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Preparation of Polyfunctional Indazoles and Heteroarylazo Compounds Using Highly Functionalized Zinc Reagents

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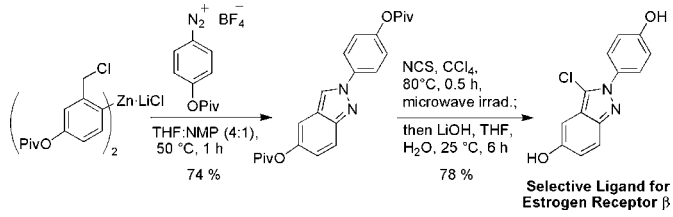
ABSTRACT



Readily available 2-chloromethylarylzinc reagents react with functionalized aryldiazonium tetrafluoroborates providing polyfunctional indazoles. Selective metalations of these 2-aryl-2*H*-indazoles afford new polycyclic aromatics. The performance of a chemoselective addition of diheteroarylzincs to aryldiazonium salts allows an efficient preparation of new heterocyclic azo compounds.

Heterocyclic compounds and in particular indazoles have found numerous applications as pharmaceuticals, agrochemicals, and polymers.[1,2] Some indazoles act as dopamine antagonists, anti-inflammatory, analgesic, or antipyretic agents.[2a,3] For the preparation of complex heterocycles, the use of organometallics as key intermediates has proven to be very useful.[4] Especially, organozinc compounds are of high importance due to their exceptional functional group tolerance and satisfactory reactivity in the presence of appropriate catalysts.[5] The compatibility of organozinc compounds with nitrogen functionalities at high oxidation degree such as nitro groups, azides, and triazenes is a remarkable feature.[6] Diphenylzinc has been reported to react with diazonium salts providing azo compounds.[7] Herein, we report the reaction of functionalized 2-chloromethylarylzinc reagents of type **1** with various aryldiazonium tetrafluoroborate salts of type **2** leading to a new general synthesis of 2-aryl-2*H*-indazoles of type **3** (Scheme 1).[8,9] Furthermore, we also report a useful preparation of heterocyclic azo compounds using heterocyclic zinc reagents.

Scheme 1. Synthesis of Aryl-2*H*-indazole Derivatives of Type **3**

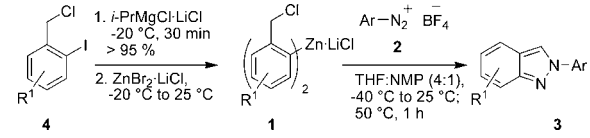


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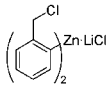
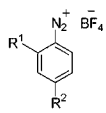
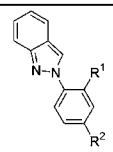
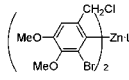
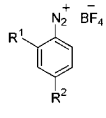
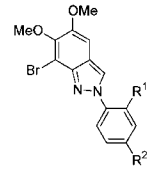
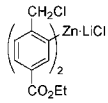
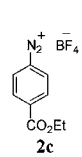
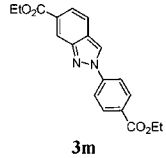
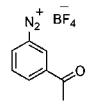
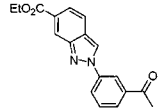
Table 1. Aryl-2*H*-indazole Synthesis by the Reaction of Di(2-chloromethylaryl) Zinc with Aryldiazonium Tetrafluoroborate

entry	zinc reagent[b]	diazonium salt	product	yield (%)[a]
				
1	**1a**	**2a**: $R^1 = R^2 = H$	**3a**	98
2	**1a**	**2b**: $R^1 = I$, $R^2 = H$	**3b**	83
3	**1a**	**2c**: $R^1 = H$, $R^2 = CO_2Et$	**3c**	97
4	**1a**	**2d**: $R^1 = H$, $R^2 = COMe$	**3d**	84
5	**1a**	**2e**: $R^1 = NO_2$, $R^2 = OMe$	**3e**	96
6	**1a**	**2f**: $R^1 = H$, $R^2 = CN$	**3f**	82
7	**1a**	**2g**: $R^1 = NO_2$, $R^2 = H$	**3g**	63
8	**1a**	**2h**: $R^1 = CO_2Et$, $R^2 = H$	**3h**	77
9	**1a**	**2i**: $R^1 = H$, $R^2 = OPiv$	**3i**	76
				
10	**1b**	**2c**: $R^1 = H$, $R^2 = CO_2Et$	**3j**	76
11	**1b**	**2b**: $R^1 = I$, $R^2 = H$	**3k**	68
12	**1b**	**2j**: $R^1 = H$, $R^2 = OMe$	**3l**	69
				
13	**1c**	**2c**	**3m**	71
				
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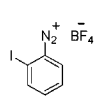
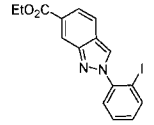
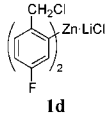
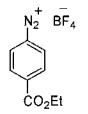
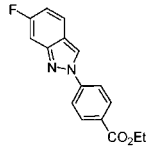
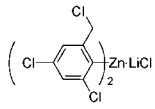
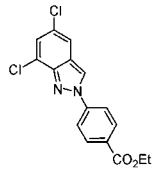
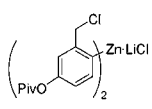
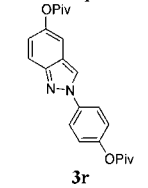
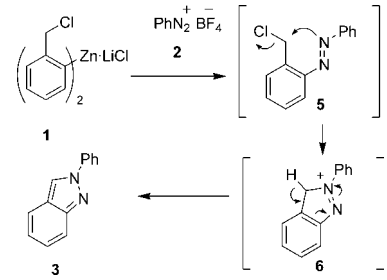
				
15	**1c**	**2b**	**3o**	90
				
16	**1d**	**2c**	**3p**	75
				
17	**1e**	**2c**	**3q**	66
				
18	**1f**	**2l**	**3r**	74

[a] Yield of analytically pure product. [b] With $ZnBr_2$·LiCl (0.55 equiv), a transmetalation was performed.

Thus, the treatment of 2-iodobenzyl chloride (**4a**) with *i*-PrMgCl·LiCl (1.05 equiv, −20 °C, 30 min) furnishes 2-chloromethylphenylmagnesium chloride.[10] Transmetalation with $ZnBr_2$·LiCl (0.55 equiv, −20 to 25 °C, 20 min) provides the diarylzinc **1a**.[11] This zinc reagent was then added to phenyldiazonium tetrafluoroborate in a 1:1 THF:NMP mixture (NMP = *N*-methyl-2-pyrrolidone) at −40 °C.[9c] After stirring the reaction mixture at 25 °C (30 min) and warming the solution to 50 °C for 1 h, 2-phenyl-2*H*-indazole (**3a**) was isolated in 98% yield (entry 1 of Table 1).

We envisioned that the diarylzinc reagent **1** chemoselectively adds to the diazonium salt **2** yielding the 2-chloromethylarylazo compound **5**. Intramolecular nucleophilic substitution at the benzylic carbon leads to the cyclic intermediate **6**. Subsequent proton abstraction furnishes the indazole **3** (Scheme 2).

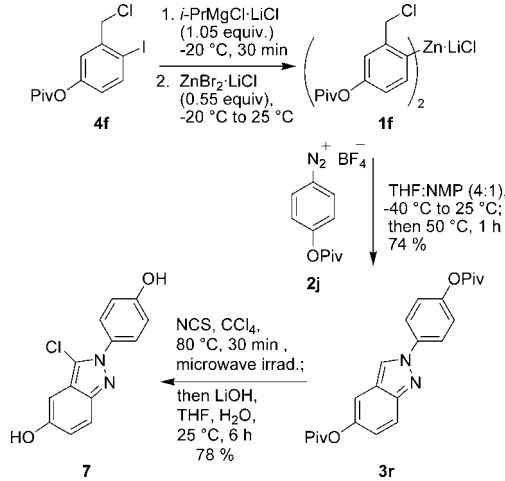
Scheme 2. Tentative Mechanism of the Indazole Synthesis



This reaction displays a remarkable functional group tolerance. Thus, a great variety of diazonium tetrafluoroborate salts and di(2-chloromethylaryl)zinc reagents can be prepared and used for the synthesis of 2-aryl-2*H*-indazole derivatives (**3a**−**r**) bearing sensitive functional groups such as halo, ester, ketone, cyano, methoxy, and nitro groups (Table 1).

As an application, a highly selective ligand for the estrogen receptor β (**7**) was prepared.[3] In the key step, the diarylzinc

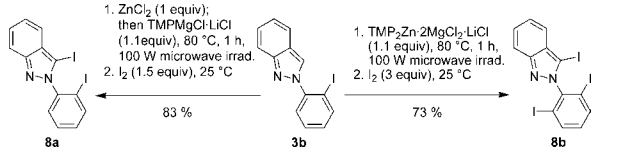
Scheme 3. Synthesis of a Selective Ligand for Estrogen Receptor β (**7**)



reagent **1f** reacted with the diazonium salt **2j** affording the indazole derivative **3r**. Selective chlorination of **3r** with *N*-chlorosuccinimide (NCS) using microwave irradiation and subsequent deprotection of the hydroxyl groups furnished the indazole derivative **7** in 78% yield (Scheme 3). Further functionalization of the indazole scaffold can be achieved by using TMP-derived bases.[12−14]

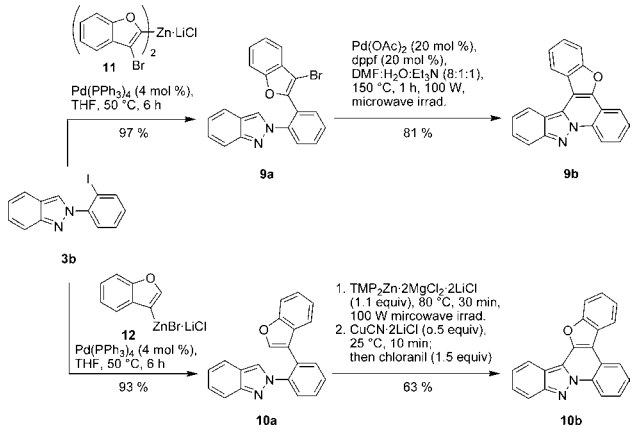
Selective zincation of the indazole **3b** was achieved using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.[12b] Subsequent trapping with iodine furnished 2-(2,6-diiodophenyl)-3-iodo-2*H*-indazole (**8b**) in 73% yield (Scheme 4). Also, the treatment of **3b** with $ZnCl_2$

Scheme 4. Direct Metalation of Indazole **3b**



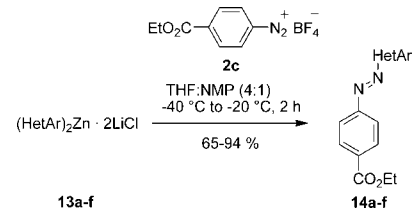
(1.0 equiv) followed by the addition of TMPMgCl·LiCl (1.1 equiv) led to a selective monozincated indazole.[13,14] After iodolysis, the diiodoindazole **8a** is obtained in 83% yield.

Scheme 5. Domino Cross-Coupling Affording the Formation of Heterocyclic Isomeric Indazole Structures of Type **9b** and **10b**



Polycyclic heteroaromatics bearing an indazole unit were prepared using domino cross-coupling[15] (Scheme 5). Thus, Pd-catalyzed cross-coupling ($Pd(PPh_3)_4$ (4 mol %), THF, 50 °C, 6 h) with 2- and 3-zincated benzofuran derivatives (**11** and **12**) gave in quantitative yields the structures **9a** and **10a**. Treatment of indazole **9a** with $Pd(OAc)_2$ (20 mol %) and dppf (20 mol %) in a 8:1:1 DMF:H_2O:Et_3N mixture at 150 °C for 1 h provided the cyclized indazole **9b**.[16] Bismetalation of indazole **10a** with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.1 equiv, 80 °C, 30 min, microwave irradiation) followed by transmetalation with CuCN·2LiCl and addition of chloranil furnished the isomeric polycyclic heterocycle **10b** in 63% yield (Scheme 5).[12a,17]

Scheme 6. Heterocyclic Organozinc Mediated Azo Coupling



Additionally, we have examined the synthesis of heterocyclic azo compounds since they are not easily accessible by conventional methods. Thus, the reaction of heteroarylzincs of type **13** with aryldiazonium tetrafluoroborate **2c** leads to various functionalized azo compounds (Scheme 6).

The required diarylzincs (**13a**−**f**) were obtained by halogen/magnesium exchange from the corresponding heteroaryl iodides or bromides followed by transmetalation with $ZnBr_2$·LiCl (−20 to 25 °C, 20 min). Reaction of these zinc, organometallics with aryldiazonium tetrafluoroborate salt **2c** in THF:NMP mixture

Table 2. Reaction of Heterocyclic Diarylzinc with Aryldiazonium Tetrafluoroborate Salt Leading to Heteroarylazo Compounds

entry	zinc reagent	diazonium salt	product	yield (%)[a]
1	**13a**: R = CO_2Et, X = O	**2c**	**14a**	89
2	**13b**: R = H, X = S	**2c**	**14b**	83
3	**13c**: R = I, X = S	**2c**	**14c**	94
4	**13d**	**2c**	**14d**	83
5	**13e**	**2c**	**14e**	94
6	**13f**	**2c**	**14f**	65

[a] Yield of analytically pure product.

(4:1) at −40 to −20 °C for 2 h furnishes the azo compounds (**14a**−**f**) in 65−94% yield (Table 2).

In summary, we have reported a short and convenient synthetic route to 2-aryl-2*H*-indazoles using highly functionalized arylzinc reagents. As an application, we have prepared a highly selective binding ligand for the estrogen receptor β (**7**). Finally, new heterocyclic azo compounds were also reported. Extensions of this method to material relevant molecules are currently underway in our laboratories.

Acknowledgment. We thank the DFG, the European Research Council (ERC), Chemetall GmbH (Frankfurt), BASF SE (Ludwigshafen), and W. C. Heraeus GmbH (Hanau) for financial support.

Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a detailed description of the formation of 2-chloromethylarylzinc reagents, see Supporting Information.

(9) (a) Varughese, D.; Manhas, M.; Bose, A. *Tetrahedron Lett.* **2006**, *47*, 6795–6797. (b) Peters, M.; Stoll, R.; Goddard, R.; Buth, G.; Hecht, S. *J. Org. Chem.* **2006**, *71*, 7840–7845. (c) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 897–897.

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(11) The use of the mixed $ZnBr_2$·LiCl has a beneficial effect on the reactivity of zinc reagents **1** with aryldiazonium salts.

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