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Rapid access to *N*-(indol-2-yl)amides and *N*-(indol-3-yl)amides as unexplored pharmacophores†

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Preparation of *N*-(indol-2-yl)amides and *N*-(indol-3-yl)amides are scarce in the scientific literature due to unstable intermediates impeding current reported syntheses. We have employed cheap and readily available substrates in the Curtius rearrangement of indole-3-carboxazide to afford *N*-(indol-3-yl)amides. The reaction is observed for alkyl and aryl carboxylic acids and both *N*-substituted or 1*H*-indole derivatives are tolerated. This approach was extended to the preparation of *N*-(indol-2-yl)amides from the corresponding indole-2-carboxazides.

Introduction

Despite what looks like a simple molecular construct, *N*-(indol-3-yl)amides **1** and *N*-(indol-2-yl)amides **2** are difficult motifs to prepare. Low yields are often reported for their preparation and only a limited number of structures are known to date. In the literature, only 162 molecules bearing the *N*-(indol-2-yl)amide **2** motif are known to exist and have been reported across 64 articles.¹ Similarly, only 899 molecules bearing the *N*-(indol-3-yl)amide **1** motif have been reported across a total of 84 articles.¹ In contrast, 37 465 and 68 422 reported structures are present in the literature for the reversed indole-3-carboxamide **3** and indole-4-carboxamide **4** motifs in 1225 and 3991 articles respectively. Additionally, compounds of type **3** and **4** have found many applications as pharmacophores. Examples include the multitude of cannabinoid receptor agonists, with APICA (**3a**) being the lead example,² and JNJ-7777120 (**4a**) a selective antagonist at the histamine H₄ receptor (Fig. 1).³ The rarity in literature and pharmacological applications of **1** and **2** is a consequence of lacking methodology to access these motifs. With the indole scaffold already being an important structure in drug discovery, improv-

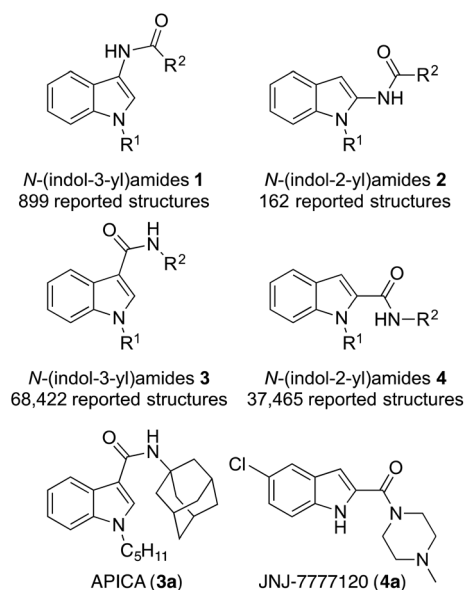


Fig. 1 General structures of *N*-indolylamides **1–2** and indolecarboxamides **3–4**.

ing the accessibility of structure classes **1** and **2** would open the door to new functionalization and could see these moieties incorporated into drug design strategies.

While only a few methods for the synthesis of *N*-(indolyl)amides **1** and **2** are known,⁴ the most commonly reported preparation is *via* an acylation 3- or 2-aminoindole respectively.^{5,6} However, we and others⁷ have found 2- and 3-aminoindoles and their precursors, 2-nitroindole and 3-nitroindole, to be unstable and poor yielding. The limited commercial availability of 2- or 3-aminoindole, and 2- or 3-nitroindole infer their apparent instability and futile synthesis. Common drawbacks to known alternative methods include a narrow substrate library or the generation of a specific subset of products (*e.g.* tertiary amides). As a feasible alternative to known methods, we have developed a mild and convenient synthetic route to *N*-(indolyl)amides **1** and **2** from easily available compounds and report our results herein.

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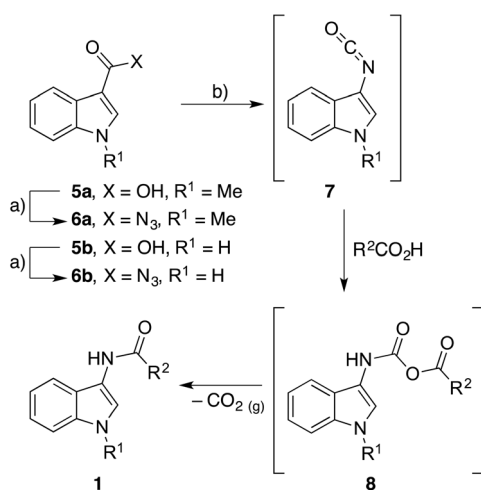
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Results and discussion

It is well documented that a Curtius rearrangement can produce an amide from a carboxylic acid,⁸ but to our knowledge, there are no reports of *N*-(indol-3-yl)amides **1** and *N*-(indol-2-yl)amides **2** being prepared in this fashion. *N*-Indol-3-yl ureas^{7a,9} and urethanes^{7a,10} have all been prepared *via* the Curtius rearrangement, as has 3-aminoindole, although its reported instability hindered its isolation and limited its subsequent use.^{7a} We decided to investigate the use and scope of the Curtius rearrangement to conveniently and rapidly prepare *N*-(indol-3-yl)amides **1** and *N*-(indol-2-yl)amides **2** from easily accessible substrates.

We began our exploration by converting the commercially available *N*-methyl indole-3-carboxylic acid (**5a**) into its carboxazide **6a** by employing diphenylphosphoryl azide (DPPA) with data matching that previously reported.¹¹ With this in hand we investigated the conditions needed to facilitate the one-step amide formation with propionic acid ($R^2 = Et$) (Scheme 1). The carboxazide **6a** was heated at reflux in toluene to facilitate isocyanate **7a** formation – which was complete after only 10 minutes (by TLC analysis). Propionic acid and triethylamine (0.05 equiv.) were added to the refluxing reaction and, after 2 h, the generation of two main products was observed, both presumably proceeding through intermediate **8a**. The first product was identified as *N*-(1-methyl-indol-3-yl)propionamide **1a** (37% yield) which confirmed the direct amide formation from indol-3-yl isocyanate **7a**. The second constituent of the reaction was identified as *N,N'*-bis(1-methyl-indol-3-yl)urea **9**. The formation of these bis-urea by-products has been reported for the analogous reaction between phenyl isocyanates and carboxylic acids.^{8a} This component fortuitously precipitates from the reaction media upon cooling but can also be effortlessly resolved from the desired *N*-(indol-3-yl)amide with flash chromatography.



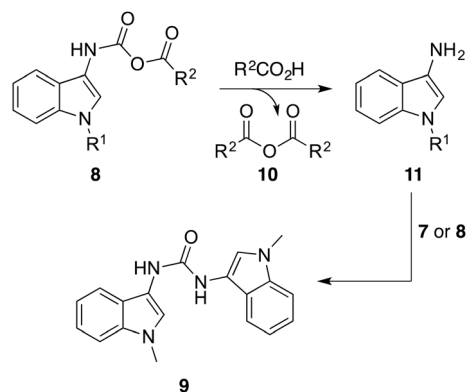
Scheme 1 Synthesis of *N*-(indol-3-yl)amides (**1**). Reaction conditions: (a) Et₃N, CH₂Cl₂, rt, 15 min then DPPA, rt 1 h, 94% ($R^1 = Me$), 97% ($R^1 = H$); (b) refer to Table 1.

With a moderate yield of the desired *N*-(indol-3-yl)amide **1a** from this initial reaction, we explored what reaction conditions could be optimized. A slight improvement in yield (39%) and convenience was achieved by merging the reaction into a one-step reaction by refluxing the indol-3-yl carboxazide **6a** with propionic acid and triethylamine. Altering the solvent from toluene to *N,N*-dimethylformamide saw an improvement in yield (49%) but isolation of the product became cumbersome.

An equal improvement in yield (49%) was observed when the equivalents of propionic acid was raised from two to five equivalents. Alternatively, the yields could be improved by conserving the carboxylic acid equivalents and performing the reactions at increased concentrations. When the reaction was performed at 10 mM (with respect to indol-3-yl carboxazide **6a**) and 2 equivalents of propionic acid, a yield of 39% was observed. When the reaction was concentrated to 100 mM, a 56% yield was recorded and finally at 500 mM, a 64% yield was observed.

It has been reported that a proton transfer reagent accelerates the decomposition of mixed anhydrides such as **8**.^{8b,c,12} To this end, the one-step reaction was repeated with an increased triethylamine concentration (from 0.05 to 0.2 equivalents) but no improvement in yield was observed. However, when triethylamine was replaced with 10 mol% of *N,N*-dimethylaminopyridine (DMAP), the desired *N*-(indol-3-yl)amide **1a** was obtained in 86% yield.

Despite the improved yields, the bis-urea **9** was still an unavoidable by-product in each of these reactions and accounted for the majority of the residual yield in each case. We first proposed it was due to water in the reaction but meticulous drying of all reagents and solvents or the incorporation of drying agents (4 Å molecular sieves) did not improve amide yields or decrease urea formation. We propose that the bis-urea **9** occurs due to the carboxylic acid substrate attacking the mixed anhydride intermediate **8** which results in a homogeneous anhydride of the carboxylic acid **10** and the 3-aminoindole **11** (Scheme 2). This 3-aminoindole **11** subsequently reacts with unreacted indol-3-yl isocyanate **7** or the mixed anhydride intermediate **8** to generate the undesired bis-urea **9**. To validate this hypothesis, we reacted the indol-3-yl isocyanate



Scheme 2 Proposed formation of bis(indol-3-yl)urea **9**.



7a with ethyl magnesium bromide to circumvent the formation of the mixed anhydride intermediate **8** and thus avoid the bis-urea by-product **9**. The desired *N*-(indol-3-yl)amide **1a** was formed in 54% yield with no bis-urea product **9** observed. Due to no significant improvement on product yield, the initially explored one-pot, single-step thermal decomposition between the indol-3-yl isocyanate **7a** and a carboxylic acid was chosen as the means of synthesizing *N*-(indol-3-yl)amides **1** given the simplicity and convenience of the method.

The substrate scope of this reaction was explored by substituting propionic acid for a variety of aliphatic and aryl carboxylic acids (Table 1). Steric hindrance appears to play a pivotal role in the amide formation. As steric bulk is increased around the carbon alpha to the carboxylic acid, we observe a reduction in yield when comparing one methyl group (**1b** 64%)¹³ to two methyl groups (**1c** 28%) to three methyl groups (**1d** 13%). This trend is also observed with phenyl groups (**1g** 75% vs. **1h** 53%) and the bulky adamantane group (**1i** 6% vs. **1j** 29%).

We were pleased that the rearrangement was also observed for sp² and sp hybridized carbons with heteroaromatic rings

tolerated. Yields were generally lower than the analogous sp³ hybridized substrates (for example benzyl **1g** 75% vs. phenyl **1k** 43% and benzyl **1p** 64% vs. phenyl **1o** 8%). Electronic effects also appear to control amide formation with electron-withdrawing substituents (**1n**, **1q**) abolishing amide formation. In these cases, the bis-urea by-product **9** was the major product which further validates the urea-forming mechanism (Scheme 2). It is proposed that the electron-withdrawing substituents on the carboxylic acid activate the carboxy carbonyl of the mixed anhydride intermediate **8** for nucleophilic attack. Acrylic acid and propiolic acid both underwent amide formation (**1r** and **1s** respectively) in similar yields.

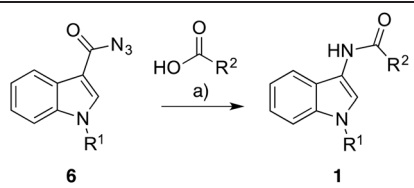
To further demonstrate the potential of this procedure, the same reaction was performed on the 1*H*-indol-3-yl carboxazide **6b** with a selection of carboxylic acids to give the corresponding amides (**1u–1z**). Under identical reaction conditions, reactions yields were generally lower but were still satisfactory given the scarcity of *N*-(1*H*-indol-3-yl) amides in the literature. The employment of the 1*H*-indole to this reaction allows for an *N*-substitution at a later stage of a synthesis and therefore allowing access to a greater range of *N*-(indolyl)amides.

A crystal of the *N*-(1-methyl-indol-3-yl)-2-(4-nitrophenyl)acetamide (**1r**) was grown and single crystal X-ray analysis confirmed the reversed amide functionality (Fig. 2). The carbonyl bond in aryl and indole carboxamides typically align parallel to the aryl rings due to extended pi orbital interactions. However, in this case, the reversed amide is disconnected and, in its lowest energy conformation state, can adopt a less sterically-hindered twisted conformation.

Given the successful preparation of *N*-(indol-3-yl)amides with the developed methodology, the focus was turned to preparation of *N*-(indol-2-yl) amides **2**. Taking commercially available indole-2-carboxylic acid (**12**), it was converted to the 1*H*-carboxazide **13a** in 93% yield using DPPA (Scheme 3). To prepare the *N*-methyl homologue **13b**, we found it convenient to alkylate the 1*H*-carboxazide **13a** with NaH and methyl iodide which resulted in the desired *N*-methyl indole-2-carboxazide (**13b**) in 64% yield.¹¹

Subjecting the indole-2-carboxazides **13a** and **13b** to the identical conditions developed for the preparation of *N*-(indol-3-yl)amides **1** resulted in moderate to excellent yields of the *N*-(indol-2-yl)amides **2** (Table 2). The reaction yields followed similar trends in substrate reactivity to the indole-3-carbox-

Table 1 Substrate scope in the synthesis of *N*-(indol-3-yl)amide **1** from indol-3-yl carboxazide **6**



Product	R ¹	R ²	Yield ^b , %
1a	Me	Ethyl	86 (64)
1b	Me	Methyl	69 (50)
1c	Me	Iso-propyl	58 (28)
1d	Me	<i>tert</i> -Butyl	3 (13)
1e	Me	Cyclopentyl	75 (27)
1f	Me	Cyclohexyl	43 (23)
1g	Me	Benzyl	88 (75)
1h	Me	Diphenylmethyl	62 (53)
1i	Me	Adamantan-1-yl	6 (6)
1j	Me	Adamantan-1-ylmethyl	41 (29)
1k	Me	Phenyl	28 (43)
1l	Me	Pyridin-2-yl	51 (13)
1m	Me	Pyridin-3-yl	41 (NR ^c)
1n	Me	Pyridin-4-yl	NR ^c (NR)
1o	Me	4-Methoxyphenyl	32 (8)
1p	Me	4-Methoxybenzyl	90 (64)
1q	Me	4-Nitrophenyl	NR ^c (NR)
1r	Me	4-Nitrobenzyl	67 (46)
1s	Me	Ethenyl	40 (23)
1t	Me	Ethynyl	45 (23)
1u	H	Methyl	75 ¹³
1v	H	Ethyl	64
1w	H	Benzyl	64
1x	H	Phenyl	24
1y	H	Adamantan-1-yl	31
1z	H	Adamantan-1-ylmethyl	26

^a Conditions: indol-3-yl carboxazide (0.5 M), carboxylic acid (2 equiv.), DMAP (0.1 equiv.), PhMe, reflux, 2 h. ^b Values in parentheses represent yields obtained when Et₃N (0.05 equiv.) was used instead of DMAP (0.1 equiv.). ^c Trace product observed.

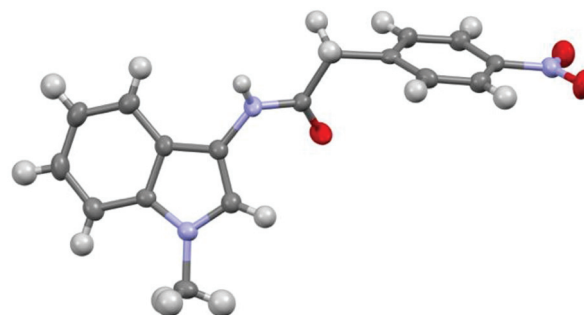
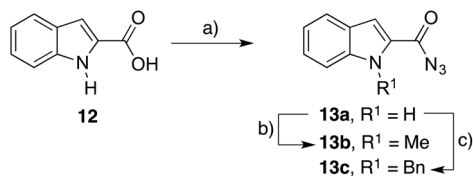


Fig. 2 ORTEP depictions of **1r** shown with 50% displacement ellipsoids.



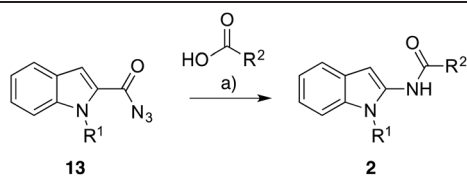


Scheme 3 Synthesis of the indole-2-carboxazides **13**. Reaction conditions: (a) Et₃N, CH₂Cl₂, rt, 15 min then DPPA, rt 1 h, 93%; (b) NaH, THF, 0 °C, 30 min, then MeI, rt, 16 h, 64%; (c) NaH, THF, 0 °C, 30 min, then BnBr, TBAI, rt, 16 h, 55%.

zide reactions (Table 1) albeit lower yields were observed relative to the respective 3-position counterpart. Nevertheless, the rapid and convenient access to these *N*-(indol-2-yl)amides *via* this methodology is a vast improvement on current approaches. An interesting observation is that substitution effects of the acid do not seem to translate between 2- and 3-substitution. For example, the formation of **1p** occurred effectively in 90% yield whereas the corresponding formation of **2d** was lower with a yield of 50%.

To further illustrate the utility of this reaction we sort to incorporate a protecting group onto the indole prior to rearrangement. Taking the 1*H*-indole-2-carboxazide **13a** the benzyl group was successfully installed (55%), with tetrabutylammonium iodide (TBAI) proving to be essential to effect the transformation. The resulting *N*-benzyl indole-2-carboxazide **13c**¹¹ was subjected to the Curtius rearrangement with a selection of carboxylic acids (Table 2, entries k–o). However, over 2 steps, the yield of the desired 1-benzyl *N*-(indol-2-yl)amides

Table 2 Synthesis of *N*-(indol-2-yl)amides **2a–o**



Product	R ¹	R ²	Yield ^b , %
2a	Me	Methyl	52
2b	Me	Ethyl	55
2c	Me	Benzyl	68
2d	Me	4-Methoxybenzyl	50
2e	Me	4-Nitrobenzyl	71
2f	H	Methyl	45
2g	H	Ethyl	45
2h	H	Benzyl	56
2i	H	4-Methoxybenzyl	91
2j	H	4-Nitrobenzyl	91
2k	Bn	Methyl	72 (40)
2l	Bn	Ethyl	70 (39)
2m	Bn	Benzyl	66 (36)
2n	Bn	4-Methoxybenzyl	62 (34)
2o	Bn	4-Nitrobenzyl	59 (32)

^a Conditions: indol-2-yl carboxazide (0.5 M), carboxylic acid (2 equiv.), DMAP (0.1 equiv.), PhMe, reflux, 2 h. ^b Values in parentheses represent yields obtained over two steps for the benzyl protection and rearrangement.

(**2k–2o**) were lower in most cases than the corresponding reactions performed with the 1*H*-indole-2-carboxazide (**2f–2j**), indicating that, unless otherwise required, it was higher yielding, more economical and more efficient to simply perform the reaction with the 1*H*-indole. When the methyl (**2a–e**) or benzyl (**2k–o**) indole amides were characterized, NMR spectra showed the presence of rotamers. When solubility allowed, these could be suppressed through the use of deuterated methanol as the solvent (see the ESI† for more details).

Conclusions

In summary, a new means of accessing *N*-(indol-3-yl)amides **1** and *N*-(indol-2-yl)amides **2** has been described. The precursory indolyl carboxazides **6** and **13** can be obtained on a high-yielding, multi-gram scale whilst the coupling carboxylic acids can be conveniently sourced from commercial supplies without prior activation or modification. Moderate yields are obtained across a wide substrate library that tolerate alkanolic, alkenolic, alkynolic and benzoic acids. This reaction is a mild and convenient route to *N*-(indol-3-yl)amides **1** and *N*-(indol-2-yl)amides **2** that avoids the isolation of unstable intermediates that impede previously reported methods. This work allows rapid access to a once limited indole motif and, with its wide substrate scope, expands the repertoire of indole-based drug design providing access to new chemical entities with potentially useful biological activity.

Acknowledgements

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