Indole Synthesis

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Fischer Indole Synthesis with Organozinc Reagents**

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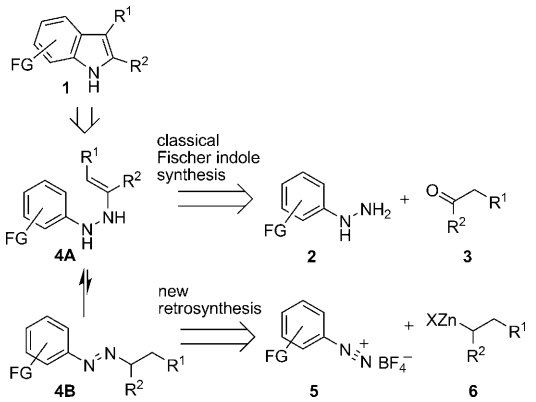
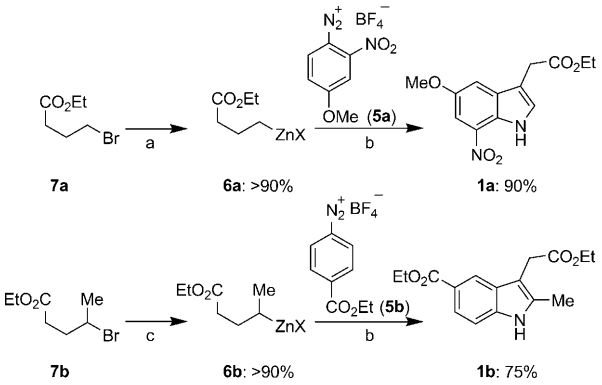
Indoles (**1**) are an important class of N-heterocycles present in many natural products and pharmaceuticals.[1] Their synthesis presents a great challenge, and a range of new synthetic approaches to indoles have been reported in recent years.[2] Metal-catalyzed or -mediated methods have proved to be especially useful.[3] The classical Fischer indole synthesis[4] starting from aryl hydrazines[5,6] **2** and ketones **3** is still extensively used, although this method suffers from several drawbacks.[7,8] The highly acidic reaction conditions combined with moderate functional-group tolerance and the poor availability of aryl hydrazines **2** strongly limit this method. Furthermore, unsymmetrical ketones result in regioisomeric mixtures of indoles.[7] Since organozinc reagents are readily available, inexpensive, and compatible with numerous functional groups,[9] we envisioned a new retrosynthetic pathway for the Fischer indole synthesis, in which the key intermediates **4A** and **4B** would not be obtained from **2** and **3**, but rather from the reaction of readily available aryldiazonium salts of type **5** and functionalized alkylzinc reagents of type **6** (Scheme 1).[10,11]



Scheme 1. Alternative retrosynthetic analysis of the Fischer indole synthesis. FG = functional group.

This approach proved to be very fruitful, since many functional groups such as ester, cyano, nitro, and keto groups are tolerated, and unexpectedly the issue of regioselectivity mentioned above is resolved. Thus, the reaction of ethyl 4-bromobutanoate (**7a**, 1.1 equiv) with zinc dust (2 equiv), $ZnBr_2$ (2 equiv),[12] and LiCl (1.1 equiv) in THF produces the expected alkylzinc halide **6a** in 90% yield (50 °C, 1 h).[13] The addition of a solution of **6a** (1 equiv) in THF to the functionalized aryldiazonium tetrafluoroborate **5a** (1.25 equiv, −60 °C to 25 °C) is thought to produce an azo compound of type **4B**, which isomerizes to the unsaturated hydrazine **4A**. Me_3SiCl (1 equiv) is added and the reaction mixture is heated using microwave irradiation (125 °C, 90 min) to furnish after standard workup the polyfunctional indole **1a** in 90% yield.[14] Similarly, a secondary alkylzinc halide such as **6b** (90% yield) was prepared from the corresponding secondary alkyl bromide **7b** (1.1 equiv; Zn, LiCl, $ZnBr_2$, 50 °C, 12 h). Its addition to ester-substituted diazonium salt **5b**[10a,12] at −60 °C to 25 °C followed by addition of Me_3SiCl and microwave irradiation (125 °C, 90 min) furnished *regioselectively* the trisubstituted indole **1b** in 75% yield (Scheme 2).



Scheme 2. Preparation of polyfunctional indoles **1a** and **1b**. a) Zn (2 equiv), LiCl (1.1 equiv), $ZnBr_2$ (2 equiv), THF, 50 °C, 1 h; b) −60 °C to 25 °C; then Me_3SiCl (1 equiv), 125 °C, 90 min, microwave irradiation; c) Zn (2 equiv), LiCl (1.1 equiv), $ZnBr_2$ (2 equiv), THF, 50 °C, 12 h.

The alkylzinc reagent **6b** also reacted with substituted aryldiazonium salts **5a**,**c**,**d** providing the functionalized indole derivatives **1c**–**e**) in 65–73% yield (Table 1, entries 1–3). By applying the same procedure to *s*BuZnBr[12] (**6c**) and to the functionalized aryldiazonium tetrafluoroborates **5a**–**g**[10a,12,15] we obtained the polyfunctional 2,3-dimethylindoles **1f**–**l**

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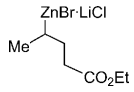
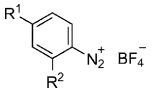
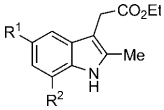
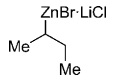
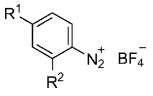
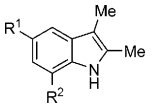
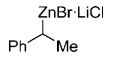
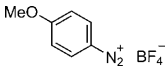
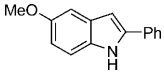
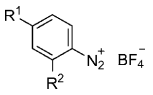
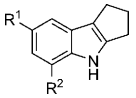
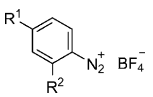
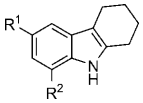
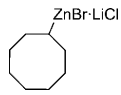
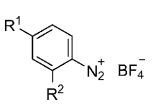
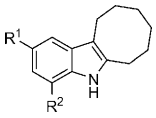
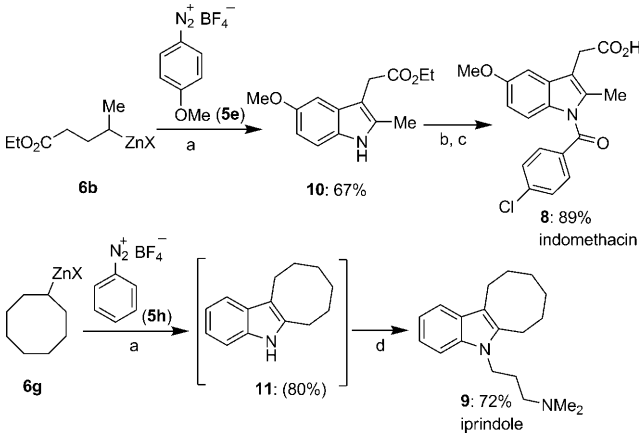
Table 1: Preparation of polyfunctional indoles **1** by the addition of alkylzinc reagents **6** to aryldiazonium tetrafluoroborates **5**.

Entry	Zinc reagent	Aryldiazonium salt	Product[a]
			
1	**6b**	**5a**: R^1 = OMe, R^2 = NO_2	**1c**: 69%
2	**6b**	**5c**: R^1 = Ac, R^2 = H	**1d**: 73%
3	**6b**	**5d**: R^1 = OPiv, R^2 = H	**1e**: 65%
			
4	**6c**	**5a**: R^1 = OMe, R^2 = NO_2	**1f**: 81%[b]
5	**6c**	**5b**: R^1 = CO_2Et, R^2 = H	**1g**: 75%
6	**6c**	**5d**: R^1 = OPiv, R^2 = H	**1h**: 78%[b]
7	**6c**	**5e**: R^1 = OMe, R^2 = H	**1i**: 84%[b]
8	**6c**	**5c**: R^1 = Ac, R^2 = H	**1j**: 81%
9	**6c**	**5f**: R^1 = I, R_2 = H	**1k**: 85%
10	**6c**	**5g**: R^1 = CN, R^2 = H	**1l**: 78%
			
11	**6d**	**5e**	**1m**: 46%
			
12	**6e**	**5a**: R^1 = OMe, R^2 = NO_2	**1n**: 68%
13	**6e**	**5b**: R^1 = CO_2Et, R^2 = H	**1o**: 78%
			
14	**6f**	**5a**: R^1 = OMe, R^2 = NO_2	**1p**: 89%[b]
15	**6f**	**5b**: R^1 = CO_2Et, R^2 = H	**1q**: 81%
16	**6f**	**5g**: R^1 = CN, R^2 = H	**1r**: 81%
17	**6f**	**5c**: R^1 = Ac, R^2 = H	**1s**: 88%
			
18	**6g**	**5a**: R^1 = OMe, R^2 = NO_2	**1t**: 86%[b]
19	**6g**	**5b**: R^1 = CO_2Et, R^2 = H	**1u**: 89%
20	**6g**	**5g**: R^1 = CN, R^2 = H	**1v**: 92%

[a] Yield of isolated product estimated to be analytically pure product by ^{1}H NMR spectroscopy. [b] No Me_3SiCl was added. Piv = pivaloyl.

regioselectively in 78–85% yield (Table 1, entries 4–10). None of the regioisomeric 3-ethylindoles were observed. The benzylic zinc reagent **6d**[16] reacted with 4-methoxybenzenediazonium tetrafluoroborate (**5e**) providing, after microwave irradiation (125 °C, 90 min), the expected 2-phenylindole derivative **1m** in 46% yield (Table 1, entry 11). Secondary cycloalkylzinc halides such as **6e**–**g**[13,12] add to functionalized aryldiazonium salts (**5a**–**g**) furnishing after microwave irradiation (125 °C, 0.5–2 h) the polysubstituted indole derivatives **1n**–**v** in 68–92% yield (Table 1, entries 12–20). For electron-rich substrates conventional heating rather than microwave irradiation was also successful, but under these conditions the cyclization to give the indole derivatives required longer reaction times.

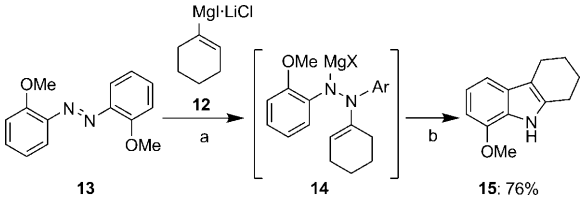
We applied this organometallic variation of the Fischer indole synthesis to prepare indomethacin (**8**), an anti-inflammatory drug,[3q,17] and iprindole (**9**),[18] an antidepressant. Thus, the reaction of the zinc reagent **6b** with the aryldiazonium salt **5e** under standard conditions produced the indole **10**, which was converted in two steps to indomethacin (**8**; Scheme 3). Similarly, cyclooctylzinc bromide (**6h**) adds to PhN_2BF_4 (**5h**) and provides after microwave irradiation the indole **11**, which was N-alkylated leading to iprindole (**9**; Scheme 3).



Scheme 3. Preparation of indomethacin (**8**) and iprindole (**9**). a) −60 °C to 25 °C; then Me_3SiCl (1 equiv), 125 °C, 30 min, microwave irradiation; b) KO*t*Bu (1.2 equiv), 0 °C, 20 min; then *p*-ClC_6H_4COCl (1.2 equiv), 25 °C, 10 h; c) LiOH (10 equiv), H_2O, THF, 25 °C, 6 h; d) KO*t*Bu (1.2 equiv), 0 °C, 20 min; then $Cl(CH_2)_3NMe_2$ (1.2 equiv), 125 °C, 3 h, microwave irradiation.

In the course of our studies, we have found that the key hydrazine intermediate of type **4A** can also be obtained by the addition of an alkenylmagnesium reagent such as cyclohexenylmagnesium iodide (**12**)[19] to a methoxy-substituted azobenzene like **13** leading to the magnesiated hydrazine **14**, which after addition of Me_3SiCl and microwave irradiation produces the carbazole **15** (Scheme 4).

In summary, we have described a new organometallic variation of the Fischer indole synthesis for the preparation of various polyfunctional indoles from readily available aryldia-



Scheme 4. Preparation of the substituted tetrahydrocarbazole **15** by the addition of alkenylmagnesium reagent **12** to azobenzene **13**. a) THF, −78 °C to 25 °C; b) Me_3SiCl (1 equiv), NMP (20 vol%), 125 °C, 30 min, microwave irradiation. NMP = *N*-methylpyrrolidinone.

zonium tetrafluoroborates and functionalized alkylzinc halides. High regioselectivity is observed in the formation of the indole ring. This variation enhances the scope of the original Fischer indole synthesis as a broad range of functionalities are tolerated and remarkable regioselectivity is achieved. Further extensions of the method for the preparation of indole-containing natural products are underway.

Experimental Section

Typical procedure: **1a**: In a flame-dried and argon-flushed Schlenk flask, a solution of **6a** (2.0 mmol, 2.7 mL, 0.74 M in THF) was added dropwise to a solution of $ZnBr_2$ (4.0 mmol, 4 mL, 1 M in THF). After the reaction mixture had been stirred at 25 °C for 10 min, the organozinc reagent was transferred slowly to a solution of **5a** (2.5 mmol, 667 mg) in THF (6 mL) at −60 °C. The reaction mixture was allowed to slowly warm to 25 °C. Subsequently, the solvent volume was reduced to half, Me_3SiCl (2.0 mmol, 217 mg) was added, and the reaction mixture was heated by microwave irradiation at 125 °C for 30 min. After cooling to 25 °C, the mixture was diluted with Et_2O (5 mL) and quenched with brine (10 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (aluminum oxide, activity II–III; pentane/EtOAc/MeOH = 95:5:1) afforded the indole **1a** as a red solid (526 mg, 90 %).

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