Non-metal-catalysed intramolecular alkyne cyclotrimerization reactions promoted by focussed microwave heating in batch and flow modes

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A number of oligomeric alkynes underwent [2 + 2 + 2] intramolecular trimerization to afford arenes under metal-free conditions using focussed microwave heating.

Although there exists an extensive literature on alkyne trimerization,[1] only a few examples have been reported for purely thermal processes.[2] Often temperatures of these reactions range between 100 and 600 °C under solvent-free conditions or they must be conducted under high pressures. More normally the reactions are performed using metal-mediated processes,[3,4] where the product outcome is highly dependent on the metal catalyst, the substitution pattern of the substrates and the reaction conditions employed.[5] In most cases careful work-up of the [2 + 2 + 2] cycloaddition products is necessary to avoid metal contamination due to their highly coordinating properties.[6,7]
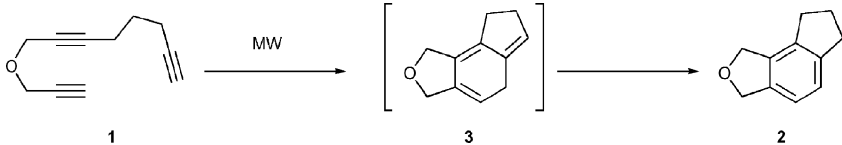
In a research programme designed to expand the chemistry of metal perovskites for organic synthesis,[8] we observed that in certain cases, such as intramolecular alkyne trimerizations, reactions proceeded well without any added metals provided that reactions were conducted using focussed microwave heating methods.[9] Here we report these results showing that the experiments can be performed in both batch and, in one case, flow modes.[10] Also, comparison with normal heating with an oil bath was shown to give inferior results.

In the first experiments we determined optimised conditions for the transformation of the oxygen-bridged triyne **1** to the fully aromatic product **2** *via* a detectable intermediate **3** using focussed microwaves (Table 1). These reactions show that water in the dimethylformamide (DMF) does not unduly effect the reaction other than create higher pressures in the microwave reaction vessel, presumably *via* enhanced decomposition of the DMF. The use of dimethyl sulfoxide (DMSO) or the ionic liquid bmin-PF$_6$ were detrimental to clean progression of the reaction (entries 6 and 7). The optimum conditions for the formation of the aromatic product **2** from **1** appears to be using neat DMF at a temperature of 200 °C for 1 h (entry 8) which proceeds with 100% conversion and in 81% yield after a work-up involving ether extraction and washing with water. This optimised microwave process should be contrasted directly with the batch reaction, which when heated by a conventional oil bath (entry 10), only showed a poor transformation to the desired aromatic product **2**. The choice of **1** as a starting point for these studies was considered to be especially favourable given the related results from previously studied metal-catalysed[6e] processes and the known propensity for oxygen in the side-chain to assist cyclisation.[11]

Next we investigated the substrate scope in these cyclotrimerization processes using a series of alkynes (Table 2) under the standardised conditions (200 °C, MW, DMF) progressing to product(s) as shown. Entry 1 constitutes the optimised conditions for converting the triyne **1** to the aromatic product **2** determined earlier. Also, we showed that it was possible to carry out this reaction in a flow process by pumping the sample through a glass coil[12] in the microwave reaction cavity, maintaining reaction pressure by using a back pressure regulator.[13] While in this example only 1 g of material was processed, it was clear that by allowing the flow to continue many grams could have been readily produced. Entry 2 constitutes

Table 1 Transformation of oxygen-bridged triyne **1** to fully aromatic product **2** *via* intermediate **3** using focussed microwaves[a]

Entry	Temp/°C	Time/h	Solvent	Pressure/bar	Conversion (%)	Comment
1	200	0.5	DMF–H$_2$O, 4 : 1	13.5	95	Clean product **2**
2	160	0.5	DMF–H$_2$O, 4 : 1	7.0	5	Intermediate **3** only product
3	160	10.0	DMF–H$_2$O, 4 : 1	7.0	95	Clean product **2**
4	200	0.2	DMF–H$_2$O, 4 : 1	13.5	65	Products **1** : **3** : **2** as 1 : 1 : 1
5	200	0.5	DMF	4.0	94	Trace of intermediate **3**
6	180	0.5	DMSO	0.7	63	Multiple products
7	200	1.0	bmin-PF$_6$	—	trace	No useful product
8	200	1.0	DMF	4.0	100	Clean product **2**
9[b]	200	0.5	DMF	n.d.	30	Products **1** : **3** : **2** as 70 : 30 : trace (<2%)
10[b]	200	1.0	DMF	n.d.	61	Products **1** : **3** : **2** as 39 : 52 : 9

[a] Biotage AG Emrys microwave synthesiser. [b] Reaction performed with oil bath batch heating; n.d. = not determined.

**Table 2** Cyclotrimerization: substrate scope

Entry	Starting material	Product	Time/h	Yield (%)	Entry	Starting material	Product	Time/h	Yield (%)
1			1	81	6			6	48
2			1	80	7			1	87
3			15	62	8			1	78
4			15	39	9			1	53
5			28	78					

a homologated version of entry 1 and as can be seen readily converts to the desired aromatic product. In the case of the sulfur-linked analogue precursors (entries 3 and 4) transformation progresses slower and less well (62 and 39% respectively) than the oxygen examples. Also in entry 3 some 24% of the thiophene product **4** accompanied the major aromatic product. A mechanistic rationale for these observations is presented later (see Scheme 2). The hydrocarbon-tethered precursor (entry 5) is converted to the aromatic product in 78% yield but also required an extended reaction time (28 h) to afford a clean product. The *N*-tosyl derivative (entry 6) affords the trimerized product but in relatively poor yield (48%). The entry 7 gives encouragement that further substituents may be carried in these cyclotrimerization reactions. Finally entry 8 constitutes a further variation of the theme leading as it does to a *bis*-furano compound while in entry 9 an alkyne was incorporated as one of the elements of unsaturation.

In view of these results it is pertinent to speculate on some of the mechanistic pathways that may be operating in these processes. Firstly in Scheme 1 for the transformation of **1** to **2** *via* the characterised intermediate **3** (X = CH$_2$) it seems reasonable that through either a diradical species or a cyclobutadiene intermediate one can access a Dewar benzene structure[14] **5** (X = CH$_2$). This could rearrange to a lower energy structure **6** or be accessed *via* the allene intermediate **7** (X = CH$_2$) and 4 + 2 electrocyclisation. The allene intermediate **7** could then fragment to a diradical species **8**, which has literature precedence,[15] and lead forward to the observed product **2** *via* intermediate **3**. However, in the example where X is replaced by oxygen (entry 8) the intermediate **6** (X = O) now has a weaker C–H bond adjacent to the oxygen that on fragmentation leads to the observed product in 78% yield. Clearly the ring strain is released and a stable aromatic furan structure is formed. In the case of the sulfur containing triyne **9** (entry 3) this leads to the expected aromatic product and thiophene **4** as a significant by-product. In order to explain this result we anticipate that **9** may first rearrange to the bis-allene intermediate **10** for which there is literature precedence.[16] Next, cyclisation leads forward *via* diradical intermediates to species which undergo prototropic rearrangement to the observed conjugated product **4** (Scheme 2).

In summary, therefore, a series of tethered trialkynes have been shown to cyclotrimerize *via* focussed microwave irradiation to
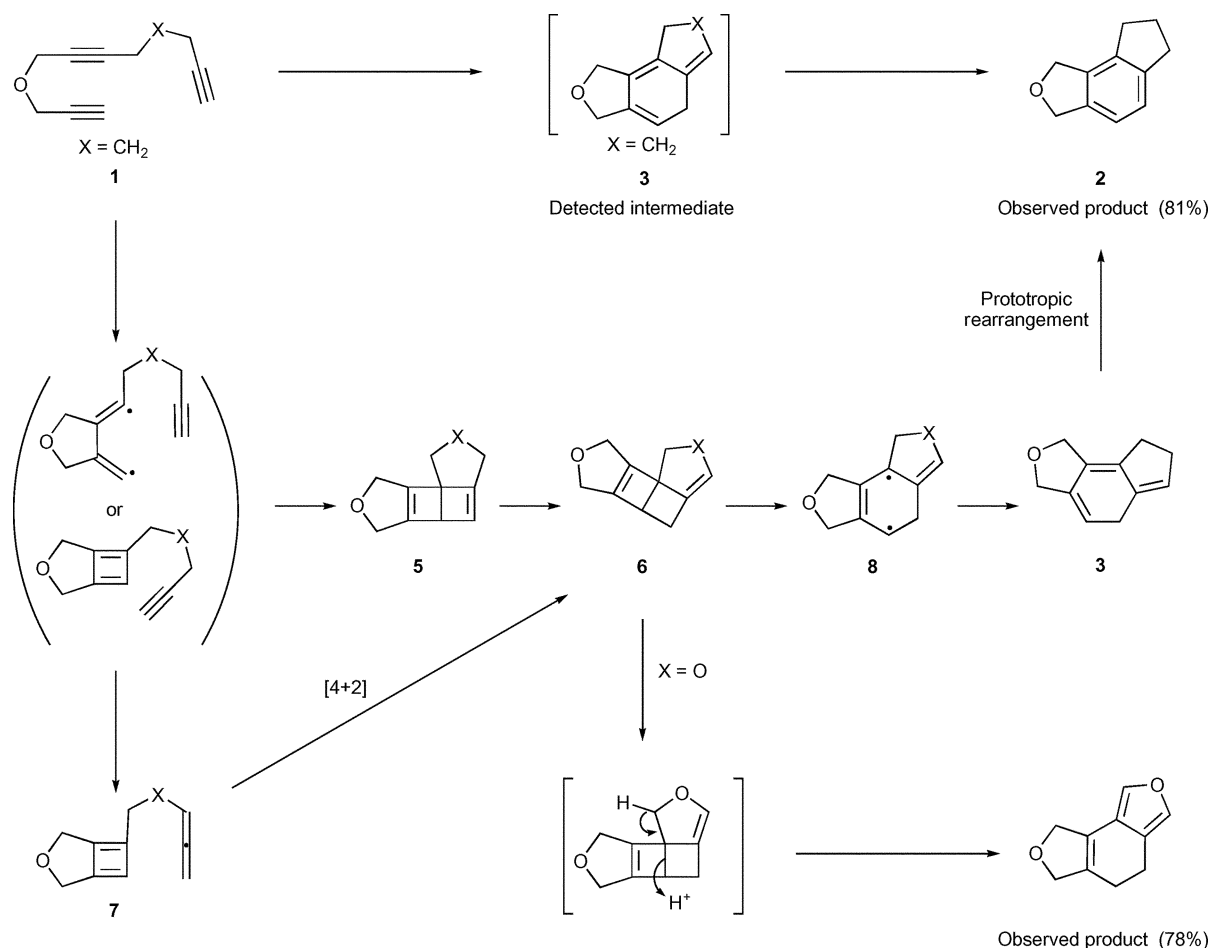
Scheme 1
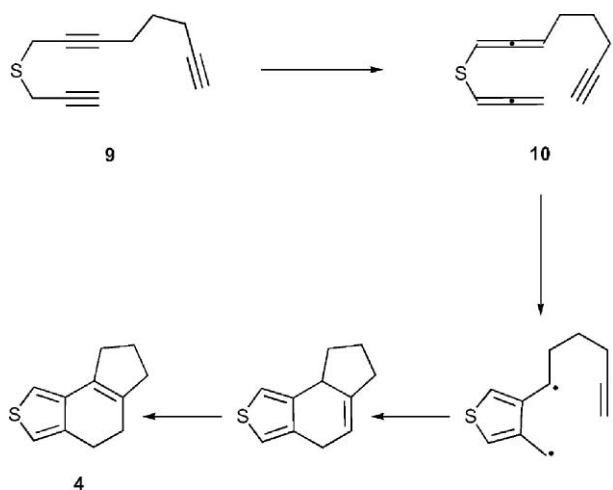
Scheme 2

give arenes in better yield than purely thermal processes and without transition metal catalysis.

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References and notes

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