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Synthesis and Functionalization of Unsymmetrical Arylsulfonyl Bisindoles and Bisbenzazoles

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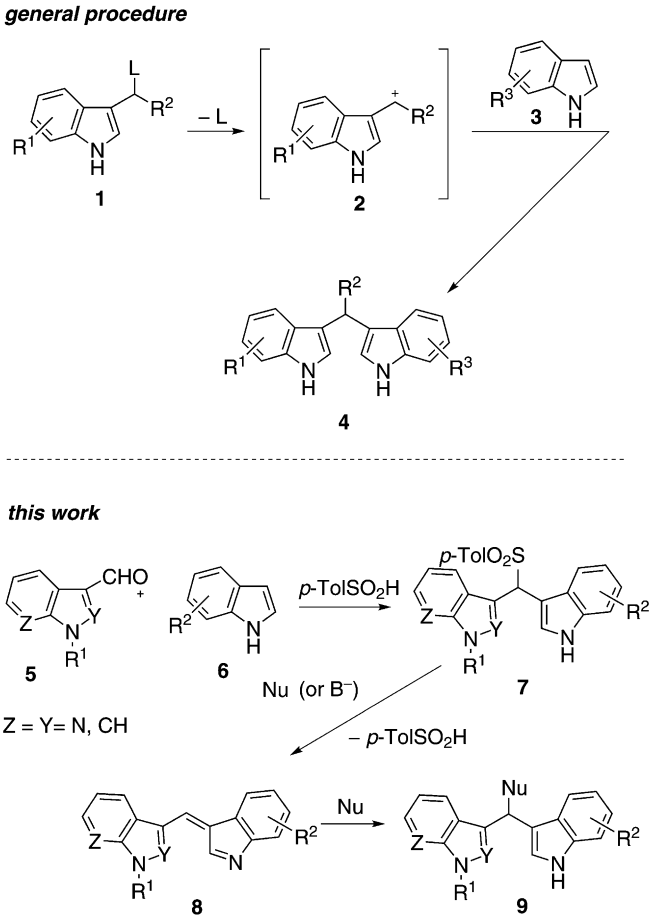
Abstract: A three-component coupling of two different benzazole compounds with *p*-toluenesulfinic acid allows the efficient preparation of unsymmetrical arylsulfonyl bisbenzazole derivatives. Substitution of the arylsulfonyl group from these adducts using sodium borohydride leads to the corresponding bisbenzazoles. Functional implementation of the bisbenzazole system can be achieved using Grignard and Reformatsky reagents.

Keywords: bisindoles; coupling reactions; Grignard reagents; reductions; Reformatsky reagents

Introduction

Compounds containing the bisindole scaffold are of paramount importance as pharmacologically active substances and for their applications in materials chemistry.[1] Symmetrical bisindoles are usually available by coupling reactions involving an aldehyde or its derivative and two equivalents of indole in the presence of acid catalysts or promoters.[2] Less commonly, aldehyde is replaced by other electrophilic groups in metal-catalysed reactions.[3] Such procedures are unfit for the preparation of unsymmetrical bisindoles since it is not possible to realise any control in the cross coupling of two different indole molecules present in the same environment. An efficient entry to unsymmetrical bisindole derivatives would be highly desirable since it provides an enlargement of compound libraries available for practical purposes. In this context, even more interesting would be the development of a synthetic procedure allowing the preparation of bisbenzazole systems embedding couples of different benzofused nitrogen heterocycles such as indoles, indazoles and azaindoles. A very general procedure for the synthesis of unsymmetrical bisindoles starts from a 3-substituted indole **1** bearing a good leaving group at the benzylic position (Scheme 1). Upon elimination of the leaving group, a stabilized carbocation **2** is generated which is able to react with indole **3** providing the bisindole compound **4**.[4] A crucial aspect of this approach lies in the limited availability and structural complexity of substrates of type **1**.[5] In this paper, a different strat-



Scheme 1. General strategies for the synthesis of unsymmetrical bisbenzazole derivatives.

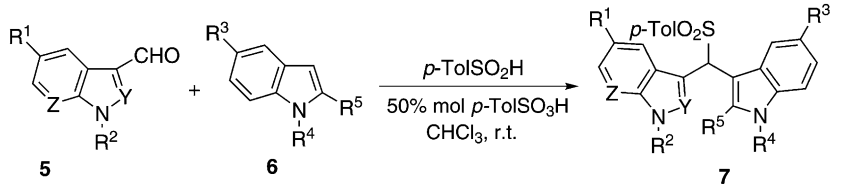
egy based on our previous work in the field of azole functionalizations is presented.[6]

Various 3-formylbenzazole derivatives **5** are eligible for a three-component coupling involving *p*-toluenesulfinic acid and a second indole molecule **6**. The mixed bisbenzazole compound **7** thus obtained works as an efficient pivotal, stable intermediate which upon reaction with a suitable nucleophile or a base generates an indolenine intermediate **8**, amenable of a nucleophilic addition to the final functionalized bisbenzazole **9**.[7]

Results and Discussion

The procedure previously disclosed by us has proved to be particularly effective also for the preparation of sulfonyl bisbenzazoles **7** (Table 1).[8] 3-Carbaldehyde derivatives of indoles, indazole and 7-azaindole **5** react with different indoles **6** and *p*-toluenesulfinic acid in a three component coupling in the presence of *p*-toluenesulfonic acid.[9] For a proper conversion, the benzazole-3-carbaldehyde nitrogen must be adequately protected since reduced yields (40–50%) of adducts are experienced with free N–H substrates. The reactivity displayed by 7-azaindole-3-carbaldehyde **5d** and its indazole analogue **5e** is particularly significant since, to the best of our knowledge, there are no examples of unsymmetrical bisbenzazole compounds including these heterocyclic systems (Table 1, entries 7–11). The enhanced pharmacological profile evidenced in many compounds having the 7-azaindole and indazole units makes bisadducts **7g–k** and their functionalized derivatives (*vide infra*), of particular interest in the realm of medicinal chemistry.[10] The preparation of compound **7** is operationally simple, does not requires harsh reaction conditions and the crude products obtained after usual work-up are easily isolated by crystallization. As previously stated, the *p*-toluenesulfonyl group in compounds **7** can be removed under basic conditions leading to a reactive vinylogous imine intermediate **8** which promptly reacts with a wide array of nucleophiles providing the corresponding substitution products **9**. Nucleophilic reagents with enough basic character are expected to assist the elimination of the sulfinate anion from **7** so that no added basic reagents are needed for the overall process as demonstrated for the reduction of compounds **7** with $NaBH_4$ which affords the expected desulfonylated bisbenzazoles **10** in good yield (Table 2).[11]

Table 1. Synthesis of arylsulfonyl bisbenzazoles **7**.[a]



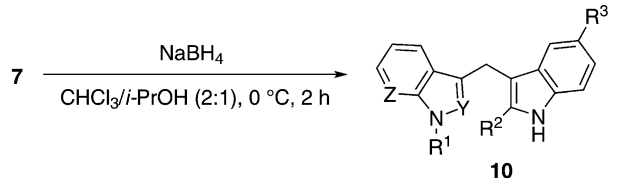
5a: Z = Y = R^1 = H, R^2 = Me
5b: Z = Y = R^1 = H, R^2 = Bn
5c: Z = Y = H, R^1 = NO_2, R^2 = Me
5d: Z = N, Y = CH, R^1 = H, R^2 = Boc
5e: Z = CH, R^1 = H, Y = N, R^2 = Bn

6a: R^3 = R^4 = H, R^5 = Me
6b: R^3 = R^4 = H, R^5 = Et
6c: R^3 = R^4 = H, R^5 = Ph
6d: R^3 = 4-OMe, R^4 = H, R^5 = Me
6e: R^3 = R^4 = H, R^5 = 4-OMePh
6f: R^3 = H, R^4 = Me, R^5 = Ph

Entry	5	6	7	Time [h]	Yield [%][b]
1	**5a**	**6c**	**7a**	4	78
2	**5b**	**6a**	**7b**	4	81
3	**5b**	**6b**	**7c**	5	90
4	**5b**	**6d**	**7d**	5.5	80
5	**5c**	**6a**	**7e**	4.5	82
6	**5c**	**6f**	**7f**	3	92
7	**5d**	**6c**	**7g**	3.5	88
8	**5d**	**6b**	**7h**	5	79
9	**5d**	**6e**	**7i**	5	80
10	**5e**	**6c**	**7j**	5	92
11	**5e**	**6e**	**7k**	5	83

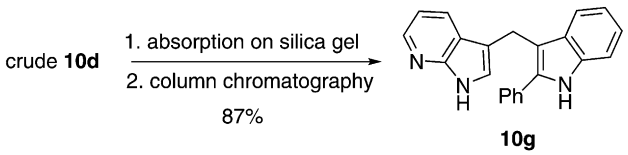
[a] *Reaction conditions:* aldehyde (3 mmol), indole (3.2 mmol), *p*-$TolSO_2H$ (3.6 mmol), *p*-$TolSO_3H{\cdot}H_2O$ (1.5 mmol), in $CHCl_3$ (10 mL) at room temperature.
[b] Yield of pure, isolated products.

Table 2. Synthesis of bisbenzazoles **10.**[a]



Entry	7	10	Yield [%][b]
1	**7a**	**10a**	76
2	**7d**	**10b**	80
3	**7c**	**10c**	72
4	**7g**	**10d**	88
5	**7h**	**10e**	72
6	**7k**	**10f**[c]	93

[a] *Reaction conditions:* sulfonyl bisazole (0.4 mmol) in $CHCl_3$/*i*-PrOH (4 mL:2 mL), $NaBH_4$ (0.8 mmol) at 0 °C.
[b] Yield of pure, isolated products.
[c] Ar = 4-$MeOC_6H_4$.

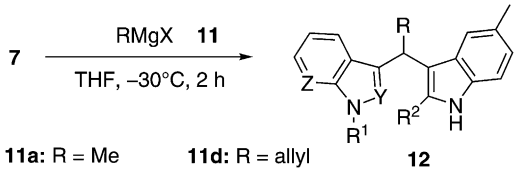


Scheme 2. Cleavage of *N*-Boc protection on the 7-azaindole moiety by absorption on silica gel.

An intriguing aspect concerns the robustness of the *N*-Boc protection in the 7-azaindole moiety which seems resistant to the acidic conditions needed for the synthesis of sulfonyl bisbenzazoles **7g–i**. However, during the purification step of crude **10d** we observed that upon absorption on silica gel and subsequent application of the solid mixture to the head of the chromatographic column, only deprotected bisbenzazole **10g** was recovered after elution (Scheme 2). The effect of silica gel on the selective deprotection of *N*-Boc-pyrrole is known, but the reported procedure requires prolonged heating (7–8 h) at 50 °C under reduced pressure (1 mmHg).[12] This evidences a superior reactivity of the azole nitrogen in 7-azaindoles compared to indole itself. The yield of **10g** is comparable to that obtained by applying crude **10d** directly to the column which results in the recovery of *N*-protected **10d**. This evidences that an almost quantitative deprotection of the *N*-Boc-7-azaindole system is achievable by simple absorption on silica gel.

Substitution of the arylsulfinyl group in compounds **7** with a carbon nucleophile would certainly represent a valid option to implement the bisbenzazole structure with the insertion of functionalized carbon frameworks. In this context different Grignard reagents **11** can be employed in the reaction with sulfonyl bisbenzazoles **7** allowing formation of the alkylated bisbenzazoles **12** (Table 3). From a synthetic standpoint, the two-step process involving formation of compounds **7** and sulfonyl substitution to derivatives **12** is equivalent to a three-component cross-coupling leading to unsymmetrical bisbenzazoles not achievable by a straightforward procedure. Primary and vinyl Grignard reagents are effective in the reaction with different sulfonyl bisbenzazoles **7**, while rather curiously allylmagnesium bromide **11d** gives a sluggish reaction with compound **7b** evidencing a double bond migration from the terminal position (Table 3, entry 4). Reaction of arylorganometallic reagents (PhMgBr and PhLi) with **7a** and **7j**, although attempted, proved to be ineffective in giving the corresponding triarylmethane derivatives. The starting arylsulfonyl bisbenzazole was totally unaffected under standard reaction conditions (−30 °C/0 °C), while upon reflux extensive decomposition of the substrate was observed after 6 h.[13] The level of functional implementation obtainable using Grignard reagents is usually quite limited because of their nucleophilic power which prevents many electrophilic functions to be present in the organometallic framework. Stabilized carbanionic systems such as zinc enolates could be profitably used for this purpose since they are prepared *in situ* from the corresponding halides and do not require carefully controlled reaction conditions. Zinc powder in the presence of a catalytic amount of iodine is able to effect the addition of different easily enolizable α-bromo derivatives **13** to sulfonyl bisbenzazoles **7** *via* the corresponding organozinc reagents (Table 4). Beside the utilization of classical α-bromo ketone and ester **13a** and **13b** it is worthy of note that also bromoacetonitrile **13c** is able to provide the corresponding adducts in high yield (Table 4, entries 3 and 7). The utilization of bromonitromethane **13d** in addition reactions as a nitromethane equivalent is rather limited in scope. This reagent is often used in cyclopropanation reactions[14] and only recently it has been involved in samarium- and indium-promoted reactions with aldehydes and imines.[15] The general reaction conditions proved effective for other bromo derivatives also, allowing the addition of bromonitro-

Table 3. Reaction of sulfonyl bisbenzazoles **7** with Grignard reagents **11**[a]

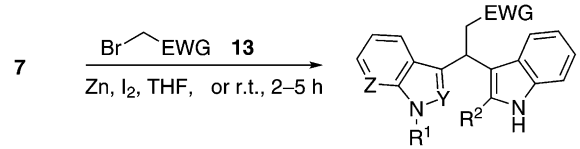


11a: R = Me **11d:** R = allyl
11b: R = *n*-Bu **11e:** R = Et
11c: R = Bn **11f:** R = vinyl

Entry	7	11	12	Yield [%][b]
1	**7a**	**11a**	**12a**	97
2	**7b**	**11b**	**12b**	95
3	**7b**	**11c**	**12c**	80[c]
4	**7b**	**11d**	**12d**	40
5	**7c**	**11c**	**12e**	78[c]
6	**7c**	**11e**	**12f**	77[c]
7	**7j**	**11f**	**12g**	82
8	**7j**	**11e**	**12h**	85

[a] *Reaction conditions:* sulfonyl bisbenzazole (0.4 mmol) in THF (6 mL) at −30 °C, Grignard reagent (1.2 mmol).
[b] Yield of pure, isolated products.
[c] 2 h at −30 °C then slowly warming to 0 °C.

Table 4. Reaction of sulfonyl bisbenzazoles **7** with bromo derivatives **13** in the presence of zinc.[a]



13a: EWG = COPh
13b: EWG = CO_2Me
13c: EWG = CN
13d: EWG = NO_2

Entry	7	13	14	Yield [%][b]
1	**7j**	**13a**	**14a**	85
2	**7b**	**13b**	**14b**	81[c]
3	**7c**	**13c**	**14c**	87
4	**7g**	**13d**	**14d**	55[d]
5	**7i**	**13b**	**14e**	83[c,d,e]
6	**7j**	**13b**	**14f**	76[c]
7	**7j**	**13c**	**14g**	89

[a] *Reaction conditions:* Zn (2 mmol), I_2 (0.1 mmol) in THF (6 mL), bromo derivative (0.8 mmol), sulfonyl bisbenzazole (0.4 mmol) at reflux for 5 h.
[b] Yield of pure, isolated products.
[c] Reaction carried out at room temperature for 5 h.
[d] *N*-Boc protection is removed in the reaction.
[e] Ar = 4-$MeOC_6H_4$.

methane **13d** to sulfonyl bisbenzazole **7g** (Table 4, entry 4). The lability of the *N*-Boc protection in the 7-azaindole moiety previously observed in the purification step of bisbenzazole **10d** is further evidenced in the synthesis of compounds **14d** and **14e** which are decarbonylated in these reaction conditions (Table 4, entries 4 and 5).

Conclusions

The new synthetic approach for the preparation of unsymmetrical bisbenzazole derivatives starts with a three-component coupling involving a heterocyclic carbaldehyde, an indole derivative and *p*-toluenesulfinic acid. This reaction generates an arylsulfonyl bisbenzazole system which acts as a pivotal intermediate for subsequent functional group implementations. Elimination of the arylsulfonyl moiety under basic conditions leaves a vinylogous imino derivative which upon reduction or reaction with organometallic reagents affords functionalized bisbenzazole systems. The described procedure is simple, viable and provides access to a class of heterocyclic derivatives hitherto unknown but with potential practical applications in the field of medicinal and materials chemistry.

Experimental Section

General Procedure for the Preparation of Sulfonyl Bisbenzazoles 7

To a stirred solution of indole **6** (3.2 mmol), *p*-toluenesulfinic acid (3.6 mmol) and *p*-toluenesulfonic acid monohydrate (1.5 mmol) in $CHCl_3$ (10 mL), the carbaldehyde **5** (3 mmol) was added. The resulting reaction mixture was stirred at room temperature for the appropriate time (see Table 1), and was then treated with saturated $NaHCO_3$ (7 mL). The aqueous layer was extracted with $CHCl_3$ (3×20 mL),[16] the combined organic extracts were dried over Na_2SO_4. The crude product **7** obtained after filtration through a short celite pad and removal of the solvent at reduced pressure, was purifed by crystallization form ethyl acetate/hexane.

General Procedure for the Preparation of Bisbenzazoles 10 by Reduction of 7 with Sodium Borohydride

To a stirred solution of sulfonyl bisbenzazole **7** (0.4 mmol) in $CHCl_3$/*i*-PrOH (4 mL/2 mL) at 0 °C was added $NaBH_4$ (0.8 mmol). The reaction mixture was stirred at room temperature for 2 h, then treated with saturated NH_4Cl (5 mL). The aqueous layer was extracted with $CHCl_3$ (3×10 mL) and the combined organic extracts were dried over $NaSO_4$. The crude product obtained after removal of the solvent at reduced pressure was purified by column chromatography (hexanes-ethyl acetate 9:1; for compounds **10d** and **10e**: hexanes-ethyl acetate 8:2).

General Procedure for the Preparation of Bisbenzazoles 12 by Reaction of Compounds 7 with Grignard Reagents 11

To a stirred solution of bisbenzazole **7** (0.4 mmol) in THF (6 mL) at −30 °C was added the selected Grignard reagent **11** (1.2 mmol). The reaction mixture was stirred at −30 °C for 2 h, then treated with saturated NH_4Cl (5 mL). The aqueous layer was extracted with $CHCl_3$ (3×10 mL) and the combined organic extracts were dried over $NaSO_4$. The crude product obtained after removal of the solvent at reduced pressure was purified by column chromatography (hexanes-ethyl acetate 8:2).

General Procedure for the Preparation of Bisbenzazoles 14 by Reaction of Compounds 7 with Bromo Derivatives 13 in the Presence of Zinc

To a stirred suspension of Zn (2 mmol), I_2 (0.1 mmol) and 2-bromo derivative **13** (0.8 mmol) in THF (6 mL) at room temperature was added the appropriate bisbenzazole **7** (0.4 mmol). The reaction mixture was stirred at reflux for 2 h (5 h at room temperature for the reactions with methyl bromoacetate **13b**). After cooling to room temperature the mixture was treated with saturated NH_4Cl (5 mL), the aqueous layer was extracted with $CHCl_3$ (3×10 mL) and the combined organic extracts were dried over $NaSO_4$. The crude product obtained after removal of the solvent at reduced pressure was purified by column chromatography (hexanes-ethyl acetate 8:2; for compounds **14d** and **14e**: hexanes-ethyl acetate 7:3).

Acknowledgements

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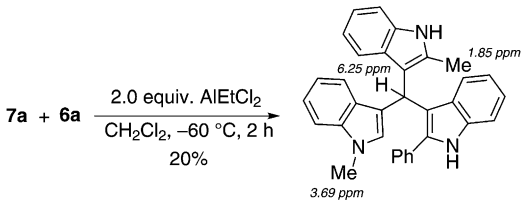
[13] The failure evidenced in the reaction of sulfonyl bisazoles **7a** and **7j** with arylorganometallic reagents is only partially due to the higher steric hindrance provided by these reagents compared to their linear analogues. As a matter of fact, reaction of compound **7a** with 2-methylindole **6a** in the presence of $AlEtCl_2$ gives the corresponding trisindole derivative **15** albeit in poor yield (20%). For a general discussion on Lewis



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[16] Some products bearing the 2-methylindolyl framework (**7b, 7d** and **7e**) show a limited solubility in $CHCl_3$. For these compounds it is advisable to extend the number of extractions (6×20 mL).

