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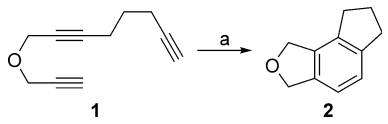
Synthetic Methods

A New Approach for the Synthesis of Highly Substituted Aromatic Rings: The Alkyne-Mediated Approach

Philip J. Parsons,*[a] Daniel R. Jones,[a] Alex C. Padgham,[a] Lewis A. T. Allen,[a] Clive S. Penkett,[a] Robert A. Green,[b] and Andrew J. P. White[a]

Dedicated to Dr. Alfred Bader on the occasion of his 91st birthday and in memory of Oxana Bennett

Abstract: Pentasubstituted aromatic rings serve as templates for drug design and can be conveniently prepared by the thermolysis of suitably substituted alkynes under microwave conditions.



1 2

Scheme 1. Ley's synthesis of a tricycle using microwave conditions. Reagents and conditions: a) DMF, 200 °C, MW (81 %).

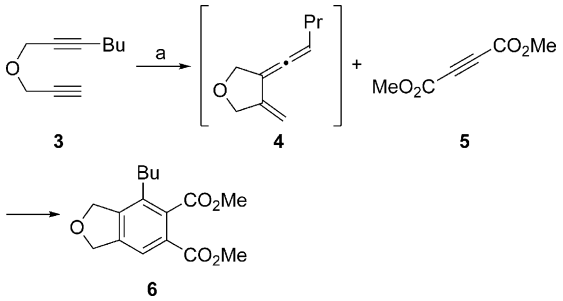
The discovery of cascade reactions added a new dimension to the science of organic synthesis. Such reactions have allowed new architectures to be synthesised, as well as providing more concise syntheses of biologically important molecules and natural products in general. Cascade sequences can proceed by invoking a number of mechanisms including thermal,[1] photochemical,[2] radical,[3] metal-catalysed[4] and organocatalysis.[5]

The synthesis of polysubstituted aromatic rings can be challenging by traditional methods.[6] In view of the importance of these polysubstituted aromatic rings, particularly in the pharmaceutical and agrochemical industries, we elected to design and carry out new and shorter methods for the preparation of these highly desirable molecules without the use of transition-metal-catalyzed cyclisation. Many syntheses of polysubstituted aromatic rings rely on transition-metal-catalyzed cyclisation reactions including gold-, palladium- and cobalt-catalyzed sequences.[7]

Ley and co-workers published an elegant methodology paper, which uses a [2+2+2] cyclisation. A triyne or ene/diyne precursor undergoes a thermal cyclisation when subjected to microwave radiation to afford a tricycle with a tetrasubstituted benzene core (Scheme 1).[8] Sakai and Danheiser extended this work to include the use of nitriles, hence forming a pyridine derivative.[9]

Parsons and co-workers have demonstrated that a thermal intramolecular cyclisation can be used to form the lactonamycin core and other interesting fused heterocyclic and carbocyclic compounds without the use of metal catalysis.[10] Further, it was found that in general, ene-diynes can cyclise to afford furans and dihydrofurans.[1]

Danheiser and co-workers showed that intermolecular cascade reactions could efficiently yield bicycles and tricycles (depending on the nature of the dienophile).[11] The diyne species (**3**) undergoes an intramolecular propargylic ene reaction to form an intermediate allene followed by the concomitant intermolecular Diels–Alder reaction in the presence of a dienophile to yield the polycyclic product (Scheme 2). Parsons and co-workers have also demonstrated that an intra/intermolecular reaction can take place.[12]



Scheme 2. Danheiser's intermolecular cascade reaction. Reagents and conditions: a) i) PhMe, 160 °C; ii) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 25 °C (72 %).

Our initial studies focused on a palladium mediated cyclisation, because we envisaged that a pentasubstituted benzene ring could be formed in one synthetic operation (Scheme 3).

To our delight, the cyclisation outlined in Scheme 3 gave rise to the pentasubstituted benzene derivative (**8**) albeit in 28 % isolated yield. To avoid the use of metals in our cyclisation reactions and to attempt to improve the yields of the cyclized products, we investigated the chemistry of propargyl ethers (Scheme 4).

[a] *Prof. P. J. Parsons, D. R. Jones, A. C. Padgham, L. A. T. Allen, Dr. C. S. Penkett, Dr. A. J. P. White*
Department of Chemistry, Imperial College London
South Kensington, London, SW7 2AZ (UK)
E-mail: p.parsons@imperial.ac.uk

[b] *R. A. Green*
School of Chemistry, University of Southampton
Southampton, SO17 1BJ (UK)

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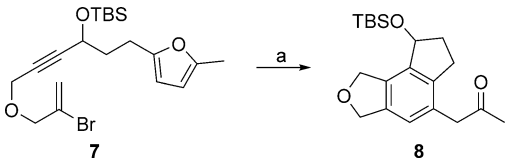
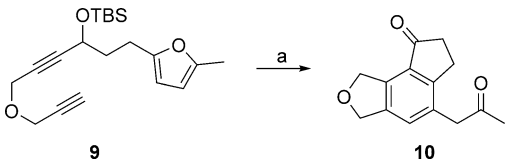


7 8

Scheme 3. Palladium-assisted cyclisation of furans. Reagents and conditions: $[Pd(OAc)_2]$, PPh_3, K_2CO_3, MeCN (28%).



9 10

Scheme 4. Thermal cyclisation of alkynes. Reagents and conditions: DMF, 200 °C, MW, 3 h (45%) or H_2O, 200 °C, MW, 1 h (50%).

Synthesis of the ether (**9**) proved to be very straightforward (Scheme 5).

With the ether (**9**) in hand, we carried out a microwave-assisted cyclisation, and to our delight, the tricycle (**10**) was formed in 45% isolated yield (Scheme 4). Alternatively, when water was used as the reaction solvent, the yield of **10** increased to 50% when subjected to microwave irradiation.

A series of analogues of the furan **9** were prepared (Table 1).

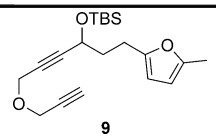
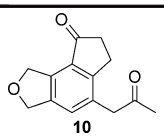
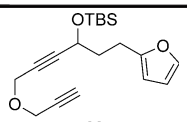
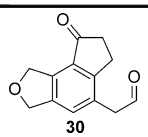
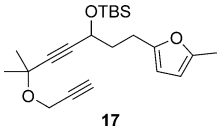
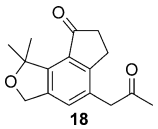
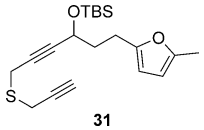
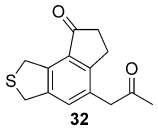
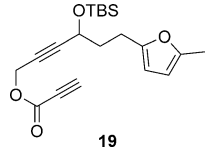
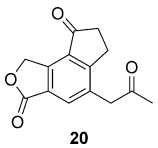
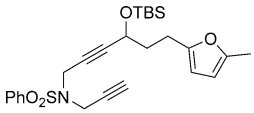
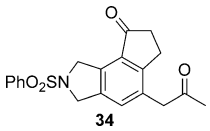
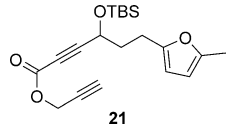
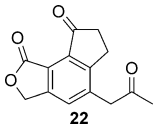
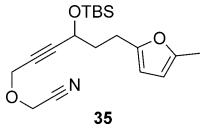
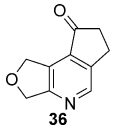
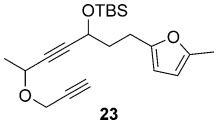
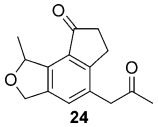
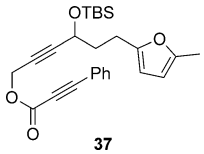
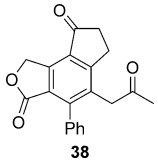
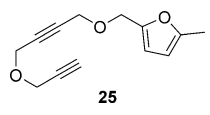
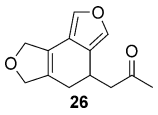
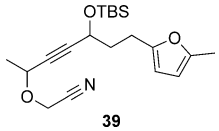
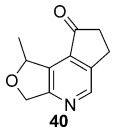
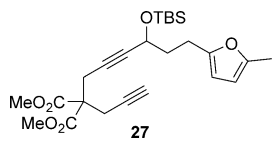
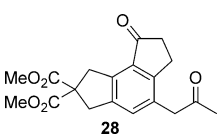
Of particular note is the conversion of the nitrile (**35** and **39**) into the pyridines (**36** and **40**) with loss of the propanone moiety. The mechanism proposed for this cyclisation is shown in Scheme 6.

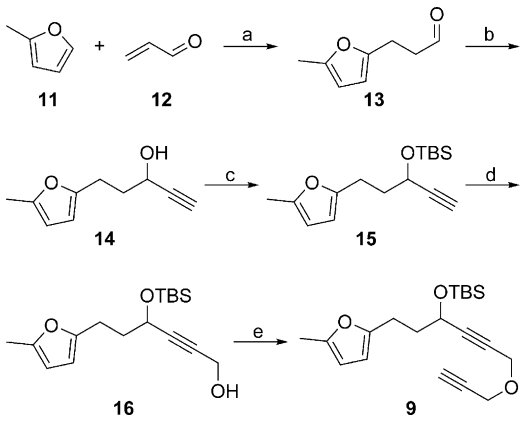
Thermal cyclisation of furan **35** resulted in the formation of the imine **41**. The azadiene then underwent a [4+2] cycloaddition with the pendant furan to give the intermediate tetracycle **42**. Fragmentation of **42** resulted in the formation of the enone **43**, which in turn lost acetone to give the pyridine **36**.

The aldehyde **30** is also an interesting product, because it would be difficult to synthesise by other means. The mechanism of the formation of **30** relies on Diels–Alder/fragmentation chemistry (Scheme 7).

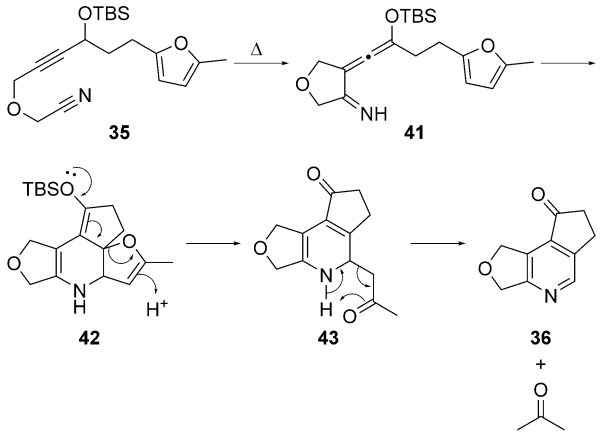
Attempted cyclisation using a palladium-mediated cascade failed to give the aldehyde (**48**; Scheme 8).

Table 1. Analogues synthesised by using new cyclisation methodology. Reagents and conditions: MeCN, 200 °C, MW, 1–6 h.

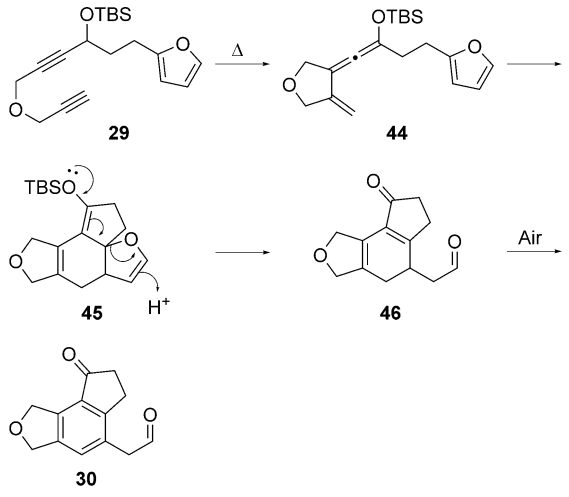
Entry	Starting material	Product	Yield [%]	Entry	Starting material	Product	Yield [%]
1	 **9**	 **10**	50	8	 **29**	 **30**	31
2	 **17**	 **18**	61	9	 **31**	 **32**	23
3	 **19**	 **20**	62	10	 **33**	 **34**	32
4	 **21**	 **22**	62	11	 **35**	 **36**	42
5	 **23**	 **24**	50	12	 **37**	 **38**	65
6	 **25**	 **26**	99	13	 **39**	 **40**	48
7	 **27**	 **28**	32				



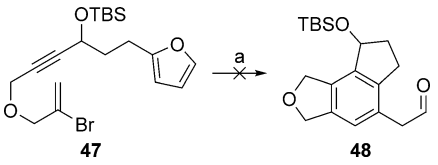
Scheme 5. Reagents and conditions: a) AcOH, HOC_6H_4OH, H_2O, 130 °C, 30 min (93%); b) ethynylmagnesium bromide (83%); c) *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, 4-dimethylaminopyridine (DMAP; 92%); d) i) *n*BuLi; ii) *para*-formaldehyde (84%); e) i) NaH, THF; ii) propargyl bromide (88%).



Scheme 6. Proposed mechanism for the formation of the pyridine derivative.

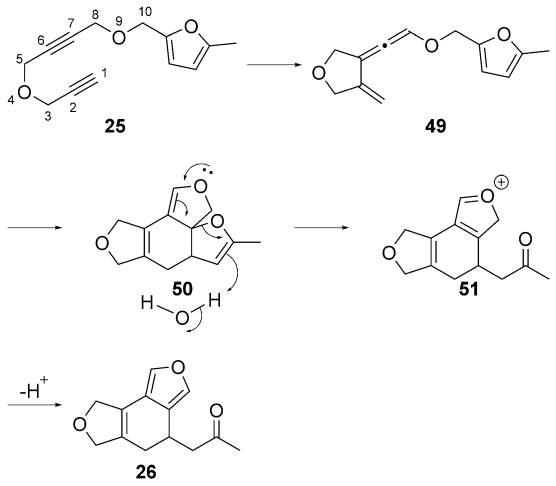


Scheme 7. Proposed mechanism for the formation of the aldehyde derivative.



Scheme 8. Attempted palladium-mediated cyclisation to for the aldehyde derivative. Reagents and conditions: a) $[Pd(OAc)_2]$, PPh_3, K_2CO_3, MeCN.

The highest yields in the cyclisation reactions were observed with those starting materials containing either a *gem*-dimethyl group, which demonstrates the Thorpe–Ingold effect to enhance cyclisation or with oxygen atoms present in the side-chain with appended lone pairs, as an example **25**.[13] Entry 6 (Table 1) is very interesting due to the high yield of the product **26** and the fact that aromatic furan ring formation is favoured in preference of benzene-ring production. This observation can be explained, because the oxygen atom at position nine of the chain appended to the furan moiety becomes the 3,4-disubstituted furan **26**. The suggested mechanism of this reaction is shown in Scheme 9.



Scheme 9. Proposed mechanism for the formation of the furan derivative.

Cyclisation of the ether **25** gave **26** in very high yield (99%). The reaction proceeded by an ene reaction followed by a Diels–Alder reaction to afford a tetracyclic intermediate **50**. The furan **26** was formed, because simple proton loss from **51** gave rise to the aromatic furan rather than the oxidative process, which would form a benzene ring. Further, oxidation of **26** would give a highly strained 10π ring system, which is unfavourable. In the other examples quoted, a carbon atom is present at position nine, and hence aromatic ring formation is not possible in a five-membered ring system.

The cyclisation of **9** to **10** was also attempted using a thermal flow technique. The initial results of which are very encouraging (these experiments were carried out with colleagues at the University of Southampton). However, isolated yields were modest compared with the batch microwave technique.

Most recently, this methodology has been extended to include the formation of hexasubstituted benzene rings (**38**; entry 12, Table 1). This was achieved by using a substituted alkyne (**37**) in place of a terminal alkyne and made little difference to the yield for the cyclisation step. Its structure was determined by X-ray crystallography (Figure 1) and showed that the newly appended phenyl ring is orthogonal to the tricycle giving potential applications in the area of molecular switches, which may be enhanced by substitution of the *ortho* or *meta* positions.[14] This also greatly expands the scope of this reaction for the synthesis of drugs templates.

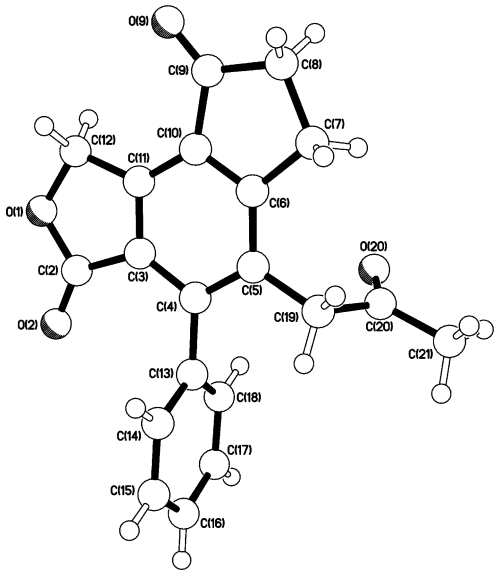


Figure 1. Crystal structure of a hexasubstituted benzene (**38**).

In conclusion, we have discovered that substituted alkynes containing a furan group can cyclise in one step to give tricyclic compounds. Although the yields of **28**, **30**, **32** and **34** are relatively low, alternative syntheses of these compounds would involve multi-step sequences, and yields would be lower than reported herein. We anticipate that the new cyclisation products will have uses in drug design.

Acknowledgements

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Keywords: alkynes · aromatic rings · cyclization · furan · microwave chemistry · thermolysis

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