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Combinatorial Synthesis of Libraries of Indole Derivatives

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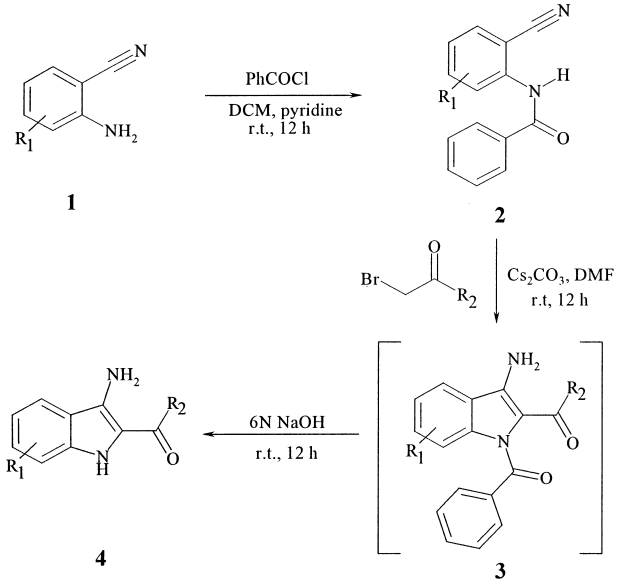
Abstract—The synthesis of two indole derivative libraries is described. 2-Acyl-3-amino-indoles **4** can easily be accessed by treatment of the intermediates **3** with bases in a one-pot reaction sequence whereas the reaction of the isolated intermediates **5** (R_3 = aromatic-, heteroaromatic, or cycloalkyl) with acid chlorides yielded the novel indole derivatives **6**. The products were purified by reversed phase column chromatography and obtained in multi-milligram quantities in acceptable yields. © 2001 Elsevier Science Ltd. All rights reserved.

Combinatorial organic synthesis[1] is still of great interest because it promises to accelerate the drug discovery process as well as speed up the development of new catalysts[2] or determine reaction protocols faster via automated techniques.[3] In the pharmaceutical industry the focus mainly lies on the synthesis of compound libraries either for general screening or for project related tasks. The synthesis of unbiased compound libraries offers the advantage of rapidly producing a considerable number of potentially active compounds resulting in diverse structures. The synthesis of smaller compound libraries supports the more rapid evaluation of hit structures, thus enabling medicinal chemistry projects to more rapidly identify potentially interesting drug candidates to be further pursued.

Indoles are known to play an important role in biology and are a frequently found motif in natural products.[4] The pharmacophoric potential is enormous and therefore the search for novel indole derivatives is a challenging and ongoing process. The work presented shows the interest in development and synthesis of novel substituted indole derivatives.[5a]

Amino-benzonitriles **1** can easily be converted to benzoylamino-benzonitriles[5b] **2** which react cleanly with various α-bromoketones in DMF with Cs_2CO_3 as base to afford the corresponding indole derivatives **3**. The benzoyl-substituent in **2** can be regarded as an activating group for the nitrogen since it was previously found that *N*-unsubstituted aminobenzonitriles themselves did not react with α-bromoketones directly under various conditions to yield the desired free indoles **4**.[5c]

However, the free indole derivatives can be liberated upon treatment of the crude DMF solutions of **3** with 6 N NaOH at room temperature in a one-pot reaction sequence.[6] Following this protocol the cleavage of the benzoyl group was easily achieved (Scheme 1).



Scheme 1.

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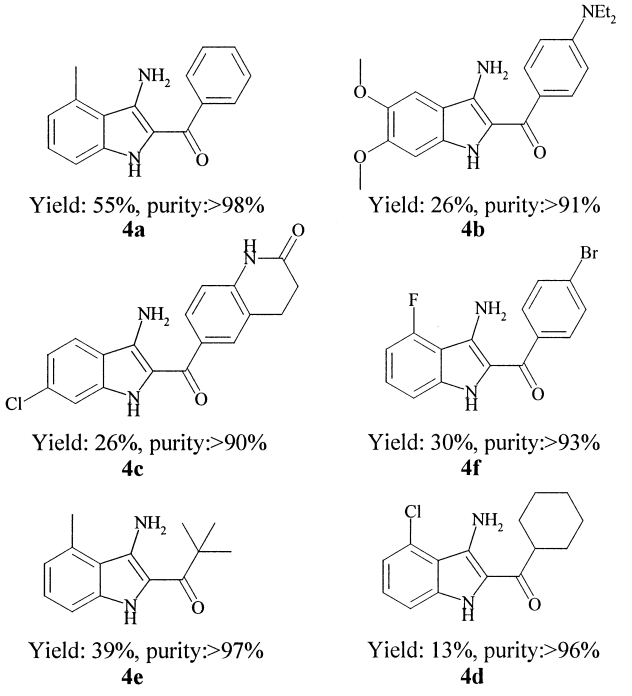
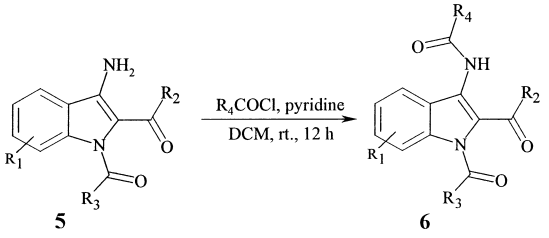
6 Alkyl- and halogen substituted 1-benzoylamino-benzonitriles **2**[5d] were reacted with 28 alkyl-, cycloalkyl-, aryl- and heteroaryl α-bromoketones, in a combinatorial fashion, to yield the indole derivatives **3** which were not isolated. Subsequently, the reaction mixtures were treated with 6 N NaOH in a one-pot process at room temperature for 12 h. This protocol allowed for an easy and straightforward access to indole derivatives **4**. The combination of this widely amenable reaction sequence with the power of parallel workup and purification of the crude DMF solutions with reversed phase HPLC yielded 89 indoles **4** with acceptable yields (2–77%; average: 25%).[7] For this reaction sequence, a wide variety of electron withdrawing and also electron donating substituents on either the α-bromoketone or the benzoylamidobenzonitriles **2** were tolerated. Representative isolated indoles are displayed in Scheme 2.



Scheme 2. Representative examples of isolated indoles **3**.

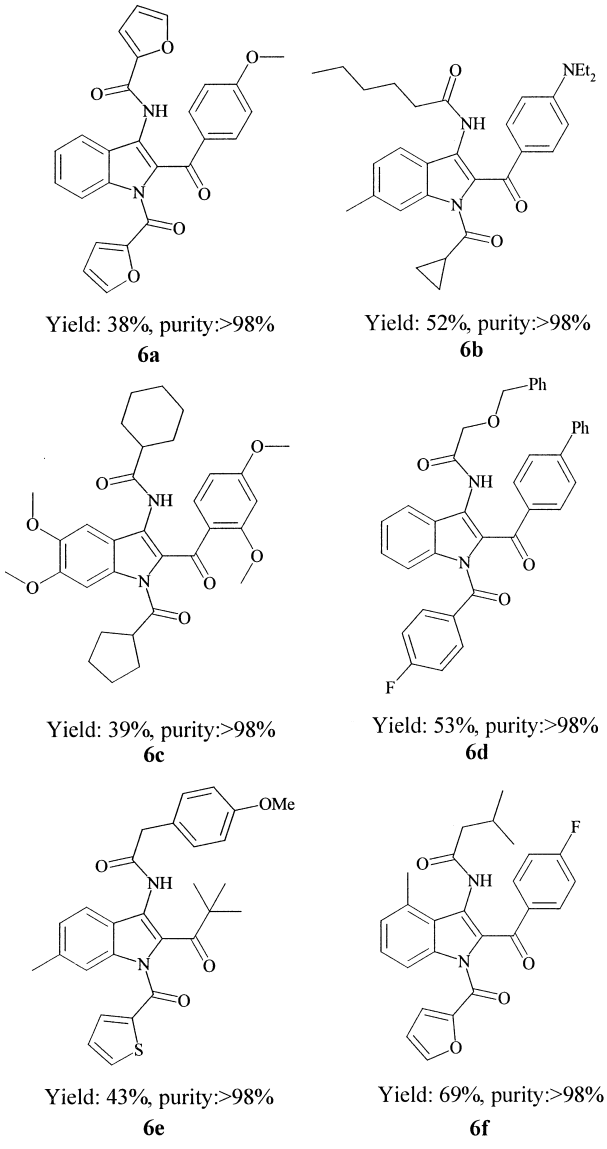
Alternatively, the intermediates **5**[5b] can, after isolation, be further derivatised to add a fourth vector of diversity. The reaction of the indoles **5** (R_3 = phenyl, substituted-phenyl, cycloalkyl) with various acid chlorides in DCM and pyridine as base yielded in acceptable yields the substituted indole derivatives **6** (Scheme 3).[8]



Scheme 3.

Out of the numerous possible combinations, 200 reactions of 159 different indoles **5** with 20 acid chlorides were performed in a combinatorial fashion. The parallel workup combined with the preparative reversed-phase HPLC purification yielded 138 previously non-described indole derivatives in multi-milligram quantities with purities generally in excess of 90%. It was found that the reaction worked unsatisfactorily in cases where the indoles **5** were substituted in the 4-position and the acid chlorides used were *ortho*-substituted benzoyl-chlorides.

The structures of the purified indoles **6** were corroborated by MS and the purity checked by HPLC at 230 nm. Representative examples are displayed in Scheme 4.



Scheme 4. Representative examples of isolated indoles **6**.

With the members of the presented indole derivative libraries **4** and **6**, biological examination will be undertaken to identify novel lead structures to be further evaluated in depth in medicinal chemistry projects.

In conclusion, the synthesis of two previously non-described indole derivative libraries in a combinatorial fashion was demonstrated. The synthesis of the intermediates **3** and **5**, respectively, was performed as earlier described in DMF with Cs_2CO_3 as base.[5b]

The resulting benzoyl-substituted indole derivatives **3** were subjected in a one-pot procedure to strongly basic conditions that effected the cleavage of the benzoyl group to liberate 89 indole derivatives **4** which were not accessible from the reaction of amino-benzonitriles with α-bromoketones directly. The purities of the final compounds were generally higher then 90% after reversed-phase HPLC purification.

The isolated intermediates **5**[5b] served as the starting point for a second previously non-described indole derivative library. Two hundred reactions of indole derivatives **5** with acid chlorides yielded 159 new indoles **6** which, after reversed-phase HPLC, were isolated with purities in excess of 90%.

Based on these results, chemistry efforts towards novel substituted indole derivatives are currently under investigation.

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References and Notes

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6. General procedure for the synthesis of **4**: To a solution of 0.3 mmol benzoyl-amidobenzonitrile **2** in 0.5 mL DMF was added 0.45 mmol α-bromoketones in 0.5 mL DMF, approximately 150 mg (0.5 mmol) Cs_2CO_3 and stirred at rt overnight (12 h). 0.5 mL (3 mmol) 6 N NaOH was added and the mixture was stirred at rt overnight (12 h). Filtration yielded a DMF solution, which was directly applied to reversed-phase column chromatography (Dynamax pumps and detector in combination with a Gilson 215 liquid handler on a YMC ODS-A column (50×20 mm)) eluting with a gradient of acetonitrile and water (20–95%). Evaporation of the elution solvents yielded the desired indoles **4**.
7. The structures of the purified indoles **4** were corroborated by MS and the purity checked by HPLC at 230 nm.
8. General procedure for the synthesis of **6**: To a solution of 1 equiv indole **5** (amount varies between 0.05 and 0.2 mmol) in DCM was added 1 equiv pyridine and 1.2 equiv acid chloride, and the mixture was stirred at rt overnight (12 h). The residues were taken up in DMF and the raw DMF solutions were subjected to reversed-phase column chromatography [Dynamax pumps and detector in combination with a Gilson 215 liquid handler on a YMC ODS-A column (50×20 mm)] eluting with a gradient of acetonitrile and water (20–95%). Evaporation of the elution solvents yielded the desired indoles **6**.