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Di- and triheteroarylalkanes *via* self-condensation and intramolecular Friedel–Crafts type reaction of heteroaryl alcohols†

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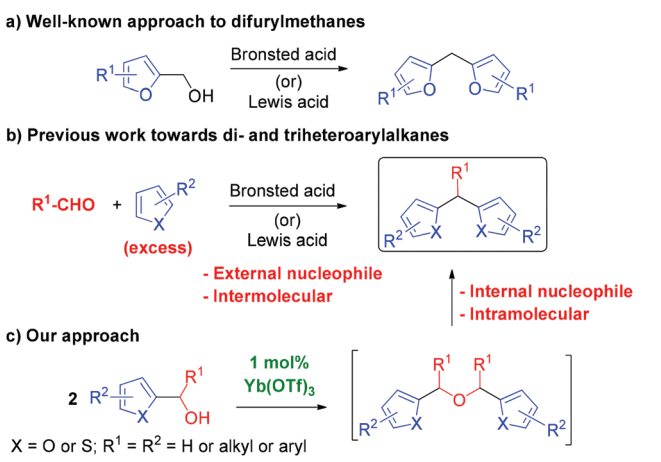
An efficient synthetic approach to diheteroarylmethanes and 1,3-diheteroarylpropenes has been developed *via* Yb(III)-catalyzed sequential self-condensation of 2-furfuryl (or 2-thienyl or 3-indolyl) alcohols followed by intramolecular Friedel–Crafts type reaction and elimination of an aldehyde. This method offers a powerful entry and a potential alternative to the traditional synthesis of diheteroarylalkanes, which are precursors to the synthesis of several intriguing heteroaryls and more significantly, to the synthesis of biofuels.

Di- and triheteroarylalkanes are the components of several bioactive natural products and pharmaceuticals, and possess significant biological activity profiles such as anticancer, antitubercular, antihyperglycemic, antiviral, antimicrobial, and analgesic properties, to mention a few.[1] Triheteroarylalkanes find applications as protective groups,[2] photochromic agents[3] and dyes[4] as well. Difuryl- and dithienylalkanes are present as natural compounds in food and beverage items such as licorice[5] and are flavor agents in coffee.[6] Dithienylalkanes are used in optoelectronic devices,[7] while bisindolylalkanes possess wide applications in material science and also act as colorimetric sensors.[8] Several natural products possessing bisindolylalkane scaffold were isolated and were found to exhibit important biological activities including anticancer activity.[9]

Among ubiquitous furan derivatives, difurylmethanes constitute a significant subclass which are important intermediates in the synthesis of heterocyclic macromolecules such as core-modified porphyrins and calixarenes.[10] As a latest development with tremendous potential, difurylalkanes are elaborated to the synthesis of biodiesel and jet fuels.[11] Unsubstituted difurylmethanes traditionally have been synthesized *via* Bronsted or Lewis acid mediated conversion of 2-(hydroxymethyl)furans (1°-alcohols) and is well-documented,[12] Scheme 1a. However, under similar conditions, conversion of 2-(hydroxyethyl)furans (2°-alcohols) to substituted difurylmethanes and triarylmethanes was either ineffective[13] or moderately successful with a limited scope.[14]

On the other hand, synthesis of difurylethanes has long been achieved by hydroalkylation–alkylation of aldehydes and furans,[15] Scheme 1b. Surprisingly, parallel strategies to access this important class of compounds from furfuryl alcohols are scarce.[14] The main disadvantage of the hydroalkylation–alkylation protocol is the usage of excess furan source (often 5–10 equiv.) against the requirement of only two theoretical equivalents and obviously the excess furan is left to the waste stream. This approach is also limited by the reliance on only aldehydes as an electrophilic source and can especially be a hindrance when complex and rather unstable aldehydes need to be employed. Herein, we delineate our efforts towards the development of a mild and efficient method for the synthesis of di- and triheteroarylalkanes that especially rely upon readily available starting materials under remarkably low catalyst loading, Scheme 1c.



Scheme 1 Contrasting difference between our work and earlier methods towards the synthesis of di- and triheteroarylalkanes.

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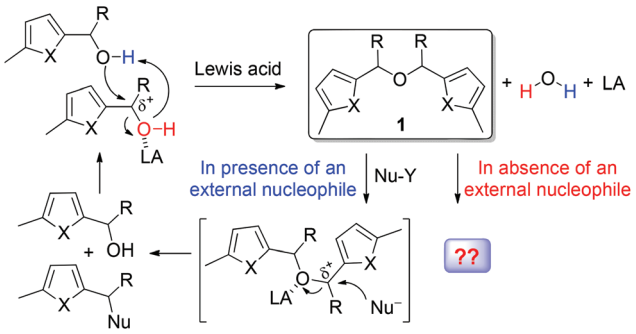
†Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of starting materials, copies of ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c3ob41945b

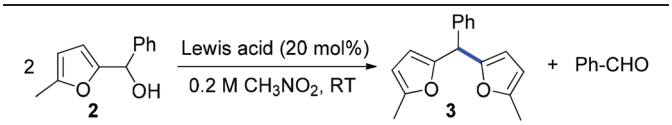


Scheme 2 General mechanism of Lewis acid catalyzed symmetric ether formation and subsequent transformations.

As part of our on-going studies towards expanding furan chemistry, we have recently communicated our preliminary results on the $BiCl_3$-catalyzed C–C, C–N, C–O, C–S bond forming reactions of a variety of furfuryl and thienyl alcohols.[16] As depicted in Scheme 2, the mechanism involves the formation of a symmetric ether intermediate of general structure **1** under the influence of Lewis acid[17] which upon reaction with an appropriate nucleophile delivers a product while regenerating starting alcohol. However, the fate of the symmetric ether **1** under Lewis acidic conditions in the absence of an external nucleophile is rather unexplored. We intended to isolate the symmetric ether **1** and subject it to further synthetic elaboration,[18] so we performed the reaction on the furfuryl alcohol **2**[16] with $BiCl_3$ as a catalyst and in the absence of an external nucleophile (Table 1, entry 1). While the respective symmetric ether (of type **1**) was not isolable, rather to our surprise, the triarylmethane **3** was isolated in 69% yield after column chromatography. To the best of our knowledge, *Lewis acid catalyzed conversion of furfuryl alcohols alone to difurylethanes or triarylmethanes* is not reported thus far and it is worth mentioning that synthetic approaches to this class of compounds especially originating in the absence of an external nucleophile are rare.[14] This prompted us to further investigate the scope of this method which provides an easy access for the synthesis of di- and triheteroarylalkanes.

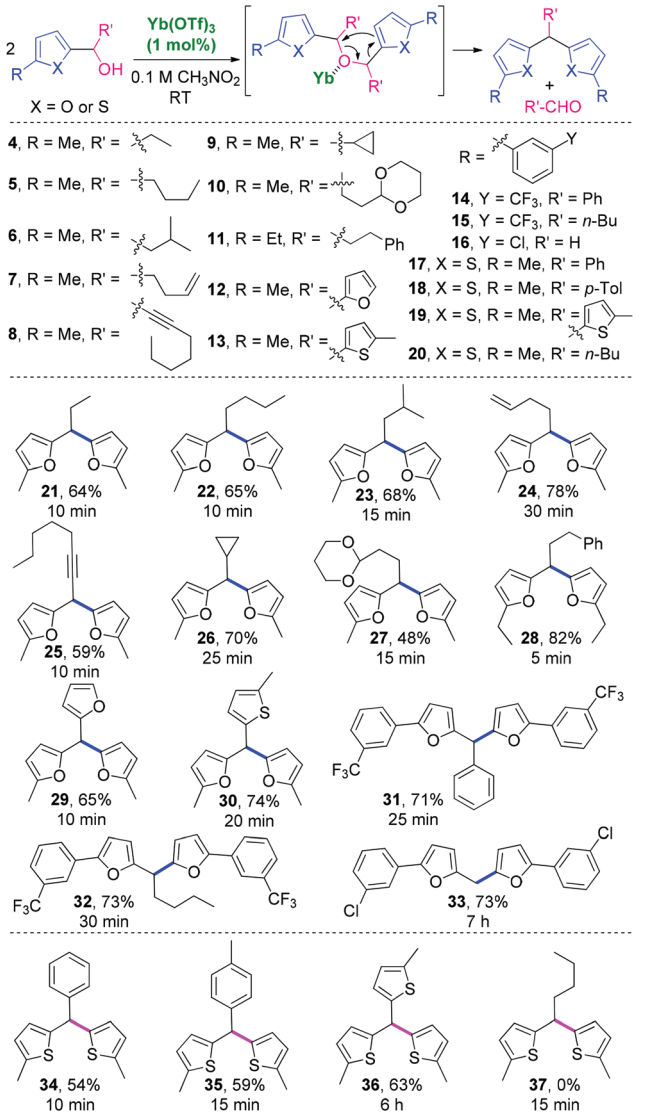
As evident from Table 1, $Yb(OTf)_3$ emerged as an effective catalyst among various Lewis acids screened, in affording **3** in

Table 1 Optimization of reaction conditions[a,b]



Entry	Lewis acid (20 mol%)	Time (min)	Yield[c] (%)
1	$BiCl_3$	10	69
2	$Bi(NO_3)_2$	10	13
3	$FeCl_3$	10	61
4	$InCl_3$	10	68
5	Ag(OTf)	15	66
6	$Cu(OTf)_2$	10	62
7	$In(OTf)_3$	10	46
8	$Sc(OTf)_3$	10	57
9	$Zn(OTf)_2$	10	63
10	$Bi(OTf)_3$	5	54
11	$Yb(OTf)_3$	10	73
12[d]	$Yb(OTf)_3$	15	73
13[e]	$Yb(OTf)_3$	15	74
14[f]	$Yb(OTf)_3$	15	75
15[g,h]	**$Yb(OTf)_3$**	**10**	**78**
16[i]	$Yb(OTf)_3$	3 h	54
17[j]	$Yb(OTf)_3$	48 h	NP[k]
18[l]	$Yb(OTf)_3$	48 h	NP
19[m]	—	48 h	NP

[a] A mixture of 0.2 M solution of alcohol in nitromethane and a catalyst was stirred for an appropriate time. [b] See ESI for detailed solvent screening results. [c] Isolated yields after silica gel column chromatography. [d] 10 mol% catalyst was used. [e] 5 mol% catalyst was used. [f] 1 mol% catalyst was used. [g] 1 mol% catalyst in 0.1 M dilution. [h] Reaction in 0.01 M dilution completes in 8 min with 75% yield. [i] Without solvent (neat). [j] In 0.2 M aqueous solution of alcohol and 20 mol% sodium dodecyl sulfate (SDS). [k] No product. [l] In 0.2 M brine solution. [m] Without any catalyst, no trace of product was observed by crude ^{1}H-NMR.



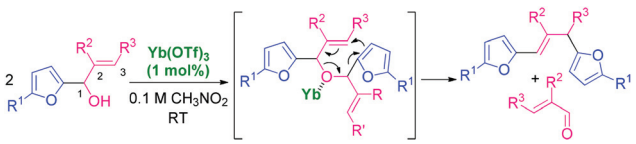
Scheme 3 Yb(III)-catalyzed etherification–fragmentation of furfuryl and thienyl alcohols.

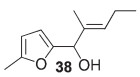
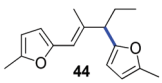
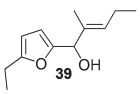
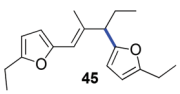
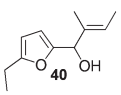
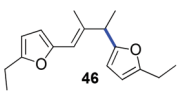
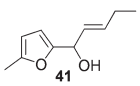
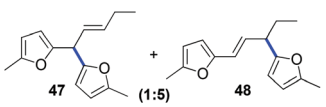
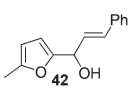
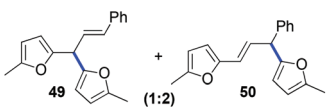
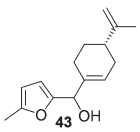
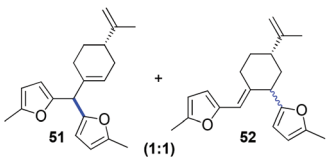
good yield within a short time (entry 11). Further optimization of catalyst loading (entries 12 to 14) established that even 1 mol% of the catalyst is sufficient to carry out the transformation, entry 14. Positive dilution effect indicates a possible intramolecular pathway during the conversion of **2** to **3**, entry 15. Our efforts to develop a neat reaction (entry 16) or an aqueous reaction were unsuccessful (entries 17 and 18). Control experiment verified that the reaction did not proceed in the absence of an Yb source, entry 19. With the optimized reaction conditions in hand (see ESI† for solvent screening results), we then investigated the substrate scope, initially with 2-furyl and 2-thienyl carbinols, Scheme 3.

Accordingly, alcohols **4** to **20** were synthesized according to the literature methods,[16] and were subjected to optimized reaction conditions. The reaction was found to be quite general with furfuryl and thienyl alcohols, but not as successful with benzofuranyl alcohols or furfuryl alcohols bearing no substitution at C-5, where decomposition or multiple product formation was observed. Significantly, as demonstrated by Corma, Dumesic and others,[11] the difurylethanes **21–28** can be easily elaborated to biodiesel or complex higher alkanes *via* simple hydrodeoxygenation. Compounds **29–31** and **34–36** belong to the class of trisubstituted methane derivatives (TRSMs),[19] which are known to be antiproliferative, antitubercular agents, non-steroidal aromatase inhibitors, *etc.* Synthesis of difurylmethanes **31–33** demonstrates the ability of this methodology in generating complex structures. Apart from 2°-furfuryl alcohols, 1°-alcohols are also found to be efficient substrates (compound **33**), but 3°-alcohols generated an inseparable mixture of products.[20] Arylthienyl carbinols are excellent substrates (compounds **34–36**) while analogous aliphatic carbinols (for example, alcohol **20**) are found to be ineffective in generating the fragmentation product, compound **37**. Remarkably, despite the presence of potential nucleophilic heteroaryls such as furan and 5-methylthiophene in alcohols **12** and **13**, respective products **29** and **30** originated only from 2-methylfuran as the migrating group.

However, when furylallyl alcohols were employed as substrates, an unexpected and to the best of our knowledge, unprecedented 1,3-difurylpropenes were isolated *via* allylic furan migration, Table 2. These compounds can be potential precursors to biofuel synthesis and in medicinal chemistry. Realizing the significance of this novel class, allyl alcohols **38–43** were synthesized and subjected to optimized reaction conditions.

Table 2 Synthesis of 1,3-difurylpropenes[a]



Entry	Substrate	Time (min)	Yield (%)	Product(s)
1		10	59	
2		10	72	
3		5	77	
4		10	70	
5		15	68	
6		10	74	

[a] Isolated yields after silica gel column chromatography.

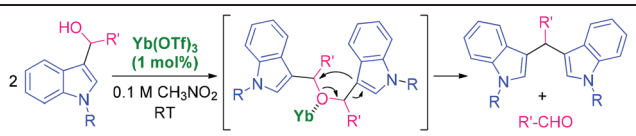
A noteworthy C-2 substituent effect is observed which is critical in the formation of a rigid cyclic six membered transition state (also in stabilizing the transient allylic cation) and is responsible in delivering exclusively the allylic furan migration products **44** to **46**. 1,3-Difurylpropenes accompanied by 1,1-difurylpropenes were obtained in cases where C-2 is either unsubstituted or part of a cyclic system, entries 4–6. Thienylallyl alcohols, on the other hand, generated multiple products at room temperature, but afforded symmetric ether intermediates at lower temperature (0–3 °C).

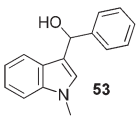
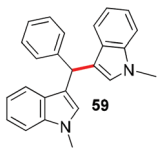
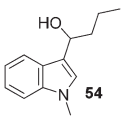
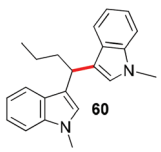
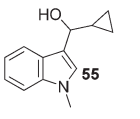
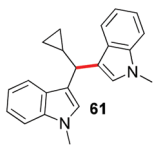
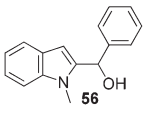
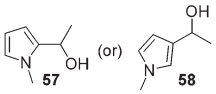
After the success with the furfuryl and thienyl alcohols, we turned our attention towards indolyl alcohols, Table 3.[21] Both aliphatic and aromatic 3-indolyl alcohols (**53–55**) are well-tolerated under the present conditions, generating the respective bisindolylmethanes **59–61** in good yields. However, 2-indolyl and pyrrolyl alcohols are found to be unsuitable substrates under the reaction conditions, entries 4 and 5.

Few representative natural products and medicinally important compounds that can be accessed *via* this methodology are depicted in Scheme 4.[22–27]

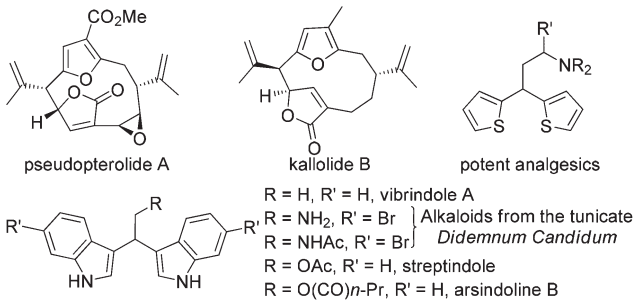
Considering the efficiency of the reaction, short reaction time and positive dilution effect, we hypothesized that the conversion of furfuryl, thienyl and indolyl alcohols under Yb(III)

Table 3 Synthesis of bisindolylmethanes[a]

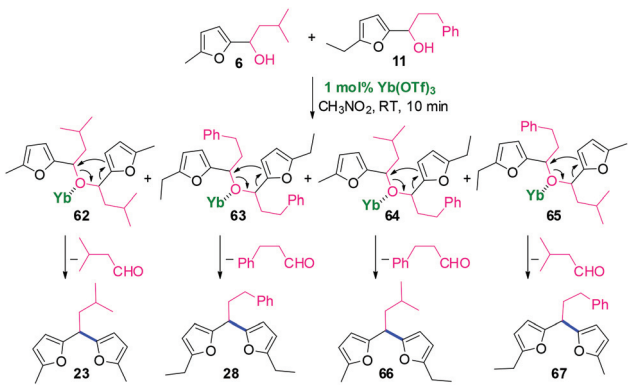


Entry	Substrate	Time (min)	Yield (%)	Product
1		15	78	
2		15	74	
3		15	67	
4		10	—	Complex mixture
5		10	—	Complex mixture

[a] Isolated yields after silica gel column chromatography, yield based on the crude weight of alcohols.



Scheme 4 Some natural products under the purview of this methodology.



Scheme 5 Cross-over experiment between alcohols **6** and **11**.

catalysis might be proceeding in an intramolecular pathway,[28] as discussed earlier, *via* the intermediacy of symmetric ether intermediates.[15a,18,29] Towards gaining some mechanistic insights, initially a cross-over experiment between alcohols **6** and **11** was conducted. Careful analysis of the crude ^{1}H-NMR and GCMS data of the reaction mixture reveals products (**23**, **28**, **66** and **67**) originating from an intramolecular fragmentation of respective *cross-over ethers* **62–65** as shown in Scheme 5 (see ESI† for ^{1}H-NMR and GCMS spectra).

Further support comes from a ^{1}H-NMR experiment with furfuryl alcohol **4** as a substrate in CD_3NO_2 at 20 °C. Our aim was to identify 2-methylfuran which was proposed to be forming in an intermolecular version.[14] ^{1}H-NMR spectra at various stages of the experiment, along with the starting alcohol **4** and 2-methylfuran are depicted in Fig. 1. Evidently, no trace of 2-methylfuran was identified by ^{1}H-NMR analysis throughout the experiment, supporting an intramolecular version (see ESI† for an enlarged picture).

A cross-over experiment between the alcohol **5** and other nucleophilic furans was also carried out. Crude ^{1}H-NMR spectra obtained after the reaction with furan, 3-bromofuran and benzofuran as external nucleophiles indicated no cross-over products. However, when 2,3-dimethylfuran was employed as an external nucleophile, cross-over product was observed (see ESI† for crude spectra) mostly because of the enhanced nucleophilicity of 2,3-dimethylfuran compared to 2-methylfuran. In such a case, the mechanism as in Scheme 2 should be operating.

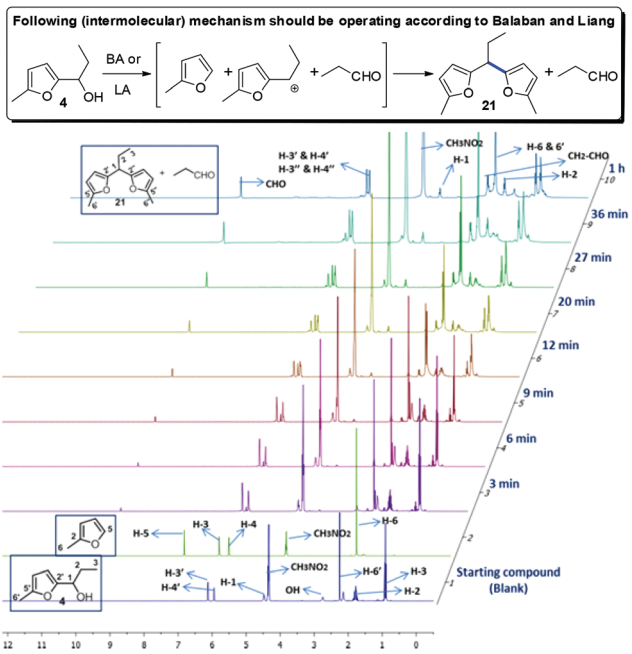


Fig. 1 ^{1}H-NMR experiment results in favour of an intramolecular pathway.

A trapping experiment was also undertaken where the reaction mixture of the alcohol **5** was connected to a continuous vacuum source and the volatiles were trapped at −70 °C. Crude ^{1}H-NMR of the residue shows no indication of 2-methylfuran (see ESI† for the crude spectrum).

From the data presented above, we believe that the reaction most likely is proceeding through an intramolecular fragmentation of the symmetric ether intermediates. Support from theoretical studies will be communicated shortly.

Conclusions

We have described a general method for the conversion of heteroaryl alcohols to di- and triheteroarylalkanes under remarkably small amounts of highly reactive $Yb(OTf)_3$ catalyst. In terms of simplicity, efficiency and ease of availability of starting materials, this reaction thus provides access to a wide variety of difurylmethanes, difurylpropenes, dithienylmethanes and bisindolylmethanes which are otherwise only accessible with difficulty. We hypothesized and found some evidence in favor of an intramolecular pathway operating *via* symmetric ether intermediates during the conversion of heteroaryl alcohols to di- and triheteroarylalkanes. Besides having synthetic and medicinal significance, these compounds find excellent applications in the synthesis of natural products, pharmaceutics and more importantly in the production of high-quality biofuels.

Notes and references

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