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Δ²-TRIAZOLINES—VI[1]

REARRANGEMENT OF TRIAZOLINES FROM 2-SUBSTITUTED-1-ARYL- AND 1-HETEROARYL-1-AMINO-ETHYLENES AND TOSYLAZIDE

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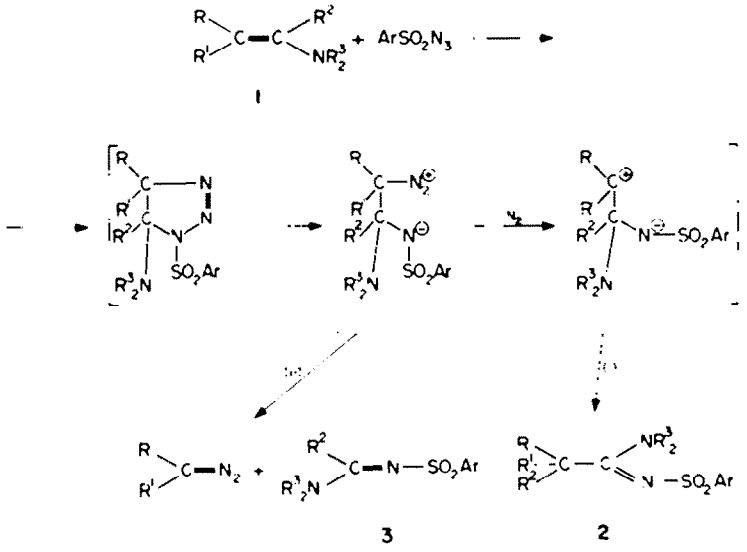
Abstract—Reaction of tosylazide with 2-substituted, 1-aryl- or 1-heteroaryl-1-amino-ethylenes affords, via unstable triazolines, a zwitterionic intermediate which can lead (i) through nitrogen loss and rearrangement to amidine (2) and (ii) through C_4–C_5 cleavage to the formation of a diazo compound and amidine (3).

Some aspects of the two mechanistic pathways are discussed.

Previous work on the reactivity of enamines toward sulfonylazides[2,3] showed that unstable triazoline intermediates are formed, which undergo cleavage to amidines according to schemes (i) or (ii):

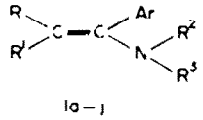


Scheme 1

It could be seen that path (i) is followed when R = alkyl and R' = H or alkyl, whereas path (ii) is the preferred rearrangement when R = R' = H.

Further work[1] pointed out that some enamines of cyclopropylalkylketones react with tosylazide following at the same time both path (i) and (ii), the former becoming more important the more substituted position 4 of the triazoline ring.

In this work 2-substituted, 1-aryl- or 1-heteroaryl-1-amino-ethylenes **1a–j** were reacted with tosylazide to study if the two separate mechanistic pathways (i) and (ii) operate concurrently. The effect, if any, of the aromatic ring, the basicity of the amine residue and the type of the substituent in the β-position of the enamine was also studied.



1a–j

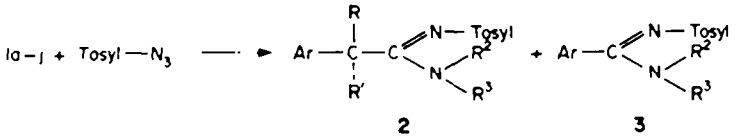
RESULTS

The enamines were reacted with tosylazide in benzene solution and at room temperature. The amidines obtained according to Scheme 2 are collected in Table 1 together with their molecular ratio and overall yields.

Table 1.

Enamine reacted	Ar	R	R	NR^2R^3	Amidine 2 No.	m.p.	Crist. Solv.	Formula	C	H	N
1a	Ph	H	Me	Morpholino	2a	156	EtOH	$C_{20}H_{24}N_2O_3S$	64.7 (64.5)	6.6 (6.5)	7.6 (7.5)
1b	Ph	H	Me	Pyrrolidino	2b	105	EtOH	$C_{20}H_{24}N_2O_2S$	67.15 (67.4)	6.75 (6.8)	8.0 (7.85)
1c	Ph	H	Me	N-methylanilino	2c	106	EtOH	$C_{23}H_{24}N_2O_2S$	70.2 (70.4)	6.1 (6.15)	7.25 (7.15)
1d	$C_6H_4OMe(4)$	H	Me	Morpholino	2d	170	EtOH	$C_{21}H_{26}N_2O_4S$	62.6 (62.7)	6.45 (6.5)	7.0 (6.95)
1e	$C_6H_4NO_2(4)$	H	Me	Morpholino	2e	218	EtOH	$C_{20}H_{23}N_3O_4S$	57.4 (57.55)	5.5 (5.55)	9.85 (10.1)
1f	Ph	H	Et	Morpholino	2f	147	iPrOH	$C_{21}H_{26}N_2O_2S$	65.0 (65.3)	6.55 (6.8)	7.3 (7.25)
1g	Ph	H	Ph	Morpholino	2g	144	EtOH	$C_{25}H_{26}N_2O_2S$	68.9 (69.1)	5.85 (6.0)	6.7 (6.45)
1h	Ph	Me	Me	Morpholino	2h	111	iPrOH	$C_{21}H_{26}N_2O_2S$	65.1 (65.3)	6.75 (6.8)	7.3 (7.25)
1i	2-Furyl	H	Me	Morpholino	2i	132	EtOH	$C_{18}H_{22}N_2O_3S$	59.8 (59.65)	6.15 (6.1)	7.4 (7.7)
1j	2-Thienyl	H	Me	Morpholino	2j	163	EtOH	$C_{18}H_{22}N_2O_2S_2$	56.95 (57.15)	5.95 (5.85)	7.4 (7.4)

†Aromatic protons and the Me group of the tosyl residue are not described owing to their low interest.



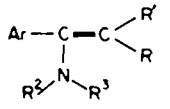
Scheme 2

DISCUSSION

The above results show that the triazolines from enamines 1 and tosylazide rearrange according to both paths (i) and (ii) at the same time, with comparable rates.

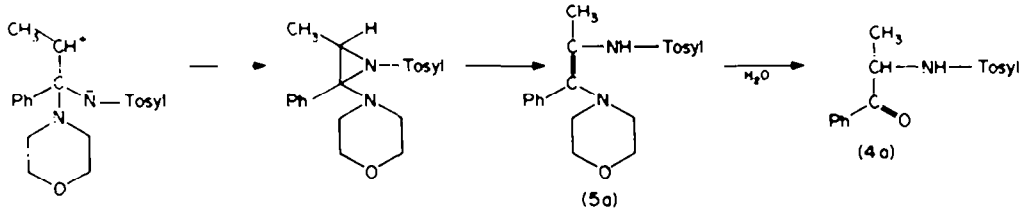
The ratios between amidines 2 and amidines 3 are always in the range from 5:5 to 7.5:2.5 for all the studied reactions.

This evidences a general effect of the substitution in the position 4 of the triazoline intermediates. In the case of acetophenone enamine[1] the rearrangement reaction according to path (i) is absent whereas in the present cases path (i) becomes the preferred mechanism. The ratio 2/3 is practically the same for all enamines reacted. This shows that the outcoming of the reaction of enamines of general formula with sulfonylazides is only determined by the



general structure of the enamine, being only weakly affected by changes of the amine residue (**1a**, **1b**, **1c**), by the kind of the Ar substituent (**1d**, **1e**, **1i**, **1j**) or by the nature and number of the substituents on th β C atom (*cf* **1a**, **1f**, **1g**, **1h**).

From the reaction mixture of enamine **1a** also 2 tosylamino - propiophenone (**4a**) was isolated in very low yields. This compound was certainly formed from the hydrolysis of β-tosyl-amino enamine (**5a**) which was derived from an aziridine intermediate.



Amidine 3									Mol ratio 2/3	Overall yield (2 + 3) (%)
NMR†	No	m.p.	Crist. solv.	Formula	C	H	N	NMR†		
1.62 (3H, d, Me) 3.37 (8H, m, morph.) 5.58 (1H, q, CH)	3a	168	EtOH	$C_{18}H_{20}N_2O_4S$	62.75 (62.8)	5.9 (5.85)	8.1 (8.15)	2.85–4.10 (8H, m, morph.)	60/40	72
1.57 (3H, d, Me) 1.40–1.90 (4H, m, CH_2CH_2) 2.50–3.80 (4H, m, CH_2NCH_2) 5.36 (1H, q, CH)	3b	150	iPrOH	$C_{19}H_{20}N_2O_2S$	65.85 (65.85)	6.0 (6.15)	8.4 (8.55)	1.90 (4H, m, CH_2CH_2) 3.05–3.70 (4H, 2t, CH_2NCH_2)	60/40	92
1.55 (3H, d, Me) 3.23 (3H, s, NMe) 5.18 (1H, q, CH)	3c	144	iPrOH	$C_{21}H_{20}N_2O_2S$	69.05 (69.2)	5.3 (5.55)	7.45 (7.7)	3.50 (3H, s, NMe)	60/40	82
1.55 (3H, d, Me) 3.42 (8H, s, morph.) 3.80 (3H, s, MeO) 5.48 (1H, q, CH)	3d	121	iPrOH	$C_{19}H_{22}N_2O_4S$	60.75 (60.95)	5.95 (5.9)	7.4 (7.5)	3.00–4.00 (8H, m, morph.) 3.80 (3H, s, MeO)	70/30	75
1.70 (3H, d, Me) 3.40 (8H, s, morph.) 5.65 (1H, q, CH)	3e	203	iPrOH	$C_{18}H_{16}N_2O_4S$	56.0 (55.5)	4.5 (4.9)	10.7 (10.8)	2.90–4.10 (8H, m, morph.)	60/40	80
1.17 (3H, t, CH_3) 1.65–2.55 (2H, m, CH_2) 3.38 (8H, m, morph.) 5.40 (1H, t, CH)	3a								60/40	70
3.00–3.80 (8H, m, morph.) 7.01 (1H, s, CH)	3a								50/50	72
1.23 (6H, s, 2Me) 3.68 (8H, s, morph.)	3a								65/35	65
1.64 (3H, d, Me) 3.50 (8H, s, morph.) 5.53 (1H, q, CH)	3f	160	iPrOH	$C_{16}H_{18}N_2O_4S$	57.1 (57.5)	5.35 (5.45)	8.2 (8.4)	3.58 (8H, m, morph.)	65/35	70
1.71 (3H, d, Me) 3.51 (8H, s, morph.) 5.68 (1H, q, CH)	3g	173	iPrOH	$C_{16}H_{18}N_2O_3S_2$	55.35 (54.85)	5.25 (5.2)	8.05 (8.0)	3.62 (8H, s, morph.)	75/25	75

The presence of enamine **5a** in the crude reaction mixture was strongly supported by a sharp singlet at 1.78δ in the NMR spectrum (CH_3–C=). Similar signals were found in the spectra of the crude reaction mixture from the other enamines. However, no effort was made to isolate these compounds because of their weak interest in the present study.

EXPERIMENTAL

All m.ps are uncorrected. The NMR spectra were recorded at 60 MHz using a Varian A-60 spectrometer. Chemical shifts are given in parts per million relative to internal TMS.

Enamines. The following enamines are reported in the literature: **1a**, **1d**, **1e**, **1i**, **1j**,[4] **1b**,[5] **1g**,[6] **1c**.[7]

The new enamines **1f**, p.e. (1 torr) 105–108°, NMR ($CDCl_3$): 0.92 (3H t, Me); 1.95 (2H, m, CH_2); 2.70 and 3.62 (8H, 2m, morph.); 4.62 (1H, t, CH); 7.30 (5H, m, Ph). (Found: C, 77.25; H, 8.85; N, 6.40. Calc. for $C_{14}H_{19}NO$: C, 77.40; H, 8.80; N, 6.45%); and **1h** p.e. (1 torr) 103–106°, NMR ($CDCl_3$): 1.50 and 1.90 (6H, 2s, Me); 2.60 and 3.68 (8H, 2m, morph.); 7.0–7.50 (5H, m, Ph). (Found: C, 77.45; H, 8.85; N, 6.35. Calc. for $C_{14}H_{19}NO$: C, 77.40; H, 8.80; N, 6.45%), were prepared by the method of White and Weingarten.[8]

Reactions with tosylazide. A soln of the enamine (10% an anyds benzene) was reacted at room temp. with an equimolar amount of tosylazide (25% in benzene). The mixture was analyzed by TLC and, at the end of the reaction, the crude mixture was chromatographed directly on a silica column (Kieselgel 60, Merck) using benzene–EtOAc (80/20) as eluent. The data of the isolated products are collected in Table 1.

2-Tosylamino-propiophenone. 1 g of the crude mixture from enamine **1a** was chromatographed on a silica column containing 80 g of Kieselgel 60 (Merck). The column was eluted with a 10% EtOAc–90% benzene at a flow rate of 3 ml/min. The first fraction collected was concentrated under reduced pressure to give 65 mg of a clear oil. Working up and recrystallization from 95% EtOH gave a white solid, m.p. 100–101°. NMR ($CDCl_3$): 1.39 (3H, d, Me–CH); 2.31 (3H, s, Me); 4.59 (1H, m, CH); 5.31 (1H, d, NH); 7.1–7.9 (9H, m, aromatics). (Found: C, 63.65; H, 5.65; N, 4.55. Calc. for $C_{16}H_{17}NO_3S$: C, 63.65; H, 5.65; N, 4.6%).

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