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Synthesis of conformationally restricted sulfonamides via radical cyclisation

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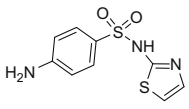
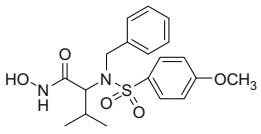
ABSTRACT

A convenient synthesis of conformationally restricted sulfonamides such as compounds (**12**) and (**40**) with seven- and eight-membered ring structures has been achieved using radical reaction. These compounds and their analogs are expected to serve as important pharmacophores in drug discovery.

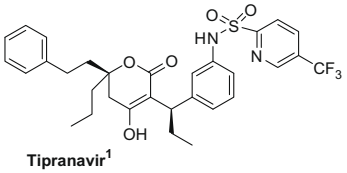
There are many drugs, used in human medicine,[1] that contain sulfonamide moiety in their structures. A few representative examples of sulfonamides that show biological activities against a variety of disease targets are illustrated below.



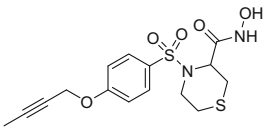
Sulfathiazole
Antibacterial[1]



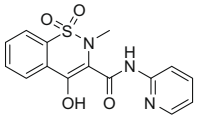
CGS 25966[1]
MMP Inhibitor



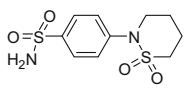
Tipranavir[1]
HIV Protease Inhibitor



TACE Inhibitor[1]

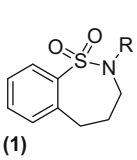


Piroxicam[2]
Antiinflammatory agent

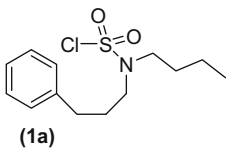


Sulthiame[3]
Anti Epileptic agent

It should be noted that several of these drugs contain an acyclic sulfonamide chain, and thus they can exist in many conformations when bound to enzymes or occupying receptors. However, there are others such as Piroxicam[2] and Sulthiame[3] that do possess cyclic sulfonamide structures. We were interested in synthesising conformationally restricted sulfonamides, which could serve as important pharmacophores in drug discovery, and in this Letter, we would like to disclose some of our results. Specifically, we were interested in synthesising compounds represented by the general structure (**1**) using radical cyclisation reaction. Katritzky et al.[4] synthesised compound (**1**) wherein, R is a butyl group by Friedel–Craft cyclisation of compound (**1a**). The cyclisation to obtain the corresponding eight-membered ring derivative yielded a trace amount of the desired compound. In this Letter, we wish to disclose a convenient synthesis of compounds represented by the structure (**1**) wherein the R could be alkyl, aryl and aryl alkyl groups. The ring size could be either seven or eight.



(1)



(1a)

Motherwell[5] and co-workers observed that a radical reaction involving substrate (**2**) yielded (**5**) and (**6**). Thus the initial radical (**3**) obtained from (**2**) cyclised onto the aromatic ring to form (**4**) which underwent loss of sulfur dioxide to yield the biphenyl (**5**) or rearranged with the loss of hydrogen radical to yield (**6**) (see Scheme 1).

We further investigated the above-mentioned reaction with (**7**) and obtained (**8**) (see Scheme 2).

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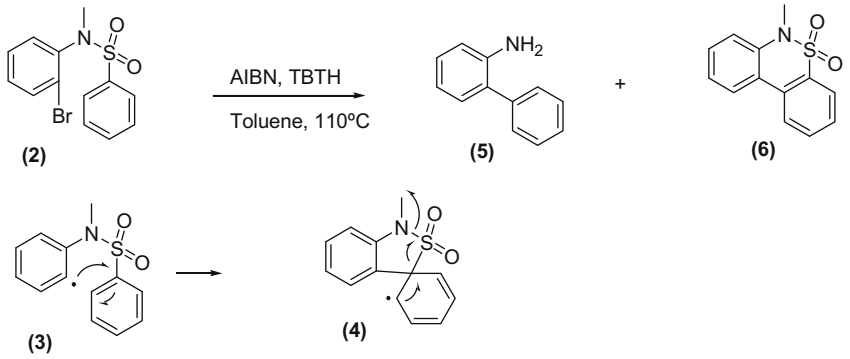


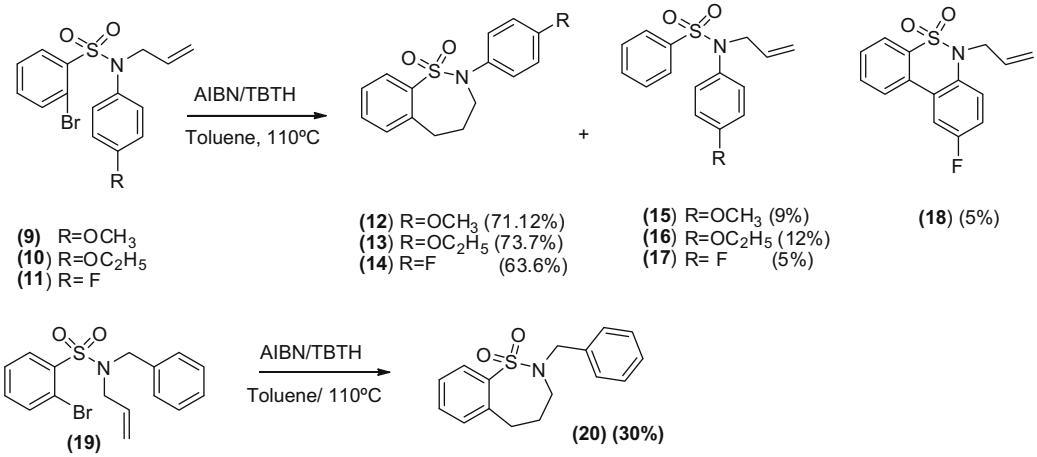
Scheme 1.

Scheme 2.

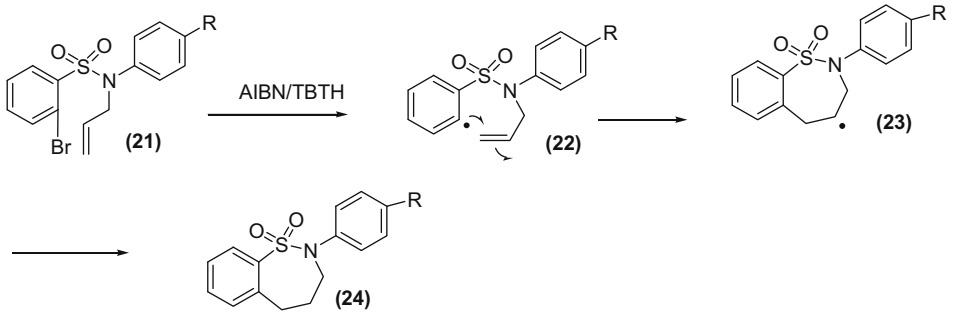
At this point we were interested in studying the radical reaction of retro sulfonamides such as (**9**). Thus treatment of compounds (**9**), (**10**) and (**11**) with AIBN/TBTH in toluene yielded unexpectedly the endocyclic addition products[6–8] (**12**), (**13**) and (**14**) as major products, respectively, along with minor amounts of the corresponding debrominated compounds (**15**), (**16**) and (**17**). In addition (**11**) also yielded a smaller amount of (**18**). Similarly, compound (**19**) yielded (**20**) (see Scheme 3). Thus, the above-mentioned reactions yielded the desired conformationally restricted sulfonamides represented by the general structure (**1**).

We believe that the mechanism of the above-mentioned reaction involves direct addition of the phenyl radical (**22**) to the terminal end of the double bond in an endocyclic sense as shown in the Scheme 4.

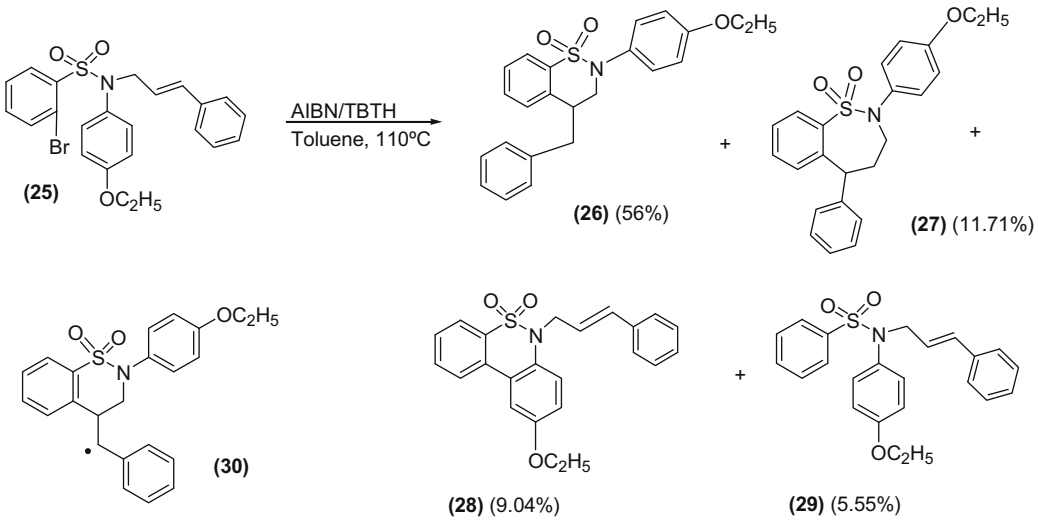
To study the scope of the above-mentioned reaction further, we treated (**25**) under radical reaction conditions and isolated compounds (**26**), (**27**), (**28**) and (**29**). (Scheme 5). The major product in this reaction was formed via benzylic radical (**30**).



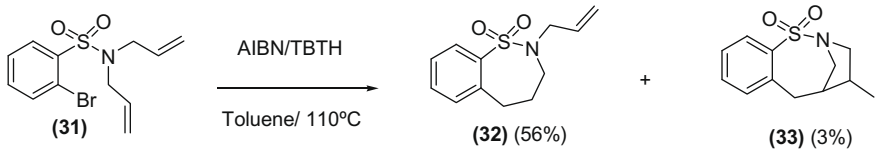
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

When compound (**31**) was subjected to the radical cyclisation reaction, it yielded (**32**) as the major product along with a minor amount of (**33**) (see Scheme 6).

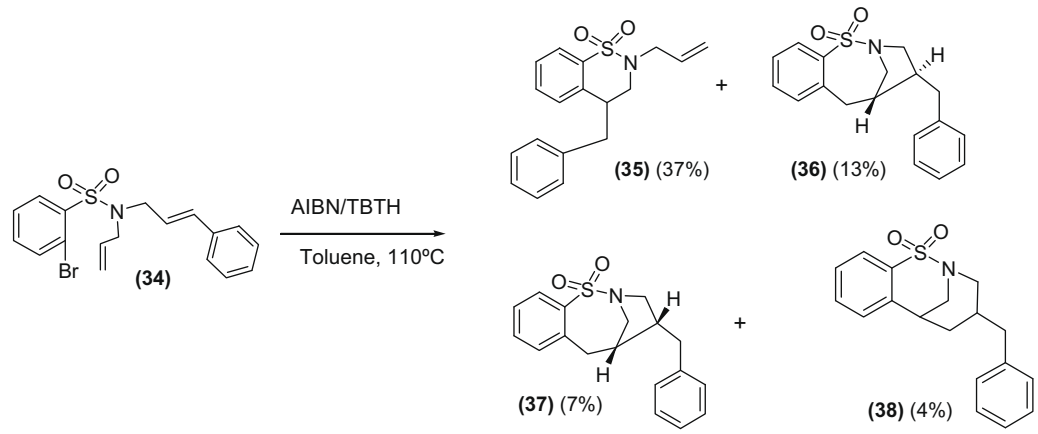
To investigate the competition of phenyl radical addition between an allyl and a cinnamyl group, we treated compound (**34**) with AIBN and TBTH and isolated compounds (**35**), (**36**), (**37**) and (**38**). The major product isolated from the reaction was compound (**35**) (see Scheme 7).

The origins of (**36**) and (**37**) could be traced to the radical derived by the addition of the initial phenyl radical to the allyl double bond in the endocyclic sense, and (**38**) is derived from the radical derived by the addition of the initial phenyl radical to the allyl double bond in the exocyclic mode.

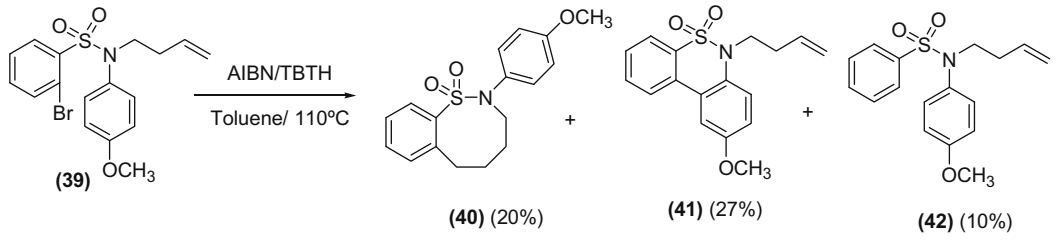
We then wanted to see the possibility of synthesising compounds of larger ring size, and thus we treated compound (**39**) with AIBN and TBTH and isolated compound (**40**), which is a eight-membered cyclic sulfonamide along with (**41**) and (**42**) (see Scheme 8).

Upon increasing the length of the carbon chain on nitrogen, compounds (**43**), (**44**) and (**45**) yielded under radical reaction condition compounds (**46**), (**47**) and (**48**), respectively, along with the corresponding debrominated compounds (**49**), (**50**) and (**51**) (Scheme 9).

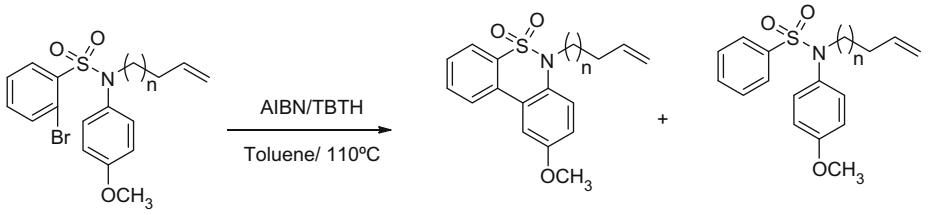
Thus, when the length of the carbon chain is increased, the distance of the terminal double bond from the phenyl radical also increases, which makes it difficult to add to the terminal double bond. Instead, the phenyl radicals take the alternative pathway of addition to the other aromatic ring followed by rearrangement and loss of a hydrogen radical to yield the observed products, or the starting compounds simply underwent debromination.



Scheme 7.



Scheme 8.



Scheme 9.

Acknowledgement

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References and notes

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6. In a typical experiment, AIBN (0.09 g, 0.7 mmol) was added to a solution of compound **10** (0.7 g, 1.8 mmol) in toluene (13 ml) with stirring. TBTH (0.9 ml, 2.9 mmol) was then added dropwise to the above-mentioned solution, which was then refluxed for around 3 h. At the end of the reaction, it was diluted with EtOAc and washed with water. The aqueous layer was extracted twice with EtOAc, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography to obtain compounds **13** (0.41 g, 73.7%) and **16** (0.069 g, 12%).
7. Yields are indicated in parentheses; however, they were not optimised. Compounds were crystallised from a mixture of dichloromethane and hexane. Melting points of the crystalline compounds are shown below: **12** (53–54 °C), **13** (57–58 °C), **14** (100–102 °C), **15** (75–77 °C), **16** (68–70 °C), **20** (81–83 °C), **26** (125–126 °C), **27** (169–171 °C), **35** (106–108 °C), **36** (143–144 °C), **37** (98–100 °C).
8. NMR and high resolution mass spectra of all the compounds described in this Letter were consistent with the assigned structures. Assignments were further confirmed using 2D NMR experiments.