4Na$ [M + Na] 430.1737; found 430.1743. LC–MS: m/z = 408.25 [M + 1]. UPLC purity: 99.33%.

[(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)indol-1-yl]methanone (3i): White solid; m.p. 80–82 °C. Purified by flash column chromatography (10–20% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3331, 3134, 2967, 2879, 2674, 1900, 1675, 1577, 1520, 1424, 1311, 1210, 1129, 1104, 915, 775, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.63 (m, 1 H), 7.63–7.55 (m, 1 H), 7.35–7.25 (m, 2 H), 7.24–7.15 (m, 1 H), 6.60 (dd, J = 3.4, 0.8 Hz, 1 H), 3.99 (s, 4 H), 3.76–3.59 (m, 4 H), 1.86–1.72 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1, 135.3, 129.5, 126.3, 123.6, 121.8, 121.0, 113.2, 106.6, 105.9, 64.5, 44.7, 35.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}N_2O_3$[M + H] 287.1390; found 287.1387. LC–MS: m/z = 287.17 [M + 1]. UPLC purity: 100%

[(2-Phenylindol-1-yl)piperidin-1-yl]methanone (3j): Yellow solid; m.p. 124–125 °C. R_f = 0.4 (EtOAc/hexane, 1:4). Purified by flash column chromatography (8–10% EtOAc/hexane). IR (KBr): $\tilde{\nu}$ = 3380, 3064, 2936, 2853, 1677, 1443, 1266, 1162, 1021, 994, 803, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.50 (m, 4 H), 7.45–7.27 (m, 3 H), 7.26–7.16 (m, 2 H), 6.71 (s, 1 H), 3.8–2.5 (br. s, 4 H), 1.56–0.55 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8, 139.3, 137.0, 132.1, 128.6, 128.4, 128.1, 127.6, 123.3, 121.5, 120.6, 111.5, 104.1, 45.2, 44.8, 25.4, 24.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{21}N_2O$ [M + H] 305.16484; found 305.16433. LC–MS: m/z = 305.25 [M + 1]. UPLC purity: 100%.

(4-Benzylpiperazin-1-yl)(5-bromoindol-1-yl)methanone (3k): Colourless sticky mass; R_f = 0.35 (EtOAc/hexane, 3:7). Purified by flash column chromatography (20–30% EtOAc/hexane). IR ($CHCl_3$): $\tilde{\nu}$ = –2814, 2771, 1681, 1319, 1270, 1000, 898 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 1.9 Hz, 1 H), 7.57 (d, J = 9.1 Hz, 1 H), 7.23–7.39 (m, 8 H), 6.52 (dd, J = 3.4, 0.8 Hz, 1 H), 3.54–3.62 (m, 6 H), 2.61–2.51 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6, 137.4, 134.1, 131.2, 129.1, 128.4, 128.3, 127.3, 127.3, 127.2, 126.5, 123.6, 115.1, 114.7, 105.2, 63.0, 52.5, 46.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{21}BrN_3O$ [M + H] 398.0863; found 398.0862. UPLC purity: 97.26%.

Ethyl 1-(5-Methoxy-2-methylindole-1-carbonyl)piperidine-4-carboxylate (3l): Green sticky mass. IR (KBr): $\tilde{\nu}$ = 2954, 2863, 2834, 2062, 1731, 1682, 1616, 1586, 1478, 1427, 1316, 1206, 1142, 1038, 1002, 945, 924, 839, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.7 Hz, 0.7 H), 7.10 (d, J = 9.1 Hz, 0.6 H), 6.96 (d, J = 2.6 Hz, 1 H), 6.81 (ddd, J = 8.8, 7.6, 2.5 Hz, 1 H), 6.30–6.23 (m,

1 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.96–3.75 (m, 2 H), 3.83 (s, 3 H), 3.24–3.02 (m, 2 H), 2.66–2.49 (m, 1 H), 2.44 (s, 1.5 H), 2.43 (s, 1.5 H), 1.94–1.64 (m, 4 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 155.1, 155.0, 153.6, 153.0, 137.3, 136.9, 130.7, 130.5, 129.4, 129.3, 111.5, 111.4, 104.3, 104.2, 60.7, 55.7, 45.5, 45.1, 40.9, 40.4, 28.4, 28.0, 14.1, 13.5, 13.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{24}N_2O_4Na$ [M + Na] 367.1628; found 367.1627. UPLC purity: 99.72%.

***N*-Benzyl-*N*-methyl-1,2,3,4-tetrahydrocarbazole-9-carboxamide (3m):** Colourless sticky mass. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, J = 7.2 Hz, 1 H), 7.36–7.30 (m, 3 H), 7.28–7.18 (m, 3 H), 7.15–7.10 (m, 2 H), 4.70–4.60 (m, 1 H), 4.55–4.50 (m, 1 H), 2.89 (s, 3 H), 2.82–2.78 (m, 2 H), 2.69–2.66 (m, 2 H), 1.88–1.86 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 136.3, 135.3, 135.0, 128.8, 128.7, 128.0, 127.8, 122.3, 120.8, 118.1, 113.9, 111.2, 53.9, 35.7, 23.1, 23.0, 22.7, 20.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{23}N_2O$ [M + H] 319.1805; found 341.1814.

Ethyl 1-(Indole-1-carbonyl)piperidine-4-carboxylate (4d): Green sticky mass. IR (KBr): $\tilde{\nu}$ = 3441, 2956, 2105, 1901, 1731, 1688, 1608, 1524, 1424, 1320, 1125, 1041, 944, 885, 861, 751, 685, 621 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (dd, J = 8.3, 0.8 Hz, 1 H), 7.64–7.52 (m, 1 H), 7.39–7.28 (m, 2 H), 7.25–7.18 (m, 1 H), 6.61 (dd, J = 3.4, 0.8 Hz, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.08–3.96 (m, 2 H), 3.25–3.11 (m, 2 H), 2.42–2.66 (m, 1 H), 2.16–1.95 (m, 2 H), 1.95–1.77 (m, 2 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 154.3, 135.3, 129.5, 126.2, 123.6, 121.9, 121.0, 131.2, 106.0, 60.7, 46.0, 40.8, 28.0, 14.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{20}N_2O_3Na$ [M + Na] 323.1366; found 323.1355.

Methyl 1-(Indole-1-carbonyl)piperidine-4-carboxylate (4e): Green sticky mass. IR (KBr): $\tilde{\nu}$ = 3448, 2953, 2104, 1902, 1731, 1683, 1524, 1452, 1421, 1320, 1267, 1125, 1040, 943, 884, 831, 751, 685, 621 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (dd, J = 8.3, 0.8 Hz, 1 H), 7.64–7.52 (m, 1 H), 7.39–7.28 (m, 2 H), 7.25–7.18 (m, 1 H), 6.61 (dd, J = 3.4, 0.8 Hz, 1 H), 4.08–3.96 (m, 2 H), 3.70 (s, 3 H), 3.25–3.11 (m, 2 H), 2.66–2.42 (m, 1 H), 2.16–1.95 (m, 2 H), 1.95–1.75 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 154.3, 135.3, 129.5, 126.2, 123.6, 121.9, 121.0, 131.1, 106.0, 51.9, 46.0, 40.8, 40.7, 28.0, 27.8 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}N_2O_3$ [M + H] 287.1390; found 287.1384.

[2-(4-Fluorobenzyl)morpholin-4-yl](5-methoxy-2-methyl-1*H*-indol-3-yl)methanone (5c): White solid; m.p. 60–62 °C. IR (KBr): $\tilde{\nu}$ = 3244, 2857, 2370, 1896, 1747, 1603, 1449, 1354, 1270, 1219, 1173, 1105, 1033, 972, 836, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1 H), 7.13 (dd, J = 8.3, 5.7 Hz, 2 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.00–6.85 (m, 3 H), 6.74 (dd, J = 8.7, 2.6 Hz, 1 H), 4.21–3.84 (m, 3 H), 3.80 (s, 3 H), 3.74–3.56 (m, 2 H), 3.25–3.05 (br. s,1 H), 2.96–2.67 (m, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3, 160.0, 154.9, 138.3, 133.1, 130.7, 130.6, 129.7, 126.7, 115.3, 115.0, 111.6, 111.4, 107.6, 101.1, 76.6, 67.2, 55.8, 49.2, 46.4, 38.8, 12.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{24}FN_2O_3$ [M + H] 383.1765; found 383.1751. LC–MS: m/z = 381.33 [M – 1]. UPLC purity: 100%.

{1-[2-(4-Fluorobenzyl)morpholine-4-carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}[2-(4-fluorobenzyl)morpholin-4-yl]methanone (5d): White solid; m.p. 92–95 °C. IR (KBr): $\tilde{\nu}$ = 2924, 2856, 1689, 1625, 1530, 1424, 1330, 1219, 1105, 1034, 835, 761 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 2 H), 7.19–7.11 (m, 3 H), 7.11–6.91 (m, 4 H), 6.91–6.53 (m, 2 H), 4.55–4.05 (br. s, 1 H), 4.1–3.74 (m, 5 H), 3.73–3.30 (m, 6 H), 3.29–3.06 (m, 3 H), 3.05–2.61 (m, 6 H), 2.55–2.43 (br. m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 166.1, 163.4, 163.3, 160.1, 155.8, 152.6, 151.8,137.1, 132.9, 132.5, 132.3, 130.8, 130.7, 129.1, 128.7, 126.6, 115.4, 115.3, 115.1, 112.7, 111.9, 111.8, 111.5, 111.4, 101.9, 101.5, 76.4, 67.2, 66.9, 66.4, 55.8, 50.3, 46.4, 38.8, 38.6, 12.3, 12.1 ppm. HRMS (ESI): calcd. for $C_{34}H_{36}F_2N_3O_5$ [M + H] 604.2618; found 604.2634.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for all key intermediates and final products

[1] For selected recent reviews on Friedel–Crafts-type reactions with indoles, see: a) C. C. J. Loh, D. Enders, *Angew. Chem.* **2011**, *123*, 46; *Angew. Chem. Int. Ed.* **2011**, *51*, 46–48; b) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449–4465.

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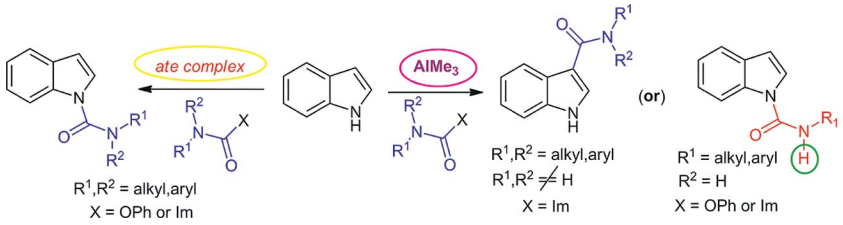
Synthetic Methods



The regioselective one-step synthesis of indole-3-carboxamide was achieved from the reaction between indole and a tertiary carbamoylimidazole in the presence of $AlMe_3$. Alternatively the reaction was diverted to the indole nitrogen when an aluminium ate complex was employed. Secondary carbamoyl electrophiles in the presence of $AlMe_3$ exclusively yielded trisubstituted ureas.

Keywords: Synthetic methods / Acylation / Regioselectivity / Chemoselectivity / Nitrogen heterocycles / Lewis acids / Aluminum

