

# Steric acceleration of an uncatalysed ene reaction at room temperature

Nandeo Choony,<sup>a</sup> Peter G. Sammes,<sup>\*a</sup> Graham Smith<sup>a</sup> and Robert W. Ward<sup>b</sup>

<sup>a</sup> Department of Chemistry, School of Physics and Chemistry, UniS, Guildford, Surrey, UK GU2 7XH.  
E-mail: p.sammes@surrey.ac.uk

<sup>b</sup> GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW

Received (in Cambridge, UK) 24th July 2001, Accepted 7th September 2001  
First published as an Advance Article on the web 27th September 2001

The bulky trityl steric buttress is used to effect an intramolecular, uncatalysed ene reaction that operates at room temperature, whilst smaller buttresses require heat.

The ene<sup>1</sup> reaction and its intramolecular counterpart<sup>2</sup> are synthetically useful processes that have been exploited in a wide range of chemistry. Normally the ene reaction requires the use of heat at temperatures greater than 140 °C to proceed and, for systems where the enophile is not activated by an electron withdrawing group, *much* higher temperatures are often required.<sup>3</sup> For systems with electron deficient enophiles, the process may be catalysed with Lewis acids, whereby the reaction has been observed to proceed at ambient temperatures<sup>4</sup> but such catalysis is not generally effective for non-activated enophiles.

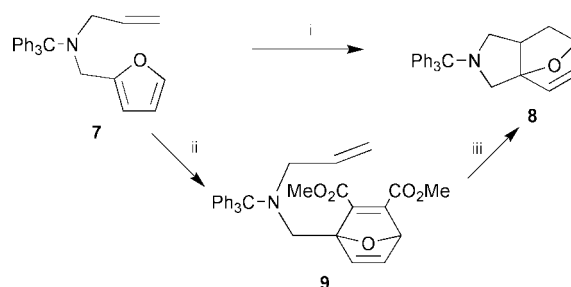
The stereochemistry of the intramolecular ene process<sup>2</sup> has also been examined and, under vigorous thermal conditions, stereocontrol is often lost. Thus, heating the simple *N*-trifluoroacetyl-*N*-allyl-*N*-dimethylallylamine compound **1** at 220 °C for 30 min effects an intramolecular ene reaction and converts it into the mixture of *cis* and *trans*-pyrrolidines **2** and **3**.<sup>5</sup> The latter compounds are of interest as members of the kainic acid family of neuroactive agents,<sup>6</sup> the kainic acid series having the *cis*-stereochemistry **2** and the *allo* series the *trans*-stereochemistry **3**.<sup>7</sup> Thus any means of controlling the stereochemistry of the intramolecular ene process would be of synthetic value.

As part of our interest in the use of steric buttressing as an aid to reactions,<sup>8</sup> herein we describe examples of use of a steric buttress that assists ene reactions to occur under uncatalysed and low temperature conditions.

Upon heating in xylene, under argon at 140 °C, for 100 h, the trityl-protected *N*-allyl-*N*-dimethylallylamine **4**, prepared by standard methods,<sup>†</sup> smoothly produced the ene product **6** in almost quantitative yield (Scheme 1). Only one isomer could be detected by <sup>1</sup>H NMR spectroscopy (>95%), assigned from <sup>1</sup>H NOE experiments, as the *cis*-isomer. The *cis*-isomer is known to be the preferred stereoisomer in analogous carbocyclic ene

reactions.<sup>2</sup> That a buttressing effect is operating was supported by the observation that no sign of any cyclisation product was obtained upon heating the parent amine **5** under the same conditions. The ease of the buttressed cyclisation, compared with the harsh conditions normally reported for unactivated ene reactions,<sup>3</sup> led us to seek other examples of the sterically assisted ene process.

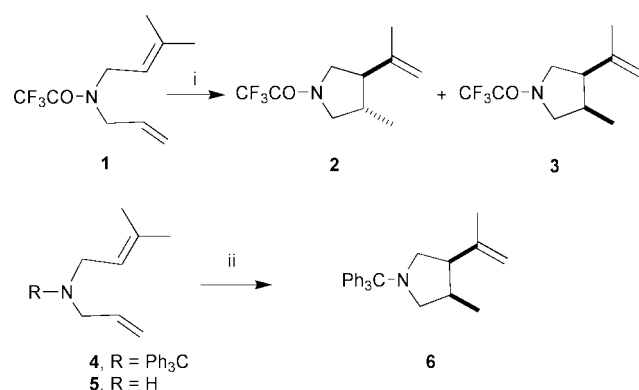
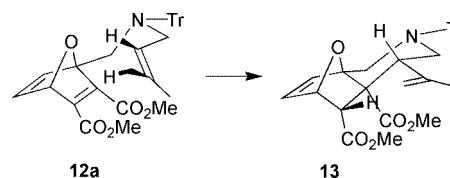
In earlier work we had shown that, on heating, the trityl protected *N*-allylfurfurylamine **7** undergoes an intramolecular Diels–Alder cycloaddition to the corresponding cycloadduct **8** in almost quantitative yield. At rt a competing intermolecular cycloaddition, with dimethyl butynedioate, is possible to give the cycloadduct **9** but, on heating, this loses the acetylenic ester by a retro-cycloaddition reaction and again forms the thermodynamically favoured cycloadduct **8** (Scheme 2).



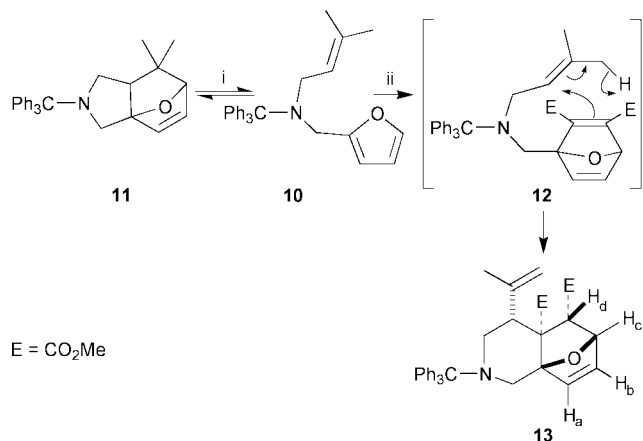
Scheme 2 i, 120 °C, 24 h; ii, MeO<sub>2</sub>C–C≡C–CO<sub>2</sub>Me, rt; iii, 120 °C.

The intramolecular process, *e.g.* **7** to **8**, is sensitive to substituents on the allyl group and the dimethylallyl derivative **10**, only undergoes partial cycloaddition to **11** on heating, to form an 80:20 equilibrium ratio of the cyclised to uncyclised components at 140 °C. A similar competing, intermolecular cycloaddition was attempted with **10** as a parallel reaction to that performed on the unsubstituted allyl compound **7**.

When the tritylated amine **10** was allowed to react with dimethyl butynedioate at rt over 5 d, a new product formed in high yield. However, the compound was *not* the expected Diels–Alder product **12** but, instead, the ene product **13**, isolated as a crystalline solid, mp 164–166 °C (Scheme 3). In its <sup>1</sup>H NMR spectrum **13** showed loss of the isopropylidene group and the furan ring protons and formation of the isopropenyl group. The ring protons, H<sub>a</sub> to H<sub>d</sub>, showed as a tightly coupled ABXY system. NOE experiments indicated the geometry shown, resulting from an approach, *via* the transition state **12a**, from the least hindered, *exo*-face of the oxabicycloheptadiene system. It should be noted that this ene reaction involves a type 1 process



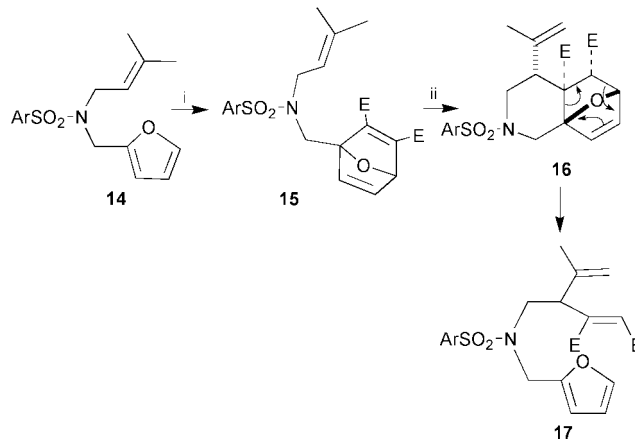
Scheme 1 i, 220 °C, 30 min; ii, 140 °C, 4 days.



**Scheme 3** i, 140 °C, xylene; ii, MeO<sub>2</sub>C–C≡C–CO<sub>2</sub>Me, rt.

of a 1,7-diene system, that normally proceed in only modest yields at very high temperatures.<sup>2,9</sup>

The striking buttressing effect of the trityl group was further illustrated by repeating the reaction using the 'smaller' buttress, the 4-toluenesulfonamide **14**.<sup>10</sup> In this case the dimethyl butynedioate adduct **15** could be isolated but showed no sign of ene products after leaving at rt for several weeks. However, on heating to 70 °C, compound **15** slowly reacted further, an ene reaction being observed, as indicated by the appearance of the compound **16** as a transient intermediate but which was unstable to the reaction conditions and underwent a subsequent retro-Diels–Alder reaction to form the furfuryl derivative **17** (Scheme 4). That this sequence of ene reaction followed by the retro-Diels–Alder process occurred, rather than an initial retro-Diels–Alder reaction, followed by an intermolecular ene process was supported by the absence of any of the starting material **14** either as a reaction product or as a transient intermediate. In contrast to the behaviour of the tosylated intermediate **16**, heating the *N*-tritylated ene product **13** at 70 °C gave no indication of the competing retro-Diels–Alder reaction, none of the open form corresponding to **17** being formed. Thus, not only does the trityl buttress assist in lowering the activation energy for the ene process but it also helps prevent the subsequent retro-Diels–Alder process from occurring. Presumably the open form (*cf.* **17**) would occupy more conformational space than is available in the presence of the sterically demanding trityl group, hence



**Scheme 4** i, MeO<sub>2</sub>C–C≡C–CO<sub>2</sub>Me, rt, 7 days; ii, heat, 70 °C, 3 days.

leaving the equilibrium firmly in favour of the closed form **13**.

We thank GlaxoSmithKline Pharmaceutical Research and the EPSRC for a research studentship (to G. S.)

## Notes and references

† Satisfactory microanalytical and spectroscopic data were recorded for all new compounds described in this communication.

- H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 556.
- W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 476.
- W. D. Huntsman, V. C. Solomon and D. Eros, *J. Am. Chem. Soc.*, 1958, **80**, 5455.
- B. B. Snider, *Acc. Chem. Res.*, 1980, **13**, 426.
- P. D. Kennewell, S. S. Matharu, J. B. Taylor and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2542.
- H. Shinozaki and S. Konishi, *Brain Res.*, 170, **24**, 368; G. A. R. Johnston, D. R. Curtis, J. Davies and R. M. McCulloch, *Nature*, 1974, **248**, 804.
- M. V. Chevliakov and J. Montgomery, *J. Am. Chem. Soc.*, 1999, **121**, 11 139.
- P. G. Sammes and D. J. Weller, *Synthesis*, 1995, 1205.
- W. D. Huntsman, P. C. Lang, N. L. Madison and D. A. Ulrick, *J. Org. Chem.*, 1962, **27**, 1983.
- N. Choony, A. Dadabhoy and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2017.