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Preparation of 5-substituted 2-carboxyindoles on solid support

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Abstract

The preparation of 5-substituted 2-carboxyindoles on solid support is reported. In the approach, the indole moiety is synthesized in solution phase, followed by nitro-group reduction, reductive amination and alkylation on solid support. The method provides a simple and convenient route for the preparation of 5-substituted 2-carboxyindoles with high purity and good yield.

Combinatorial chemistry is a method by which large numbers of structurally distinct molecules may be synthesized in a time- and resource-effective manner, and then be submitted for pharmacological tests.[1,2] Our synthetic efforts in the area of lead discovery has led to the exploration of synthesis routes for the high throughput preparation of structurally diverse compound libraries. As part of an ongoing project, we required a flexible synthetic protocol for the preparation of 5-substituted 2-carboxyindoles.

Several indole-structures featuring a 5-substituent group have been reported.[3–5] It has been suggested that a substituent at C-5 would increase the binding affinity at various bioreceptors, for instance at the NMDA-receptor,[6] and at the rHLGPa-receptor.[7] Moreover, the 5-substituent has been shown to be important in structure–activity relationship (SAR) studies for improving the affinity and selectivity at the 5-HT_{1D} receptor:[8] a 5-substituent capable of participating in hydrogen bonding could be critical for the binding affinity.[9] In addition, at least one heteroatom attached to C-5 has been reported in several 5-HT_{1D} receptor agonists.[10]

Herein, we report a convenient method for a simple and inexpensive route for the modification of the 5-substituent in an indole moiety. The route we chose to study is illustrated in Scheme 1.

The template 5-nitro-2-carboxyindole (**1**)[11] (Scheme 2) was synthesized by a Japp–Klingemann reaction[12] followed by Fisher indolization.[13] The hydrazone (**2**) obtained in the reaction as an intermediate was isolated, recrystallized from EtOH in 75% yield, and characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS.[14] The cyclization was performed in polyphosphoric acid producing the desired indole (**1**) in 83% yield. An attempt to utilize a modified Fisher indole synthesis on a solid support as described

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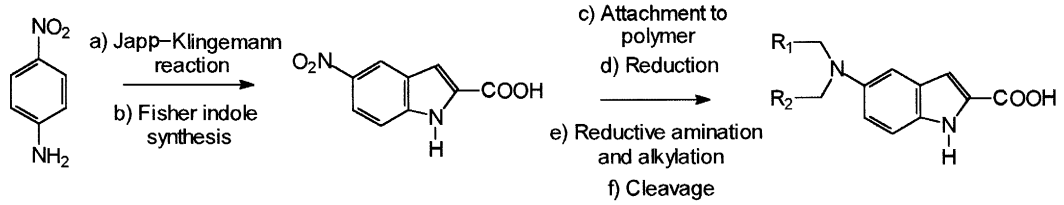
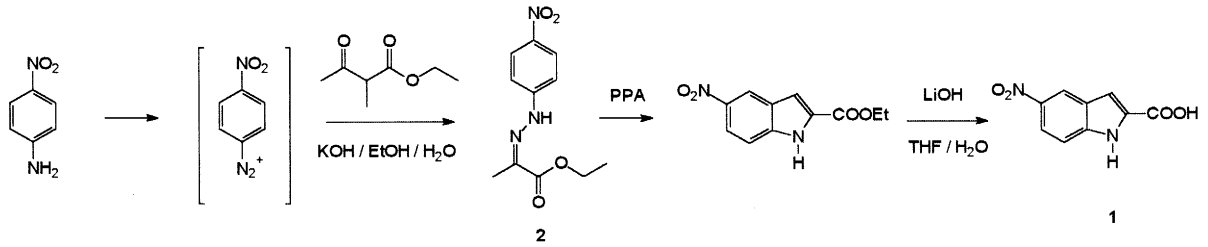


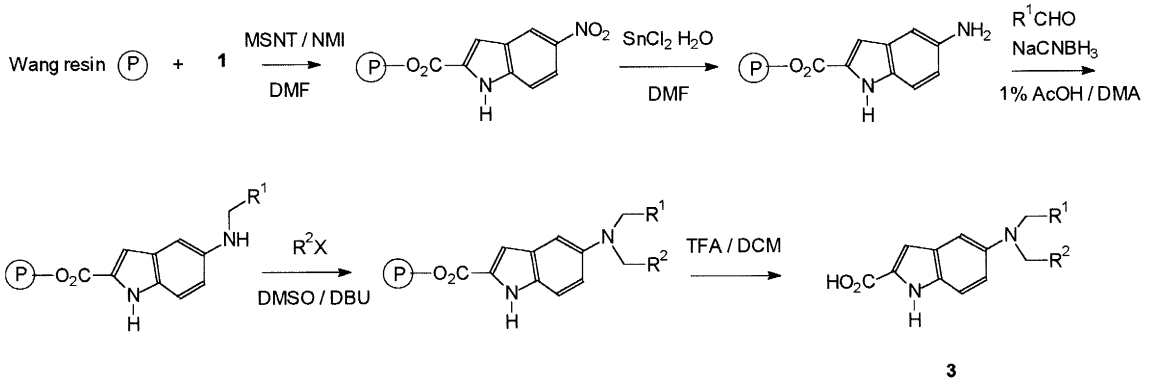
Scheme 1.

by Hutchins and Chapman[15] did not produce the desired results and therefore we decided to prepare the indole nucleus in solution followed by immobilization onto the resin.



Scheme 2.

The solid phase procedure is described in Scheme 3. The indole (**1**) was attached to Wang resin using 1-(2-mesitylene-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) and *N*-methylimidazole (NMI) in dichloromethane[16] followed by nitro-group reduction.[17] The attachment was monitored by IR and characteristic bands at 1350 cm^{-1} (NO_2) and at 1700 cm^{-1} (RCOOR) could be observed. In the first combinatorial step a reductive amination with several aromatic aldehydes in the presence of $NaCNBH_3$ in DMA was performed.[18] The polymer bound secondary amines obtained were not further characterized. However, IR analyses and cleavage of a small amount of the product revealed that no starting material could be observed. A further alkylation with benzylic bromides, thus providing the next combinatorial step,[18] was performed. Cleavage using the standard TFA–DCM method produced the final products in 40–75% total yield (calculations based on the commercially announced loading).

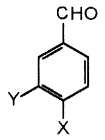
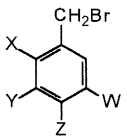
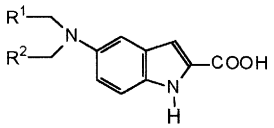
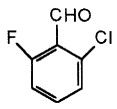
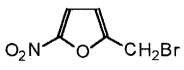
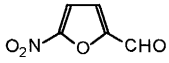
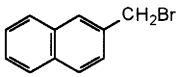


Scheme 3.

All products **3a**[19,20]–**3h** were characterized by ^1H NMR, and ESI-MS to assure that the reaction procedure had been succesfully accomplished. The preparation of **3a** was also accomplished by attachment of **1** to Merrifield resin. Attachment and cleavage was performed according to Frenette and Friesen.[21] All

compounds were purified by preparative TLC and in Table 1 the components used for the combinatorial synthesis, the structures of products and total yields are summarized.

Table 1
Starting materials, products and yields summarized

Aldehydes R^1	Alkyl halides R^2	Product	Yield (%)[a]
			
X = CF_3 , Y = H	X = OMe , W = NO_2 , Y = Z = H	3a	51
X = NO_2 , Y = H	W = NO_2 , X = Y = Z = H	3b	73
X = H , Y = Me	X = Y = Z = W = H	3c	55
X = OMe , Y = H	W = NO_2 , X = Y = Z = H	3d	69
X = Cl , Y = H	W = NO_2 , X = Y = Z = H	3e	74
X = H , Y = NO_2	X = NO_2 , Y = H , Z = W = OMe	3f	40
		3g	60
		3h	45

a) Isolated yield (calculated based on the commercially announced loading)

In summary, we have demonstrated a simple and convenient method for the preparation of 5-substituted-2-carboxyindoles on solid support. After cleavage from the support, only one product can be observed and due to high purity, a preliminary screening in biological assays is possible. We are now in a process of extending our studies toward using aliphatic aldehydes and bromides making this route more useful for preparation of combinatorial libraries.

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11. The data for compound (**1**) is as follows: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 (d, *J*=1 Hz, 1H), 7.58 (d, *J*=9 Hz, 1H), 8.11 (dd, *J*=9 and 2.5 Hz, 1H), 8.71 (d, *J*=2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 109.6, 113.0, 119.0, 119.4, 125.9, 131.9, 139.8, 141.2, 161.9; mass spectrum (ESI) *m*/*z* 205 ($M-H^+$).
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14. The data for compound (**2**) is as follows: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.28 (t, *J*=7 Hz, 3H), 2.12 (s, 3H), 4.23 (q, *J*=7 Hz, 2H), 7.39 (d, *J*=9 Hz, 2H), 8.20 (d, *J*=9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.5, 14.2, 60.7, 113.1, 113.1, 125.7, 125.7, 137.0, 140.3, 164.3; mass spectrum (ESI) *m*/*z* 252 ($M+H^+$).
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16. Nielsen, J.; Lyngso, L. *Tetrahedron Lett.* **1996**, *37*, 8439.
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19. Typical procedure (**3a**): the attachment of **1** (2 equivalent) to Wang resin (0.2 g, 0.56 mmol/g) followed the procedure by Nielsen and Lyngsjo,[16] except that DMF was used instead of DCM in the reaction. Following filtration and washing of the derivatized resin several times with DMF, THF, MeOH, and DCM, the reduction of the nitro-group was performed according to the method by Wei and Phillips.[17] Reductive amination with 4-trifluoromethyl benzaldehyde and alkylation with 2-methoxy-5-nitrobenzylbromide was performed in a similar manner to that described by Green.[18] Cleavage was performed in DCM/TFA (1:1) for 2 h at room temperature. Following filtration, the resin was washed with DCM and the filtrate was evaporated to dryness. The residue was purified on silica gel ($CHCl_3$/EtOAc, 1:1+1% AcOH) to obtain 17 mg (51%) of pure **3a**.
20. The data for compound (**3a)** is as follows: ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.97 (s, 3H), 4.62 (s, 2H), 4.80 (s, 2H), 6.77 (m, 1H), 6.81 (m, 1H), 6.87 (m, 1H), 7.26 (d, *J*=9 Hz, 2H), 7.49 (d, *J*=8 Hz, 2H), 7.58 (d, *J*=8 Hz, 2H), 7.92 (m, 1H), 8.18 (dd, *J*=9 and 3 Hz, 1H); mass spectrum (ESI) *m/z* 498 ($M-H^+$).
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