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One-pot two step synthesis of unsymmetrically substituted indenes from 3,4-diarylbutadiene sulfones

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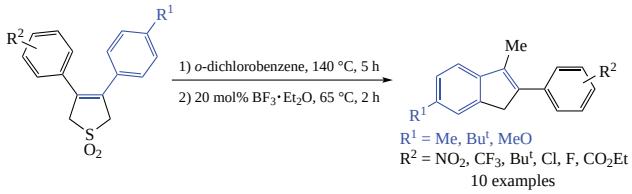
A new one-pot two step synthesis of unsymmetrically substituted indenes from available 3,4-diarylbutadiene sulfones involves SO_2 thermal extrusion followed by acid-catalyzed cyclization of the diene formed, the cyclization proceeding selectively at the more electron-rich aryl rings. The procedure is efficient for substrates bearing donor, acceptor, as well as bulky substituents.



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Compounds containing indene moiety possess diverse biological activities,[1–4] exhibit antiviral,[5] anti-inflammatory,[6,7] cytotoxic[8] and antiproliferative[9,10] effects as well as estrogen receptor modulation.[11,12] Indene fragment can be easily found in natural compounds and different materials[13,14] or metallocene complexes for olefin polymerization catalysis.[15,16] Regarding this, it is of high importance to develop not only efficient and high yielding synthetic route to this class of compounds, but the one to solve the possible selectivity issues in case of multisubstituted indenes.

There are many examples of different approaches to make an indene core.[17,18] Among recently investigated ones there are Nazarov type cyclizations of aryl vinyl ketones with ethyl acetate[19] or CF_3-TMS,[20] or arylacetylenes with carbonyl compounds;[21] the Prins cyclization of 4-alkynyl alcohols followed by the ring opening and Friedel–Crafts reaction;[22,23] coupling between alkynes and *o*-bromophenylzinc bromide[24] or 2-chloromethylphenylboronic acid;[25] and some other methods involving intramolecular cyclization.[26–29] It should be noted that the particular synthesis of 2-arylindenes is presented in limited number of pathways (reaction of 2-indanone with Grignard reagent,[30] 2-bromoindene cross-coupling,[31] selective Heck reaction of indenes[32]) not allowing to call these methods simple and common. Despite the high efficiency and selectivity of these methods in the synthesis of the simple indenes, some significant limitations should be emphasized, namely, the use of harsh conditions and expensive or uncommon reagents that lead to a limited scope of allowed functional groups. The above circumstances make an introduction of diverse substitutes problematical especially in case of unsymmetrical indenes containing both donor and acceptor groups. Thus, it was of particular interest to develop the simple and general synthetic procedure to access unsymmetrical multisubstituted indenes bearing different functional groups.

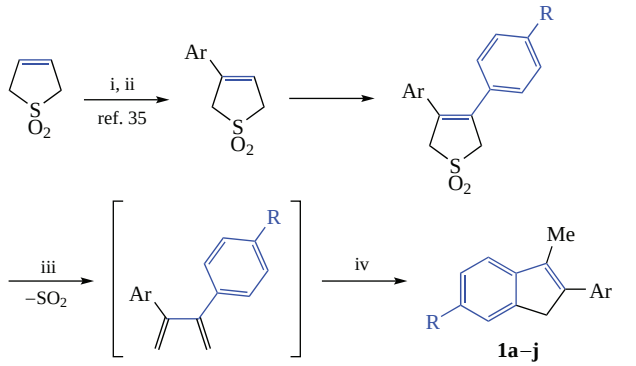
It was previously shown[33,34] that indenes could be obtained from the corresponding 2,3-diaryl-1,3-butadienes, however, those studies have limited number of examples mainly due to the inaccessibility of the starting materials bearing different substitutes. Based on our previous works where the possibility for the synthesis of unsymmetrical 2,3-diaryl-1,3-butadienes from available unsymmetrical 3,4-diarylbutadiene sulfones *via* SO_2 thermal extrusion was investigated, we assumed that such sulfones might also appear as the initial compounds in indene synthesis.[35,36] In continuation of our research on catalytic methods in synthesis,[37–43] we report herein one-pot two step preparation of unsymmetrically substituted indenes from available 3,4-diarylbutadiene sulfones allowing to introduce a wide range of different substituents into the indene ring system.

We started our search for optimal conditions for one-pot two step indene synthesis by testing different reaction conditions for the one-pot procedure, obtaining the 2,3-diaryl-1,3-butadienes from the corresponding 3,4-butadiene sulfones with their further catalytic cyclization to indenes. We used 3-(4-methylphenyl)-4-(4-nitrophenyl)buta-1,3-diene sulfone as the model substrate. The conditions for the SO_2 thermal extrusion stage have already been tested in our previous work.[36] It was shown that heating *o*-dichlorobenzene solutions at 140 °C for more than 6 h leads to product decomposition and extensive by-products formation, so heating for 5 h was the best choice for this stage. The cyclization of the obtained *in situ* 2-(4-methylphenyl)-3-(4-nitrophenyl)-buta-1,3-diene was investigated under different conditions to form the corresponding indene (Table 1). Aluminium chloride and TFA (Table 1, entries 1–5) required a longer time heating or

Table 1 Optimization of the second step of the indene synthesis.[a]

Entry	Catalyst (mol%)	*T*/°C	*t*/h	Conversion (%)
1	$AlCl_3$ (20)	20	1	40
2	$AlCl_3$ (20)	65	4	100
3	TFA (20)	20	1	0
4	TFA (20)	65	1	20
5	TFA (120)	65	3	100
6	$BF_3 \cdot Et_2O$ (10)	20	1	30
7	$BF_3 \cdot Et_2O$ (10)	65	2	50
8	$BF_3 \cdot Et_2O$ (20)	65	2	100

[a] Reaction conditions: (1) 3-(4-methylphenyl)-4-(4-nitrophenyl)butadiene sulfone, *o*-dichlorobenzene, 140 °C, 5 h; (2) catalyst, 20–65 °C, 1–4 h.



a Ar = 4-$O_2NC_6H_4$, R = MeO (78%) **f** Ar = 4-$EtO_2CC_6H_4$, R = Me (92%)
b Ar = 4-$F_3CC_6H_4$, R = MeO (78%) **g** Ar = 2-FC_6H_4, R = Bu^t (75%)
c Ar = 4-ClC_6H_4, R = MeO (67%) **h** Ar = 4-$EtO_2CC_6H_4$, R = Bu^t (68%)
d Ar = 4-$Bu^tC_6H_4$, R = MeO (76%) **i** Ar = 2-FC_6H_4, R = MeO (69%)
e Ar = 4-MeC_6H_4, R = Me (80%) **j** Ar = 3-ClC_6H_4, R= MeO (64%)

Scheme 1 *Reagents and conditions (one-pot)*: i, ArN_2BF_4, $Pd(OAc)_2$, MeOH, 50 °C, 2 h; ii, DBN, 1,4-dioxane, 100 °C, 2–24 h (see ref. 35); iii, *o*-dichlorobenzene, 140 °C, 5 h; iv, $BF_3 \cdot Et_2O$ (20 mol%), 65 °C, 2 h.

larger catalyst loadings to achieve the excellent conversion compared with $BF_3 \cdot Et_2O$ (entries 6–8). Temperature decrease has led to significant drop in conversion in all cases (entries 1, 3, 6).

To show the versatility of investigated conditions, nine more representatives of unsymmetrical indenes bearing electron-withdrawing and electron-donating groups were obtained (Scheme 1).† It should be noted that indenes we got by the one-pot two step syntheses are hard to obtain by other reported procedures. The products were isolated with the high yields and excellent selectivity. The structure of indene **1d** was unambiguously confirmed by ^1H–^1H NOESY NMR (see Online Supplementary Materials, Figure S26). Moreover, the regioselectivity of the reaction is fully consistent with the proposed cyclization mechanism,[34] the interaction of Lewis acid with 1,3-diene produces a more stable carbocation (a benzylic cation of the more donor aryl), which, in turn, undergoes cyclization at the more donor aryl ring.

It is worth mentioning that most of the indenes (except for **1f**) obtained in this work were synthesized for the first time. To summarize, a new one-pot two step procedure for the synthesis of unsymmetrically substituted indenes from synthetically available 3,4-diarylbutadiene sulfones was elaborated. The scope of unsymmetrical indenes bearing electron-withdrawing and electron-donating groups hard to access by other reported procedures were obtained in good yields with the excellent selectivity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.006.

† *General procedure.* 3,4-Diarylbutadiene sulfone (1 mmol) was heated in *o*-dichlorobenzene (5 ml per mmol, or 10 ml per mmol for **1a**–**d**,**i**,**j**) in a round-bottom flask under inert atmosphere for 5 h. After that the reaction mixture was cooled to 65 °C, and $BF_3 \cdot Et_2O$ (0.2 mmol) was added. The reaction mixture was stirred at 65 °C for 2 h, allowed to cool to room temperature, quenched with methanol (2 ml), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/hexane, from 3:1 to 1:1 by volume).

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