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ARTICLE

Facile synthesis of biarylmethanes and tetrasubstituted arenes *via* base-mediated [3+3] benzannulation reaction of Morita-Baylis-Hillman adducts and unsaturated sulfones

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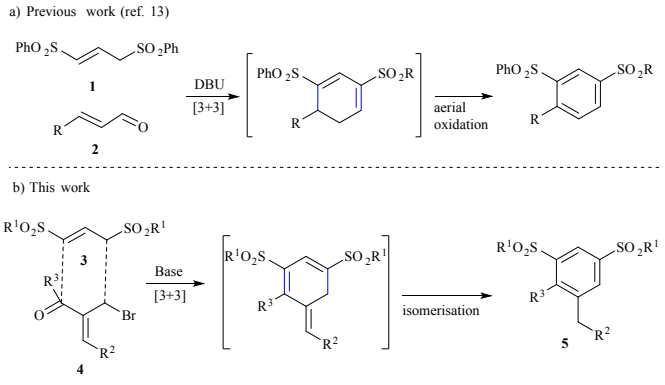
A facile DBU-mediated [3+3] benzannulation reaction of 1,3-*bis*-sulfonyl propenes and Morita-Baylis-Hillman (MBH) bromides is described. The benzannulation reaction afforded *bis*-sulfonyl biarylmethanes/arenes with complete regioselectivity. The products may be converted readily into corresponding benzophenones via site-selective benzylic oxidation.

Introduction

Phenyl derivatives constitute important building blocks in organic synthesis due to their abundance and the ease of carrying out aromatic electrophilic substitution reactions. Regiochemical outcome of the substitution reactions is determined by the directing influences of groups present on the aryl ring.[1] This very virtue may, however, prevent the formation of a desired regioisomer when the construction of poly-substituted arenes is attempted. Deactivating effects of electron withdrawing groups and steric crowding also pose serious challenges to this approach. Availability of methods such as transition-metal mediated cross-coupling reactions[2] and directed metallation reactions[3] helps to overcome these issues significantly. These reactions, however, employ arenes pre-functionalised with groups which engage in coupling reactions or anchor the metal catalyst at the desired position. Such pre-functionalised arenes are mostly assembled via standard aromatic substitution reactions which occasionally bring the above-mentioned roadblocks back, especially when a non-trivial, poly-substituted arene building block is required.

Benzannulation reactions, an unconventional approach, wherein acyclic precursors are combined to afford substituted arenes, addresses some of the above-mentioned concerns. The acyclic building blocks can be of various types or sizes; their assembly may be catalysed/mediated by acid, base, light or metal complexes and the arene may result from the combination of two, three or more building blocks. Important and well-known transformations such as the Dötz reaction[4] and Danheiser benzannulation[5] amply demonstrate the power of benzannulation strategy in synthesis. Benzannulation reactions are generally classified based on the number of carbons contributed by each building block, such as [5+1], [4+2], [3+3], [2+2+2] etc. More pertinent to the work presented here are [3+3] benzannulation reactions.[6] Elegant applications of benzannulation reactions in the total synthesis of a number of structurally intriguing, arene-containing natural products demonstrate the power of this approach.[7]

Arylsulfones are important synthetic targets owing to their well-described biological activities as well as synthetic utility.[8] In addition, some arylsulfones also exhibit excellent coordinating properties.[9] Common methods for the construction of arylsulfones include oxidation of aryl sulfides,[10] sulfonylation of arenes[11] and coupling of sulfinates with aryl halides.[12] These protocols invariably require arene building blocks and the challenges associated with their availability and functionalisation (*vide supra*) often necessitate lengthy routes and cumbersome procedures. We and others have attempted to address these challenges by developing new *benzannulation* methods for the convenient synthesis of arylsulfone derivatives.[13]



Scheme 1: a) [3+3] benzannulation reactions of enals/enones; b) The present work

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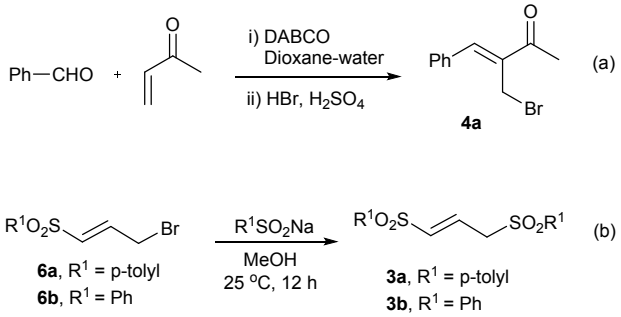
This mild, base-mediated, aerial-oxidative, [3+3] benzannulation method afforded substituted arylsulfones from two simple 3-carbon building blocks, viz., the *bis*-nucleophile **1** and the *bis*-electrophile **2** (Scheme 1a). The innate simplicity of this approach along with the richly functionalised nature of the arene products prompted us to explore this method further. We surmised that union of symmetric, sulfone-bearing, bis-nucleophile **3** and a multifunctional electrophilic partner, such as **4**, could potentially afford tetra-substituted bis-sulfonylarenes **5** (Scheme 1b). The easy generation of the substrate **4** via the versatile Morita-Baylis-Hillman (MBH) reaction[14] was indeed a key driving factor behind the design of this route. In addition, it was intriguing to examine the reactivity of the MBH bromide **4** which incorporated three reactive electrophilic centers in a benzannulation reaction.

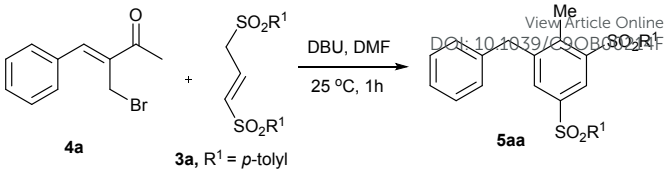
Results and Discussion

The required MBH adduct **4a** was prepared from benzaldehyde and methyl vinyl ketone in two steps as reported earlier (Scheme 2a).[14a] The nucleophilic reaction partners, 1,3-*bis*-toluenesulfonylpropene **3a** and 1,3-*bis*-phenylsulfonylprpopene **3b** were prepared from the corresponding bromides **6a, 6b** as depicted in Scheme 2b.[15]



Scheme 2: Preparation of substrates for benzannulation reactions

Following the synthesis of the precursors **3a** and **4a**, their union in a benzannulation reaction was attempted. In a pilot reaction, **3a** and **4a** were subjected to the conditions of our previously reported benzannulation protocol.[13a] Pleasingly, a facile reaction was observed and a crystalline product was obtained after work-up and column chromatography. The diphenylmethane structure **5aa** was assigned to the product on the basis of spectroscopic analysis. In the ^{1}H NMR spectrum of the product, a singlet at δ 3.99 corresponding to two protons indicated the presence of the benzylic methylene group. Another singlet at δ 2.35 (3H) was assigned to the methyl group on the newly formed arene. The presence of signals at δ 39.7 and δ 16.3 in the ^{13}C NMR spectrum confirmed the presence of these methylene and methyl groups respectively. The two aromatic protons on the newly formed aryl ring resonated as mutually coupled doublets (J = 2.0 Hz) at δ 8.63 and δ 7.87. Other spectroscopic data were also in complete agreement with the assigned structure.

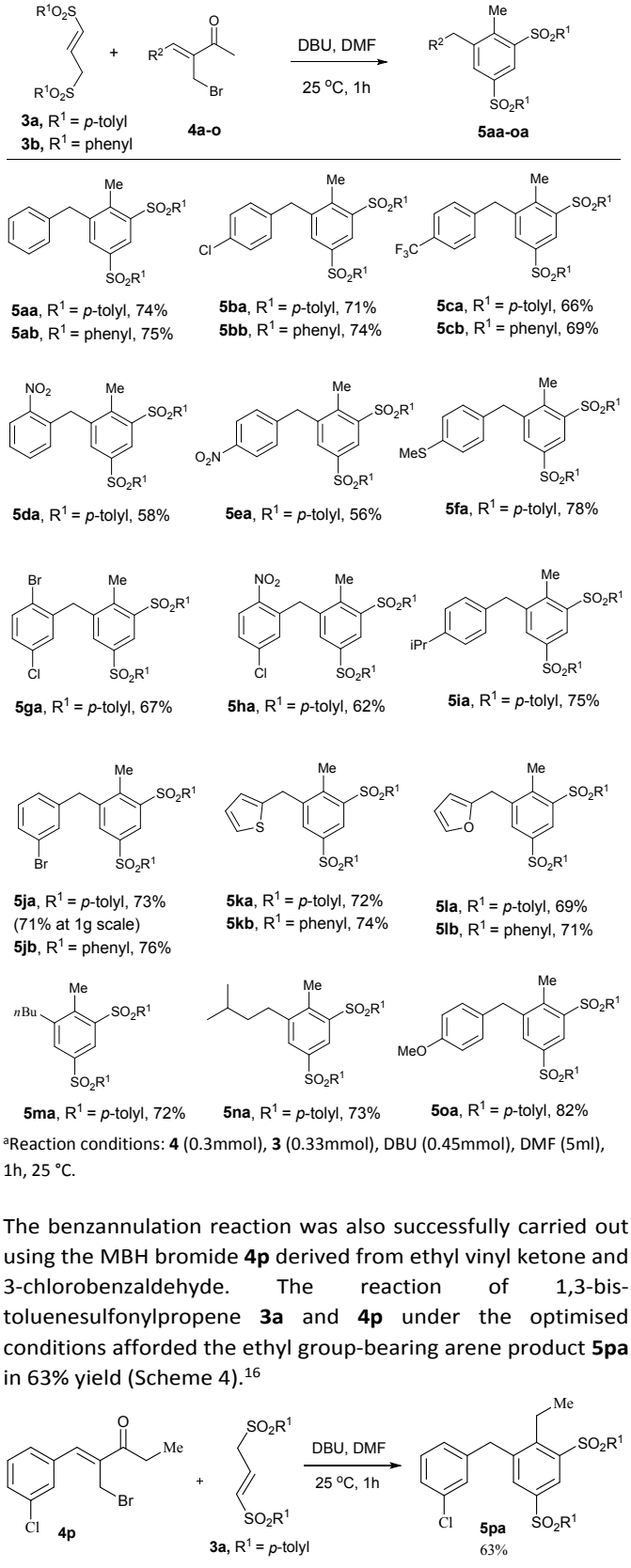


Scheme 3: DBU-mediated benzannulation reaction of **4a** and **3a**

The facile formation of a tetrasubstituted phenyl ring from two simple acyclic precursors prompted us to investigate the scope and generality of the benzannulation reaction. To this end, a variety of MBH-bromides were prepared in the same manner as described in Scheme 2. They were treated with 1,3-*bis*-arylsulfonylpropenes **3a** and **3b** under the conditions for benzannulation reaction. The results are summarised in table 1.

All of the MBH adducts **4a**-**4n** employed in the study reacted smoothly to afford the corresponding *bis*-sulfonylarenes. MBH-adducts derived from substituted benzaldehydes afforded biarylmethane products **5aa**-**5na** endowed with nitro, trifluoromethyl, thiomethyl, bromo and chloro groups. Heterocyclic residues such as thiophene and furan may also be incorporated in the final products (**5ka**, **5kb**, **5la** and **5lb**) by employing the corresponding heteroaryl MBH-adducts. Electron donating aryl units such as *p*-methoxyphenyl ring is also tolerated in the benzannulation reaction (**5oa**). It is noteworthy that the benzannulation is not limited to aryl MBH adducts. Alky group bearing substrates reacted uneventfully to generate the corresponding tetrasubstituted arenes **5ma** and **5na** in very good yields. To test the scalability of the benzannulation method, a representative reaction was carried out using 1g of the MBH bromide **4j** (R^2 = 3-bromophenyl). Pleasingly, the desired product **5ja** was obtained in 71% yield.

Table 1: Substrate scope of the benzannulation reaction[a]

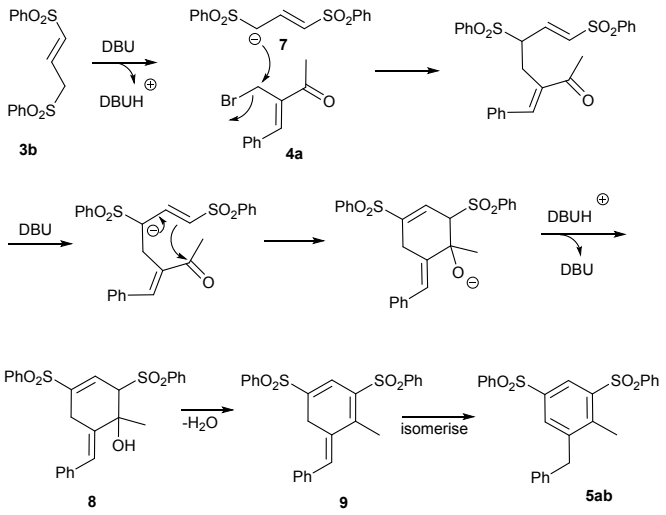


[a]Reaction conditions: **4** (0.3mmol), **3** (0.33mmol), DBU (0.45mmol), DMF (5ml), 1h, 25 °C.

The benzannulation reaction was also successfully carried out using the MBH bromide **4p** derived from ethyl vinyl ketone and 3-chlorobenzaldehyde. The reaction of 1,3-bis-toluenesulfonylpropene **3a** and **4p** under the optimised conditions afforded the ethyl group-bearing arene product **5pa** in 63% yield (Scheme 4).[16]

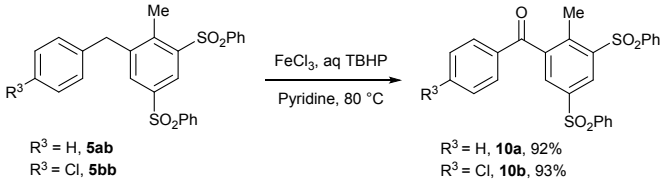
Scheme 4: Benzannulation reaction of MBH bromide derived from ethyl vinyl ketone

A simplified mechanistic rationalisation for the formation of biaryl methane derivatives in the benzannulation reaction is advanced as depicted in Scheme 5. The reaction is initiated by the displacement of the primary allylic bromide in **4a** by the stabilised carbanion **7** generated from **3b** and DBU. This is presumably because the bromine containing carbon is the least hindered electrophilic site in **4a**. Further deprotonation and intramolecular Julia-type cyclisation affords the cyclohexenol derivative **8** (Intramolecular Michael addition of the stabilized carbanion to the enone moiety is presumably less favoured due to higher steric demands). The carbinol **8** then undergoes dehydration to produce the cyclohexadiene derivative **9**. The final product **5ab** is then formed via the aromaticity-driven isomerisation of **9**.



Scheme 5: Plausible mechanism of the benzannulation reaction

The biarylmethane derivatives are amenable to further synthetic modifications. For example, tert-butyl hydroperoxide (TBHP) and $FeCl_3$-mediated benzylic oxidation[17] of two representative biarymethanes **5ab, 5bb** afforded the corresponding benzophenone derivatives **10a, 10b** in excellent yields (Scheme 6). It may be noted that the benzylic oxidation proceeded exclusively at the methylene group and the methyl group was unaffected.



Scheme 6: Benzophenone synthesis via site-selective oxidation of biarylmethanes

Conclusions

In conclusion, a [3+3] benzannulation reaction of 1,3-*bis*-sulfonyl propene derivatives and MBH-bromides has been developed. A series of highly substituted *bis*-sulfonyl arene derivative were synthesised in good yields. The

benzannulation reactions are mediated by a common base (DBU), proceed rapidly at room temperature and generate significant levels of molecular complexity. The biaryl derivatives thus obtained are readily converted into corresponding benzophenone derivatives by site-selective benzylic oxidation. It is presumable that the method may find applications in the targeted synthesis of sulfonyl arenes and benzophenones.

Conflicts of interest

There are no conflicts to declare.

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