Pergamon

Tetrahedron Letters, Vol. 36, No. 22, pp. 3901-3904, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00594-3

(2*E*,4*E*)-5-Tosyl-2,4-pentadienamides: New Dienic Sulfones for the Stereoselective Synthesis of (2*E*,4*E*)-Dienamides

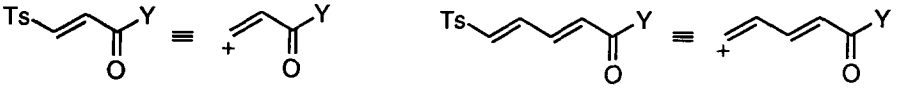
M. Carmen Bernabeu, Rafael Chinchilla and Carmen Nájera*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Abstract: The iodosulfonylation of (2*E*)-pentadienamides **1** affords stereoselectively (2*E*,4*E*)-5-tosylpentenamides **2**. These dienic sulfones suffer nucleophilic vinylic substitution of the tosyl group by sodium thiolates and Grignard reagents to give regio- and stereo-selectively (2*E*,4*E*)-dienamides **3**. This methodology has been applied to the synthesis of sarmentine (**3bg**) and an Achillea amide (**3cg**).

(2*E*,4*E*)-Unsaturated amides derived from piperidine, pyrrolidine and isobutylamine are interesting synthetic targets[1] because they belong to an important class of natural products, which are common flavour constituents and show also both physiological and insecticidal activities. The bigest difficulty to synthetise these compounds is the regio- and stereo-selective introduction of the double bonds. Several synthetic methods for dienamides create double bonds by: (a) Knoevenagel condensations[2], (b) Wittig type approaches[3] and (c) palladium-catalysed coupling reaction of β-bromoacrylamides with alkenylboronates[4]. Other methodologies are based on: (a) elimination reactions of β-substituted sulfones[5] and allyl carboxylates[6], (b) isomerization of 2-ynoic amides[7] and 3,4-dienamides[8] and (c) cross-coupling reactions of silylated glutaconaldehyde[9] or (2*E*,4*E*)-5-iodo-2,4-dienamides[10] with organomagnesium compounds.

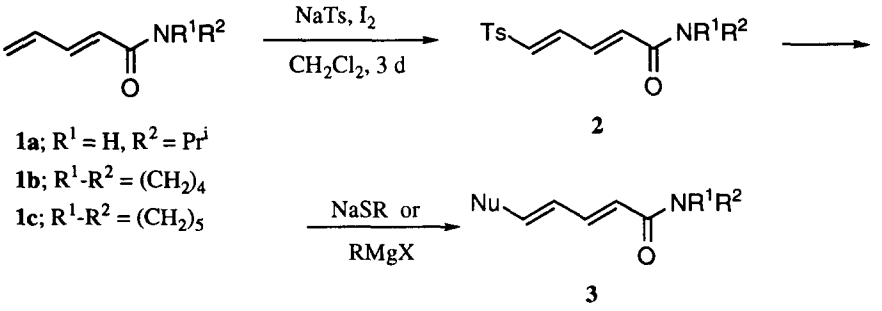
Continuing our studies on vinylic nucleophilic substitution of the sulfone group in β-tosylacrylic derivatives **I** and their application, as β-acylvinyl cation equivalents **II**, to the synthesis of β-substituted acrylates and acrylamides[11], we report here a straightforward method for the transformation of (2*E*)-pentadienamides into (2*E*,4*E*)-dienamides using δ-tosyl dienamides of the type **III** as δ-acyldienyl cation equivalents **IV**.



I **II** **III** **IV**

When (2*E*)-2,4-pentadienamides **1**, prepared from (2*E*)-2,4-pentadienoic acid[12], were allowed to react with sodium *p*-toluenesulfinate and iodine in dichloromethane[14], the corresponding (2*E*,4*E*)-5-tosyl-2,4-pentadienamides **2** were obtained (Scheme 1 and Table 1). Surprisingly the dehydroiodination process took place spontaneously in the reaction medium without the presence of triethylamine[14] or other bases. These dienic sulfones **2** are stable crystalline compounds which can be stored at room temperature for months. As secondary

products were isolated in some cases (2*Z*,4*E*)-2,5-ditosyl-2,4-pentadienamides **4** which can be easily separated by column chromatography. The configuration of these disulfones **4**, which were formed by iodosulfonylation of compounds **2** followed by spontaneous dehydroiodination, was established according to NOE experiments.



Scheme 1.

Table 1. Preparation of Dienic Sulfones **2**.

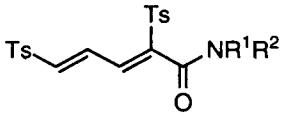
no.	R^1	R^2	yield (%)[a]	mp (°C)[b]
2a	H	Pr^i	43[c]	175-177
2b	$(CH_2)_4$		31	173-175
2c	$(CH_2)_5$		42[d]	185-187

[a] Based on dienamides **1** after column chromatography on silica gel [all compounds were fully characterized by their spectroscopic data (IR, ^1H and ^{13}C NMR, and mass spectra)]. [b] Hexane/EtOAc. [c] A 12% of compound **4a** was also obtained. [d] A 7% of compound **4c** was also obtained.

The nucleophilic vinylic substitution of the tosyl group took place with two equiv. of sodium thiolates or organomagnesium compounds at low temperatures in THF to give (2*E*,4*E*)-dienamides **3** in a regio- and stereoselective manner (Scheme 1 and Table 2). The reaction was first at all studied with sulfones **2a** and **2c** as models of mono- and di-alkylated amides, respectively. In the case of compound **2a**, derived from isopropylamine, the substitution occurred only with thiolates, so with sodium benzylthiolate at room temperature compound **3aa** was obtained (Table 2, entry 1). However, in the case of the dienic sulfone **2c** derived from piperidine the reaction with sodium benzylthiolate at 0°C afforded compound **5** (Table 2, entry 4) due to the 1,6-Michael addition of the nucleophile to the first formed compound **3ca**. The dienamide **3ca** was prepared carrying out the reaction at -40°C. With the bulkier sodium (1*S*-*exo*)-2-bornanethiolate[15] the substitution product **3cb** was formed exclusively at 0°C (Table 2, entry 5). The substitution reaction took place also with disulfone **4c** at the δ-position to let to the formation of compound **6** (Table 2, entry 6). When compound **2c** was allowed to react with other heteronucleophiles such as alcoholates and amines only decomposition reactions were observed.

The alkylation reaction was studied with the dienic sulfone **2c**, derived from piperidine, and different alkyl or vinyl Grignard reagents, in all cases the substitution occurred at the δ-position to yield stereoselectively (2*E*,4*E*)-dienamides **3** (Scheme 1 and Table 2, entries 6-10 and 12). With the monoalkylated amide **2a**, derived

from isopropylamine, the reaction failed.



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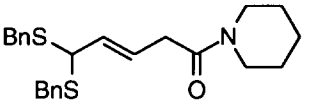

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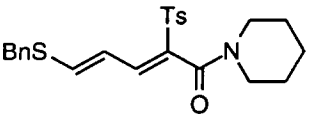

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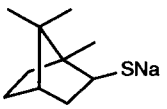
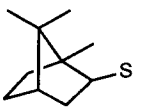
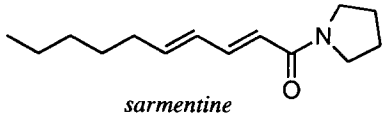
Table 2. Reaction of Dienic Sulfones **2** with Nucleophiles. Synthesis of (2*E*,4*E*)-Dienamides **3**.

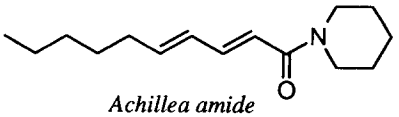
				product					
Entry	sulfone	nucleophile	reaction conditions	no.	R^1	R^2	Nu	yield (%)[a]	R_f[b]
1	**2a**	NaSBn	rt, 1 h	**3aa**	H	Pr^i	SBn	65	0.42[c]
2	**2c**	NaSBn	-40°C, 2 h	**3ca**	$(CH_2)_5$		SBn	52	0.53
3	**2c**	NaSBn	0°C, 1.5 h	**5**				42	0.60
4	**4**	NaSBn	rt, 2 h	**6**				53	0.58[d]
5	**2c**		0°C, 3 h	**3cb**	$(CH_2)_5$			58	0.30[e]
6	**2c**	EtMgCl	-40°C, 5 h	**3cc**	$(CH_2)_5$		Et	47	0.39[f,g]
7	**2c**	Pr^iMgCl	-40°C, 3 h	**3cd**	$(CH_2)_5$		Pr^i	22	0.40[f]
8	**2c**	Bu^nMgCl	0°C, 1 h	**3ce**	$(CH_2)_5$		Bu^n	25	0.75
9	**2c**	Bu^iMgBr	-20°C, 2 h	**3cf**	$(CH_2)_5$		Bu^i	43	0.50[f]
10	**2b**	$Pent^nMgCl$	-40°C, 2 h	**3bg**	$(CH_2)_4$		$Pent^n$	53	0.42[h,i]
11	**2c**	$Pent^nMgCl$	-40°C, 4 h	**3cg**	$(CH_2)_5$		$Pent^n$	60	0.60[j]
12	**2c**	CH_2=CHMgBr	-40°C, 2 h	**3ch**	$(CH_2)_5$		CH_2=CH	48	0.62

[a] Isolated yield after flash chromatography (silica gel) based on starting sulfone; all compounds were fully characterized by their spectroscopic data (IR, ^1H and ^{13}C NMR, and mass spectra). [b] From hexane/EtOAc: 1/1. [c] Mp 158-160°C (hexane/EtOAc). [d] Mp 128-130°C (hexane/EtOAc). [e] $[\alpha]_D^{25}$ = +100.3 (c 1.2, EtOH). [f] Hexane/ether: 1/4. [g] Lit.[7a] bp 110°C/0.01 torr. [h] Hexane/EtOAc: 1/3. [i] Lit.[1g] R_f 0.42 (30% EtOAc/petrol). [j] Lit.[7a] colorless liquid.

This methodology has been applied to the synthesis of naturally occurring unsaturated amides *N*-[(2*E*,4*E*)-decadienoyl]pyrrolidine (**3bg**), sarmentine[1g] and *N*-[(2*E*,4*E*)-decadienoyl]piperidine (**3cg**) an Achillea amide[1a], by reaction of n-pentylmagnesium chloride with sulfones **2b** and **2c**, respectively (Table 2, entries 10 and 11).



sarmentine



Achillea amide

In conclusion, this procedure is a direct and stereoselective route to (2*E*,4*E*)-dienamides, starting with (2*E*)-pentadienamides and using the new reagents (2*E*,4*E*)-5-tosylpentadienamides as δ-acyldienyl cation equivalents.

Synthesis of Compounds **2**. *Typical Procedure:* To a stirred suspension of amide **1** (1.8 mmol) and sodium *p*-toluenesulfinate (0.435 g, 1.7 mmol) in CH_2Cl_2 (150 mL) was added iodine (0.45 g, 1.8 mmol) in small portions during 3 d. The resulting suspension was washed with aqueous 0.1 M $Na_2S_2O_3$ and the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel to afford compounds **2** and/or **4** (see Table 1).

Synthesis of Dienamides **3**. *Typical Procedure:* To a stirred solution of dienic sulfone **2** (0.3 mmol) in dry THF (4 mL) was added under argon the corresponding solution of the sodium thiolate or the Grignard reagent (0.7 mmol) in THF at the temperature and for the time indicated in Table 2. The reaction was monitorized by TLC and quenched with water and saturated NH_4Cl. The reaction mixture was extracted with ether, dried (Na_2SO_4) and evaporated to give crude compounds **3**, which were purified by column chromatography on silica gel[16].

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16. We are grateful to DGICYT of the Spanish Ministerio de Educación y Ciencia (MEC, Project no. PB91-0751) for financial support. R. C. thanks MEC for a postdoctoral fellowship.

(*Received in UK* 20 *March* 1995; *accepted* 31 *March* 1995)