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Regioselective Hydrodebromination of Polybrominated Indoles

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The mixture of sodium borohydride and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in combination with a palladium catalyst is a mild and efficient system for the regioselective hydrodebromination of polybrominated indoles with both *N*-donating and *N*-withdrawing substituents [*N*-methyl- and *N*-(methoxycarbonyl)indoles, respectively].

Introduction

Indoles bearing bromine substituents are valuable synthetic intermediates, as well as important units in many biologically active alkaloids and potential candidates for pharmaceuticals.[1,2] Moreover, brominated indoles have been isolated from a range of marine sources.[3] As a result, considerable efforts have been devoted to the bromination of indoles, which has resulted in a number of convenient approaches.[4]

Regioselectively substituted bromoindoles are generally prepared by selective sequential bromination reactions. However, this synthetic approach does not allow access to all possible regioisomers. We considered that a possible solution to this problem could be to reverse the process. In other words, the heterocyclic ring could be polybrominated, and then the bromine atoms could be progressively removed by selective hydrodebromination. To achieve this goal a process for the metal-catalyzed hydrodehalogenation of halogenated heterocycles[5] is needed.

There are only a few reports about regioselective metal-catalyzed reactions concerning *N*-substituted polybrominated indoles. All these reactions are cross-coupling reactions that employ palladium complexes as catalysts and involve regioselective discrimination between the 2- and 3-position of the indole ring. Thus, Gribble and Liu reported that all attempts to prepare monocoupling products or unsymmetrical 2,3-diarylindole derivatives, which contain two different aryl groups, by Suzuki–Miyaura reactions of *N*-phenylsulfonyl-substituted 2,3-dibromoindole were unsuccessful.[6] Recently, Langer described that the Heck reaction of 2,3-dibromo-*N*-methylindole proceeded without selectivity,[7] whereas the Suzuki–Miyaura reactions on these substrates occurred regioselectively to afford unsymmetrical 2,3-diarylindoles.[4d] Only one example that concerns the competitive substitution between other differently substituted bromoindoles has been reported. On that occasion Ohta and co-workers demonstrated that the first attack in Suzuki–Miyaura reactions of *N*-*tert*-butyldimethylsilyl-protected 3,6-dibromoindole occurred at C-6 to give 6-aryl-3-bromo-*N*-(*tert*-butyldimethylsilyl)indoles.[8]

From these results it appears that the regioselectivity depends on both the nitrogen protective group and the type of reaction. The key step in metal-catalyzed coupling reactions is the oxidative addition of palladium, which usually occurs first at the most electron-deficient carbon atom.[9] In 2,3-dibromo-*N*-methylindole the electron-donating character of the *N*-methyl substituent increases the electronic density on C-3, thus favoring site-selective transformations at C-2. However, the strong electron-withdrawing effect of the sulfonyl group causes increased reactivity of both C-2 and C-3 of the indole moiety, thus generating a less pronounced difference between their electronic characters.

Based on this information we decided to examine the regioselective hydrodebromination of polybrominated indoles by a metal-catalyzed process. We recently demonstrated that a sodium borohydride/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine ($NaBH_4$/TMEDA) mixture as the hydride source in combination with a palladium catalyst is a mild and efficient system for the hydrodehalogenation of halogenated heterocycles.[10] The good results obtained in that study prompted us to assess this reducing system for the synthesis of regioselectively substituted bromoindoles, which resulted in the regioselective removal of bromine substituents from polybrominated indoles with both *N*-donating and *N*-withdrawing substituents, namely *N*-methyl- and *N*-(methoxycarbonyl)indoles, respectively.

Results and Discussion

To begin with we examined the reduction of polybrominated *N*-(methoxycarbonyl)indoles, which were easily avail-

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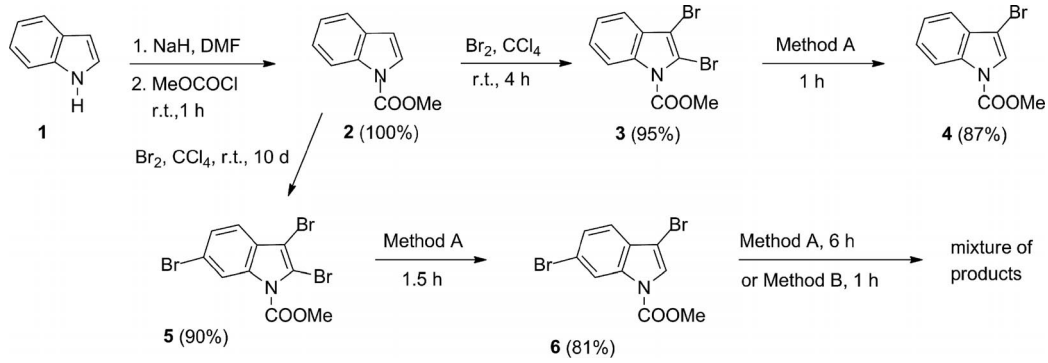
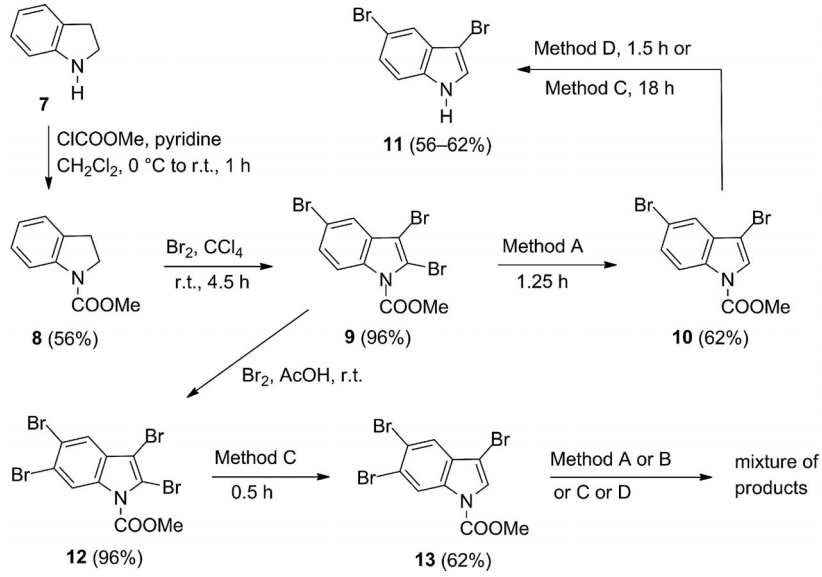


Scheme 1. Method A: Heterocycle (0.66 mmol), $Pd(OAc)_2$ (5.0 mol-%), PPh_3 (20.0 mol-%), $NaBH_4$ (3.4 equiv.), TMEDA (3.4 equiv.), THF (13.2 mL) at room temp. Method B: Heterocycle (0.66 mmol), $PdCl_2$(dppf) (5.0 mol-%), $NaBH_4$ (3.4 equiv.), TMEDA (3.4 equiv.), THF (13.2 mL) at room temp. DMF = dimethylformamide.

able in high yields from *N*-(methoxycarbonyl)indole (**2**)[11] (Scheme 1). The first reduction was of methyl 2,3-dibromoindole-1-carboxylate (**3**) that was prepared by bromination of indole **1** (95% yield).[4e] After careful examination of various reaction conditions, we concluded that the best results for hydrodehalogenation were achieved by using $Pd(OAc)_2$ (5 mol-%) with PPh_3 (20 mol-%) in combination with $NaBH_4$ (3.4 equiv.) and TMEDA in tetrahydrofuran (THF) at room temperature (Method A). Under these reaction conditions selective removal of the 2-bromine atom from **3** occurred within 1 h to afford methyl 3-bromo-1*H*-indole-1-carboxylate (**4**) in 87% yield (Scheme 1). Next we examined the hydrodebromination of methyl 2,3,6-tribromo-1*H*-indole-1-carboxylate (**5**) that was readily obtained from **2** (90%).[4e] With Method A the 2-bromine atom from indole **5** was selectively removed to give, after 1.5 h, 3,6-dibromo analogue **6** in 81% yield (Scheme 1). Further reduction of **6** was problematic (Scheme 1). In fact, when Method A was employed, the disappearance of starting material occurred after 6 h as determined by TLC, but led to a complex mixture of products. The ^{1}H NMR spectrum of this mixture showed signals corresponding to both methyl 3-bromo- and 5-bromo-1*H*-indole-1-carboxylate and indolic products derived from *N*-carbodemethoxylation. When $Pd(OAc)_2/PPh_3$ was replaced by the more active catalyst $PdCl_2$[1,1′-bis(diphenylphosphanyl)ferrocene] (dppf; 5 mol-%) in combination with 3.4 equiv. of the reducing system (Method B), complete conversion occurred



Scheme 2. Method A: Heterocycle (0.66 mmol), $Pd(OAc)_2$ (5.0 mol-%), PPh_3 (20.0 mol-%), $NaBH_4$ (3.4 equiv.), TMEDA (3.4 equiv.), THF (13.2 mL) at room temp. Method B: Heterocycle (0.66 mmol), $PdCl_2$(dppf) (5.0 mol-%), $NaBH_4$ (3.4 equiv.), TMEDA (3.4 equiv.), THF (13.2 mL) at room temp. Method C: Heterocycle (0.66 mmol), $Pd(OAc)_2$ (5.0 mol-%), PPh_3 (20.0 mol-%), $NaBH_4$ (2.0 equiv.), TMEDA (2.0 equiv.), THF (13.2 mL) at room temp. Method D: Heterocycle (0.66 mmol), $PdCl_2$(dppf) (5.0 mol-%), $NaBH_4$ (2.0 equiv.), TMEDA (2.0 equiv.), THF (13.2 mL) at room temp.

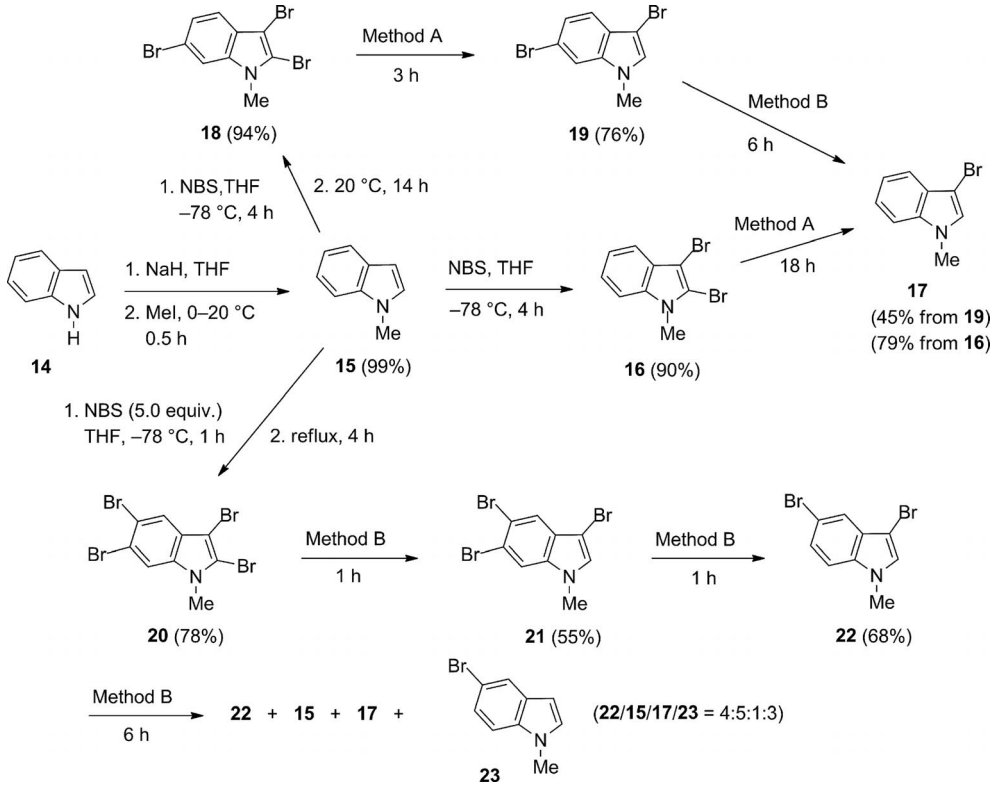
after 1 h, but the result was the same and indicated no selectivity in this reduction.

Next, the reduction of polybrominated *N*-(methoxycarbonyl)indoles was investigated, which are easily available in high yields from *N*-(methoxycarbonyl)indoline (**8**) obtained in turn from indoline (**7**) (Scheme 2). The first one to be examined was methyl 2,3,5-tribromo-1*H*-indole-1-carboxylate (**9**)[4e] (Scheme 2). Surprisingly, the reduction of this indole was less satisfactory than that of isomer **5** with the bromine atom in 6-position of the benzene condensed ring. In fact, the removal of the 2-bromine atom was obtained after 1.25 h reaction time with Method A, but expected methyl 3,5-dibromo-1*H*-indole-1-carboxylate (**10**) was isolated in lower yield (62%). After many reaction permutations (which included the amount of $NaBH_4$/TMEDA and the reaction temperature), no improvement in the yield and selectivity was found. Thus, the use of $NaBH_4$/TMEDA (1.2 equiv.) gave only partial conversion of the starting material (about 50%) after 24 h both at room temperature and 50 °C. Moreover, by performing the reduction with $NaBH_4$/TMEDA (2 equiv.) for 2 h, dibromo compound **10** was isolated in about 50% yield.

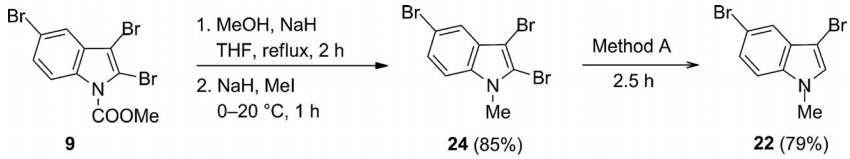
Next, we devoted our attention to more demanding tetrabromoindole **12**[4e] that was obtained by bromination of tribromoindole **9** (Scheme 2). With this indole the best compromise between yield and selectivity was obtained by using $NaBH_4$/TMEDA (2 equiv.) for 30 min. Thus, 3,5,6-tribromo-1-methyl-1*H*-indole (**13**)[4e] was formed in 62% yield. Further reduction of **13** occurred with no selectivity. A mixture of products that contained various brominated *N*-(methoxycarbonyl)indoles and bromoindoles derived from the *N*-carbodemethoxylation reaction was obtained.

The final reduction in this series was that of 3,5-dibromo-1*H*-indole-1-carboxylate (**10**)[4e] that was performed with $PdCl_2$(dppf) (5 mol-%) in combination with 2.0 equiv. of the reducing system (Method D). Under these reaction conditions disappearance of the starting material occurred after 1.5 h as determined by TLC analysis, but the major isolated product was 3,5-dibromo-1*H*-indole (**11**;[4e] 56% yield), derived from *N*-carbodemethoxylation of **10**. By employing $Pd(OAc)_2$/PPh_3 (Method C) a longer reaction time was required (18 h), but a similar final result was obtained with **11**, which was isolated in 62% yield.

The next *N*-substituted indoles to be examined were polybrominated *N*-methylindoles, prepared by selective bromination of *N*-methylindole (Scheme 3). The reduction of 2,3-dibromo-1-methyl-1*H*-indole (**16**)[7] was successfully accomplished with Method A, which afforded 3-bromo-1-methyl-1*H*-indole (**17**)[12] in 79% yield[10] (Scheme 3). The reduction of **16** was slowest (18 h) relative to methyl 2,3-dibromoindole-1-carboxylate (**3**; 1 h), which confirms the lower reactivity of C-2 with *N*-donating substituents on the



Scheme 3. Method A: Heterocycle (0.66 mmol), $Pd(OAc)_2$ (5.0 mol-%), PPh_3 (20.0 mol-%), $NaBH_4$ (3.4 equiv.), TMEDA (3.4 equiv.), THF (13.2 mL) at room temp. Method B: Heterocycle (0.66 mmol), $PdCl_2$(dppf) (5.0 mol-%), $NaBH_4$ (3.4 equiv.), TMEDA 3.4 equiv.), THF (13.2 mL) at room temp. NBS = *N*-bromosuccinimide..



Scheme 4. Method A: Heterocycle (0.66 mmol), $Pd(OAc)_2$ (5.0 mol-%), PPh_3 (20.0 mol-%), $NaBH_4$ (3.4 equiv.), TMEDA (3.4 equiv.), THF (13.2 mL) at room temp.

indole ring. Unexpectedly, the reduction of 2,3,6-tribromo-1-methylindole (**18**)[13] was faster than **16**, and under Method A the removal of the 2-bromine atom occurred selectively within 3 h to give 3,6-dibromo-1-methylindole (**19**) in 76% yield.

For the hydrodebromination of 3,6-dibromoindole **19** the use of $Pd(OAc)_2/PPh_3$ as catalyst was unsatisfactory; thus, the more active catalyst $PdCl_2$(dppf) was employed (Method B). Under these reaction conditions the disappearance of the starting material was observed within 6 h, which gave a complex mixture of products from which 3-bromo-1-methylindole (**17**) was isolated in 45% yield.

We then turned our efforts to 2,3,5,6-tetrabromo-1-methyl-1*H*-indole (**20**);[14] the reduction was most challenging and required a number of experiments. With Method A, complete conversion of **20** was achieved within 1 h, but the selectivity was very low. The reaction product was a mixture of products that contained 3,5,6-tribromo-1-methyl-1*H*-indole (**21**;[4b] 66%), 3,5-dibromo-1-methyl-1*H*-indole (**22**; 31%) and 5,6-dibromo-1-methyl-1*H*-indole (3%)[15] in a molar ratio of about 22:10:1. When the amount of $NaBH_4$/TMEDA was reduced, the ratio **21/22** increased significantly from 2.2:1 to 4.6:1 (by using 1.2 equiv.), but the conversion was incomplete. Also, the use of the catalytic system formed by $Pd_2(dba)_3$/XantPhos (2.5 and 5 mol-%, respectively) with $NaBH_4$/TMEDA (3.4 equiv.) was unsatisfactory and gave **21** and **22** in a 1.4:1 ratio. Surprisingly, when $PdCl_2$(dppf) was used as catalyst (Method B), complete conversion was observed after 1 h, and the **21/22** ratio increased dramatically to 13:1 and afforded **21** in 55% isolated yield. On this basis, tribromoindole **21** was reduced under Method B and led to dibromoindole **22** in 68% yield after 1 h.

The hydrodebromination in this series was completed through the examination of 3,5-dibromo-1-methyl-1*H*-indole (**22**). By carrying out the reduction by using $PdCl_2$(dppf) (Method B) until disappearance of the starting material (18 h) as determined by TLC, the major observed product was 1-methyl-1*H*-indole (**15**). However, by stopping the reaction after 6 h, a mixture which consisted of starting indole **22**, and products **15**, 3-bromo-1-methyl-1*H*-indole (**17**) and 5-bromo-1-methyl-1*H*-indole (**23**),[6] in a 4:5:1:3 ratio was obtained. Although some selectivity in favor of bromoindole **23** (**23/17** = 3:1) has been achieved in this reaction, further fast reduction of the initially formed monobromoindoles to fully debrominated indole **15** makes this hydrodebromination impractical.

Finally, we examined the selective hydrodebromination of 2,3,5-tribromo-1-methylindole (**24**), which was conveniently prepared in two steps from parent tribromoindole **9** according to a well-described procedure (Scheme 4).[4e] For this reduction the use of Method A was effective, and dibromoindole **22** was obtained in 79% yield after 1 h.

Conclusions

The use of sodium $NaBH_4$/TMEDA in combination with a palladium catalyst is a mild and efficient system for the regioselective hydrodebromination of polybrominated indoles with both *N*-donating and *N*-withdrawing substituents [*N*-methyl and *N*-(methoxycarbonyl)indoles, respectively]. The results obtained in this study show that the polybromination followed by selective hydrodebromination is a valuable procedure, which should be taken into account for the selective synthesis of complex bromoindole-containing molecules.

Experimental Section

General Information: All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^1H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Indoline (**7**), indole (**14**) and 1-methyl-1*H*-indole (**15**) were commercial compounds. Methyl-1*H*-indole-1-carboxylate (**2**),[11] 2,3-dibromoindole-1-carboxylate (**3**),[4e] methyl 2,3,6-tribromo-1*H*-indole-1-carboxylate (**5**),[4c] *N*-(methoxycarbonyl)indoline (**8**),[17] methyl 2,3,5-tribromo-1*H*-indole-1-carboxylate (**9**),[4e] methyl 2,3,5,6-tetrabromo-1*H*-indole-1-carboxylate (**12**),[4e] 2,3-dibromo-1-methyl-1*H*-indole (**16**),[7] 2,3,6-tribromo-1-methyl-1*H*-indole (**18**)[13] and 2,3,5,6-tetrabromo-1-methyl-1*H*-indole (**20**)[14] were prepared according to reported procedures. Analytical and spectral data of

products methyl 3,5-dibromo-1*H*-indole-1-carboxylate (**12**),[4e] 3,5-dibromo-1*H*-indole (**11**),[4e] 3-bromo-1-methyl-1*H*-indole (**17**),[12] 3,5,6-tribromo-1-methyl-1*H*-indole (**21**),[4b] 5-bromo-1-methyl-1*H*-indole (**23**)[16] and 5,6-dibromo-1-methyl-1*H*-indole[15] were identical to those reported in the literature.

General Procedures for the Hydrodebromination of Polybrominated Indoles

Method A: Anhydrous THF (13.2 mL) was degassed by bubbling argon for a few minutes, then $Pd(OAc)_2$ (7.2 mg, 0.033 mmol, 5 mol-%) and PPh_3 (17.7 mg, 1.132 mmol, 20 mol-%) were added, and the resulting mixture was stirred at room temperature for 30 min. The halogenated heterocycle (0.66 mmol), TMEDA (0.260 g, 2.24 mmol, 3.4 equiv.) and finally $NaBH_4$ (85.0 mg, 2.24 mmol, 3.4 equiv.) were introduced in sequence. The mixture was stirred at room temperature under argon for the proper time. The residue was taken up in brine and extracted with ethyl acetate. The organic phase was separated, dried, the solvent was evaporated, and the residue was purified by flash chromatography (mixtures of petroleum ether/ethyl acetate) to give pure bromoindoles.

Method B: A mixture of the halogenated heterocycle (0.66 mmol) in anhydrous THF (13.2 mL) was degassed by bubbling argon for a few minutes. Then, $PdCl_2(dppf)\cdot CH_2Cl_2$ (27.0 mg, 0.033 mmol, 5.0 mol-%), TMEDA (0.260 g, 2.24 mmol, 3.4 equiv.) and finally $NaBH_4$ (85.0 mg, 2.24 mmol, 3.4 equiv.) were introduced in sequence. The mixture was stirred at room temperature under argon for the specific time and then worked up as described above.

Method C: The procedure of Method A was applied except that TMEDA (0.133 g, 1.32 mmol, 2.0 equiv.) and $NaBH_4$ (50.0 mg, 1.32 mmol, 2.0 equiv.) were used.

Method D: The procedure of Method B was applied except that TMEDA (0.133 g, 1.32 mmol, 2.0 equiv.) and $NaBH_4$ (50.0 mg, 1.32 mmol, 2.0 equiv.) were used.

Methyl 3-Bromo-1*H*-indole-1-carboxylate (4): Oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.14 (d, J = 0.8 Hz, 1 H), 7.63 (s, 1 H), 7.51 (d, J = 7.6 Hz, 1 H), 7.37 (dt, J = 7.6, 1.2 Hz, 1 H), 7.31 (dt, J = 7.6, 1.2 Hz, 1 H), 4.01 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.6, 134.5, 129.3, 125.6, 124.3, 123.5, 119.5, 115.0, 98.8, 54.0 ppm. $C_{10}H_8BrNO_2$ (254.08): calcd. C 47.27, H 3.17, N 5.51; found C 47.65, H 3.13, N 5.56.

Methyl 3,6-Dibromo-1*H*-indole-1-carboxylate (6): White solid. M.p. 106–107 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 7.60 (s, 1 H), 7.43 (dd, J = 8.4, 1.6 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 1 H), 4.05 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.3, 135.0, 128.3, 126.9, 124.8, 120.8, 119.6, 118.2, 98.6, 54.3 ppm. $C_{10}H_7Br_2NO_2$ (332.98): calcd. C 36.07, H 2.12, N 4.21; found C 36.35, H 2.15, N 4.18.

Methyl 3,5,6-Tribromo-1*H*-indole-1-carboxylate (13): White solid. M.p. 134–136 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.42 (s, 1 H), 7.72 (s, 1 H), 7.60 (s, 1 H), 4.06 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 150.0, 133.7, 129.9, 125.8, 123.9, 121.6, 119.9, 119.5, 97.3, 54.5 ppm. $C_{10}H_6Br_3NO_2$ (411.87): calcd. C 29.16, H 1.47, N 3.40; found C 29.44, H 1.43, N 3.45.

3,6-Dibromo-1-methyl-1*H*-indole (19): Oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.43 (d, J = 1.6 Hz, 1 H), 7.31 (d, J = 8.4 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 1 H, 0.8 Hz), 6.99 (s, 1 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 136.9, 128.3, 126.2, 123.4, 120.6, 116.4, 112.5, 89.6, 33.1 ppm. $C_9H_7Br_2N$ (288.97): calcd. C 37.41, H 2.44, N 4.85; found C 37.88, H 2.41, N 4.81.

3,5-Dibromo-1-methyl-1*H*-indole (22): White solid. M.p. 59–60 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.67 (d, J = 2.0 Hz, 1 H), 7.31 (dd, J = 8.8, 2.0 Hz, 1 H), 7.13 (d, J = 8.8 Hz, 1 H), 7.00 (s, 1 H), 3.72 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 134.9, 128.9, 128.8, 125.5, 121.8, 113.5, 111.0, 88.5, 33.2 ppm. $C_9H_7Br_2N$ (288.97): calcd. C 37.41, H 2.44, N 4.85; found C 37.22, H 2.48, N 4.89.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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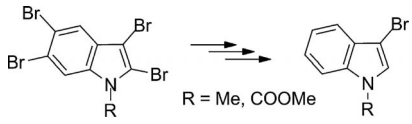
The mixture of $NaBH_4$/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine in combination with a palladium catalyst is a mild and efficient system for the regioselective hydrodebromination of polybrominated indoles with both *N*-donating and *N*-withdrawing substituents [*N*-methyl- and *N*-(methoxycarbonyl)indoles].



Keywords: Synthetic methods / Nitrogen heterocycles / Bromine / Reduction / Palladium

