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A combinatorial approach towards 2-acyl-3-amino-indole derivatives

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Abstract

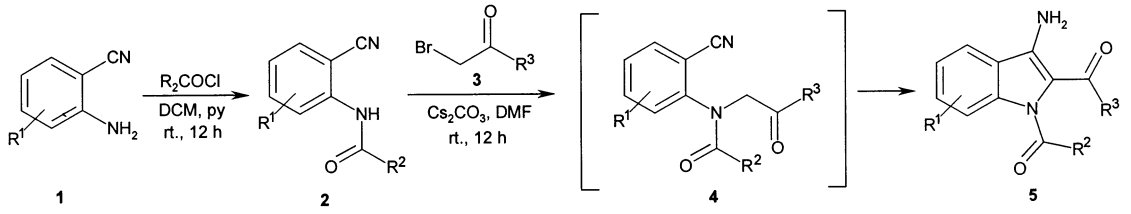
A widely applicable reaction sequence towards functionalised 2-acyl-3-amino-indole derivatives is presented. A set of 205 indole derivatives were prepared, in a solution phase combinatorial fashion, by coupling a reliable reaction protocol to a rapid purification system employing parallel filtration and application of automated reversed phase HPLC. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: combinatorial chemistry; solution phase synthesis; indole derivative library; HPLC purification.

Combinatorial chemistry[1] is currently under intense investigation and the search for new pharmacophore containing scaffolds is an ongoing process. Indole ring systems are ubiquitously found within pharmaceutical agents as well as in natural products[2] and therefore access to novel functionalised indole derivatives in a combinatorial fashion would be of great interest.

A facile approach to 3-amino-indoles was first disclosed in 1991 by Viti and coworkers,[3] who described the synthesis of such compounds as intermediates of a multistep synthesis leading to indolobenzoazepin-6-ones. Complementary to this route, our efforts were concerned with the evaluation of the potential of 3-amino-indole derivatives in combinatorial library synthesis.

The synthetic approach is outlined in Scheme 1 and comprised the coupling of eight different aminobenzonitriles **1** with a selected set of acid chlorides, which yielded a matrix of 90 amides



Scheme 1.

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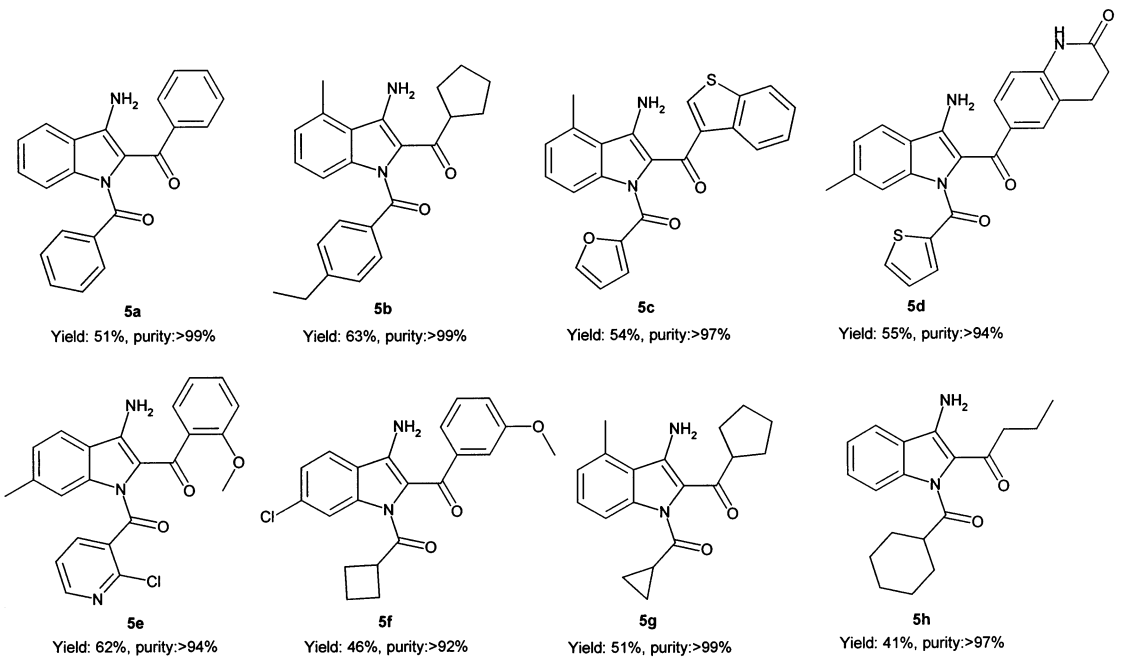
2. A total of 83 were successfully isolated in yields from 70 to 99% with purities in the range of 66 to 99%. The aminobenzonitriles were variously substituted with alkyl or halogen groups and the acid chlorides employed were either cycloalkyl, substituted benzoyl or heteroaromatic acid chlorides. The acid chlorides all reacted smoothly whereas the nature of the aminobenzonitrile dramatically affected the yield and the purity of the amide products. The unsubstituted and monosubstituted aminobenzonitrile reacted cleanly whereas polysubstituted aminobenzonitriles generally gave poorer yields and purities of the desired amides **2**.

From the 83 amides **2** isolated, the 48 with the highest purity were selected and used in the consecutive step without further purification.[4]

α-Bromoketones are known to react under various reaction conditions with, for example sulfides,[5] alcohols,[6] amines[7] and amides.[8] Interestingly, the reaction of amide **2** with α-bromoketones **3** could not be affected in CH_2Cl_2 or DMF with pyridine as a base or even in neat pyridine. Use of other bases such as KOH, $NaHCO_3$, KO*t*Bu, NEt_3 or DIPEA did not change the outcome. It has been previously described that the deprotonation can be achieved in DMF using NaH as the base.[3] In a model, the reaction of **2** ($R^1=H$ and $R^2=Ph$) with **3** ($R^3=Ph$) in DMF with 1 equiv. NaH as the base indole **5** ($R^1=H$, $R^2=R^3=Ph$) was obtained in 53% yield. Employing NaH in this synthetic array was considered to be impractical due to the moisture sensitive nature of the reagent. Therefore, a subsequent search for alternative conditions revealed Cs_2CO_3 as a base in DMF at room temperature to be a suitable protocol in this reaction sequence, which has not been reported earlier.[9] The use of DMF as a solvent was advantageous since it allowed the preparation of stock solutions of the starting material for both poorly soluble amides as well as α-bromoketones. The yield of **5** ($R^1=H$, $R^2=R^3=Ph$) employing the Cs_2CO_3 protocol was comparable (51%)[10] to that of using NaH as the base, which indicated that this new procedure could be readily applied in parallel array synthesis.

A library was prepared from 280 reactions, consisting of seven separate arrays, each containing eight amides **2** reacting in parallel with five α-bromoketones **3** in DMF with Cs_2CO_3 as a base at room temperature overnight (12 h). Tedious work-up was avoided by simple parallel filtration of the DMF solutions to remove the Cs_2CO_3, which were then submitted to preparative reversed phase HPLC purification. UV controlled collection allowed the rapid purification of the products, which were UV active at 400 nm. Subsequent removal of the elution solvents yielded a total of 205 isolated indole derivatives **5** in multi-milligram quantities (2–30 mg). Predictably, no intermediate **4** was isolated in any case. The yields varied between 10–92%, depending on the nature of the substituents. Representative examples are shown in Scheme 2.

It was found that the nature of R^1 affected the reaction only to a minor degree, whereas R^2 and R^3 had a large impact. The reactions of aryl- or heteroaryl substituted amides **2** with aryl- or heteroaryl substituted α-bromoketones which proceeded smoothly in 80% of the cases, yielded the desired indoles **5** in a range of 4 to 92% (average yield: 47%) (Table 1, entry 1). Amides that were substituted with electron withdrawing groups, however, afforded the products in lower average yields. Aryl- and heteroaryl substituted amides **2** also reacted smoothly with cycloalkyl- and alkyl substituted α-bromoketones (13–69%, average yield: 35%), and generally showed a good reactivity in 57% of the reactions producing indoles **5** (Table 1, entry 2). Cycloalkyl substituted amides also reacted nicely in 67% respectively 73% of the examples with a variety of α-bromoketones (Table 1, entries 3 and 4) affording the products in 4–66% yield. It is believed that this scope demonstrates the broad applicability of this reaction sequence.



Scheme 2. Representative examples of isolated indoles **5**

Table 1
Library reaction statistics

Entry	R^2	R^3	No. of performed reactions[a]	Yield (%)
1	Aryl-/heteroaryl-	Aryl-/heteroaryl-	148 (118) 80%	4–92 average: 47
2	Aryl-/heteroaryl-	Cycloalkyl-/alkyl-	28 (16) 57%	13–69 average: 35
3	Cycloalkyl-	Aryl-/heteroaryl-	89 (60) 67%	4–66 average: 39
4	Cycloalkyl-	Cycloalkyl-/alkyl-	15 (11) 73%	16–66 average: 45

[a] No. in parentheses indicates the number of reactions that yielded detectable amounts of product.

In conclusion, it was shown that out of 280 reactions of various amides with α-bromoketones in a combinatorial fashion, the desired product was isolated in multi-milligram quantities, in acceptable yields in 205 (73%) of the reactions. The novel reaction conditions (Cs_2CO_3 in DMF) employed proved to be the key for successful synthesis of the 2-acyl-3-amino-indole library **5**. The Cs_2CO_3 was easily handled and DMF proved to be the solvent of choice due to its high solublising properties. The crude products from this library were efficiently and rapidly purified by automated reversed phase HPLC. To the best of our knowledge this is the first report of library synthesis of 3-amino-2-acyl-indole derivatives. Based on these encouraging results the chemistry efforts towards novel substituted and functionalised indole derivatives are currently under investigation.

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4. Typical procedure for the synthesis **2**: A mixture of 10 mmol of aminobenzonitrile in 15 ml of DCM and 15 mmol of pyridine was treated with 11 mmol of acid chloride and reacted over night (12 h) at room temperature. In the cases where the product was soluble in 15 ml of DCM, water was added and the layers were separated by filtration through hydrophobic filter devices (Macherey & Nagel) and the volatiles removed in vacuo. In the cases where the product was not soluble in 15 ml of DCM, hexane was added and the precipitate collected, washed with hexane and dried in vacuo. MS and HPLC at 230 nm corroborated the structures and purities.
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9. General procedure: To a solution of 0.3 mmol substituted benzonitrile **2** in 0.5 ml DMF was added 0.45 mmol of α-bromoketones **3** in 0.5 ml of DMF, approximately 150 mg (0.5 mmol) of Cs_2CO_3 and stirred over night (12 h) at rt. Filtration yielded a DMF solution, which was directly applied to reversed phase column chromatography (Dynamax pumps and UV detector in combination with a Gilson 215 liquid handler on a YMC ODS-A column (50×20mm)) eluting with a gradient of acetonitrile and water (20–95%). Evaporation of the elution solvents yielded the desired indoles **5**. MS corroborated the structures and the purities were determined by HPLC at 230 nm.
10. **5a** (R^1 = H, R^2 = R^3 = Ph) Yield: 51%; 250 MHz ^{1}H NMR ($CDCl_3$): δ = 8.28 (d, J = 7.2 Hz, 1H, Ind-H7), 7.70 (d, J = 7.2 Hz, 1H, Ind-H4), 7.60 (t, J = 7.2 Hz, 1H, Ind-H6), 7.40 (t, J = 7.2 Hz, 1H, Ind-H5), 7.35 and 7.15 (m, 10H, 2×Ph), 5.88 (s, br, 2H, NH_2).