Tetrahedron Letters 50 (2009) 3446–3449

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A dramatic effect of double bond configuration in *N*-oxy-3-aza Cope rearrangements—a simple synthesis of functionalised allenes

Luis F. V. Pinto [a], Paulo M. C. Glória [a], Mário J. S. Gomes [a], Henry S. Rzepa [b], Sundaresan Prabhakar [a,*], Ana M. Lobo [a,*]

[a] Chemistry Department, REQUIMTE/CQFB, Faculty of Sciences and Technology, New University of Lisbon, and SINTOR-UNINOVA, 2829-516 Monte de Caparica, Portugal
[b] Chemistry Department, Imperial College London, South Kensington Campus, SW7 2AY London, UK

ARTICLE INFO

Article history:
Received 24 February 2009
Accepted 25 February 2009
Available online 14 March 2009

Keywords:
3-Aza Cope rearrangements
Hydroxylamines
Enamines
Allenes
Configuration
Intermediates
Transition states

ABSTRACT

The first examples of low temperature *N*-oxy-3-aza Cope rearrangements, leading to functionalised allenes are described, where the *Z*-configuration of the enaminic double bond in the rearranging system proves critical.

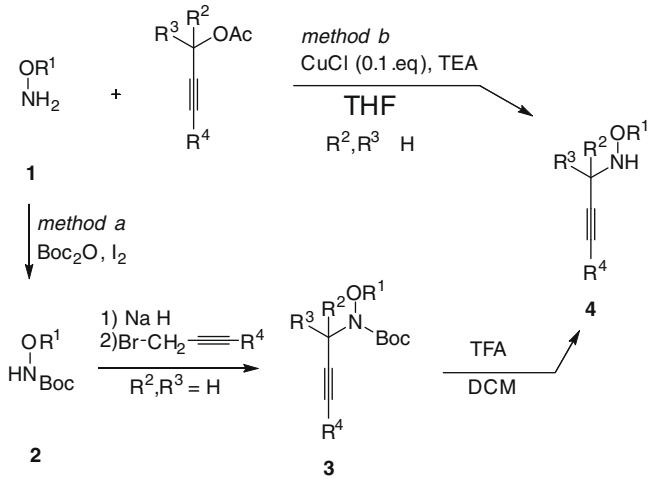
With the decrease in the availability of fossil fuels and the necessity to guarantee the sustainability of life in the planet, chemists' attention has been increasingly focused in low and room temperature reactions that can provide access to functionalised molecules with a minimum of energy expenditure, and a maximum of atom economy.[1,2] Among [3,3]-sigmatropic rearrangements the 3-aza Cope (also known as the 3-aza Claisen) rearrangement is especially flexible for the different types of molecules that it can lead to.[3,4] The caveat for its wider use resides in its need for high temperatures and prolonged reaction times, associated with sometimes modest yields. We report in this Letter an *N*-oxy-3-aza Cope rearrangement occurring at or below room temperature, which is gated by the configuration of the rearranging *N*-oxy-enaminic double bond, and which leads to functionalised oxime-allenes.[5]

The required hydroxylamine derivatives **4** (R^1,R^2 = H) could be routinely obtained from the O-substituted hydroxylamines **1** by propargylation of the corresponding *N*-Boc derivatives[6] **2** followed by deprotection of **3** with TFA (Scheme 1, *method a*), whereas by adapting Imada procedure[7] (Scheme 1, *method b*) compounds **4** (R^1,$R^2 \neq$ H) were easily made available from the corresponding *tert*-propargyl acetate. Next they were added to an activated acetylenic sulfone and the products were analysed. For example addition of **4a** to the acetylenic *p*-toluylsulfone[8] in DCM at rt gave rise after 60 h to allene **6a** in 95%, the only other product detected being enamine *E*-**5a** in 5%. The allene showed the characteristic IR absorption at 1954 cm^{-1} and a ^{13}C NMR high chemical shift at δ 211.5 for the allene carbon.[9] The results obtained with other hydroxylamine derivatives are summarised in Table 1. Good to excellent yields of functionalised allenes are found in reactions where the hydroxylamine oxygen substituent is tertiary and bulky [e.g., adamantyl, *tert*-butyl, 1,1-dimethyl-3-phenylpropyl and 1-methyl-cyclohexyl], or is attached to a tertiary silyl group as in Table 1, entries (*Z*) 1, 8, 11–13. Similar results are obtained when the hydroxylamine derivatives are disubstituted in the α-carbon of the propargyl [entries (*Z*) 2, 7, 9, 10], a marked decrease being, however, observed when the disubstitution is achieved through a *spiro* carbon, by incorporation of a six- or specially a five-membered ring [entries (*Z*) 5, 6]. When the triple bond of **2** bears a terminal substituent (entries 3, 4) no allene product is obtained at rt, the only product isolated being the unrearranged *E*-enamine Michael adduct *E*-**5**. The obtention of allenes **6** can be rationalised by invoking a sigmatropic 3-aza Cope rearrangement, as shown in Scheme 2, through either a zwitterionic intermediate[10] such as *Z*-**5A** or a neutral enaminic *Z*-**5**.

In order to detect possible intermediates the reactions were followed by ^1H NMR in CD_2Cl_2. Immediately after addition of **4a** to the

* Corresponding authors. Fax: +351 212948550 (A.M.L.).
E-mail address: aml@fct.unl.pt (A. M. Lobo).
URL: http://www.dq.fct.unl.pt/qoa/lpg.html (A. M. Lobo).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.228



a: R^1 = adamantyl; R^2,R^3,R^4 = H
b: R^1 = adamantyl; R^2,R^3 = Me; R^4 = H
c: R^1 = adamantyl; R^2,R^3 = H; R^4 = Me
d: R^1 = adamantyl; R^2,R^3 = H; R^4 = Et
e: R^1 = adamantyl; $R^2,R^3 = CH_2(CH_2)_3CH_2$; R^4 = H
f: R^1 = adamantyl; $R^2,R^3 = CH_2(CH_2)_2CH_2$; R^4 = H
g: R^1 = adamantyl; R^2 = Me; R^3 = Et; R^4 = H
h: R^1 = *tert*-butyl; R^2,R^3,R^4 = H
i: $R^1 = CMe_2(CH_2)_2Ph$; R^2,R^3 = Me; R^4 = H
j: R^1 = 1-methylcyclohexyl; R^2,R^3 = Me; R^4 = H
k: $R^1 = Si(i\text{-}Pr)_3$; R^2,R^3,R^4 = H
l: $R^1 = SiMe_2CMe_3$; R^2,R^3,R^4 = H
m: $R^1 = SiPh_2CMe_3$; R^2,R^3,R^4 = H
n: R^1 = benzyl; R^2,R^3,R^4 = H

Scheme 1.

acetylenic sulfone enamine *Z*-**5** is formed in a fast reaction, and this intermediate then suffers the rt rearrangement to yield allene **6**. When the rearrangement of *Z*-**5** is slower, competition from isomerisation to *E*-**5** occurs and such enamine accumulates. For the rearrangement of *E*-**5** to take place heating at above 70 °C (typically at 180 °C) is now needed [Table 1, entries (*E*) 2–4, 8, 12, 14]. At that temperature allene **6** is no longer stable and a cascade of reactions may lead to different compounds through triene **7**. For example if there are no substituents on the α-carbon of the propargylic unit, a substituted pyridine **8** is formed as shown in Scheme 3, resulting from elimination of R^1OH in the dihydropyridine after N–O bond cleavage [entries (*E*) 1, 3, 4, 8, 12, 14]. If, however, R^2 and R^3 are not hydrogens, then triene **9** is isolated [entry (*E*) 2] (cf. Scheme 4).

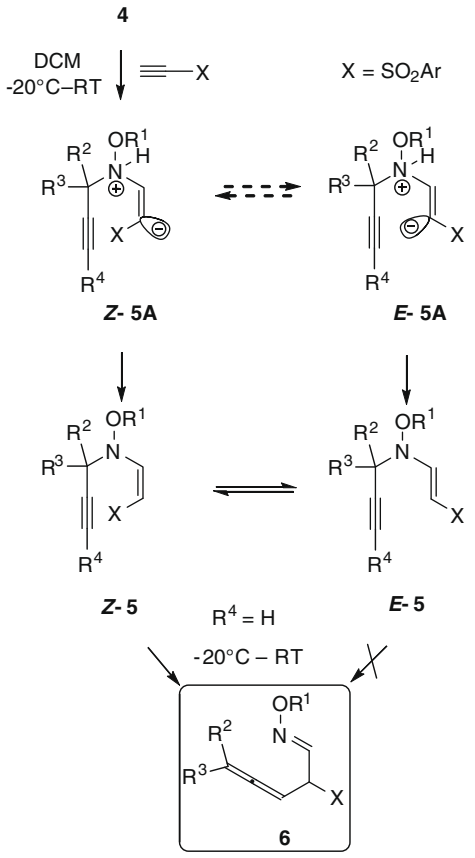
The oxime allenes **6** are themselves liable to acid-catalysed isomerisation, when, for example, in prolonged contact with silica gel at room temperature (as while being subjected to purification), in which case triene-type **7** is obtained by prototropy. Upon heating **6** at 180 °C the same isomeric triene **9** as above is obtained as in Scheme 4, which can be due to the facile formation of an ion-pair **6′**, followed by attack of the leaving sulfone moiety to the allene central carbon.

To gain insight into the stereoelectronic influences for the reaction path outlined in Scheme 5, the potential energy surface was modelled at the B3LYP/6-31G(d) level (Web Table), reaction barriers being computed from thermal and entropy corrected free energies. The initial transition state (TS1) involves a zwitterionic product, and this was modelled with a continuum solvation field applied (CPCM, specifying water or dichloromethane).[11] The subsequent non-ionic intermediates and transition states were modelled for the gas phase. We first note that nucleophilic addition by the amine to the arylsulfonylalkyne is predicted to exhibit a more stable transition state TS1 (by ~1.6 kcal mol^{-1}/water and 0.9 kcal mol^{-1}/dichloromethane in the solvation free energy) if the developing vinyl carbanion in the transition state is oriented *anti* rather than *syn* to the nucleophile. The effect arises predominantly from the greater solvation stabilisation in the *anti* configuration (dipole moment 14.1 D) compared to *syn* (dipole moment 11.2 D). This result agrees with an earlier suggestion by Evans and Kirby[12] that such nucleophilic

Table 1
3-Aza-Cope rearrangements of enamines **5** produced via Scheme 2.

#	O-Substituted hydroxylamines **4**	Configuration of enamines **5**	Conditions	Product Yield[a] (%)	
			Temp/Time	Allene **6**	Others
1	**a**: R^1 = adamantyl; $R^2 = R^3 = R^4$ = H	*Z*	rt/60 h	95[b]	*E*-**5a** (5[c])
		E	180 °C/15 min	–	**8a** (80)
2	**b**: R^1 = adamantyl; $R^2 = R^3$ = Me; R^4 = H	*Z*	−20 °C/90 d	91, 99[b]	–
		Z	−4 °C/25 d	98, 99[b]	–
		Z	rt/48 h	90, 99[b]	–
		E	70 °C/200 h	50, 54[b]	*E*-**5b** (15[c])
		E	180 °C/15 min	–	**9b** (70)
3	**c**: R^1 = adamantyl; $R^2 = R^3$ = H; R^4 = Me	*E*	180 °C/1 h	–	**8c** (80)
4	**d**: R^1 = adamantyl; $R^2 = R^3$ = H; R^4 = Et	*E*	180 °C/1 h	–	**8d** (71)
5	**e**: R^1 = adamantyl; $R^2 = R^3 = CH_2(CH_2)_3CH_2$; R^4 = H	*Z*	rt/96 h	61, 64[b]	*E*-**5e** (28[c])
6	**f**: R^1 = adamantyl; $R^2 = R^3 = CH_2(CH_2)_2CH_2$; R^4 = H	*Z*	rt/96 h	27, 28[b]	*E*-**5f** (70[c])
7	**g**: R^1 = adamantyl; R^2 = Me; R^3 = Et; R^4 = H	*Z*	rt/96 h	70, 93[b]	–
8	**h**: R^1 = *tert*-Bu; $R^2 = R^3 = R^4$ = H	*Z*	rt/72 h	64[b]	*E*-**5h** (30[c])
		E	180 °C/15 min	–	**8h** (71)
9	**i**: R^1 = 1,1-dimethyl-3-propyl; $R^2 = R^3$ = Me; R^4 = H	*Z*	rt/72 h	80, 99[b]	–
10	**j**: R^1 = 1-methylcyclohexyl; $R^2 = R^3$ = Me; R^4 = H	*Z*	rt / 72 h	78, 96[b]	-
11	**k**: $R^1 = (i\text{-}Pr)_3Si$; $R^2 = R^3 = R^4$ = H	*Z*	rt/24 h	64, 98[b]	–
12	**l**: $R^1 = (Me)_2(tert\text{-}Bu)Si$; $R^2 = R^3 = R^4$ = H	*Z*	rt/24 h	65, 68[b]	*E*-**5l** (32[c])
		E	180 °C/15 min	–	**8l** (88)
13	**m**: $R^1 = Ph_2(tert\text{-}Bu)Si$; $R^2 = R^3 = R^4$ = H	*Z*	rt/96 h	75, 92[b]	–
14	**n**: R^1 = benzyl; $R^2 = R^3 = R^4$ = H	*Z*	rt/72 h	60[b]	*E*-**5n** (30[c])
		E	180 °C/15 min	–	**8n** (77)

[a] Isolated yields after flash-chromatography.
[b] Yields calculated from ^{1}H NMR of crude reaction mixtures.
[c] Recovered *E*-enamine after chromatography.

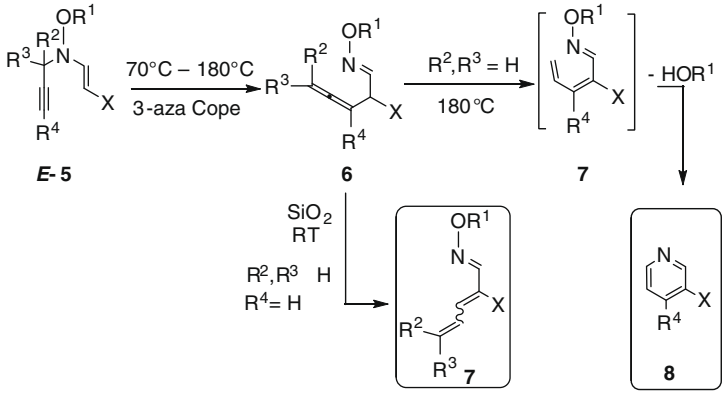


Scheme 2.

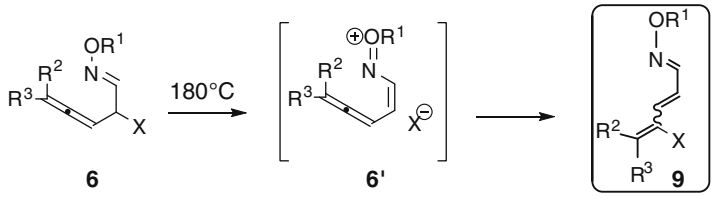
addition does indeed proceed via a vinylcarbanion intermediate in antiperiplanar fashion. The transition state for *Z*-**5A**/*E*-**5A** isomerisation by inversion at the vinyl carbanion centre (TS3) has a free energy 8.1 kcal mol^{-1} higher than that for TS1/*Z*-**5A**. The stereospecific anti-carbanion is thus presumed to be rapidly and irreversibly quenched with a proton to produce the *Z* enamine before any isomerisation to the *syn*-carbanion *E*-**5A** can occur. This stereochemistry represents a classical example of kinetic rather than thermodynamic control, since the alternative enamine *E*-**5** is in fact 9.1 kcal mol^{-1} more stable in free energy.

Either enamine now undergoes a [3,3] sigmatropic rearrangement (via TS2) to give **6**, the more facile reaction being that commencing from the less stable *Z*-**5** enamine with a free energy barrier of 20.2 kcal mol^{-1} and the less facile from the (more stable) *E* enamine, the barrier for which is 27.8 kcal mol^{-1}. The free energy barrier for double-bond isomerisation of the neutral *Z*-**5**/*E*-**5** intermediates (TS4) is too high to compete (free energy barrier 34.6 kcal mol^{-1}, 14.4 kcal mol^{-1} higher than that for [3,3]-rearrangement (TS2) of *E*-**5**). A viable mechanism for *Z*-**5**/*E*-**5** isomerisation, a process which is in fact observed to slowly take place, may in fact occur by prior protonation of the enamine on the *sulfonyl oxygen*, enhancing the electronic push/pull, and reducing the free energy barrier for double-bond rotation (TS5) down to a more feasible 20.0 kcal mol^{-1} (from protonated *Z*-**5**). This would allow *Z*-**5** to isomerise at a similar rate to the competing [3,3] rearrangement. This overall free energy analysis rationalises the experimental observations that initial product *Z*-enamine reacts at low temperatures, whereas the more stable *E*-enamine has an observable lifetime, and only undergoes Cope rearrangement at >70 °C.

In conclusion, it has been shown that for *low to room temperature N*-oxy-3-aza Cope rearrangements, leading to oxime allenes, the *Z*-configuration of the rearranging enaminic double bond proves to be a critical factor.

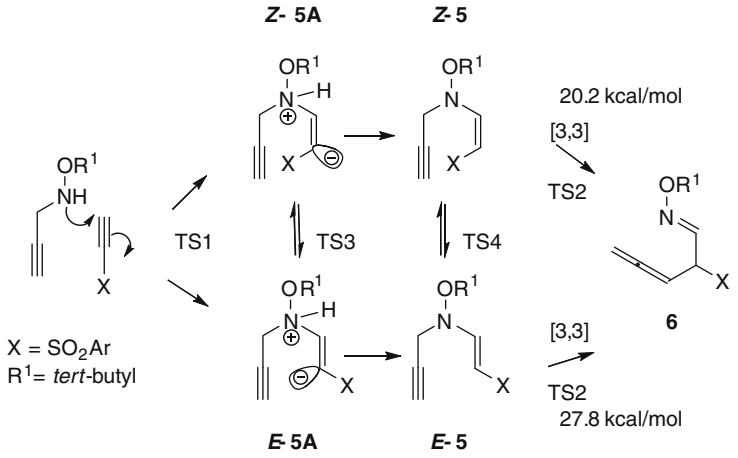


Scheme 3.



R^1 = adamantyl R^2,R^3 = Me X = SO_2Ar

Scheme 4.



Scheme 5.

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia (FC&T, Lisbon, Portugal) for partial financial support (Project POCTI/QUI/36456). Three of us (L.F.V.P., P.M.C.G., M.J.S.G.) are grateful for the award of doctoral fellowships from FC&T. A.J.G. Bento is thanked for the preparation of some starting materials.

Supplementary data

Supplementary data associated with this article can be at http://www.ch.imperial.ac.uk/rzepa/j.tetlet. 2009.02.228.

References and notes

1. Baum, R. M. *Chem. Eng. News* **2008**, 42–46; Ritter, S. K. *Ibidem* **2008**, 59–68.
2. Deffeyes, K. S. *Beyond Oil—The View from Hubbert's Peak*; Hill and Wang: London, 2006; Clark, J.; Macquarrie, D. *Handbook of Green Chemistry and Technology*; Blackwell: London, 2002.
3. For reviews, see: Majundar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597–643; Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149–213; Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002; Majumdar, K. C.; Ghosh, S.; Ghosh, M. *Tetrahedron* **2003**, *59*, 7251–7271; Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50; Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882; Blechert, S. *Synthesis* **1989**, 71–82; Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452; Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–246; Nubbemeyer, U. In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, 2007; pp 461–523.
4. For 3-aza-Cope rearrangements, see: Weston, M. H.; Nakajima, K.; Back, T. G. *J. Org. Chem.* **2008**, *73*, 4630–4637; Gonzalez, I.; Bellas, I.; Souto, A.; Rodriguez, R.; Cruces, J. *Tetrahedron Lett.* **2008**, *49*, 2002–2004; Glória, P. M. C.; Prabhakar, S.; Lobo, A. M. *Tetrahedron Lett.* **2008**, *49*, 7355–7357; Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138–4139; Craig, D.; King, N. P.; Mountford, D. M. *Chem. Commun.* **2007**, 1077–1079; Hemming, K.; O'Gorman, P. A.; Page, M. I. *Tetrahedron Lett.* **2006**, *47*, 425–428; Fiedler, D.; Van Halbeek, H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 10240–10252; Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748–6751; Zheng, J.-F.; Jin, L.-R.; Huang, P.-Q. *Org. Lett.* **2004**, *6*, 1139–1142; Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Savory, E. D.; Smith, A. D. *Chem. Commun.* **2003**, 2134–2135; Kang, J.; Kim, T. H.; Yew, K. H.; Lee, W. K. *Tetrahedron: Asymmetry* **2003**, *14*, 415–418; Winter, R. F.; Rauhut, G. *Chem. Eur. J.* **2002**, *8*, 641–649; Gomes, M. J. S.; Sharma, L.; Prabhakar, S.; Lobo, A. M.; Glória, P. M. C. *Chem. Commun.* **2002**, 746–747; Lindstrom, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, *7*, 94–98; McComsey, D. F.; Maryanoff, B. E. *J. Org. Chem.* **2000**, *65*, 4938–4943; Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545–3547.
5. *Modern Allene Chemistry*; Krauser, A., Stephen, A., Hashmi, K., Eds.; Wiley-VCH: Weinheim, 2004.
6. Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283–8286.
7. Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S. *J. Org. Chem.* **1994**, *59*, 2282–2284.
8. For acetylenic sulfones, see: Back, T. G. *Tetrahedron* **2001**, *57*, 5263–5301; Chen, Z.; Trudell, M. L. *Synth. Commun.* **1994**, *24*, 3149–3155; Bhattacharya, S. N.; Josiah, B. M.; Walton, D. R. M. *Organomet. Chem. Synth.* **1971**, *1*, 145–149.
9. *Typical experimental procedure*: To a 0.5 M solution of *tert*-butyl *N*-(*O*-adamantyl)carbamate **2a** (mp 99–100 °C), under N_2 atmosphere in dry DMF, were added NaH (1 equiv, 60% dispersion in oil) and after 5 min propargyl bromide (1 equiv). The reaction was left at rt for 2 h. After work-up the product was purified by flash chromatography to yield the hydroxylamine derivative **3a** as a yellowish oil (95%). Next this oil (1 equiv) was dissolved in DCM, TFA (4 equiv) was added and the mixture was left to react at rt for 24 h, after which the reaction was stopped and compound **4a** was obtained as a white solid (77%), mp 50–51 °C (Et_2O). *Addition to sulfone*: A DCM 0.4 M solution of **4a** (Table 1, entry 1) (20 mg) and ethynyl *p*-toluylsulfone (1 equiv) were left to react at rt for 60 h, when only allene **6a** (95%) and enamine ***E*-5a** (5%) could be identified. After ca. 30 h of reaction enamine ***Z*-5a** was clearly visible in the ^{1}H NMR of the mixture, but no trace was observed at the end. After completion of the reaction the solvent was evaporated and the products were purified by flash chromatography (silica, Et_2O/*n*-hex, 1:4).*Selected data*: ***Z*-5a**, ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 7.81 (2H, d, J = 8.2 Hz), 7.35 (2H, d, J = 8.2 Hz), 6.59 (1H, d, J = 10.1 Hz), 5.43 (1H, d, J = 10.1 Hz); ***E*-5a**, mp 138–9 °C; ^{1}H NMR (CD_2Cl_2) δ: 7.71 (2H, d, J = 8.2 Hz), 7.36 (1H, d, J = 12.7 Hz), 7.30 (2H, d, J = 8.2 Hz), 5.77 (1H, d, J = 12.7 Hz); HRMS *m/z*: 386.17882 (M^++1) ($C_{22}H_{28}NO_3S$ requires 386.17899); **6a**, IR (neat) 1954 (C=C=C) cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ: 7.68 (2H, d, J = 7.8 Hz), 7. 37 (2H, d, J = 7.8 Hz), 7.29 (1H, d, J = 7.3 Hz), 5.48–5.43 (1H, m), 4.92–4.85 (2H, m), 4.36 (1H, t, J = 6.0 Hz), 2.44 (3H, s), 2.10 (3H, br s), 1.69–1.50 (12H, m); ^{13}C NMR δ: 211.5; **8a**, IR (neat) 1317, 1158 (SO_2); ^{1}H NMR ($CDCl_3$) δ: 9.12 (1H, d, J = 1.0 Hz), 8.77 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.0 Hz), 8.20 (1H, d, J = 8.0 Hz), 7.85 (2H, d, J = 8.0 Hz), 7.44 (1H, dd, J_1 = 8.0 Hz, J_2 = 5.0 Hz), 7.33 (2H, d, J = 8.0 Hz), 2.42 (3H, s); HRMS *m/z*: 233.05170 (M^+) ($C_{12}H_{11}NO_2S$ requires 233.05105).
10. For zwitterionic intermediates, reported earlier in low-temperature 3-aza Cope rearrangements, see Refs. 3 (Nubbemeyer) and 4 (Weston et al.). In our reactions the *Z*-**5**/*E*-**5** isomerisation occurs after an *irreversible* protonation. It is unlikely that the reaction conditions could result in the deprotonation of the vinyl proton of the enamines, which would require a very strong base to be present.
11. Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001.
12. Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1269–1275.