Pergamon

Tetrahedron Letters 42 (2001) 4937–4939

TETRAHEDRON LETTERS

Highly diastereoselective dimerisation of alkenylthiazolines

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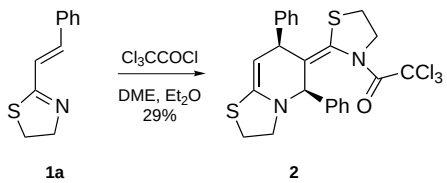
Received 11 April 2001; revised 14 May 2001; accepted 24 May 2001

Abstract—Alkenylthiazolines undergo a highly diastereoselective novel dimerisation when treated with trichloroacetyl chloride or with trifluoroacetic anhydride.

During the course of our recent investigations into the aza-Diels–Alder reactions of alkenylazolines,[1] we attempted the reaction of alkenylthiazoline **1a** with dichloroketene generated in situ from trichloroacetyl chloride. In reactions where the dichloroketene was not allowed to form fully, we were able to isolate a new product to which we were eventually able to assign structure **2**. Using only trichloroacetyl chloride, this compound was the sole product observed in the ^{1}H NMR spectrum of the crude reaction mixture. However, it proved somewhat difficult to purify, hence the relatively low yield presented (Scheme 1).

The assignment of structure **2** is based on extensive NMR data to confirm the stereochemistry of the core ring system. In particular, a significant W coupling (3.5 Hz) between the benzylic hydrogens establishes the stereochemistry around the six-membered ring; this is supported by NOE data on compound **3a** below. Compound **2** is formed as a single diastereoisomer (within the detection limits of 400 MHz ^{1}H NMR) although we have been thus far unable to obtain unambiguous data supporting the double bond geometry. The only precedent which we have been able to find for this transformation is from the work of Abdel-Rahman (Scheme 2).[2]

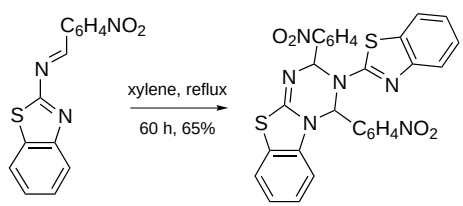


1a **2**

Scheme 1.

Given this encouraging preliminary result, and the interesting array of functionality within this molecule, we sought to investigate the scope and limitations of this new reaction. A brief survey of other acylating agents showed that only trifluoroacetic anhydride and trichloroacetyl chloride promote this dimerisation, with acetic anhydride, acetyl chloride and benzoyl chloride being ineffective, even at elevated temperatures. The reaction with trifluoroacetic anhydride was more convenient, and so attention was focused in this direction. This reaction was unsuccessful for alkyl-substituted vinylthiazolines, but proved effective for a range of substituted styrylthiazolines[3] (Table 1).[4] A similar reaction on the analogous styryloxazoline met with failure.

One interesting feature of the ^{1}H NMR spectrum of **3a** is the presence of two protons in the aromatic region at δ 6.85, slightly upfield of the rest. Nuclear Overhauser experiments established that these were the *ortho* hydrogens on the phenyl ring in the piperidine 2-position. We tentatively attribute this shielding as due to the proximity of the amide carbonyl and hence assign the double bond geometry as shown. Treatment of **3a** with trifluoroacetic acid in refluxing chloroform for 8 hours showed no double bond isomerisation, although significant decomposition was observed.



Scheme 2.

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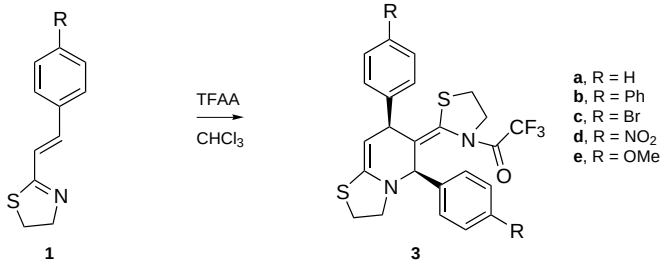
PII: S0040-4039(01)00886-3

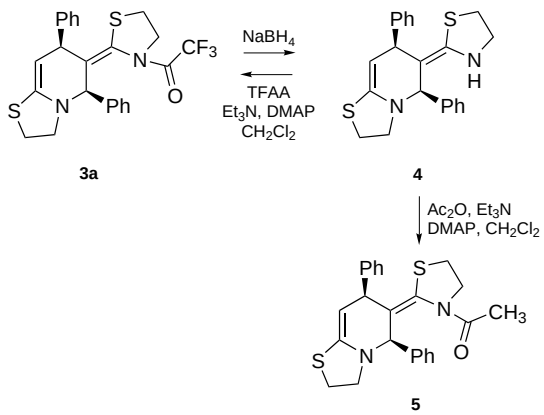
Table 1.



Product	Reaction time/h	Solvent (temperature)	Yield/%
3a[5]	3	1:4 Et_2O/DME (25°C)	49
3b	3	$CHCl_3$ (25°C)	25[a]
3c	6	$CHCl_3$ (75°C)	43
3d	3	$CHCl_3$ (75°C)	50
3e	3	1:4 Et_2O/DME (25°C)	31

[a] Compound **3b** was isolated with difficulty from a complex mixture, and was not obtained analytically pure.

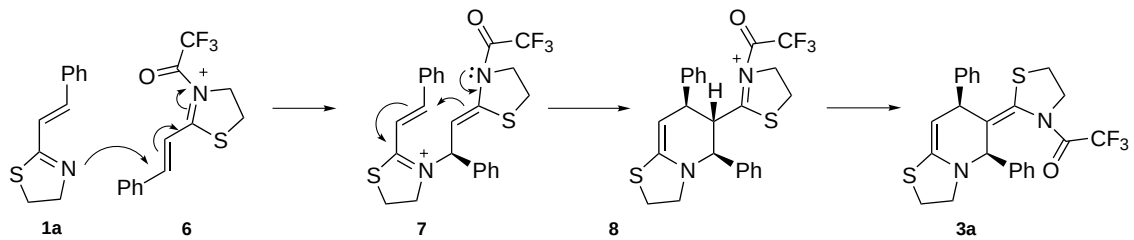
Unfortunately none of these compounds provided crystals suitable for X-ray analysis, so we elected to replace the trifluoroacetyl group with other acyl groups in the hope of obtaining further data. Reaction of **3a** with sodium borohydride in ethanol gave **4**, existing solely as the enamine tautomer.[6] Re-acylation with trifluoroacetic anhydride returned **3a** with no isomerisation of the double bond, verifying the validity of the method. Reaction of **4** with acetic anhydride gave a relatively impure sample of **5** with no loss of stereochemical integrity, although the only NOE enhancements observed for the methyl group were to the adjacent methylene. This can be attributed to the conformation of the amide group, so that again elucidation of the double bond geometry was unsuccessful (Scheme 3).



Scheme 3.

Clearly given the near-symmetry of the products, formation of a single double bond isomer is surprising to say the least. Our desire to confirm and rationalise the double bond geometry prompted us to carry out a computational study. This investigation supported our initial feeling that the reaction is stepwise as shown in Scheme 4.[7] In our previous work[1b] we found that the relatively large size of the molecules involved in these reactions and the large amount of conformational flexibility limited the level of theory used to semi-empirical methods. Here too, calculations have been carried out at the semi-empirical level using the PM3 Hamiltonian[8] within the MOPAC package.[9]

Acylation of **1a** will give the cationic intermediate **6**, in which the conformer shown is favoured by 13 kJ mol^{-1}. To give a calculation in which charge neutrality was ensured we included a single trifluoroacetate anion ($CF_3CO_2^-$) at all stages. This also allowed the proton loss from **8** to be modelled as the transfer of a proton to a base. Following Scheme 4, conjugate addition of **1a** to **6** will lead to **7**. Due to the conformational preference of **6**, only the double bond isomer shown need be considered, although we have carried out calculations on both isomers and reached identical conclusions. The location of transitions states corresponding to the closure of **7** to **8** in a stepwise mechanism was straightforward, and indeed showed that **7** should cyclise more readily than its double bond isomer. In either case, formation of the *cis*-2,4-diphenyl stereochemistry was overwhelmingly favoured. In the intermediate formed, the C=N bond of the acylated five-membered ring virtually eclipses the adjacent C–H bond. This intermediate immediately following ring closure is shown in Fig. 1, in which it can be seen that the pyramidalisation of the nitrogen means that the two phenyl groups are sufficiently distinguished in their spatial orientation. The phenyl group shown on the right is held further from the thiazoline ring as shown, allowing clockwise rotation of the thiazoline to give the double bond isomers as previously drawn, and tentatively assigned from the NMR data. These conclusions have been supported by a detailed study of the rotational barriers in **8**, to be published elsewhere.



Scheme 4.

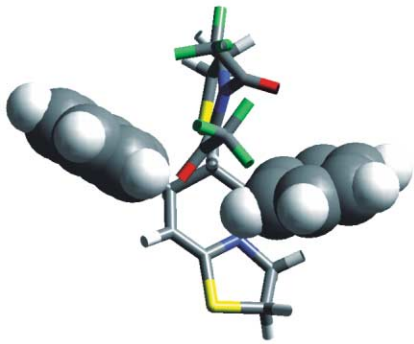


Figure 1. View of **8** directly down the C–H bond. The C–C bond is vertical.

Acknowledgements

We would like to thank the EPSRC for studentships (to N.M.G. and M.S.L.) and The Royal Society for additional support. We gratefully acknowledge support of our computational facilities by EPSRC, ICI Katalco and OCF, and thank the EPSRC Mass Spectrometry service, University of Wales Swansea, for the provision of high resolution mass spectrometric data.

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2. Abdel-Rahman, M. A. *Synth. Commun.* **1993**, *23*, 1427.
3. Styrylthiazolines were prepared by the direct condensation of 2-methylthiazoline with aromatic aldehydes: Wehrmeister, H. L. *J. Org. Chem.* **1962**, *27*, 4418.
4. All new compounds were characterised by ^{1}H and ^{13}C NMR, IR and HRMS. One notable feature of compounds **3a**, **3c**, **3d** and **3e** is the coincidence of peaks corresponding to the *ortho* carbons on the individual aromatic rings, and similarly the *meta* carbons, in the ^{13}C NMR spectra.
5. **Preparation of 2-(5,7-diphenyl-2,3,6,7-tetrahydro-5*H*-[1,3]-thiazolo[3,2-*a*]pyridin-6-ylidene)-3-(2,2,2-trifluoroacetyl-4,5-dihydro-1,3-thiazole (3a)**: (*E*)-2-[2-phenylethenyl]-4,5-dihydro-1,3-thiazole **1a** (150 mg, 0.8 mmol) was dissolved in dry ether (1 ml) and dimethoxyethane (4 ml). Trifluoroacetic acid anhydride (0.06 ml, 0.42 mmol) was added dropwise with stirring under N_2 at 25°C. After stirring for 3 h, the solution was washed with aqueous $NaHCO_3$ solution then with brine, dried over magnesium sulfate and concentrated in vacuo to yield a glassy orange solid. Column chromatography on neutral alumina (eluent, CH_2Cl_2) then gave the *title compound* (80 mg, 49%) as a colourless solid, mp 196–198°C (found, $[M+H]^+$, 475.1127; $C_{24}H_{22}F_3N_2OS_2$ requires M, 475.1125); ν_{max} (CH_2Cl_2) 1725 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.3–7.1 (8H, m, aromatic CH), 6.85 (2H, dd, *J* 7.5 and 1.7, aromatic CH), 4.6 (1H, d, *J* 11.1, alkene CH), 4.5 (1H, d, *J* 4.1 PhC*H*-N), 3.7 (2H, m, CH_2NCO), 3.4 (1H, dd, *J* 4.1 and 11.1 PhC*H*), 3.35 (2H, m, NCH_2) and 2.95 (4H, m, 2×S-CH_2); δ_C (100 MHz, $CDCl_3$) (carbonyl carbon not observed) 166.6, 166.2 (thiazoline-*C*), 139.5, 136.9 (aromatic *C*), 127.5, 127.0, 126.8, 126.2 (all aromatic-*C*H; peaks not fully resolved), 117.1 ($^2J_{C\text{-}F}$ 290 Hz, *C*F_3), 97.9 (alkene *C*), 70.7 (*C*H_2-NCO), 59.1 (alkene-*C*H), 51.8, (N-*C*H_2), 48.8, (Ph*C*H), 40.7 (Ph*C*H-N), 32.3 (one of S-*C*H_2) and 29.2 (one of *C*H_2-S); *m*/*z* (APCI) 475.2 (MH^+, 100%) and 102.5 (29).
6. With removal of the trifluoroacetyl groups, the protons assigned as the *ortho*-phenyl hydrogens at the piperidine 2-position moved downfield to merge with the rest of the aromatic protons, supporting our earlier hypothesis.
7. We have been unable to locate a transition state for the direct Diels–Alder reaction of **1** with **6** to give **8**.
8. Stewart, J. P. P. *J. Comp. Chem.* **1989**, *10*, 209.
9. Stewart, J. P. P. *J. Computer-aided Mol. Des.* **1990**, *4*, 1.