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An Informal Synthesis of an En-yn-en-yn-ol

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Abstract: We made some molecules and stuff.

Specific: An inefficient, laborious and time consuming synthetic method for the preparation of an en-yn-en-yn-ol is reported. Yields were low, chemoselectivity was poor, and protecting groups were essential. The synthetic route is not amenable to derivatization, and is taxing in terms of both funds and mental health.

This last century has been a good one for organic chemistry. It has seen the arrival of a host of new analytical techniques and a whole phonebook of named reactions. Thousands of groups world-wide now pursue research in this field, alongside the hosts of industry. This upwelling of knowledge comes with a downside however; we're running out of things to synthesise. Bio-prospectors are desperately extracting anything they can lay hands on, in the hope of finding some new sucrose derivative, for which they can perform the first formal synthesis. We, like Alexander the Great, wept, for we saw no worlds left to conquer. This has led us to prowl the fringes of utility, and the depths of obscurity in the search for something new to make. In our desperation, we stumbled upon the class of molecules known as en-yn-en-yn-ols (such as **1**), first hypothesised to exist by Dennis Ryan in 1997 (Figure 1).¹

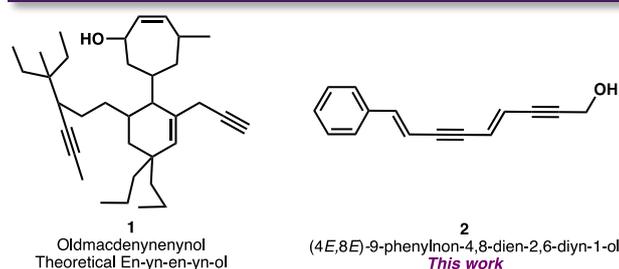


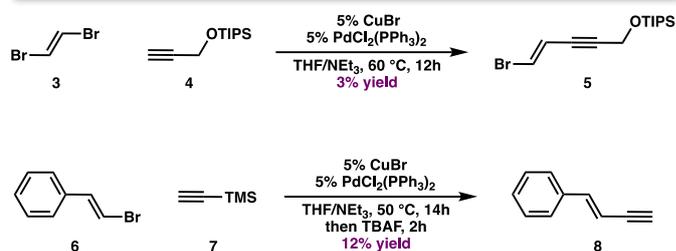
Figure 1 Ryan's first proposed yn-en-yn-en-ol and the target of this work

These molecules have eluded the covetous claws of synthetic chemists for over 20 years. This is likely because these molecules have no purpose whatsoever. None. They are entirely pointless. No applications for them exist, nor will any be found. Secondly, they are fiendishly difficult to make. In a process best described as "death-by-Diels-Alder," they literally tie themselves in knots.² This process is initiated by exposure to light, heat, air, water, shock/vibration and the colour yellow. Even looking at them funny can trigger a violent decomposition. Despite these challenges, we were compelled to attempt the first synthesis of **2**, as grant applications close next month and we needed some runs on the board. Herein, we report the first informal synthesis of (4E,8E)-9-phenyl-non-4,8-dien-2,6-diyn-1-ol (**2**).

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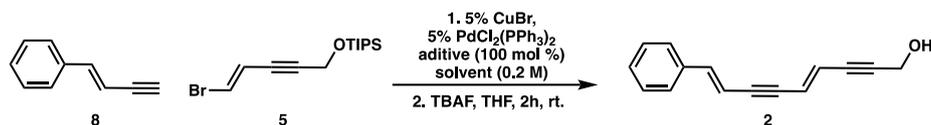
Results and Discussion

A convergent synthetic pathway to **2** was envisaged. The parent molecules of **2** were prepared by Sonogashira reactions (Scheme 1). The coupling of dibromoethene³ **3** with protected propargyl alcohol **4** gave **5** in apocalyptic yield. The progress of the reaction was monitored by smell, using Ho's method of odour analysis.⁴ The reaction is complete when the smell of bin juice is replaced by that of burning tyres. The mixture was purified by flash column-chromatography on silica, alumina, silica again and then more alumina. Elution of the product was achieved with silicon oil/DMSO. It was necessary to conduct this reaction on kilogram scale to obtain useable quantities of en-yn-ol **5**.



Scheme 1 Synthesis of coupling partners **5** and **8**

In a comparatively simple process, vinyl bromide **6** and acetylene **7** were reacted under standard conditions, and the product en-yne **8** was obtained by cooling the reaction mixture to $-20\text{ }^{\circ}\text{C}$ for four months.⁵ With these precursors in hand, suitable conditions were sought for the coupling of en-yn **8** with en-yn-ol **5** (Table 1). Conventional conditions for the Sonogashira reaction failed to deliver any trace of en-yn-en-yn-ol **2**. The use of diisopropylamine as base, or 1,4-dioxane as solvent gave only a trace amount of product. Notably, switching to methanol pushed the yield into double figures. Conscious of the principles of green chemistry, a water/methanol mixture was employed, which surprisingly led to an increase in yield, and an increase in funding. Such a result is atypical of green chemistry. A mixture of methanol and water is already commercially available as a solvent, in the form of Blundaburg Rum. As expected, Blundaburg Rum also furnished **3** in 16% yield. We hypothesised that low yields were a result of inactivation of the palladium catalyst. The fate of the catalyst was interrogated by forensic chromatography,⁶ which yielded



Entry	Solvent	Additive	T (°C)	Time (h)	Yield (%)
1	THF/NEt ₃	-	70	12	0
2	THF/HN ⁱ Pr ₂	-	70	24	1
3	1,4-dioxane/HN ⁱ Pr ₂	-	100	24	2
4	MeOH/NEt ₃	-	80	24	12
5	MeOH/NEt ₃ /H ₂ O	-	100	24	16
6	Blunderburg Rum/NEt ₃	-	100	24	16
7	Blunderburg Rum/NEt ₃	verbal encouragement	100	24	23
8	Blunderburg Rum/NEt ₃	abuse	100	24	13
9	Blunderburg Rum/NEt₃	peer pressure	100	24	31

Table 1 Optimisation of the yield of **2**

large quantities of palladium brown.⁷ Evidently, the catalyst was poisoning itself, a common side-reaction induced by this solvent. This problem was recently encountered by Crosby and Stills in their synthesis of mobile phenones.⁸ They found that verbal encouragement of the catalyst helped it to turn over. By working in six-hour shifts, it was possible to provide the reaction with a constant stream of positive incitement. This produced a jump in yield to 23%. Switching from encouragement to abuse dropped the yield to 13%, affirming the widely held belief that profanity achieves nothing.⁹ Peer pressure proved to be a particularly potent activator of the catalyst system, in conjunction with rum as solvent (entry 9). These conditions were accepted as “good enough,” and furnished en-yn-en-yn-ol **2** in 31% yield. The product takes the form of a fuming brown liquid, with the consistency of crude oil, and the odour of melting E-waste. It’s half-life at ambient temperature is around 30 minutes, with decomposition beginning by isomerisation of the propargylic alcohol to the corresponding en-yn-en-en-ol followed by “death by Diels-Alder.” Nonetheless, this represents the first informal synthesis of an en-yn-en-yn-ol.

Conclusions

En-yn-en-yn-ol **2** has been synthesised in 0.9% yield over two steps. The character of the product was determined, and it was found to be an arsehole. Given how tedious the preparation of **2** proved to be, combined with its complete lack of applications, it is unlikely to be of use to anybody, but we are awaiting toxicological study results. Work on other useless molecules such as en-amine-amide-aminones and moronic acid derivatives has already begun in our laboratory.

Experimental data, spectra and reaction conditions are available for a limited charge from behind the loose brick in the 4th floor toilet of the chemistry building.

Author Contributions

R. B. conducted the experimental work, characterised the products and prepared the unsupported information. P. G. sanctified the glassware. M.H. contributed fuck all. O. M. conceived the synthesis in a moment of drunken passion.

Conflicts of Interest

R.B. has a long-term partner. P. G. thinks that the book is always better than the movie, but really liked the Lord of The Rings films. M. H. finds the Crimean war to be fascinating. O. M. holds the patent for the synthesis of **2**, shares in Blundaburg Rum®, and a farm.

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O. M. acknowledges himself for helpful discussions.

Notes and references

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- 7 Palladium brown is a colloidal suspension of palladium oxide/hydroxide in crude oil
- 8 D. Crosby, S. Stills, G. Nash, N. Young, *J. Mus. Chem.* 1969, **4**, 6743
- 9 Even though it is satisfying.