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STEREOSELECTIVE SYNTHESIS OF (E)-β-ALKYL ACRYLATES AND ACRYLAMIDES

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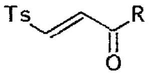
Summary: β-Tosyl-α,β-unsaturated esters and amides react regio and stereoselectively with carbanionic reagents to afford β-alkyl, alkenyl, or alkynyl substituted α,β-enoates or enamides with an E configuration.

β-Sulfonyl-α,β-unsaturated carbonyl compounds **1**[1] are interesting molecules because they exhibit dual reactivity at their β-position: they can act either as β-acylvinyl cation equivalents **2a**[1] or as β-acylvinyl anion ones **2b**[2], according to a normal or umpoled reactivity, respectively. In both cases the sulfone group directs the attack at the β-position either by nucleophilic or electrophilic reagents, when the last process was preceded by the corresponding metallation reaction. The reactivity of compounds of the type **1** as β-acylvinyl cation equivalents involves the substitution of the sulfone moiety by a nucleophile and has been mainly described for β-sulfonylvinyl ketones and nitrogen or sulfur containing nucleophiles;[1,3] this process is facilitated by other electron-withdrawing groups such as nitro[4] or sulfone.[5] We now report the synthesis of β-alkyl substituted α,β-enoates[6] and enamides from β-tosylacrylic derivatives and carbanionic reagents, the sulfone group acting as a leaving one.



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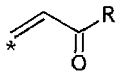

2a, * = +
2b, * = -

The reaction of the (E)-β-tosyl-α,β-unsaturated esters **3a**,**b** and (E)-N-(β-tosylacryloyl)piperidine (**3c**) with two equivalents of the corresponding organomagnesium compound[7] at 0°C in tetrahydrofuran led regio and stereoselectively to (E)-α,β-unsaturated esters or amides **4** (Scheme 1 and Table 1). When vinylmagnesium bromide was used as nucleophile the

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Table 1 . Reaction of β-tosylated acrylic derivatives **3** with organometallic reagents. Preparation of β-alkyl-α,β-unsaturated esters and amides **4** or compounds **5**.

Starting material			Organometallic	Reaction	Product[a]		
No.	R^1	X	R^2M	time (h)	No.	Yield (%)[b]	B.p. (°C)[c] or R_f[d]
3a	H	OEt	$CH_2{=}CHMgBr$	3	**4a**	79	80
3c	H	$\overline{\mathrm{N(CH_2}}\mathrm{)_5}$	$CH_2{=}CHMgBr$	2	**4b**	90	160
3c	H	$\overline{\mathrm{N(CH_2}}\mathrm{)_5}$	i-PrMgBr	14	**4c**	56	0.25
3a	H	OEt	n-BuMgBr	1	**4d**	75	60
3b	Me	OMe	n-BuMgBr	4	**4e**	89	60
3a	H	OEt	$n\text{-}C_6H_{13}C{\equiv}CMgBr$[e]	24	**4f**	55	0.75
3b	Me	OMe	$(EtO_2C)_2CHNa$[f]	15	**4g**	70	160
3a	H	OEt	$(EtO_2C)_2CHNa$[f]	1	**5a**	60	0.65[g]
3c	H	$\overline{\mathrm{N(CH_2}}\mathrm{)_5}$	$(EtO_2C)_2CHNa$[f]	24	**5b**	78	0.46[g]

[a] All compounds are >95% pure (g.l.c.) and gave satisfactory spectral data (i.r., ^{1}H and ^{13}C n.m.r., and mass spectra).

[b] Based on the starting sulfone **3**. Yields after distillation or flash chromatography. Products **4** were isolated as pure (E)-stereoisomers (g.l.c. or/and 300 MHz ^{1}H n.m.r.).

[c] Bath temperature at 0.1 torr.

[d] Silica gel; hexane/ether: 1/2.

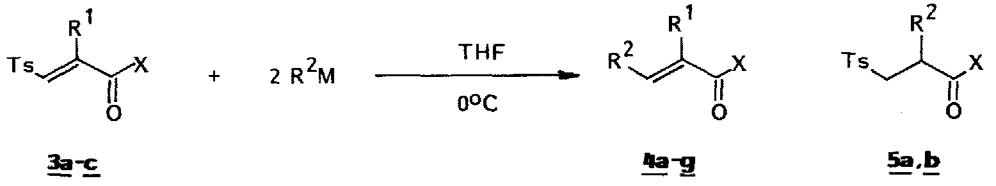
[e] Prepared from 1-octyne and isopropylmagnesium bromide.

[f] Prepared from diethylmalonate and sodium hydride.

[g] Silica gel; hexane/ether: 1/10.

corresponding dienoate **4a** and dienamide **4b** were obtained; this method for **4a**,**b** constitutes a new direct and simple approach to the synthesis of this important class of compounds.[8]

When sodium diethyl malonate was used as nucleophile, only the methyl methacrylate derivative **3b** afforded the corresponding substituted ester **4g** as a mixture of Z/E stereoisomers. In the case of the acrylate derivatives **3a** and **3c**, Michael type reaction products **5** were exclusively obtained (Scheme 1 and Table 1).



Scheme 1.

The methodology described in this paper allows the two steps stereoselective alkylation of simple acrylic or methacrylic derivatives: a tandem iodosulfonylation-dehydroiodination reaction[1] followed by the alkylation with the appropiate alkyl, alkenyl, or alkynyl Grignard reagent or sodium malonate.

In a typical reaction the ethereal solution of the Grignard reagent (2 mmol) or sodium diethyl malonate[9] was dissolved in tetrahydrofuran (5 ml) and cooled at 0°C. To the resulting solution was added the corresponding substituted β-tosyl ester or amide **3** in small portions. The reaction mixture was stirred at 0°C (see Table 1) and monitored by t.l.c. When the reaction was finished the resulting solution was hydrolysed with water and a saturated aqueous solution of ammonium chloride, and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated (15 torr) to afford crude products **4** or **5**, which were purified by distillation in vacuo (0.1 torr) or by flash chromatography on silica gel (see Table 1).[10]

References and Notes

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9. In this case sodium hydride was added to the solution of diethyl malonate in tetrahydrofuran.

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