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A new strategy for 2-substituted indolylalkylamines: synthesis of 2-aryldihomotryptamines

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Abstract—Substituted homologues of tryptamines were synthesized in one step in high yields under mild conditions. The key intermediates are arylhydrazones of 6-aminohexanones, which undergo Fischer rearrangement readily in glacial acetic acid. An easy and ready for scale-up procedure is developed and formerly unknown 2-substituted dihomotryptamines are obtained. © 2002 Published by Elsevier Science Ltd.

Indolylalkylamines have importance as a main structural unit of indole alkaloids, many biologically active substances and remedies.[1] Recently, derivatives of 2-substituted tryptamines attracted a lot of attention because of their high selectivity for serotonin,[2] melatonin[3] and gonadotropin releasing hormone[4] receptors.

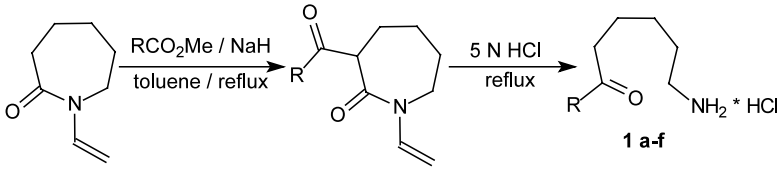
Three general approaches exist to 2-substituted tryptamines. The first consists of attaching the alkylamine fragment to the indole core.[5] The second involves multi-step modification of the 3-indole substituent into the alkylamine chain.[6,7] The third lies in the synchronous creation of the selected alkylamine fragment and the indole core and is the method of choice because it should provide a shortened and simplified procedure.

To fulfil such an approach there are Fischer, Grandberg or Japp–Klingemann reactions. The last one limits the range of products to 2-carboxyindolylalkylamines.[8] It has been shown[9,10] that 2-arylindolylalkylamines cannot be obtained by the Grandberg approach, but the authors[11] were able to obtain 2-aryltryptamines in a low yield using the reaction of 4-chlorobutyrophenone with phenyl hydrazines. The Fischer reaction has often been applied to the synthesis of 2-unsubstituted indolylalkylamines from aminoaldehydes,[12] which are very labile compounds and need to be protected before being used. This drawback increases the total expense and time of this method.

In this investigation we propose and elaborate a new general method for the synthesis of homologues of tryptamine, substituted in 2-position. The starting compounds are various aminoketones and arylhydrazines.

Our approach is the first example of the Fischer's reaction of aminocarbonyl compounds containing an unprotected amino group.

The synthesis of various arylhydrazines is well-known, therefore we aimed at developing a convenient synthesis of 6-aminohexanones from readily available and inexpensive substances. We chose α-acyllactams as the starting materials for synthesis of the aminoketones on the basis of literature analysis: they can be easily



Scheme 1.

Keywords: Fischer reaction; amino ketones; indolisation; biologically active compounds.

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Table 1. Aminohexanones obtained via Scheme 1

Entry	Aminohexanone, R	Isolated yield (%)	Entry	Aminohexanone, R	Isolated yield (%)
1a	C_6H_5	66	**1d**	4-ClC_6H_4	81
1b	3-MeC_6H_4	86	**1e**	4-BrC_6H_4	85
1c	3-$MeOC_6H_4$	70	**1f**	3,4-$Cl_2C_6H_3$	78

Table 2. 2-Aryldihomotryptamine **2a–j** produced via Scheme 2

Entry	R	R′	Isolated yield (%)
2a	C_6H_5	H	85
2b	C_6H_5	5-Br	78
2c	C_6H_5	5-MeO	80
2d	C_6H_5	4,6-Me_2	84
2e	C_6H_5	5-*n*-Bu	85
2f	3-MeC_6H_4	H	65[a]
2g	3-$MeOC_6H_4$	H	57[a]
2h	4-ClC_6H_4	H	72[a]
2i	4-BrC_6H_4	H	62[a]
2j	3,4-$Cl_2C_6H_3$	H	77[a]

[a] Glacial acetic acid, saturated by HCl, was used.

obtained by Claisen condensation of an *N*-protected lactam and ester.[13] We used a *N*-vinylcaprolactam, which is commercially available, and methyl esters of substituted benzoic acids. It is known that the *N*-vinyl protecting group is stable for the condensation (and isolation of α-acyllactams) and can be easily removed during subsequent acidic hydrolysis and decarboxylation. We modified this method to obtain the 6-aminohexanones **1a–f** as hydrochloride salts (Scheme 1, Table 1).

All the aminohexanones obtained reacted easily with arylhydrazines (as their HCl salts) forming the corresponding hydrazones in quantitative yields. The use of isolated hydrazones in the reaction of indolisation or their preparation in situ did not effect the yield of the target compounds.

We found that heating under reflux of the hydrazones or a mixture of the arylhydrazine and the aminoketones **1a–f** in glacial acetic acid gave the 2-substituted dihomotryptamines in high yields up to 85% (Table 2). The procedure is extremely simple and readily scaled-up (Scheme 2).[14]

To investigate the scope of the method and the effect of substituents on the yield of the Fischer reaction, various arylhydrazines with donor and acceptor groups were synthesized.[15] It was found that in all cases dihomotryptamines were isolated in good to high yields.[16] The experimental data obtained allow the anticipation that development of this work can make this approach a new general method for the synthesis of substituted indolylalkylamines (tryptamines, homotryptamines and isotryptamines) from other aminoketones.

In conclusion, we propose a new general method for synthesis of various dihomotryptamines with desired substituents in all positions of the indole core. This work is in progress in our laboratory and the results will be reported in due course.

Acknowledgements

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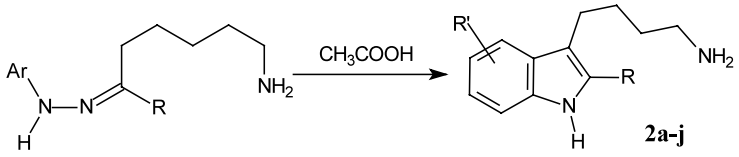

Scheme 2.

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14. General procedure: A mixture of 6 mmol arylhydrazine hydrochloride and 5 mmol aminoketone was refluxed in glacial acetic acid. The progress of the reaction was monitored by TLC (MeCN:EtOH:NH_3 (aq) = 80:12:8). After the reaction was finished, the mixture was concentrated in vacuo and recrystalized from water. If the hydrochloride was soluble in water, it was basified with 3 M K_2CO_3, extracted with CH_2Cl_2 2×30 ml, and the organic phase was washed with water, 2×50 ml, dried (Na_2SO_4) and evaporated in vacuo. The residue was dissolved in 10 ml of MeOH and 5 mmol of oxalic acid dihydrate was added in 15 ml of hot MeOH. The solvent was removed under reduced pressure and the oxalate was recrystalized from 10 ml of EtOH, filtered and washed with Me_2CO:Et_2O (1:1).
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16. All new compounds were fully characterized on the basis of complementary spectral (^1H and ^{13}C NMR) and microanalysis data. Selected data: compound **2a**, **4-(2-phenyl-1*H*-indol-3-yl)-1-butylamine hydrochloride)**: Yield 85%. R_f 0.25. Mp 236°C. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 1.60–1.71 (m, 4H), 2.75 (t, 2H, J = 6.95 Hz), 2.85 (t, 2H, J = 7.11 Hz), 6.95–7.65 (m, 9H), 7.94 (bs, 3H), 11.21 (s, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 23.94 (CH_2), 27.29 (CH_2), 27.60 (CH_2), 38.71 (CH_2), 111.16 (C), 111.45 (CH), 118.57 (CH), 118.67 (CH), 121.42 (CH), 127.21 (C), 127.74 (CH), 128.60 (CH), 128.72 (CH), 133.03 (C), 133.93 (C), 135.99 (C). Anal. calcd for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04. Found: C, 72.04; H, 6.91%.