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Environmentally benign, microwave-assisted chemoselective *N*-hydroxyalkylation of indoles with trifluoroacetaldehyde methyl hemiacetal

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Dedicated to Prof. Kenneth Laali on the occasion of his 65th birthday and life-long contributions to chemistry

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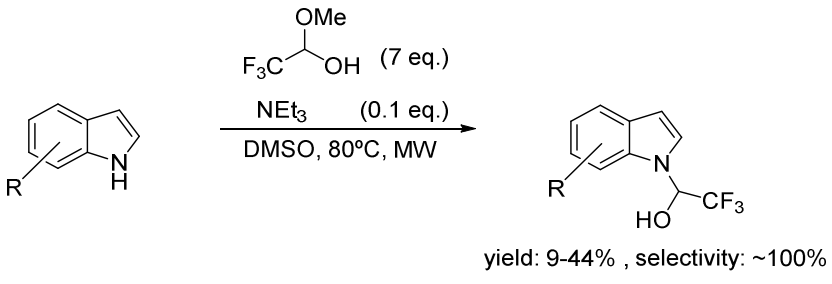
Abstract

The chemoselective microwave-activated N-hydroxyalkylation of indoles using trifluoroacetaldehyde methylhemiacetal as the alkylating agent under mild conditions is described. The chemoselectivity of this reaction is determined by the solvent used. In dimethyl sulfoxide, the reaction occurs without the use of a strong base or a metal catalyst. This approach can be applied to a variety of different substituted indoles to obtain the corresponding N-alkylated products with high selectivity. The product 2,2,2-trifluoro-1-(1-*H*-indol-1-yl)ethanols combine two moieties of frequent pharmacological interest: the indole core and a CF_3-group containing a hydroxyalkyl substituent.



yield: 9-44% , selectivity: ~100%

Keywords: Indole, hydroxyalkylation, trifluoroalkylation, microwave activation, solvent effect

Introduction

Indole as a structural moiety can be found in a broad range of natural products (i.e. alkaloids and peptides).[1] As these compounds are often biologically active they serve as a core in many drugs and potential pharmaceutical synthons. Thus, their synthesis is of high interest for the pharmaceutical industry.[1-3] Indoles are also known as potential inhibitors of various pathogenic pathways leading to fatal neurodegenerative diseases such as prion[4] or Alzheimer's disease.[5,6] While it is possible to synthesize these molecules by building the indole core with substituents already in place,[7-11] the functionalization of the existing indole core also represents a versatile strategy. The introduction of a CF_3- group to indole using trifluoromethyl group-containing substrates can further enhance the drug like properties of bioactive compounds.[12-15]

The importance of organofluorine compounds has steadily increased over the last few decades due to their frequent use in pharmaceutical and agrochemical applications, as well as in the synthesis of advanced materials. Currently, an estimated 20 percent of pharmaceuticals prescribed or administered contain at least one fluorine atom. Their improved potential, such as enhanced affinity towards biological targets, increased metabolic stability, bioavailability and membrane permeability is due to the unique physiochemical and biological properties of organofluorine compounds[16-18].

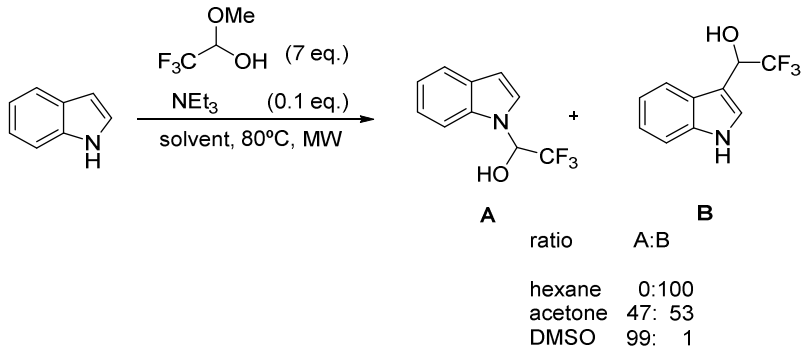
Substitution on the 5-membered ring of indoles can occur at the N1, C2 and C3 positions. With C3 being the most reactive position in aromatic electrophilic substitutions, numerous methods for the synthesis of 3-substituted indoles are reported in literature.[19-22] However, achieving a selective introduction of substituents to the N1- or C2-position of indoles is a more challenging task.[23,24] N-Substituted indoles are mainly obtained by direct N-alkylation. This involves the initial formation of an indolyl anion, but due to its ambident nature, both N- and C- alkylated products can form. As deprotonation makes the nitrogen atom the most reactive nucleophilic site, procedures for N-substitution commonly involve base-catalyzed nucleophilic substitution or conjugate addition reactions.[25,26] Accordingly, there is only a limited number of broadly applicable procedures for the synthesis of N-alkylated indole derivatives.[27] In order to obtain chemoselectivity between the reactive centers several factors have to be carefully considered, e.g. the type of metal counter ion, the use of metal catalysts[28] or phase transfer catalyst,[29] the use of base[30] and the type of solvent used.[31] Some advances toward selective N-arylation have recently been made applying Cu-nanoparticles.[32] However, the use of a stoichiometric amount of base, harsh reaction conditions or multistep synthesis[33] is commonly required for these methods.

Extending our recent efforts on the development of sustainable synthesis methods,[34-38] herein we report the environmentally benign synthesis of 2,2,2-trifluoro-1-(1-*H*-indol-1-yl)ethanols by a direct N-hydroxyalkylation of indoles with trifluoroacetaldehyde methyl hemiacetal under mild conditions without the use of strong bases or metal catalysts.

Results and Discussion

Based on our earlier results the alkylation of indole using trifluoroacetaldehyde methyl hemiacetal occurs preferentially at the C3 position yielding the thermodynamically favored product.[39,40] The N-substituted product can be obtained under kinetic control using a strong base or metal mediated reactions.[25] However, our recent mechanistic and DFT investigations showed that the outcome of this hydroxyalkylation reaction is highly dependent on the choice of the reaction conditions, especially the selection of the solvent.[41] It was found that the use of non-polar solvents, such as hexane, resulted in the exclusive hydroxyalkylation at the C3

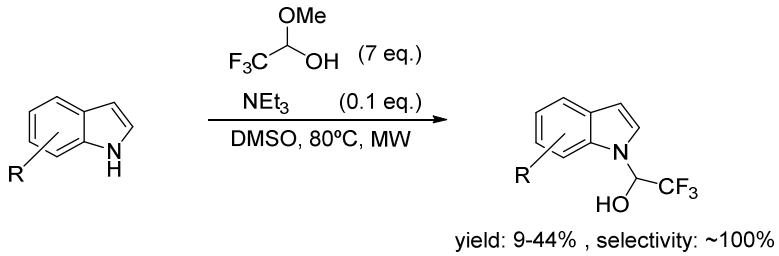
position. As the polarity of the solvent increases, the reaction tends to favor the formation of the N-alkylated product. Using DMSO as the solvent, almost exclusive N-alkylation was observed (Scheme 1). The product can be obtained under completely base-free conditions, however, the use of a catalytic amount of triethylamine led to a 2-fold increase in yield.



Scheme 1. Solvent dependence of indole hydroxyalkylation.

This solvent dependence can be applied to synthesize selectively indol-1-yl-trifluoromethyl ethanols without the use of harsh reaction conditions and/or additional reagents. Following these findings for the selective N-alkylation of indole we decided to broaden the scope of the reaction by using various substituted indoles.

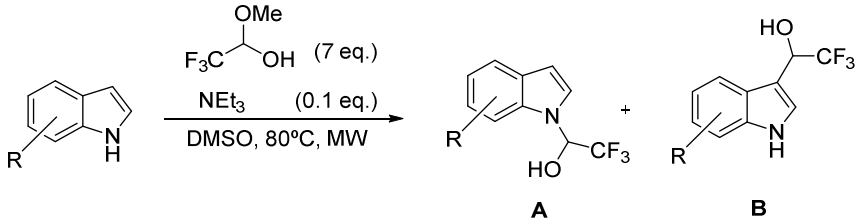
The reactions were performed according to our previously optimized conditions (Scheme 2).[41]

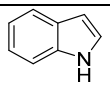
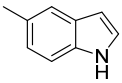
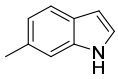
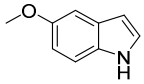
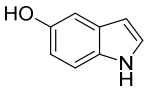
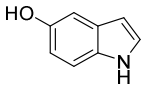
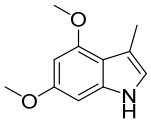
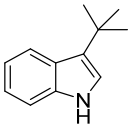
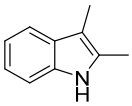
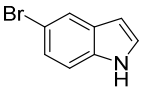
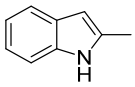
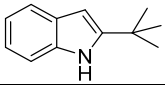


Scheme 2. General reaction scheme for the chemoselective synthesis of indol-1-yl trifluoromethyl ethanols.

The indoles were dissolved in DMSO, and then a catalytic amount of triethylamine (NEt_3) and excess trifluoroacetaldehyde methylhemiacetal were added. While trifluoroacetaldehyde ethylhemiacetal can also be used for the generation of trifluoroacetaldehyde (fluoral) under acidic conditions,[40] the methylhemiacetal, appeared to be more reactive and could be used under these mild conditions to achieve the selective conversion of the starting material. A variety of substituted indoles were submitted to these conditions and the results are summarized in Table 1. With few exceptions, the products were obtained with complete chemoselectivity. It is worth noting that while the yields are only moderate, the reaction resulted in the exclusive formation of the hydroxyalkylation-product; no other byproduct formation was observed and the unreacted starting indole was recovered and reused.

Table 1. Reaction of different substituted indoles with trifluoroacetaldehyde methylhemiacetal



Entry	Substrate	Product	Yield[a]	Ratio **A**:**B**
1		A	44%	99:1
2		A	34%	99:1
3		A	22%[c]	99:1
4		A	19%	99:1
5		A+B	40%	1:1
6[b]		A	9%	99:1
7		A	32%	99:1
8		A	20	100:0
9		A	10%	99:1
10		-	0%	-
11		B	99%	0:100
12		-	0%	-

[a]GC yield. >99% selectivity was obtained; the starting indole was recovered after the reaction. [b]Reaction was performed at 60 [o]C for 30 min; [c]due to stability issues the product was only identified by its EI-MS spectrum.

As it can be seen in Table 1 the reaction can be performed successfully with indole and indoles bearing an electron-donating (alkyl or oxygen-containing) substituent on the 6-membered ring of the indole (entries 1-7). The yields obtained are generally in the range of 20-40%, which is due to the relatively low conversion of the reaction. When the reaction is driven to achieve higher conversions (increased temperature and/or reaction time) the selectivity of the reaction decreases and C-alkylation, as well as the formation of other

byproducts occur. It should be noted that 5-hydroxyindole is highly reactive under the standard reaction conditions yielding in a mixture of N- and C-substituted product (entry 5). Lowering the reaction temperature and reaction time restored the chemoselectivity of the reaction for exclusive N-hydroxyalkylation, albeit with lower conversion (entry 6). When indoles with an electron-withdrawing (EWD) substituent are tested (e.g. 5-Br-indole, entry 10) under the reaction conditions, no product formation was observed, the starting material could be recovered completely. This is probably due to the deactivating effect of the substituent reducing the reactivity of the aromatic system.

When placing substituents to the C2 position of indole, the outcome of the reaction is strongly dependent on the nature and size of the substituent. Similarly to the effect of electron withdrawing substituents on the carbocyclic ring, adding EWD substituents to the five-membered ring deactivates the ring and no product formation occurs. Submitting 2-*tert*-butyl substituted indole to the reaction conditions (entry 12) does not result in product formation either. Using 2-methylindole (entry 11) as a starting material results in the formation of the C3 hydroxyalkylated product in quantitative yield. While the latter observation can be explained by the activating effect of the methyl-group, the lack of reactivity of 2-*tert*-butylindole can be interpreted by the steric strain imposed by the bulky substituent overcoming its activating effect and preventing the reaction from taking place at either of the N1- and C3-positions. Blocking the C3 position on the indole leads to a selective transformation yielding the N-alkylated product even with bulky substituents such as *tert*-butyl (entry 8).

Conclusions

N-Hydroxyalkylated indoles were synthesized selectively using trifluoroacetaldehyde methylhemiacetal as the hydroxyalkylating agent. The reactions can be performed under mild conditions without the use of a strong base or a metal catalyst. The reaction can be performed with a variety of substituted indoles and the selectivity can be strongly influenced by the choice of the solvent. DMSO was found to act as a strong directing solvent and reactions carried out in DMSO yielded the chemoselective formation of the N-substituted products.

While the yields are only moderate at this level of the research, the results described clearly indicate that the method allows for the preparation of the target compounds via a simple, one-step method that is reasonably more environmentally benign than the known literature procedures. In addition, the reaction did not yield other byproducts, thus the unreacted starting material could be recovered and recycled.

Experimental Section

General. All reagents used were obtained from commercial sources (Alfa Aesar, Sigma-Aldrich) and used as received. Reactions were monitored by gas chromatography – mass spectrometry (GC-MS) with an Agilent 6850 gas chromatograph-5973 mass spectrometer system (70 eV electron impact ionization) using a 30 m long DB-5 type column (J&W Scientific). Microwave heating was performed in a CEM-Discover microwave reactor using closed-vessel setting. Product separation was performed by preparative thin-layer chromatography using Merck silica gel PF_{254} containing gypsum binder. Nuclear Magnetic Resonance (NMR) spectra were recorded on an Agilent MR400DD2 spectrometer, with a multinuclear probe with two RF channels and variable temperature capability. The measurements were carried out at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C

NMR) and 376 MHz (^{19}F NMR). The NMR signals are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or the residual signal of the solvent. The high resolution mass spectrometry analysis (HR-MS) was performed using a AB SCIEX Qtrap 5500 instrument in negative ion mode.

General reaction conditions. Indole (0.35 mmol, 1 eq.), trifluoroacetaldehyde methylhemiacetal (270 µL, 7 eq.), triethylamine (7 µL, 10 mol %), and DMSO (0.5 mL) were mixed together in a microwave vial (10 mL). The solution was irradiated in the microwave reactor at 80˚C for 45 min. After cooling to room temperature the reaction mixture was diluted with 2 mL of dichloromethane and washed with water (3x 5 mL). The solvent was evaporated under vacuum and the crude product was purified by preparative thin layer chromatography.

2,2,2-trifluoro-1-(1-*H*-indol-1-yl)ethanol (Table 1, entry 1). MS (EI) m/z 215 (54%, M^+), 146 (41%), 118 (85%), 117 (100%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): *δ* (*ppm*) 7.66 (d, *J* 8.4 Hz, 1H), 7.58 (dt, *J* 8.0, 1.2 Hz, 1H), 7.47 (d, *J* 3.2 Hz, 1H), 7.16-7.22 (m, 1H), 7.06-7.12 (m, 1H), 6.55-6.59 (m, 1H), 4.04 (q, *J* 6.8 Hz, 1H), 2.94 (br s, 1H); ^{13}C NMR (101 MHz, $(CD_3)_2CO$): *δ* (*ppm*) 137.0, 130.0, 126.0, 124.3, 123.0, 121.7, 121.3, 111.3, 104.6, 77.0 (q, *J* 36.3 Hz); ^{19}F NMR (376 MHz, $(CD_3)_2CO$): *δ* (*ppm*) -81.05 (d, *J* 5.2 Hz). HR-MS (ESI-TOF) (M-1): calcd. for $C_{10}H_7F_3NO$, 214.0480; found: 214.0051.

2,2,2-trifluoro-1-(5-methyl-1*H*-indol-1-yl)ethan-1-ol (Table 1, entry 2). MS (EI) m/z 229 (68%, M^+), 160 (32%), 131(71%), 130 (100%); ^{1}H NMR (400 MHz,$(CD_3)_2SO$): *δ* (*ppm*),), 8.24 (d, *J* 4.3 Hz, 1H), 7.59 (d, J= 6.1 Hz, 1H), 7.41 (t, *J* 4.3 Hz, 1H), 7.34(m, 1H), 6.98 (dd, *J* 8.4, 1.7 Hz, 1H), 6.85 (d, J 5.5Hz, 1H), 5.74 (s, 1H), 2.35 (s, 3H) ; **^{13}C NMR** (100 MHz, solvent): *δ* (*ppm*) 133.1, 129.1, 128.8, 128.1, 127.0, 125.5, 121.0, 111.6, 104.3, 54.4 ; **^{19}F NMR** (376 MHz, solvent): *δ* (*ppm*) -77.99 (d, *J* 3.5 Hz). HR-MS (ESI-TOF) (M-1): calcd. for $C_{11}H_{11}F_3NO$, 228.0636; found: 228.0009.

2,2,2-trifluoro-1-(5-methoxy-1*H*-indol-1-yl)ethan-1-ol (Table 1, entry 4).[6] MS (EI) m/z 245 (100%, M^+), 176 (32%), 147 (65%), 132 (58%), 104 (50%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 8.28 (s, 1H), 7.63 (m, 1H), 7.44 (d, J 5.3 Hz, 1H), 7.07 (d, J 4.8 Hz, 1H), 6.81 (dd, J 9.0, 2.5 Hz, 1H),6.55(d, J 6.6 Hz, 1H), 6.48 (dd, J 3.4, 0.5, 1H), 3.74 (s, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 154.0, 136.1, 133.9, 129.7, 124.3, 112.3, 110.5, 109.0, 104.6, 102.2, 68.9 ; **^{19}F NMR** (376 MHz, $(CD_3)_2SO$): *δ* (*ppm*) -79.43 (d, J 5.2 Hz). Known compound. Spectral data are agreement with ref 6.

1-(2,2,2-trifluoro-1-hydroxyethyl)-1*H*-indol-5-ol (Table 1, entry 5). MS (EI) m/z 231 (74% M^+), 133 (100%), 104 (37%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 7.80 (d, *J* 5.5Hz, 1H), 7.56 (d, *J* 5.1 Hz, 1H), 6.99 (d, *J* 6.6 Hz, 1H), 6.61 (t, J 5.5 Hz, 1H), 6.59 (t, J 5.1 Hz, 1H) 6.52 (d, J 6.6Hz, 1H), 5.5 (s, 1H), 4.0 (s, 1H);**^{13}C NMR** (100 MHz, $(CD_3)_2SO$): *δ* (*ppm*): δ (ppm) 152.3, 131.5, 127.2, 124.4, 121.6, 118.8, 104.9, 103.4, 101.3, 86.4; **^{19}F NMR** (376 MHz, $(CD_3)_2SO$): *δ* (*ppm*) -82.71 (d, *J* 4.2 Hz). HR-MS (ESI-TOF) (M-1): calcd. for $C_{10}H_9F_3NO_2$, 230.0429; found: 230.0340.

1-(4,6-dimethoxy-3-methyl-1*H*-indol-1-yl)-2,2,2-trifluoroethan-1-ol (Table 1, entry 7). MS (EI) m/z 289 (45%, M^+), 191 (100%), 176 (99%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): 8.08 (d, *J* 4.5 Hz, 1H), 6.91 (s, 1H), 6.86 (d, *J* 1.6 Hz, 1H), 6.44 – 6.40 (m, 1H), 6.18 (d, *J* 1.6 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.37 (s, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 157.6, 155.0, 138.7, 125.2, 120.1, 112.8, 112.2, 94.5, 92.2, 92.0, 75.3, 55.6; **^{19}F NMR** (376 MHz, $(CD_3)_2SO$): *δ* (*ppm*) -79.21 (d, *J* 5.1 Hz). HR-MS (ESI-TOF) (M-1): calcd. for $C_{13}H_{13}F_3NO_3$, 288.0848; found: 288.0938.

1-(3-(tert-butyl)-1*H*-indol-1-yl)-2,2,2-trifluoroethan-1-ol (Table 1, entry 8). MS (EI) m/z 271 (18%, M^+), 256 (55%), 173 (32%), 158 (100%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 8.17 (d, *J* 5.6Hz, 1H), 7.74 (d, *J* 7.4Hz, 1 H), 7.4 (d, *J* 7.4 Hz, 1 H), 7.05 (m, 1 H), 6.51 (m, 1 H), 5.75 (s, 1H), 5.04 (m, 1H), 2.53 (s, 9H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 136.7, 128.4, 125.7, 121.7, 120.8, 119.2, 118.7, 109.1, 43.0, 36.3; ^{19}F NMR (376 MHz,

$(CD_3)_2SO$): *δ* (*ppm*) -79.14 (d, *J* 4.8 Hz). HR-MS (ESI-TOF) (M-1): calcd. for $C_{14}H_{15}F_3NO$, 270.1106; found: 270.1074.

1-(2,3-dimethyl-1*H*-indol-1-yl)-2,2,2-trifluoroethan-1-ol (Table 1, entry 9). MS (EI) m/z 243 (30%, M^+), 145 (70%), 144 (100%), 130 (56%); ^{1}H NMR (400 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 8.43 (d, *J* 7.2Hz, 1H), 8.13 (t, *J* 7.2Hz, 1H), 8.09 (d, *J* 7.2 Hz, 1H), 8.07 (t, *J* 3.9Hz, 1H), 6.22 (q, *J* 4.6Hz, 1H), 3.20 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): *δ* (*ppm*) 135.2, 132.1, 129.6, 121.1, 119.9, 118.2, 110.7, 105.5, 97.8, 76.6 (q, J 35.1 Hz), 10.7, 8.5; ^{19}F NMR (376 MHz, $(CD_3)_2SO$): *δ* (*ppm*) -84.34 (d, *J* 4.6 Hz). HR-MS (ESI-TOF) (M-1): calcd. for $C_{12}H_{11}F_3NO$, 242.0793; found: 242.0028.

Synthesis of 3-*t*-butyl indole. Indole (100 mg), K-10 montmorillonite (250 mg) and 2 mL of *tert*-butanol were mixed together in a microwave vial (10 mL). The solution was irradiated in the microwave reactor at 100˚C for 60 min. After cooling to room temperature the reaction mixture was diluted with 2 mL of dichloromethane and washed with water (5 mL). The solvent was evaporated under vacuum and the crude product was purified by preparative thin layer chromatography.

3-(tertbutyl)-indole[42] MS (EI) m/z 173 (31%, M^+) 158 (100%); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ (ppm) 10.70 (s, 1H), 7.67 (d, *J* 8.0 Hz, 1H), 7.32 (d, *J* 8.0 Hz, 1H), 7.06 – 6.87 (m, 3H), 1.38 (s, 9H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): δ (ppm) 137.7, 125.9, 124.9, 120.9, 120.8, 120.5, 118.3, 112.4, 31.6, 31.2 (3C). Known compound. Spectral data are agreement with ref. 42.

Acknowledgements

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